FDA Oncologic Drugs Advisory Committee Meeting

BRIEFING DOCUMENT PREPARED BY MYLAN

MYL-1401O (Mylan's proposed biosimilar to trastuzumab)

ADVISORY COMMITTEE BRIEFING MATERIALS:
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
BLA	Biologics Licensing Application
BWFI	Bacteriostatic water for injection
CI	Confidence interval
CD	Circular dichroism
DP	Drug product
DS	Drug substance
DSC	Differential scanning calorimetry
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
FDA	Food and Drug Administration
FPER	false-positive error rate
FTIR	Fourier transform infrared
HMWP	High molecular weight protein
HPLC	High-performance liquid chromatography
ICH	International Council for Harmonisation
IEX	Ion exchange
IOP	Inhibition of proliferation
IRS	Internal reference standard
ITT	Intent-to-Treat
IV	Intravenous
LVEF	Left ventricular ejection fraction
MBC	Metastatic breast cancer
MOA	Mechanism of action
NP-HPLC	Normal phase high-performance liquid chromatography
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic
PFS	Progression-free survival
PK	Pharmacokinetic
PP	Per Protocol
PSUR	Periodic safety update report
PV	Process validation
QR	Quality range
RP-HPLC	Reverse phase high-performance liquid chromatography
SAE	Serious adverse event
SD	Standard deviation
SPR	Surface plasmon resonance
US	United States
TEAE	Treatment-emergent adverse event
TK	Toxicokinetic
T/R	Test/reference
TTP	Time to progression
UV	Ultraviolet

1 EXECUTIVE SUMMARY

Mylan, in partnership with Biocon, has developed MYL-1401O as a proposed biosimilar to the United States (US)-licensed reference product, Herceptin® (trastusumab). Mylan submitted a Biologics License Application (BLA) under Section 351(k) of the Public Health Service Act seeking approval of MYL-1401O for the treatment of the same indications as Herceptin. MYL-1401O is the first proposed trastuzumab biosimilar and as such represents an important addition to the armamentarium for the treatment of cancer. Mylan looks forward to the review of this product by the Oncologic Drugs Advisory Committee (ODAC).

The development of MYL-1401O followed a step-wise approach as outlined in the Food and Drug Administration's guidance document for establishing biosimilarity. As the development was also intended to support registration in the European Union (EU), Mylan incorporated European guidance into its development program, including the evaluation of both US- and EU-approved Herceptin.

The step-wise development approach began with the structural and functional characterization of Herceptin protein using a wide array of sensitive methods. This understanding was used to develop and manufacture MYL-1401O to match Herceptin. The extensive data from the analytical similarity assessment demonstrated that MYL-1401O is highly similar to US-licensed Herceptin and European Union (EU)-approved Herceptin (hereafter referred to as US-Herceptin and EU-Herceptin, respectively). Any differences detected from the physicochemical and structural studies were determined to have no impact on biological activities measured *in vitro*, thereby supporting the conclusion that MYL-1401O would have the same clinical safety and efficacy profile as Herceptin.

This was followed by a nonclinical program that included safety pharmacology studies and toxicology studies. The safety pharmacology studies focused on assessing the effects of MYL−1401O and EU-Herceptin on mitochondrial function in human and rat cardiomyocytes. The toxicology studies were conducted in Cynomolgus monkeys with the objective of evaluating the toxicological effects and exposure between products prior to dosing human subjects. Overall, the nonclinical program demonstrated a comparable safety and toxicology profile between the products.

Finally, the clinical program was conducted to establish bioequivalence and to confirm that MYL-1401O and Herceptin are therapeutically equivalent with no clinically meaningful differences in safety and immunogenicity profiles. These studies included a 3-way pharmacokinetic (PK) bridging study comparing MYL-1401O, EU-Herceptin, and US-Herceptin to each other, one 2-way supportive PK study with EU-Herceptin in healthy volunteers, and

1 confirmatory efficacy and safety study (HERITAGE) in patients with metastatic breast cancer (MBC). The use of EU-Herceptin in the HERITAGE study was justified through the establishment of a 3-way analytical and bioequivalence bridge among MYL-1401O, US-Herceptin, and EU-Herceptin. An additional supportive study in patients with MBC was conducted in India. The confirmatory clinical studies established bioequivalence and therapeutic equivalence and confirmed that there are no clinically meaningful differences between MYL-1401O and Herceptin with respect to safety, immunogenicity, and effectiveness.

Building on the results of the above-mentioned development program, Mylan seeks approval for all of Herceptin's indications. The rationale for seeking approval for indications not specifically evaluated in the MYL-1401O program is based on an understanding that once biosimilarity is established through structural, functional, nonclinical, and clinical activity, an extrapolation can be made to other indications for which the reference product has been tested and approved. Extrapolation from molecule to molecule is scientifically justified based on a) high similarity in molecular structure; b) highly similar HER2 binding that is relevant for mechanism of action (MOA), efficacy, safety, and immunogenicity; c) a common mechanism of action central to all indications; and d) common conditions of use including the same dose across all approved indications. This same regulatory philosophy applies to the approval of new dosage forms or changes in manufacturing processes for novel biologics.

The totality of the evidence from analytical, nonclinical, and clinical studies shows that MYL-1401O is highly similar to Herceptin and that there are no clinically meaningful differences between MYL-1401O and Herceptin in terms of the purity, potency, and safety of the product. As such, the totality of evidence supports the approval of MYL-1401O as a biosimilar to Herceptin for the full range of Herceptin indications, including HER2-overexpressing breast cancer and HER2-overexpressing metastatic gastric cancer or gastroesophageal junction adenocarcinoma.

2 INTRODUCTION

On July 13, 2017, the ODAC will be asked to provide its recommendation to the FDA on the approvability of MYL-1401O, Mylan's proposed biosimilar to Herceptin (trastuzumab; Genentech, Inc.). The application for MYL-1401O is the first proposed trastuzumab biosimilar to be assessed by the ODAC.

Mylan, in partnership with Biocon Limited, developed MYL-1401O with the mission of improving access to this important life-saving therapeutic. Mylan and Biocon are leaders in product innovation and have a long tradition of enhancing access to high-quality, affordable medicine in markets around the world, including the US.

Mylan conducted a comprehensive step-wise development program based on advice and guidance from both the FDA and European health authorities to demonstrate biosimilarity of MYL-1401O to Herceptin. Key program findings included the following:

- State-of-the-art analytics demonstrated that the physicochemical and biological characteristics of MYL-1401O are highly similar to those of Herceptin. The amino acid sequence is identical, and the higher order structures including secondary, tertiary structure, and product variants were shown to be highly similar between MYL-1401O and Herceptin.
- A range of *in vitro* functional assays relevant to MOA, efficacy, safety and immunogenicity were conducted to evaluate the biological activity and determine the effects of trastuzumab on breast cancer cells. HER2 binding and HER2 dependent activity including induction of antibody (trastuzumab)-dependent cellular cytotoxicity and inhibition of proliferation confirmed conservation of the same mechanism of action. All functional assays demonstrated that MYL-1401O is highly similar to Herceptin. The high functional similarity also addressed any potential residual uncertainties in minor differences in the glycan composition.
- Nonclinical *in vivo* studies included a single-dose PK study in female Cynomolgus monkeys and a repeat-dose toxicity study with 5 weekly administrations of test articles in male and female Cynomolgus monkeys. In addition, safety pharmacology studies to evaluate the relative cardiotoxicity potential were conducted using human and rat cardiomyocytes. Overall the data from these studies indicated similar exposure, safety and toxicity profiles for MYL-1401O and Herceptin.
- The clinical development program was designed to establish bioequivalence and therapeutic equivalence and to confirm the similarity established in the previous steps of development and to demonstrate no clinically meaningful differences in comparison to Herceptin.
    - Results from a robust well powered 3-way bridging bioequivalence study in healthy volunteers demonstrated PK equivalence between MYL-1401O, US-Herceptin, and EU-Herceptin. An additional 2-way supportive PK study with Herceptin sourced from the EU also demonstrated similar PK equivalence. In combination with the analytical similarity data showing high similarity between US-Herceptin and EU-Herceptin, these results established a scientific bridge between US- and EU-Herceptin, thereby allowing the use of EU-sourced Herceptin in the comparative clinical safety and efficacy study used to confirm that there are no clinically meaningful differences between MYL-1401O and US-Herceptin.

- A globally conducted confirmatory safety, efficacy and immunogenicity study in 500 patients with HER2-positive MBC demonstrated therapeutic equivalence in both combination and mono therapy setting, confirming the similarity established with the analytical and nonclinical data. MBC patients who received MYL-1401O or Herceptin as a first-line treatment along with taxanes for at least 8 cycles, followed by monotherapy until disease progression represents a sensitive population for detecting any possible differences in safety and efficacy between the products, both in combination with taxanes and as monotherapy. An additional supportive study was also conducted in India, in patients with MBC.

Collectively, the data from the analytical, nonclinical and clinical programs confirm high similarity and, demonstrate that there are no clinically meaningful differences between MYL-1401O and Herceptin. The totality of evidence supports MYL-1401O to be biosimilar to Herceptin.

3 TREATMENT LANDSCAPE AND MECHANISM OF ACTION

Breast cancer is the most common cancer in women worldwide. Advances in molecular biology and immunotherapy have made targeted therapeutic interventions possible and have allowed physicians to tailor treatments to the specific characteristics of the disease (Maximiano et al., 2016). The over-expression of human epidermal growth factor receptor (HER)2 is implicated in the pathophysiology of approximately 25% of breast cancer tumors and is therefore a clinically relevant biomarker for its treatment. In addition to breast cancer, HER2 overexpression has also been demonstrated across multiple other cancers including gastric and ovarian cancers. Trastuzumab (Herceptin) was one of the first targeted biological therapy specifically shown to be effective in patients with HER2 overexpression. The regulatory approvals for Herceptin are as follows:

- In 1998, Herceptin was approved for the treatment of metastatic breast cancer in patients who overexpress the human epidermal growth factor receptor 2 (HER2) protein. Since the approval of trastuzumab, other anti-HER2 molecules have been approved. Nonetheless, trastuzumab remains the gold standard for treatment of HER2-positive breast cancer (Denduluri et al., 2016).

- In 2006, Herceptin was approved as part of a treatment regimen of doxorubicin, cyclophosphamide, and paclitaxel for the adjuvant treatment of patients with node-positive, HER2-overexpressing breast cancer. This approval was based on 2 large clinical trials, which demonstrated that the combination of trastuzumab and standard chemotherapy cut the risk of HER2-positive breast cancer recurrence by more than 50% compared with chemotherapy alone (NCI, 2013).

- In 2010, Herceptin was approved for its third indication, in combination with cisplatin and a fluoropyrimidine (either capecitabine or 5-fluorouracil), for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal (GE) junction adenocarcinoma who have not received prior treatment for metastatic disease. Trastuzumab was the first biologic approved for the treatment of gastric cancers, an important step in targeted therapy as HER2 is overexpressed in 10–25% of gastric cancers (Gunturu et al., 2013).

The proposed clinical use of MYL-1401O is identical to that of the reference product, Herceptin. MYL-1401O is proposed for the treatment of adult patients with HER2-overexpressing breast cancer and for the treatment of adult patients with HER2-overexpressing metastatic gastric cancer (MGC) or gastroesophageal junction adenocarcinoma.

The key criteria prior to initiating treatment with Herceptin in patients with breast or gastric cancer is demonstration of HER2 overexpression or HER2 gene amplification. Across indications, the MOA is the same, in that, the antibody binds to HER2 receptors and initiates downstream effects which lead to inhibition of proliferation of human tumor cells that overexpress HER2. In addition, the antibody also initiates cell-mediated tumor cell lysis through the antibody dependent cell-mediated cytotoxicity (ADCC) mechanism. Furthermore, the dose and dosing regimen across indications is also similar. Since Herceptin has been studied and shown to be safe and effective in each of these indications, and since MYL-1401O will be shown to be highly similar to Herceptin and will access the same mechanism of action, its efficacy and safety can be presumed to be the same across all indications for which the reference product is approved (Ismael et al. 2012; Goldhirsch 2013; Tolaney et al. 2015; Gunturu et al. 2013).

3.1 MYL-1401O Overview

MYL-1401O is a proposed biosimilar to Herceptin (trastuzumab). Trastuzumab is a humanized immunoglobulin G1-kappa monoclonal antibody produced in mammalian Chinese hamster ovary cell suspension culture. It is directed against an epitope of the extracellular domain (ECD) of the HER2 protein, sub-domain IV.

The final MYL-1401O formulation is identical to that of US-Herceptin, except for a change in 2 excipients. The US- and EU-Herceptin formulation includes polysorbate 20 and trehalose dihydrate. Due to intellectual property considerations, these excipients were replaced with PEG 3350 and sorbitol in the MYL-1401O formulation (see Section 5.2). The analytical, nonclinical, and overall similarity assessments have demonstrated that these formulation differences have no meaningful effect on the similarity of MYL-1401O and Herceptin. The products showed highly similar clinical PK profiles despite the formulation differences, and a

comprehensive clinical evaluation in patients with metastatic breast cancer demonstrated similarity with respect to safety, effectiveness, immunogenicity and population PK.

3.1.1 Reference Product

The reference product for MYL-1401O is Herceptin (trastuzumab), which was initially approved in the US in 1998. In April 2017, Herceptin's label was updated from a presentation of 440 mg to 420 mg presented in a multi-dose vial. A 150-mg single use vial presentation was also added in this update. In Europe, Herceptin was approved in 2000 and is marketed as a single-dose, 150-mg vial presentation.

Mylan used EU-Herceptin in its global confirmatory clinical study to support demonstration of biosimilarity to Herceptin. In accordance with the FDA's guidance on biosimilars, a sponsor may use a non-US-licensed comparator product to support a demonstration that the proposed biological product is biosimilar to the US-licensed reference product. However, as a scientific matter, 3-way comparative analytical studies and at least one clinical PK study intended to support a demonstration of biosimilarity must be performed to provide an adequate comparison of the proposed biosimilar product directly with the US-licensed reference product and to establish a "bridge" of similarity across the three products. Mylan fulfilled this requirement through robust 3-way analytical studies and a 3-way PK study comparing MYL-1401O, US-Herceptin, and EU-Herceptin. Therefore, the use of EU-Herceptin in place of US-Herceptin in the confirmatory clinical similarity study with MYL-1401O has been scientifically justified.

3.1.2 Mechanism of Action

MYL-1401O and Herceptin are HER2 antagonists and act by binding to HER2, thereby blocking downstream effects. HER2 is a type I transmembrane tyrosine kinase receptor belonging to a family of four epidermal growth factor receptors (EGFRs; HER1–HER4). Upon ligand binding to the extracellular domain, the HER receptors undergo a structural change from a closed inactive form to an open active conformation that induces dimerization with other family members. HER2 is unique in that it lacks a known endogenous ligand; instead it is locked in an open, constitutively active conformation that forms dimers with itself (homodimerization) or other HER members (heterodimerization) without the need for ligand binding. Activation and dimerization results in tyrosine kinase phosphorylation of the receptor's intracellular domain and subsequent activation of second messenger systems including mitogen activated protein (MAP) and phophoinositide-3 kinase/protein kinase B (PI3K/Akt) pathways that promote cell migration and proliferation as well as cell survival.

Overexpression of HER2 in human tumor cells leads to increased constitutive HER2 activity, dimerization and subsequent dysregulated tumor cell growth. The binding of trastuzumab to

HER2 is the key mechanism critical for all downstream effects, including inhibition of dimerization and downstream signaling, thereby inhibiting tumor cell proliferation and decreasing tumor survivability.

Additionally, through the constant domain of the antibody, trastuzumab can attract effector cells of the immune system, such as natural killer cells, to tumor sites that overexpress HER2. Binding of the Fc portion of trastuzumab to receptors on effector cells induce antibody-dependent cell-mediated cytotoxicity (ADCC), a mechanism in which the effector cell releases cytokines that results in lysis of the tumor cells. Trastuzumab has also been proposed to induce HER2 internalization and degradation, which would in turn decrease HER2-mediated positive effects on tumor cells. Importantly, the mechanism of action is identical across all approved indications of Herceptin. See Figure 20 in Section 6.2.3 for an illustration of trastuzumab's primary mechanism of action in HER2-positive cancer cells.

3.1.3 Indications and Dose Regimen

The presentation of MYL-1401O is identical to Herceptin. Each multi-use vial of lyophilized powder will deliver at least 420 mg of trastuzumab following reconstitution with bacteriostatic water for injection (BWFI) for intravenous (IV) infusion. The proposed indications for MYL-1401O are identical to those for which Herceptin is approved and are as follows:

Metastatic Breast Cancer
MYL-1401O is indicated for the treatment of adult patients with HER2-positive metastatic breast cancer (MBC):

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer.

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

Adjuvant Breast Cancer

MYL-1401O is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative with one high risk feature) breast cancer:

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

Metastatic Gastric Cancer

MYL-1401O is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.

3.2 Medical Need

The benefits of trastuzumab treatments have been clearly demonstrated. Trastuzumab is deemed to be the gold standard in the treatment of HER2 positive breast cancer. An estimated 252,710 women in the US will be diagnosed with breast cancer in 2017 (NCI, 2017), but the patient access to biologic treatments like trastuzumab may be limited by cost and along with other breakthrough biologic treatments represent a significant cost burden to the health care system overall. The introduction of biosimilar treatments like trastuzumab is of crucial importance to increase competition, increase affordability, and increase overall access and use. Savings achieved for the healthcare system may further benefit the patient by enabling earlier or additional treatment options including other biologic treatments.

4 BIOSIMILAR DEVELOPMENT APPROACH

4.1 Regulatory Framework for the Approval of a Biosimilar

The Biologics Price Competition and Innovation Act of 2009 (BPCIA) was signed into law with the Affordable Care Act (ACA) in 2010. The BPCIA created an abbreviated licensure pathway for biological products shown to be highly similar to a currently licensed biologic (the reference product). Specifically, section 351(k) allows a sponsor to rely on existing safety and efficacy of the reference product and allows for the biosimilar product to be licensed with an abbreviated nonclinical and clinical data package. The BPCIA defines biosimilars as a biological product that is highly similar to the reference product, notwithstanding minor difference in clinically inactive components, and for which 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. The

specific provisions of the 351(k) regulatory pathway, and how the MYL-1401O application satisfies these provisions, is reviewed in Section 4.3.

4.2 Biosimilar Development

The FDA has emphasized 2 concepts in the guidance for biosimilar developers: 1) that the demonstration of biosimilarity be based on the *totality of the evidence*, and 2) in developing a biosimilar product, a sponsor should utilize a *stepwise approach* to demonstrate biosimilarity including an evaluation of *residual uncertainties* at each step. Mylan has considered and applied both concepts in the development of MYL-1401O.

Utilization of the stepwise approach in the development of MYL-1401O will be apparent in review of the data package. The structural and functional analytical data established that the proposed biosimilar and its reference product were highly similar, containing essentially the same molecules and formed the basis for the next development step (i.e., the nonclinical program). The results of the nonclinical program demonstrated similarity in relevant *in vitro* and *in vivo* models. Finally, the efficacy and safety of MYL-1401O was assessed in a targeted clinical program.

4.3 Fulfillment of Statutory Requirements of MYL-1401O

This application is submitted under Section 351(k) of the Public Health Service Act. The following table shows specific elements in this application that meet the requirements outlined in the BPCIA for establishing biosimilarity.

Table 1: MYL-1401O Application Addressing all Requirements as Per the Biologics Price Competition and Innovation Act of 2009

BPCIA 351(k) [2][A] Part	**Provision**	**Compliance by MYL-1401O Application**
Biosimilarity to the Reference Product must be demonstrated by:		
[i]I (aa)	Analytical studies demonstrating high similarity to the reference product	Comprehensive quality and analytical similarity studies using suitable, and as required, orthogonal methods showed that the physicochemical and biological characteristics of MYL-1401O are highly similar to those of Herceptin.
[i]I (bb)	Animal studies, including the assessment of toxicity	One single-dose pharmacokinetic study as well as a repeat- dose toxicity study in Cynomolgus monkeys showed no significant toxicity for MYL-1401O or EU-Herceptin. A similar PK profile was demonstrated for MYL-1401O and Herceptin.

BPCIA 351(k) [2][A] Part	Provision	Compliance by MYL-1401O Application
[i]I (cc)	Clinical study(ies), including assessment of immunogenicity, PK, and PD, that are sufficient to demonstrate safety, purity, and potency in an appropriate condition of use that the reference product is licensed for	Two studies were conducted in healthy volunteers (MYL-Her-1001 and MYL-Her-1002) and 1 safety, efficacy, and immunogenicity study in patients with metastatic breast cancer (MYL-Her-3001) showed that MYL-1401O, US-Herceptin, and EU-Herceptin are bioequivalent and produce equivalent responses in healthy volunteers, with a similar immunogenicity profile. MYL-1401O is similar in safety and efficacy to Herceptin for the treatment of HER2-overexpressing breast cancer. These findings are supported by Study BM200-CT3-001-11, conducted in patients with metastatic breast cancer in India.
[i]II	Information showing that the proposed biosimilar uses the same mechanism(s) of action as the reference product	Highly sensitive *in vitro* assays were used to measure biological activities known to be critical to the action of Herceptin. *In vitro* Inhibition of Proliferation and ADCC studies showed highly similar potency and surface plasmon resonance-based assays showed that multiple batches of MYL-1401O and Herceptin had highly similar binding kinetics to Fcγ receptors.
In addition:		
[i]III	The conditions of use being requested for the proposed biosimilar must have been approved for the reference product	The conditions of use requested for MYL-1401O are those approved for Herceptin: For adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with 1 high-risk feature) breast cancer o as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel o with docetaxel and carboplatin o as a single agent following multi-modality anthracycline based therapy. In combination with paclitaxel, for first-line treatment of HER2-overexpressing metastatic breast cancer and as a single agent for treatment of HER2-overexpressing breast cancer in patients who have received 1 or more chemotherapy regimens for metastatic disease. 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
[i]IV	The route of administration, the dosage form, and the strength of the proposed biosimilar must be the same as those of the reference product	The route of administration, the dosage form, and the strength of the MYL-1401O is identical to US-Herceptin.

BPCIA 351(k) [2][A] Part	Provision	Compliance by MYL-1401O Application
[i]V	The facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent.	MYL-1401O drug substance and drug product are manufactured and packaged under strict quality control in a cGMP-compliant multiproduct facility. The formulated bulk drug substance is filtered through a 0.2 µm filter in to a Celsius-Pak bag and stored at -20°±5°C. The drug product is manufactured according to a standard aseptic manufacturing process that starts with thawing of formulated drug substance, pooling and mixing of drug substance, pre-filtration followed by sterile filtration, aseptic filling, lyophilization, and sealing of vials containing lyophilized product.
[iii]I	The application shall include publicly-available information regarding the Secretary's previous determination that the reference product is safe, pure, and potent	Data for the BLA were obtained from the USPI for Herceptin, the product monograph for Herceptin from the Health Canada, and the European Public Assessment Report scientific discussion published by the European Medicines Agency. The US FDA Summary Basis of Approval Review for Herceptin (trastuzumab; BLA 103792) is not publicly available.

4.4 Extrapolation of Indications

As noted, this application seeks approval for all indications for which the reference product, Herceptin, is approved. The rationale for extrapolation is based on a strong scientific justification taking into account the demonstration of biosimilarity at the molecule level. In addition, the underlying pathology for all the three indications is the same in that, there is overexpression of HER2 protein or HER2 gene amplification. The mechanism of action by which trastuzumab demonstrates its effect is common across these indications and requires the binding of the antibody to HER2 receptors. Finally, the doses and dosing regimen used across these indications are similar.

Thus, extrapolation from molecule to molecule is scientifically justified with the expectation that essentially the same molecule, working through the same mechanism of action and used in a comparable way across all indications will perform in the same way as the reference product in all indications for which the reference product has been tested and approved.

5 PRODUCT DEVELOPMENT

The manufacturing process of MYL-1401O was systematically developed to be highly similar to its reference product, Herceptin, with respect to both the drug substance (DS) and drug product (DP). The following sections provide a summary of the MYL-1401O manufacturing process which includes fermentation, harvesting, and purification of the DS/active pharmaceutical ingredient, and formulating and packaging of the DP.

5.1 MYL-1401O Drug Substance Development

MYL-1401O is produced using recombinant DNA technology in Chinese hamster ovary-derived cell line, which is same as that of Herceptin. After screening several clones, the master clone was selected and established based on the productivity, cell line stability, and product quality. Further, a comprehensive cell bank system was established and qualified according to International Council for Harmonisation (ICH) Guidance Q5A and Q5D.

A step-wise approach for manufacturing process development was followed to ensure that the manufacturing process would produce product that met the desired quality profile and to ensure that the DS produced from this process would be highly similar to the reference product (Herceptin) in terms of quality, safety, and efficacy.

MYL-1401O is manufactured by a fed-batch process using a production bioreactor followed by harvesting by centrifugation and depth filtration. The harvested cell culture supernatant is processed in downstream purification unit operations to remove product- and process-related impurities prior to the additions of excipients and buffers. The resulting formulated DS is filtered and stored at -20ºC ±5º.

The manufacturing process for MYL-1401O DS was scaled up to the commercial scale from which material for the 3-way clinical PK study and confirmatory efficacy and safety study were manufactured. Based on further manufacturing experience, some process improvements were made before the start of process validation. Mylan has demonstrated extensive comparability of MYL-1401O DS that were manufactured over the duration of process development. The process characterization studies were conducted to have an in-depth understanding of the process prior to process validation. The process was successfully validated at the commercial scale at the commercial manufacturing site. Thus, the DS material used in the clinical studies is representative of the commercial material.

5.2 MYL-1401O Drug Product Development

Herceptin is available as 2 presentations: 150 mg in the EU and 420 mg in the US. Herceptin 150 mg is a single-use vial and Herceptin 420 mg is a multi-use vial intended for reconstitution with 20 mL of the appropriate diluent, bacteriostatic water for injection or sterile water for injection. Both 150 mg and 420 mg when reconstituted yield a solution containing 21 mg/mL of trastuzumab.

The early product development was focused to develop a formulation having a same excipient that of EU-Herceptin. This formulation was referred to as the Bmab-200 reference product formulation (Bmab-200 RPF), and was used in the clinical studies conducted in India (supportive clinical study BM200-CT3-001-11), and was then approved and commercialized in India. This

formulation included identical excipients as the Herceptin product and utilized trehalose and polysorbate 20 as lyoprotecant and surfactants, respectively.

Subsequently, as a part of the global development and owing to patent considerations of the Herceptin formulation, sorbitol and PEG 3350 were selected as an alternative lyoprotectant and cryoprotectant, respectively, instead of trehalose and polysorbate 20. BPCIA and FDA guidance on biosimilarity (2015) allow the differences between the formulation of a proposed product and the reference product. The development program, including Mylan's nonclinical and clinical studies, have confirmed that there is no impact of these minor differences in formulation. Sorbitol and PEG 3350 are commonly used in pharmaceutical preparations and comply with the United States Pharmacopeia and European Pharmacopeia standards. This formulation with sorbitol and PEG 3350 is referred to as MYL-1401O. Based on this formulation, Mylan has developed 2 presentations of the finished DP: MYL-1401O 150 mg a single-use vial (intended commercial formulation in the EU and other countries) and MYL-1401O 420 mg, a multi-dose vial (intended commercial formulation in the US). The MYL-1401O DP was developed to be highly similar to the reference product, Herceptin, with respect to quality attributes and stability.

The global nonclinical, clinical PK, and the confirmatory efficacy and safety studies were conducted with MYL-1401O 150 mg. In parallel, the MYL-1401O 420 mg presentation was developed and share the similar manufacturing process of 150 mg. Both 150 and 420 mg presentations are derived from the same DS, and share identical DP manufacturing processes, except for vial size, fill volume, and minor differences in the primary drying stage of lyophilization. Both the proposed dose formulations are sterile lyophilized powders for reconstitution, containing the same quantitative and qualitative composition after dissolution with BWFI or WFI. The strength of the dissolved medicinal product, defined as the ratio of solid powder to solvent, remains unchanged for both presentations (trastuzumab 21 mg/mL).

Extensive comparability studies were conducted between MYL-1401O 150 mg and 420 mg and based on these studies, it was demonstrated that both presentations are highly comparable.

After completion of process characterization studies, the DP manufacturing process has been successfully validated at the commercial scale and at the commercial manufacturing site.

6 ANALYTICAL DEMONSTRATION OF BIOSIMILARITY

Mylan has used extensive state-of-the-art analytical techniques to characterize and compare the physicochemical and biological properties of MYL-1401O and Herceptin. A stepwise approach was used to demonstrate analytical similarity of MYL-1401O with US-Herceptin and EU-Herceptin. This included the following evaluations:

1) Identification of quality attributes that impact safety and efficacy.
2) Criticality risk ranking and classification of quality attributes.
3) Quantitative evaluation of similarity based on the likely impact on clinical activity.
4) Demonstration of comparability between the 2 presentations, MYL-1401O 420 mg and MYL-1401O 150 mg since data from both presentations were combined to demonstrate analytical similarity.
5) Performance of a 3-way comparative analytical assessment to show similarity of MYL-1401O, US-Herceptin, and EU-Herceptin.

The following sections review these findings of the analytical similarity assessments, which demonstrate a high level of similarity between MYL-1401O and Herceptin.

6.1 Criticality Assessment, Risk Ranking, and Tiering of Quality Attributes

Mylan's approach to establishing analytical similarity included a comprehensive ranking of quality attributes (protein characteristics) that are relevant to clinical outcomes of safety and efficacy. These quality attributes fall into 2 major categories: product variants and product attributes. Product variants are present due to post-translational modifications such as charge variants and glycosylated variants. Product attributes are structural and specific functional attributes. These quality attributes were ranked based on the risk assessment principles set forth in the ICH Quality Guidelines Q8 and Q9. The relative importance/ranking was assigned based on a thorough scientific literature review and in-house experiments in which quality attributes were varied and assessed.

Using this Criticality Risk Ranking approach, quality attributes were initially evaluated and placed into 1 of 4 risk categories: Very High, High, Moderate, and Low, based on their potential impact on clinical efficacy, immunogenicity, safety, or PK/PD.

As recommended by the FDA, the risk ranked quality attributes were then assigned to one of three tiers based primarily on the likelihood of the attribute to impact clinical activity, the type of analytical method employed, and the level of the attribute in the product. The tiers then determine the type of quantitative analysis that needs to be performed for the determination of similarity. For example, *in vitro* potency testing is considered most reflective of clinical efficacy, so the key bioassays are assigned to Tier 1 and similarity is assessed using statistical equivalence

testing. While many other attributes are considered highly critical to clinical activity, most are assigned to the next Tier 2, wherein similarity is assessed by determining the percent of biosimilar lots that fall within 2 or 3 standard deviations (σ) of the mean, depending on the criticality rank of the attribute and the variability of the analytical method[a]. Finally, attributes that are determined not to be critical for clinical activity, or that are not amenable to statistical analysis, are placed into Tier 3. These attributes, which include primary amino acid sequence, higher order structure, and low level non-critical variants, are analyzed by visual examination of the raw data.

A summary of the tiering approach and grouping of attributes is shown in Table 2.

a If the criticality risk rank was Very High and/or the analytical method variability was >15%, ±2 SD was used. For all others, ±3 SD was applied.

Table 2: Summary of the Tiering Approach Used in the Analytical Similarity Assessment

Tier	Description	Criteria for High Similarity	Attributes/Tests in Tier
1	**EQUIVALENCE TESTING** ➢ Attributes with the highest clinical relevance (Criticality Risk) using assays that reflect the mechanism of action. ➢ Equivalence acceptance criteria (EAC) were calculated based on ± 1.5x the standard deviation of the reference product.	Products were highly similar if the 90% confidence intervals (CI) of the mean difference was within the defined EAC.	• HER2 binding • Inhibition of Cell Proliferation • Antibody Dependent Cellular Cytotoxicity (ADCC)
2	**QUALITY RANGES** ➢ Attributes with comparatively lower clinical relevance (Criticality Risk). ➢ Quality ranges (QRs) were set based on the mean ± 2 or 3 standard deviations of the of the reference product (depending on criticality rank and method variability).	Products were highly similar if at least 90% of the lots fell within the Quality Range.	• Protein Content • 2° structure (Far UV CD) • Aggregates (SEC-UV) • Fragments (Non-reduced CE-SDS) • Glycoforms ▪ Non-glycosylated ▪ Afucosylated ▪ Terminal galactose ▪ High mannose ▪ Terminal sialic acid • Charge Variants • FcγRIIIa binding • FcRn binding
3	**QUALITATIVE COMPARISONS** ➢ Characteristics with lowest clinical relevance (Criticality Risk) or those evaluated with non-quantitative analytical methods	Similarity assessed based on visual comparison of qualitative profiles.	• Amino acid sequence • Intact mass and HC/LC mass • 2° structure (Far UV CD) • Disulfide bridging • Free cysteine • Higher order structure ▪ Near UV CD ▪ Differential scanning calorimetry ▪ Intrinsic fluorescence ▪ Hydrophobic interaction chromatography • Subvisible particles (MFI) • Aggregates • Analytical ultracentrifugation • SEC-MALS (multi-angle light scattering) • Glycation • Methionine oxidation • Deamidation • C-terminal lysine • FcγRIa binding • FcγRIIa binding • FcγRIIb binding • FcγRIIIb binding • C1q binding

6.2 Results of the Analytical Similarity Assessments

The following subsections describe key results for structural and functional attributes from the analytical similarity assessment.

6.2.1 Structural Attributes

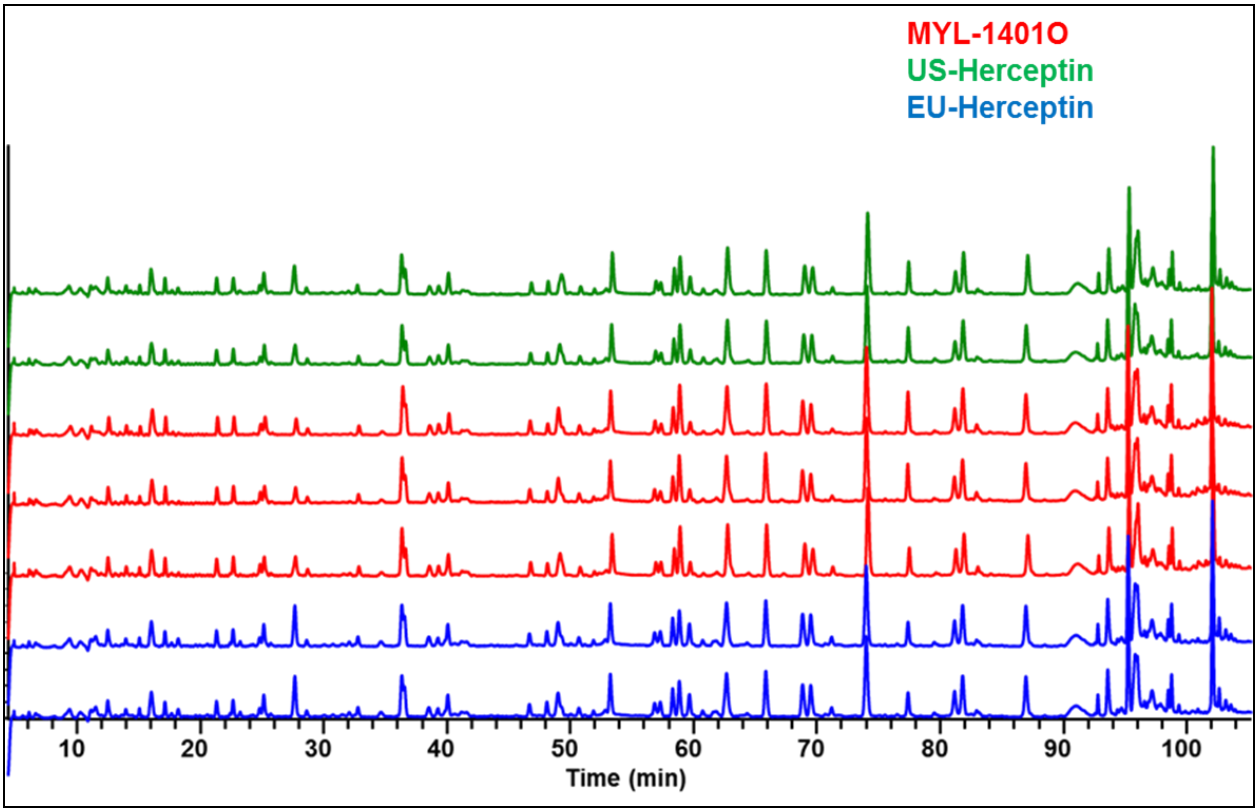
The intact molecular mass of trastuzumab is approximately 148 kDa. It is composed of 2 identical heavy chains and 2 identical light chains, which are cross-linked by disulfide bonds. The 2 heavy chains are further cross-linked by 2 disulfide bonds. Four intra-chain disulfide bonds are also found in each heavy chain, while light chains have 2 intra-chain disulfide bonds. The heavy chain sequence is made of 450 amino acids and the light chain sequence is composed of 214 amino acids.

Refer to Table 2 for details on the test methods utilized to assess the similarity of MYL-1401O and Herceptin with respect to the structure attributes of trastuzumab. Results from several of these methods are described herein.

Primary Structure (amino acid sequence)
Primary structure of the products was determined by reduced peptide mapping and orthogonally confirmed by intact mass analysis and reduced mass analysis.

The amino acid sequence analysis of MYL-1401O, US-Herceptin, and EU-Herceptin was performed by non-reduced peptide mapping. Samples were reduced and alkylated followed by digestion with trypsin or Glu-C. The resulting protein fragments were separated by reverse phase high-performance liquid chromatography (RP-HPLC) and the ultraviolet (UV) profile was compared. The peptide fragments were further analyzed by mass spectrometry to confirm the amino acid sequence in each peptide fragment. A representative overlaid UV profile of reduced peptide mapping analysis of MYL-1401O, US-Herceptin, and EU-Herceptin is shown in Figure 1.

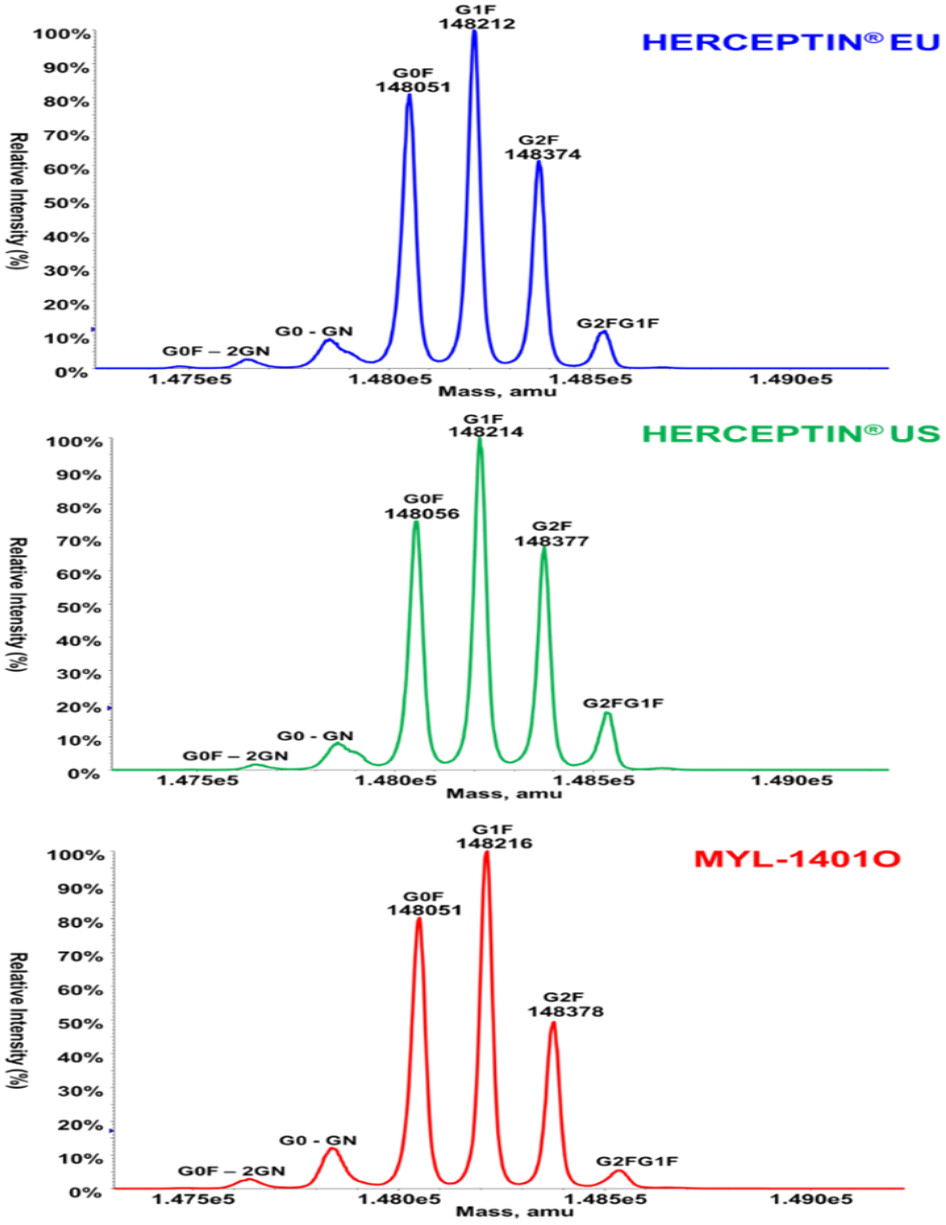
Figure 1: Representative Overlaid Chromatograms of Peptide Mapping for MYL-1401O, US-Herceptin, and EU-Herceptin Lots



The peptide map UV profiles of MYL-1401O, US-Herceptin, and EU-Herceptin were highly similar in terms of number of peaks and their position. Analysis of the peptide fragments by mass spectrometry confirmed the identical primary sequence of MYL-1401O, US-Herceptin, and EU-Herceptin. Between the trypsin and Glu-C digests, 100% sequence coverage for each product was obtained.

Intact and reduced mass analysis of MYL-1401O, US-Herceptin, and EU-Herceptin was conducted on a high-resolution hybrid quadrupole time-of-flight mass spectrometer. Representative deconvoluted mass spectra from this analysis are shown in Figure 2.

Figure 2: Representative Deconvoluted Mass Spectra for MYL-1401O, US-Herceptin, and EU-Herceptin (Intact Mass)



Further, in the mass analysis of reduced MYL-1401O and Herceptin lots, the observed masses for heavy chains and light chains closely matched with the expected masses. Addtionally, the masses obtained for MYL-1401O lots were highly similar to those obtained for US-Herceptin and EU-Herceptin. This result supports the idential amino acid sequence of the products as determiend in the peptide mapping analyses.

Secondary and Higher Order Structure (3-Dimensional Structure; Folded Protein Conformation)

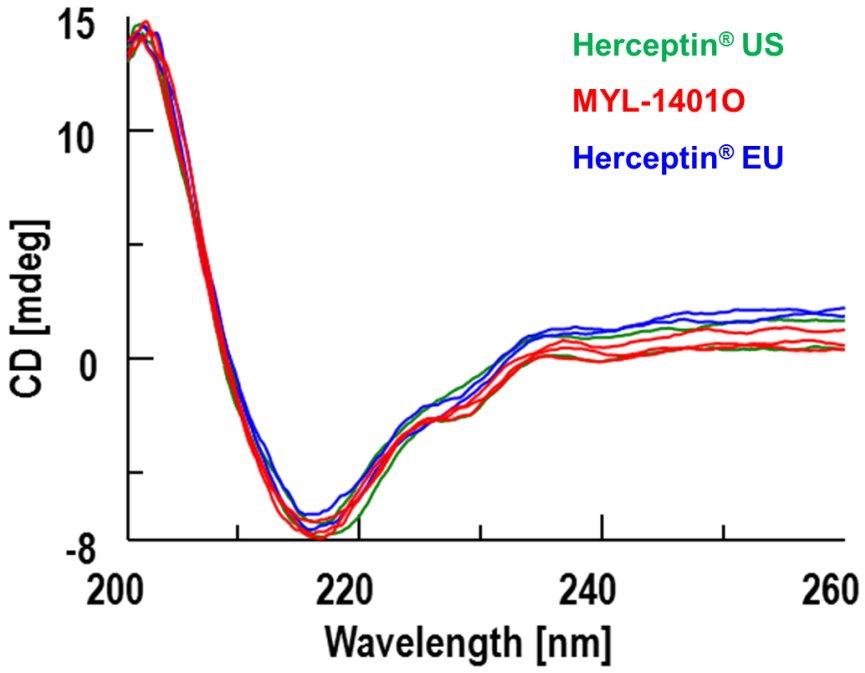
Secondary and higher order structure were assessed using multiple spectroscopic techniques, including Far UV and Near UV circular dichroism (CD), Fourier transform infrared (FTIR), and intrinsic fluorescence. Extensive characterization of the multiple disulfide linkages in the antibodies was performed using HPLC-mass spectrometry and complemented free cysteine analysis. Higher order structure was further characterized using Differential Scanning Calorimetry (DSC), which measures the characteristic unfolding of a protein as a function of temperature. Results from these analyses, a subset of which are summarized below, demonstrate that the secondary and higher order structure of MYL-1401O is highly similar to US- and EU-Herceptin.

Secondary Structure

CD relies on the differential absorption of left and right circularly polarized radiation by chromophores is one of the most commonly used techniques to characterize the structure of proteins and other biomolecules. Secondary structure information can be obtained from CD spectroscopy in the "Far-UV" spectral region (190-250 nm). At these wavelengths, the chromophore is the peptide bond, and a signal arises when it is located in a regular, folded environment. In the Far-UV CD analysis, alpha-helix, beta-sheet, and random coil structures each give rise to a characteristic shape and peak magnitude within a CD spectrum.

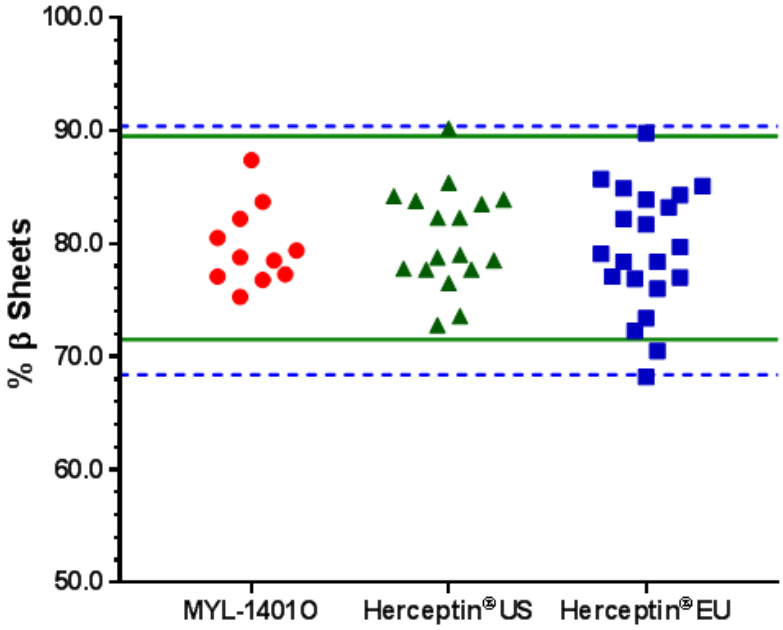
Representative Far UV CD spectra for MYL-1401O, US-Herceptin, and EU-Herceptin are presented in Figure 3 and show high similarity across the 3 products.

Figure 3: Representative Far UV CD Spectra for MYL-1401O, US-Herceptin, and EU-Herceptin



The Far UV CD analysis showed that the predominant (~80%) secondary structural configuration in trastuzumab was a β-sheet. Figure 4 shows the β-sheet content in the products as well as the respective Quality Ranges (Tier 2 attribute).

Figure 4: β-Sheet Content in MYL-1401O, US-Herceptin, and EU-Herceptin

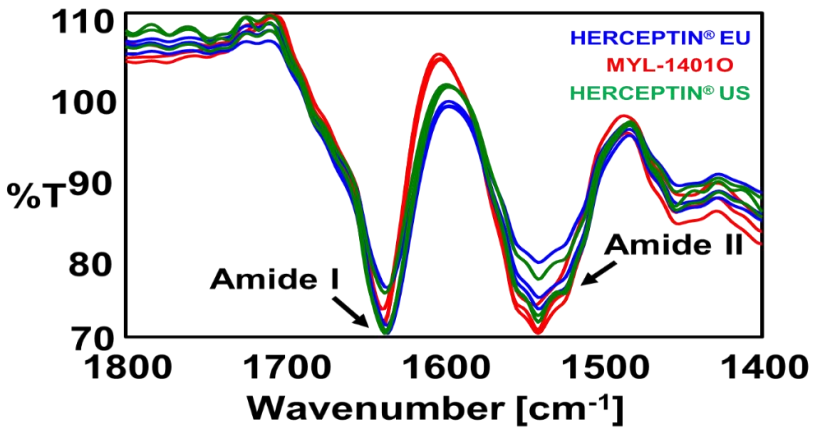


β-sheet content in MYL-1401O was highly similar to both US-Herceptin and EU-Herceptin. EU-Herceptin fell slightly outside of the Quality Range criteria owing to increased inter-lot variation, however, this was not deemed significant as the mean values were in close agreement (US-Herceptin 80.5%; EU-Herceptin 79.4%).

Fourier transform infrared (FTIR) spectroscopy is an orthogonal tool for secondary structure characterization. Proteins typically exhibit two characteristic signals in FTIR that are sensitive to secondary structure: an Amide I band at approximately 1600 – 1700 cm^{-1}, which predominantly reflects C=O bond stretching and an Amide II band near 1550 cm^{-1} primarily due to N-H bond bending. The precise location of these bands is a characteristic of the individual protein and its secondary structure.

FTIR representative overlay spectra of MYL-1401O, US-Herceptin, and EU-Herceptin are shown in Figure 5.

Figure 5: Overlay of FTIR Spectra Profiles for MYL-1401O, US-Herceptin, and EU-Herceptin Lots



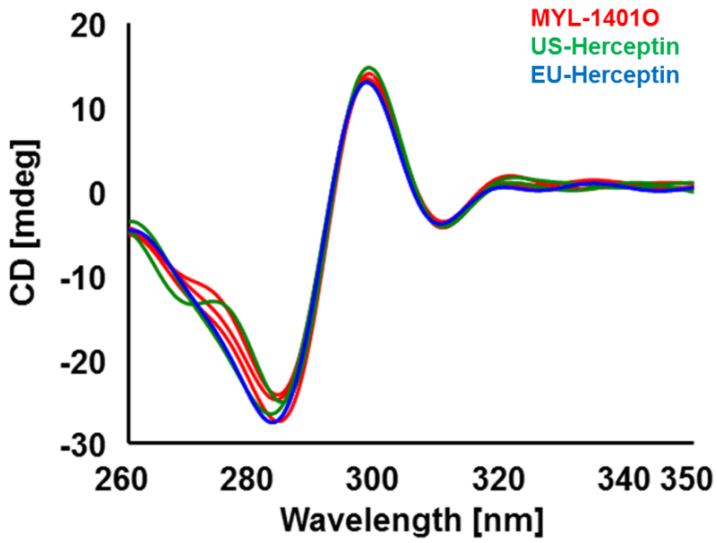
FTIR was a Tier 3 test in which similarity was assessed by qualitative data comparisons. The wavenumbers of the Amide I and Amide II bands were consistent across all 3 products, supporting high similarity in terms of secondary structure.

Higher Order Structure

Near UV-CD spectroscopy can be used for tertiary structural information. In constant to the far UV wavelengths used to characterize secondary structure, the CD spectrum in the near UV region (320-260 nm) reflects the environments of the aromatic amino acid side chains (tyrosine, tryptophan, phenylalanine), which are affected by folding of the protein, and thereby provides information regarding the tertiary structure of the protein.

Near UV-CD was a Tier 3 test in which similarity was assessed by qualitative data comparisons. As shown in Figure 6, the near UV CD spectra obtained for MYL-1401O and US-Herceptin and EU-Herceptin lots were highly similar, providing evidence of high similarity of tertiary structure.

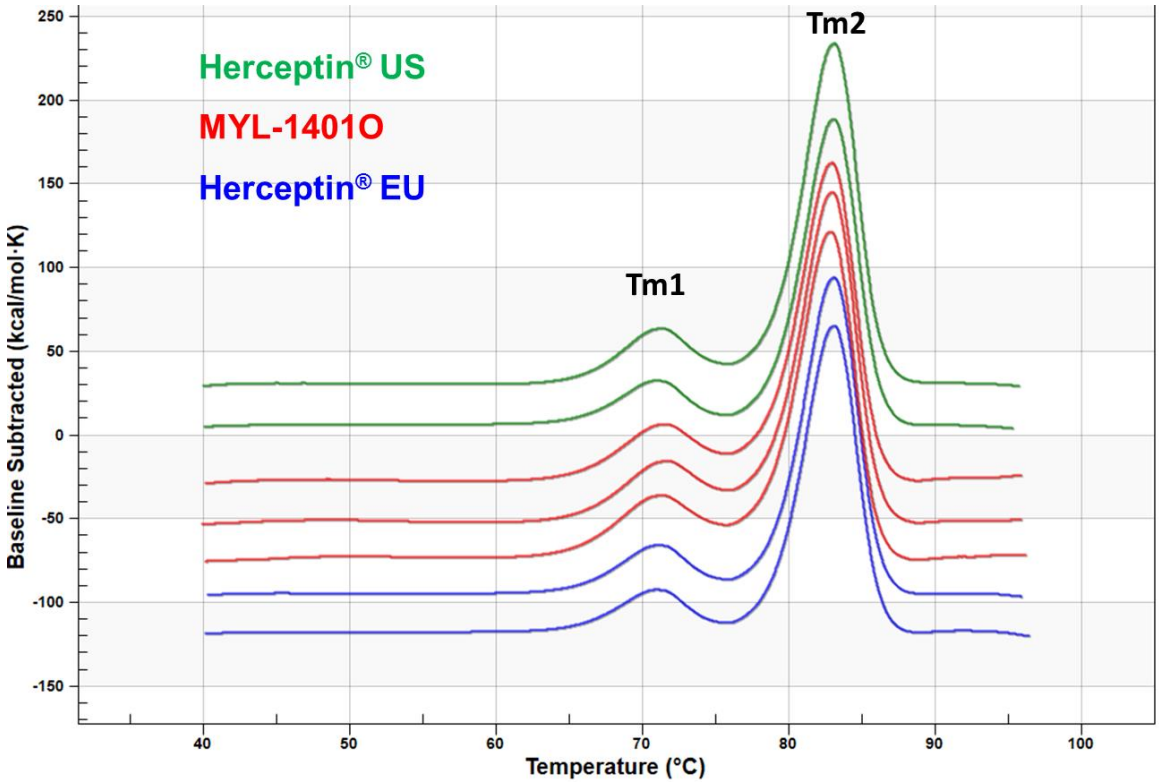
Figure 6: Representative Overlays of Near UV CD Spectra Profiles for MYL-1401O, US-Herceptin, and EU-Herceptin Lots



DSC interrogates the structure of a protein from a thermodynamic perspective. DSC measures the heat capacity required to induce unfolding of the molecule. The temperature at which half of the protein molecules are unfolded is called the melting temperature (mid-point of DSC peak, Tm). A thermodynamic difference in this test would therefore indicate structural differences. The thermal properties and structural-phase transitions of MYL-1401O, US-Herceptin, and EU-Herceptin were evaluated by measuring their Tm values by DSC.

Representative thermograms of MYL-1401O, US-Herceptin, and EU-Herceptin are provided in Figure 7.

Figure 7: Representative Overlays of DSC Thermograms for MYL-1401O, US-Herceptin, and EU-Herceptin Lots



Upon thermal denaturation, the Fab region usually unfolds first followed by the CH3 domain, which would result in 2 endothermic transitions. DSC was a Tier 3 test in which similarity was assessed by qualitative data comparisons. The expected 2 endothermic transitions, transition temperatures T_m1 and T_m2 for MYL-1401O, US-Herceptin, and EU-Herceptin were highly similar, providing evidence that the folder structure and conformation of the 3 products are highly similar.

Disulfide bridging is another important structural feature of proteins that plays a key role in defining a protein's folding pattern and overall higher order structure. Trastuzumab, an IgG1 monoclonal antibody, is known to contain 16 disulfide linkages, 12 intra-chain and 4 inter-chain bridges. For this reason, Mylan's characterization of higher order structure in MYL-1401O, US-Herceptin, and EU-Herceptin also entailed mapping of the disulfide bonds. In this analysis, the native (non-reduced) products were digested with trypsin and analyzed by HPLC/mass spectrometry.

A summary of the disulfide linkage peaks determined by HPLC-mass spectrometry (MS) is shown in Table 3.

Table 3: Disulfide Linkages Detected in MYL-1401O, US-Herceptin, and EU-Herceptin

Di-sulfide linked peptide	Location	Theoretical [M+H] mass	Mass Found		
			EU-Herceptin	MYL-1401O	US-Herceptin
1	H_{C22}-H_{C96}	2385.6	2385.1	2385.1	2385.1
2	H_{C264}-H_{C324}	2329.6	2329.2	2329.2	2329.2
3	H_{C370}-H_{C428}	3847.3	3847.9	3847.9	3847.9
4	L_{C134}-L_{C194}	3558.0	3557.8	3557.8	3557.8
5	L_{C23}-L_{C88}	4822.3	4822.3	4822.3	4822.3
6	H_{C229}-H_{C229}	5458.5	5458.9	5458.9	5458.9
	H_{C232}-H_{C232}				
7	H_{C147}-H_{C203}	7921.8	7922.1	7922.1	7922.1

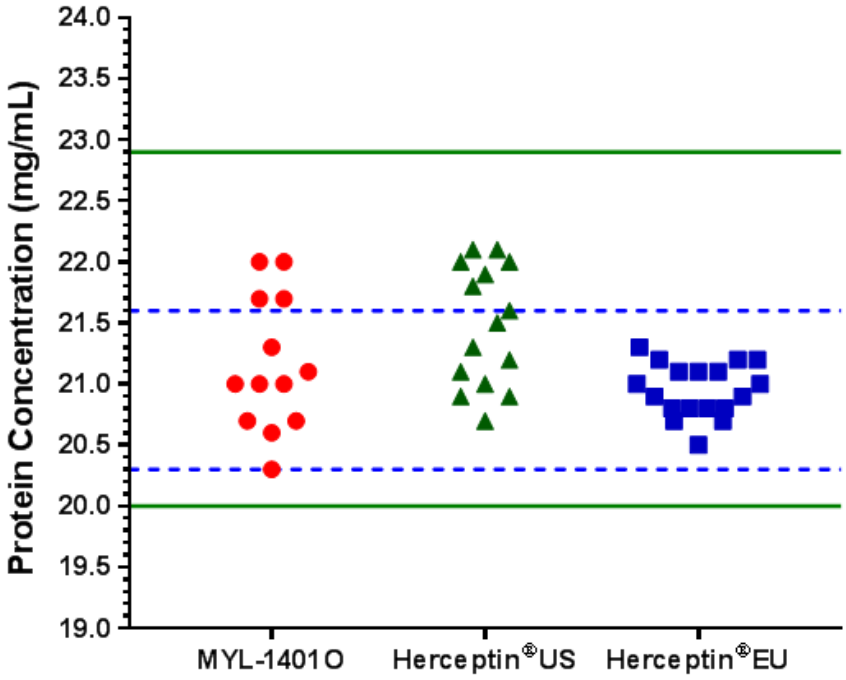
All the expected disulfide linked peptide fragments were found in MYL-1401O, US-Herceptin, and EU-Herceptin, except for the small (< 1 kDa) fragment corresponding to the inter-chain bridge linking LC214 and HC223, which due to its low reversed-phase retentivity and weak electrospray MS response was not detected in any of the products. Importantly, no misfolded (scrambled) linkages were detected in MYL-1401O, US-Herceptin, or EU-Herceptin. These data provide strong evidence that the same disulfide bridges exist in the 3 products and further support the high similarity of MYL-1401O, US-Herceptin, and EU-Herceptin with respect to higher order structure.

Protein Content

The protein content of MYL-1401O, US-Herceptin, and EU-Herceptin was determined spectrophotometrically by measuring absorbance at UV 280 nm using the theoretical extinction coefficient, which was confirmed experimentally.

Results are shown in Figure 8 along with the respective Quality Ranges, as protein content was classified as a Tier 2 attribute.

Figure 8: Protein Content in MYL-1401O, US-Herceptin, and EU-Herceptin



Solid Green Lines represent the Quality Range established for US-Herceptin; Dotted Blue Lines represent the Quality Range established for EU-Herceptin

The protein content in MYL-1401O was highly similar to US-Herceptin, with all MYL-1401O lots falling within the Quality Range. However, although all EU-Herceptin lots were within the Quality Range of US-Herceptin, the protein content of the EU product trended lower than both MYL-1401O and US-Herceptin. Given the low magnitude of the difference (mean differences relative to EU-Herceptin were 1.4% and 2.9%, respectively for MYL-1401O and US-Herceptin), the marginally lower protein content of EU-Herceptin was deemed not to be significant.

6.2.2 Product Variants

Monoclonal antibodies can undergo post-translational or chemical modifications during production and storage. Modifications including deamidation of asparagine and glutamine residues, oxidation of histidine, tryptophan and methionine, cyclization of N-terminal glutamine residues, processing of C-terminal lysine of the heavy chains, and fragmentation are commonly observed in therapeutic monoclonal antibodies.

Other post-translational modifications such as glycated variants, and hydrophobic variants are quantified by sensitive and specific methods.

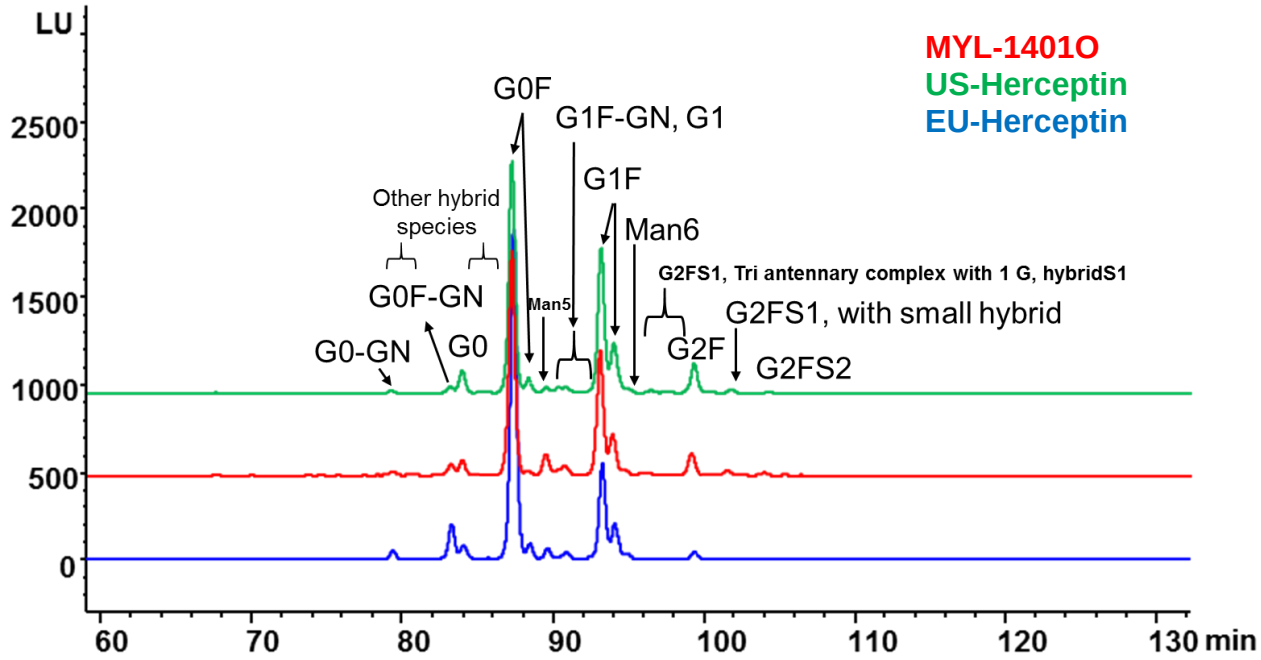
6.2.2.1 *Glycoform Variants*

IgG1 antibodies such as trastuzumab contain various carbohydrate (sugar) molecules linked to the protein at the CH2 domain in the heavy chain. Glycoform variants of MYL-1401O, US-Herceptin, and EU-Herceptin were characterized by qualitative and quantitative analysis of released glycans following PNGaseF enzyme treatment, total afucose content, and terminal sialic acid content. These analyses are described below.

N-linked glycan profile analysis was performed by treating the products with PNGaseF, a glycosidase enzyme that cleaves N-linked glycans at their site of attachment to the antibody. The released glycans were then labeled and quantified by normal phase (NP) HPLC.

Representative N-glycan profiles for MYL-1401O, US-Herceptin, and EU- Herceptin are provided in Figure 9.

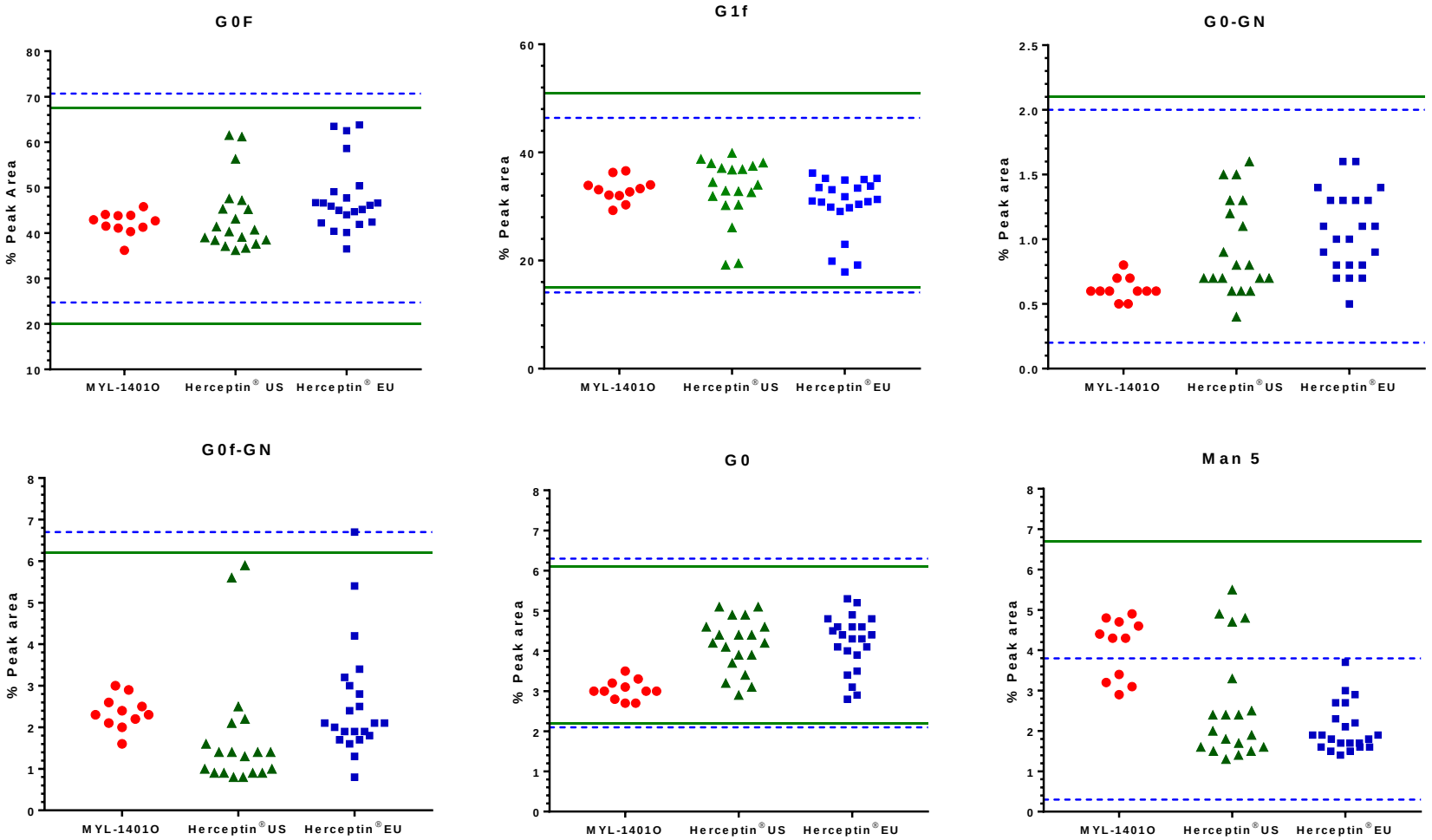
Figure 9: Representative Overlaid N-Glycan Profiles of MYL-1401O, US-Herceptin, and EU-Herceptin

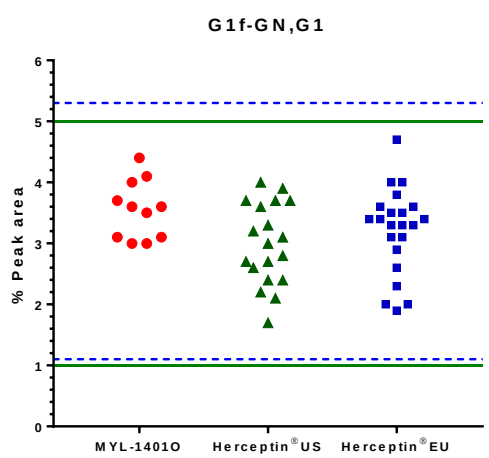


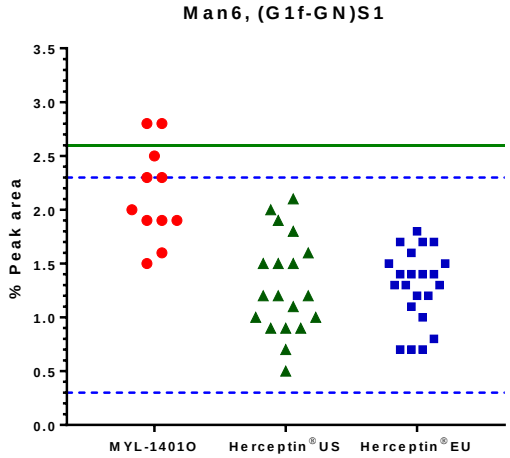
The glycan profiles obtained for MYL-1401O, US-Herceptin, and EU Herceptin were highly similar. No unique glycan species were detected in any product.

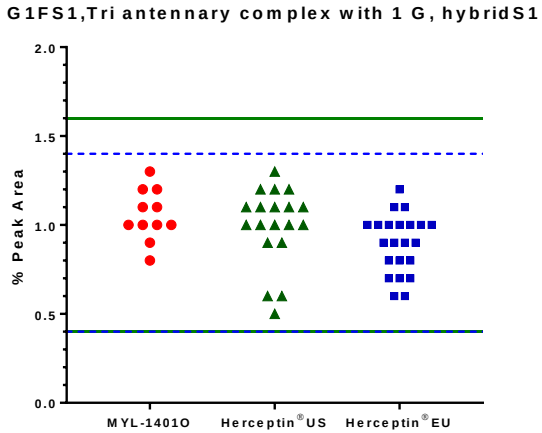
Quantitatively, of the 13 individual species detectable with the NP-HPLC method, high similarity between MYL-1401O and US-Herceptin was observed for 12 species (Man6 levels were marginally higher in MYL-1401O). Eleven species were highly similar between MYL-1401O and EU-Herceptin, with marginally higher levels of Man5 and Man6 seen). These results are summarized Figure 10.

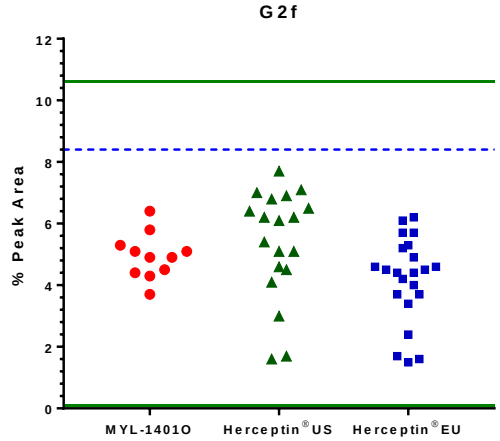
Figure 10: Summary of Quantitative Analysis Results for the Individual N-Glycan Peaks Determined by NP-HPLC

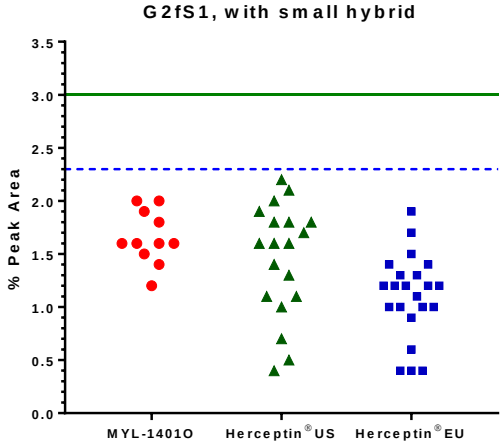


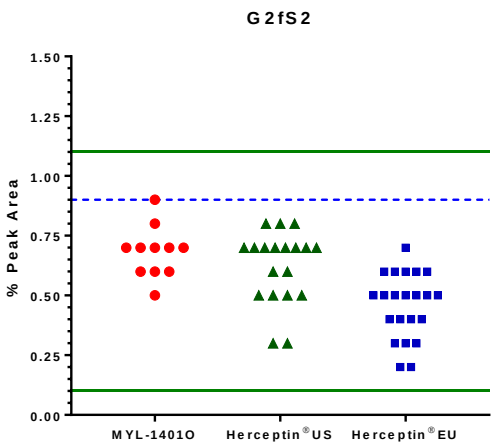

G1f-GN,G1
% Peak area
MYL-1401O
Herceptin® US
Herceptin® EU

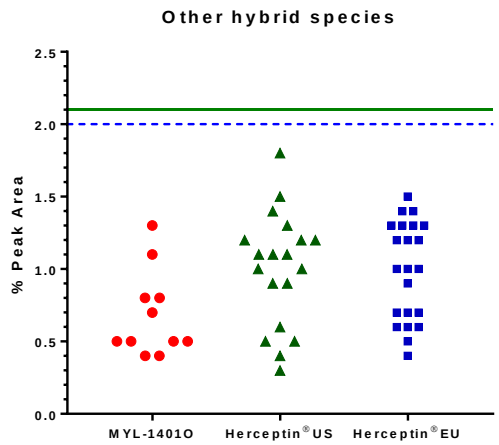

Man6, (G1f-GN)S1
% Peak area
MYL-1401O
Herceptin® US
Herceptin® EU


G1FS1,Tri antennary complex with 1 G, hybridS1
% Peak Area
MYL-1401O
Herceptin® US
Herceptin® EU


G2f
% Peak Area
MYL-1401O
Herceptin® US
Herceptin® EU


G2fS1, with small hybrid
% Peak Area
MYL-1401O
Herceptin® US
Herceptin® EU

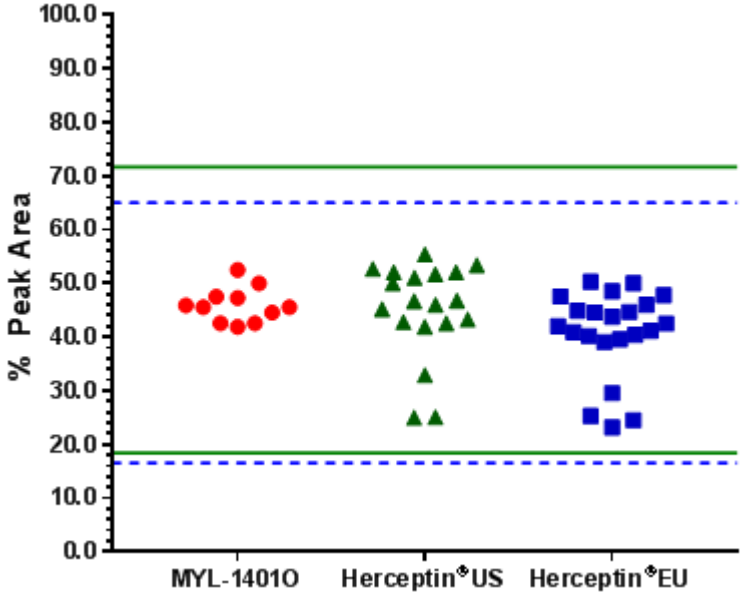

G2fS2
% Peak Area
MYL-1401O
Herceptin® US
Herceptin® EU



Solid Green Lines represent the Quality Range established for US-Herceptin; Dotted Blue Lines represent the Quality Range established for EU-Herceptin

Given that terminal galactose species accounted for nearly half of the released glycan abundance based on NP-HPLC responses, the N-glycan data were also evaluated in terms of total terminal galactose content, represented by the sum of the individual terminal galactose species. The results of this analysis are shown in Figure 11. As total terminal galactose was classified as a Tier 2 attribute, the respective Quality Ranges established for US-Herceptin and EU-Herceptin are also shown in the figure.

Figure 11: Total Terminal Galactose in MYL-1401O, US-Herceptin, and EU-Herceptin

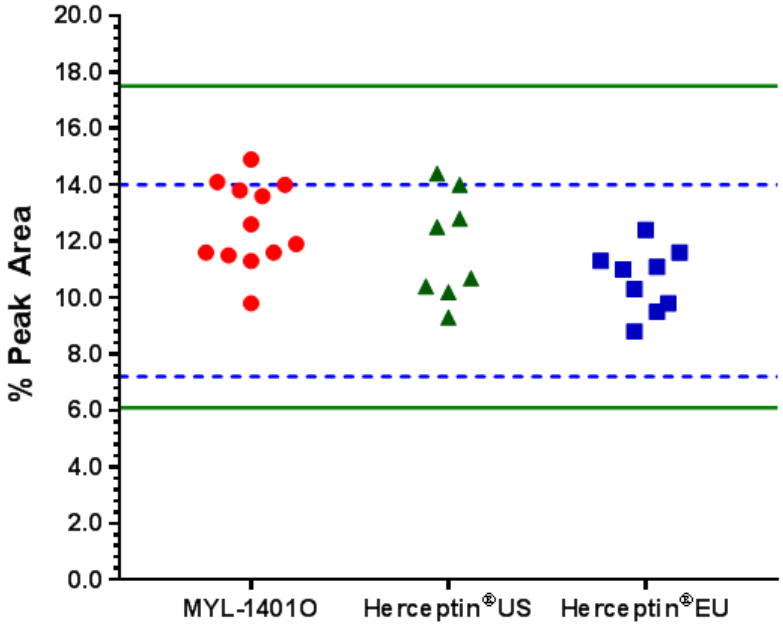


Solid Green Lines represent the Quality Range established for US-Herceptin; Dotted Blue Lines represent the Quality Range established for EU-Herceptin.

MYL-1401O, US-Herceptin, and EU-Herceptin were highly similar with respect to total terminal galactose content, further supporting the overall high similarly of the products with respect glyan variants.

Glycoform characterization also included an evaluation of total afucosylated species using RP-HPLC linked with mass spectrometry (RP-HPLC-MS). Fucose content of IgG1 monoclonal antibodies is known to affect binding to the FcγRIIIa receptor, and in turn, effector function. Total afucose content in MYL-1401O, EU-Herceptin, and US-Herceptin is shown in Figure 12. Along with the respective Quality Ranges established for US-Herceptin and EU-Herceptin (total afucose was a Tier 2 attribute).

Figure 12: Total Afucosylation in MYL-1401O, US-Herceptin, and EU-Herceptin



Solid Green Lines represent the Quality Range established for US-Herceptin; Dotted Blue Lines represent the Quality Range established for EU-Herceptin.

The afucose content of MYL-1401O met the Quality Range criteria and thus was highly similar to US-Herceptin. With respect to EU-Herceptin, both MYL-1401O and US-Herceptin contained marginally higher afucose levels.

As the products are derived from a CHO expression system, both MYL-1401O and Herceptin contain low levels of sialic acid glycans in the form of N-acetyl neuraminic acid (NANA), a structure also found in human glycoproteins. Despite the low amounts expected to be present, comparative sialic acid analysis was performed using HPLC with fluorescence detection to further characterize the glycan structures in the products.

Expectedly, the levels of total sialic acid in MYL-1401O, US, and EU Herceptin were low (≤0.1 moles per mole protein). However, the content was observed to be marginally higher for most of the MYL-1401O lots compared with US and EU Herceptin (mean of 0.08 moles per mole protein for MYL-1401O vs. 0.05 moles per mole protein for both US and EU Herceptin).

Overall, Mylan's comprehensive characterization of the glycan variants in MYL-1401O, US-Herceptin, and EU Herceptin demonstrate high similarity of the products. The very minor quantitative differences observed in high mannose and sialic acid content were demonstrated in a series of key functional assays (Section 6.2.3), including HER2 binding, inhibition of cell

proliferation, and ADCC, not to impact functional activity. Likewise, Fc receptor binding assays (including FcγRIIIa) and C1q binding analyses provided additional evidence that these minor differences did not impact effector function.

With respect to the marginally higher afucose levels observed in MYL-1401O and US-Herceptin as compared with EU-Herceptin (Section 6.2.3), these slight variations did not translate into differences in FcγRIIIa binding or ADCC activity and thus were determined not to be significant.

6.2.2.2 *Charge Variants*

Cation exchange chromatography (IEX-HPLC) is a technique capable of resolving species with minor charge differences and is the primary technique to assess charge variants. The predominant species which is considered as unmodified variant, is categorized as the main peak. Variants that elute earlier and are less positively charged than the main peak are referred to as acidic variants. These are mainly the deamidated variants, or sialic acid modifications etc. Variants that elute later than the main peak are referred to as basic peaks/variants, and commonly include C-terminal lysine variants.

Representative IEX-HPLC chromatograms for MYL-1401O, US-Herceptin, and EU-Herceptin are shown in Figure 13. Summarized results for acid, main, and basic species are shown in Figure 14, along with the respective Quality Ranges (charge variants were a Tier 2 attribute).

Figure 13: Representative IEX Chromatograms Showing Charge Variants in MYL-1401O, US-Herceptin, and EU-Herceptin

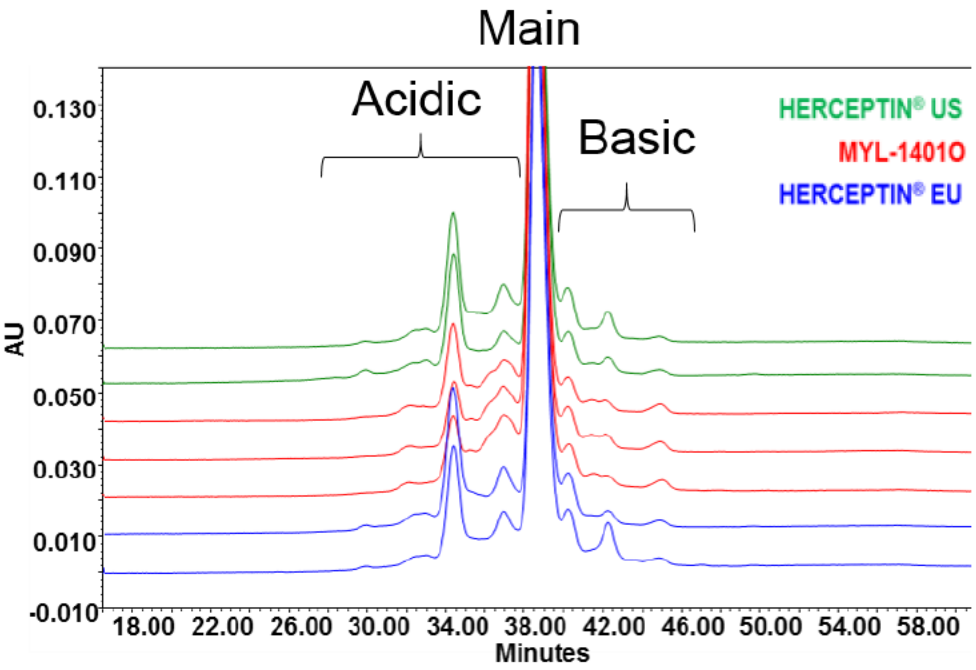
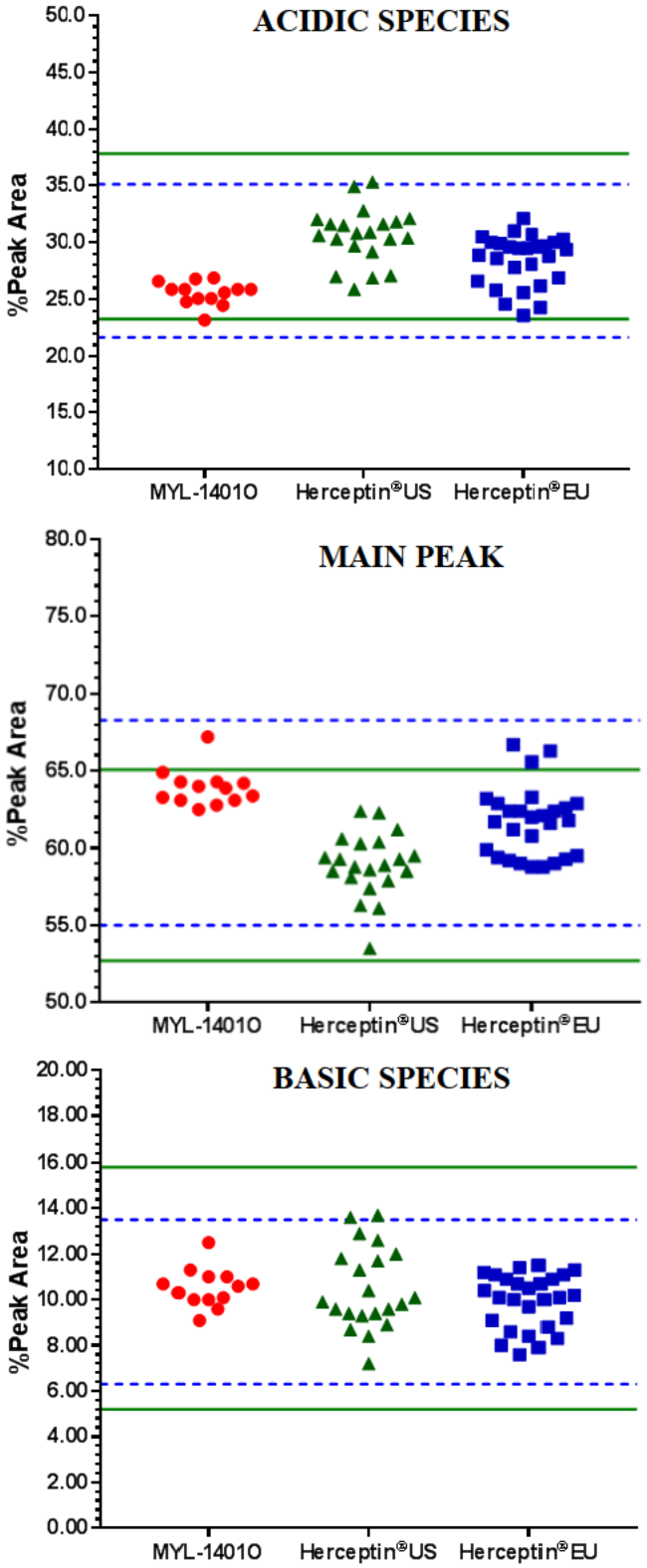


Figure 14: Acidic, Main, and Basic Species in MYL-1401O, US-Herceptin, and EU-Herceptin Determined by IEX-HPLC



Solid Green Lines represent the Quality Range established for US-Herceptin; Dotted Blue Lines represent the Quality Range established for EU-Herceptin

High similarity, as evaluated using Quality Ranges, was observed for the acidic, main, and basic species of MYL-1401O compared to both US- and EU-Herceptin. Likewise, US- and EU-Herceptin were highly similar except for a slightly higher main peak content for EU-Herceptin (mean 61.7% vs. 58.9%), which was determined not to be significant based on the small magnitude of the difference and the fact that no differences were observed in the battery of functional assays (Section 6.2.3).

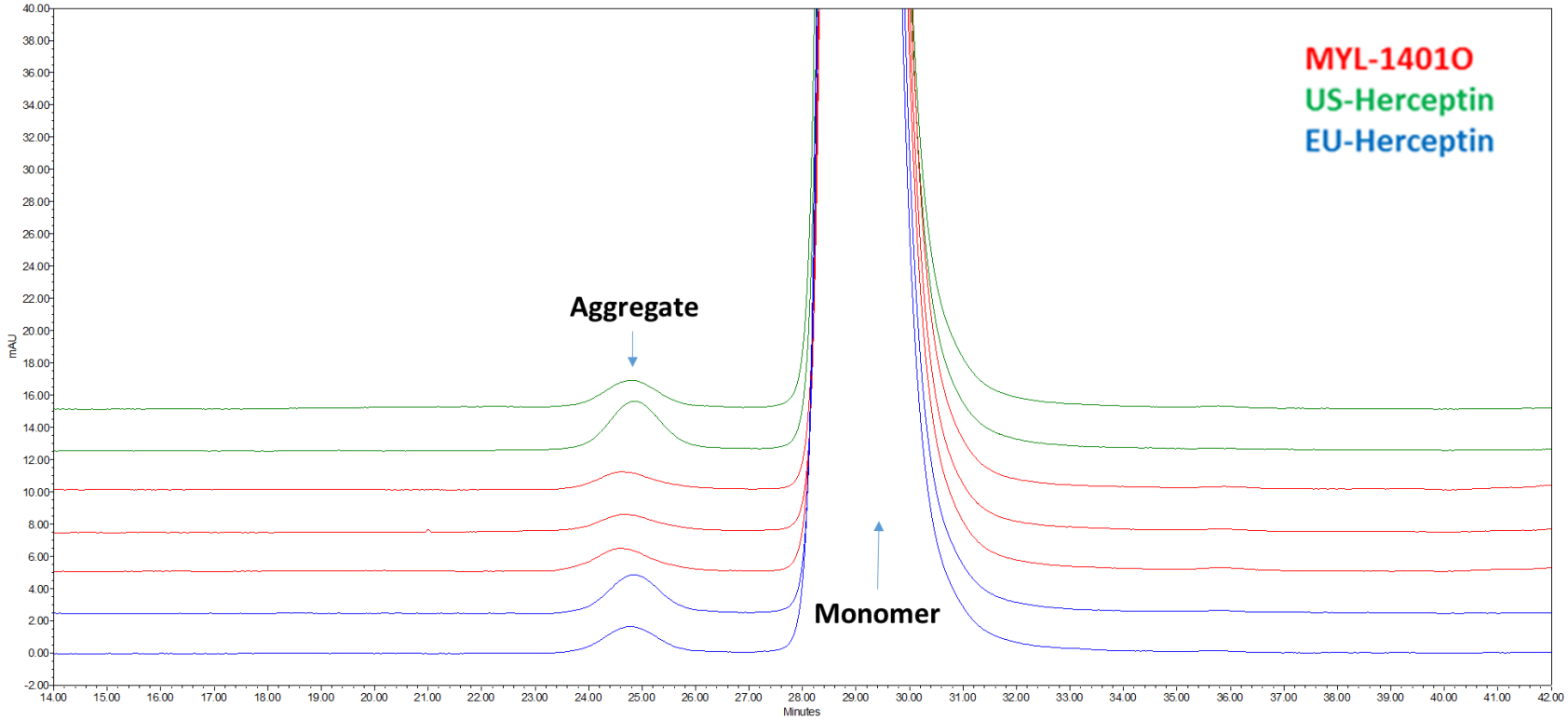
6.2.2.3 *Size Variants*

Aggregates

High molecular weight protein (HMWP) variants in MYL-1401O and both US- and EU-Herceptin were evaluated using SEC. The species resolved by this method were further characterized and found to be dimer/oligomers/higher order oligomers (aggregates).

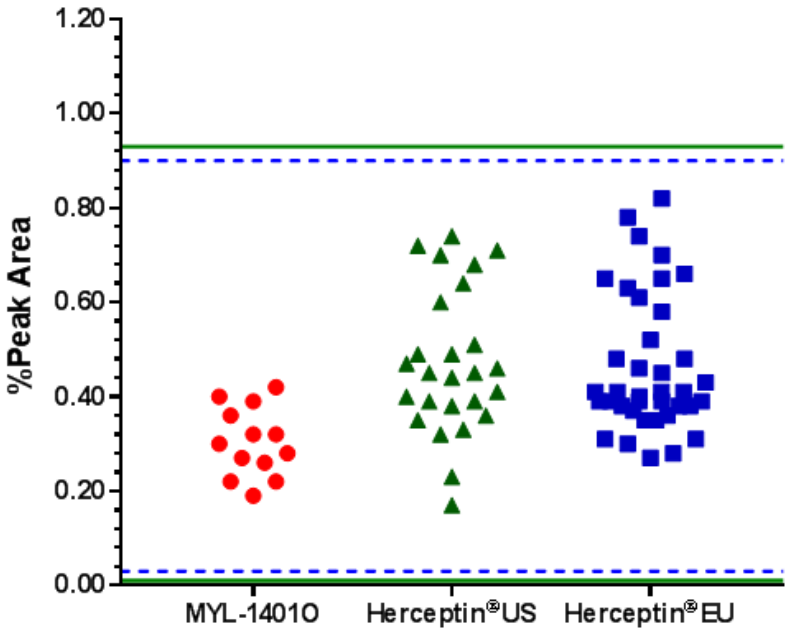
Representative overlaid SEC chromatograms are provided in Figure 15.

Figure 15: Representative SEC-HPLC Chromatograms for MYL-1401O, US-Herceptin, and EU-Herceptin



Aggregates were classified as Tier 2 attribute and were assessed using Quality Ranges. Results are shown in Figure 16 and demonstrate that MYL-1401O, US-Herceptin, and EU-Herceptin were highly similar.

Figure 16: Aggregates in MYL-1401O, US-Herceptin, and EU-Herceptin

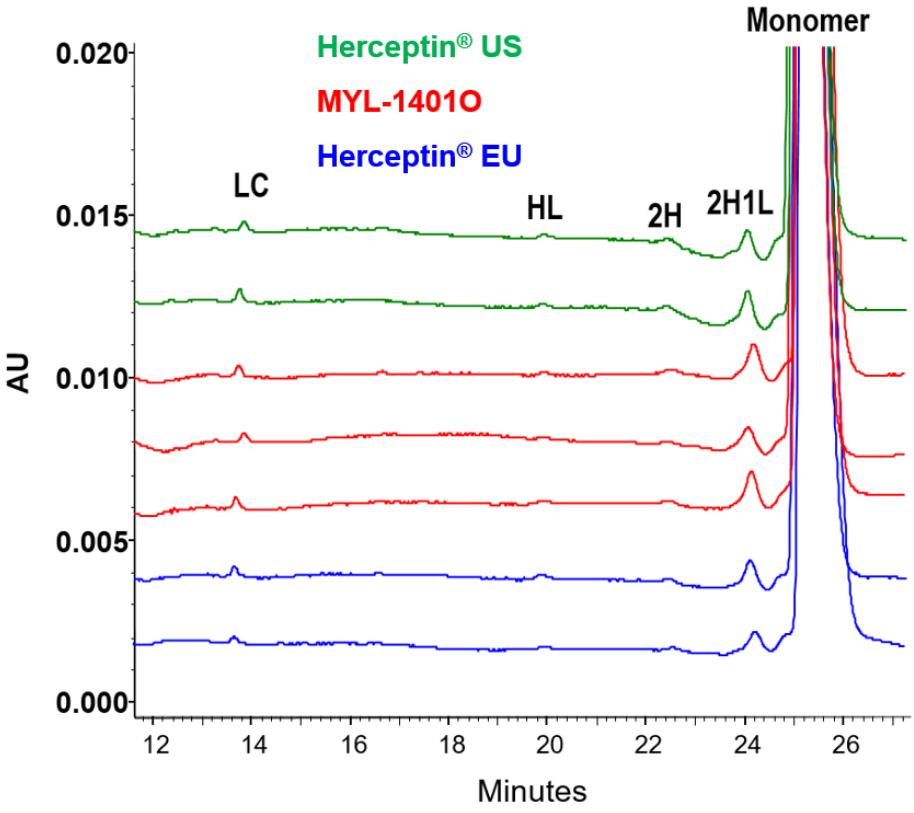


Solid Green Lines represent the Quality Range established for US-Herceptin; Dotted Blue Lines represent the Quality Range established for EU-Herceptin

Fragments

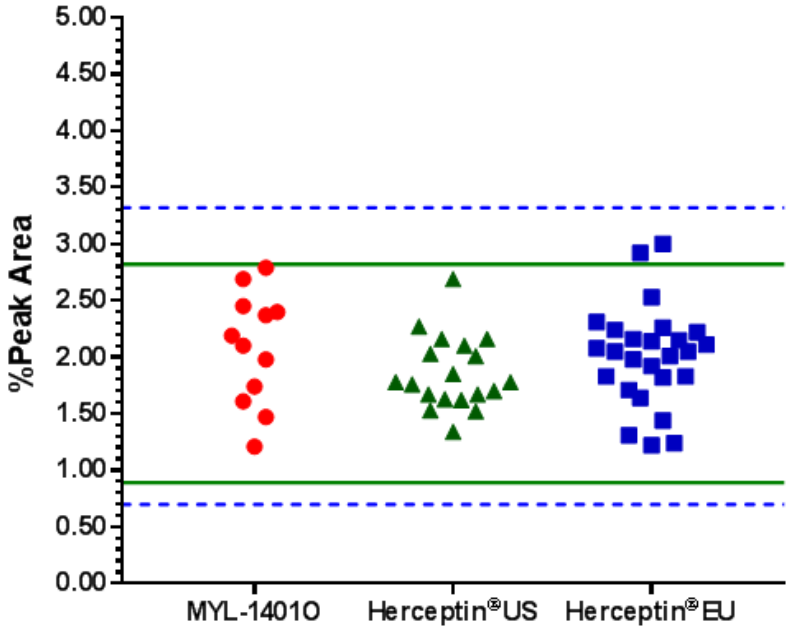
Low molecular weight variants (fragments) in the products were assessed using non-reduced CE-SDS. Figure 17 shows overlaid electropherograms for MYL-1401O, US-Herceptin, and EU-Herceptin.

Figure 17: Representative CE-SDS Electropherograms Showing Fragments in MYL-1401O, US-Herceptin, and EU-Herceptin



The same fragment species were detected in each product and as shown in Figure 18, total levels of fragments were found to be highly similar for MYL-1401O, US-Herceptin, and EU-Herceptin, as assessed using Quality Ranges (Tier 2 attribute).

Figure 18: Total Fragments in MYL-1401O, US-Herceptin, and EU-Herceptin



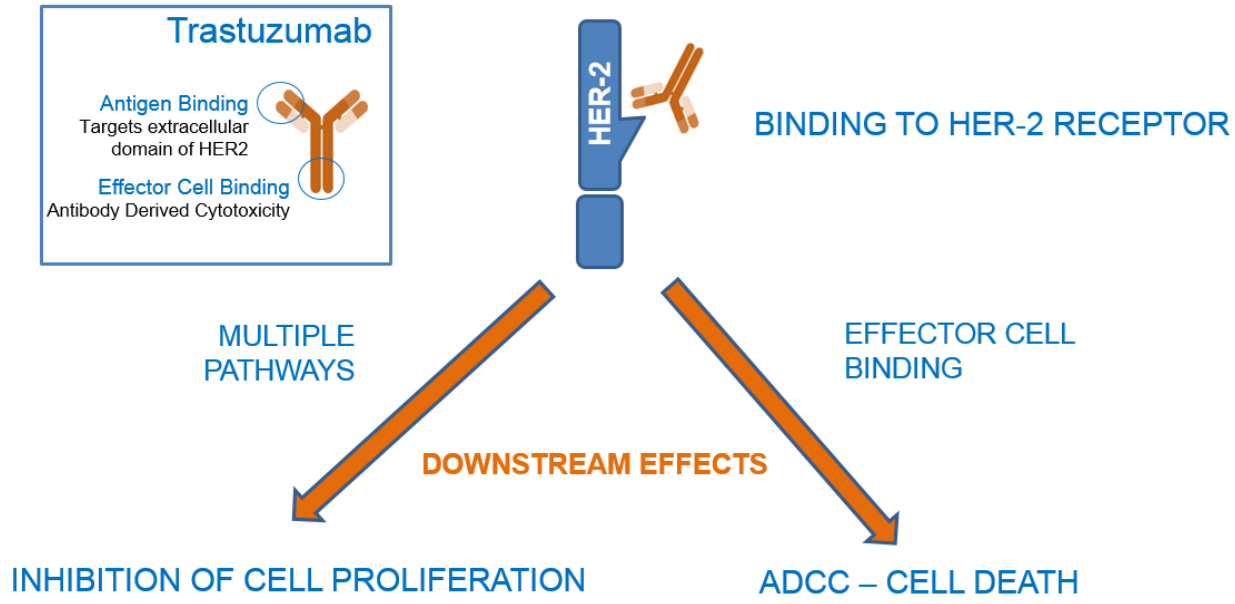
Solid Green Lines represent the Quality Range established for US-Herceptin; Dotted Blue Lines represent the Quality Range established for EU-Herceptin

6.2.3 Functional Attributes

The biological and functional similarity of MYL-1401O was compared with US- and EU-Herceptin using multiple assays to measure both the target binding (Fab) and effector (Fc-mediated) functionality of the antibody.

As illustrated in Figure 19, trastuzumab's mechanism of action in each indication involves the key step of binding to the HER2 extracellular domain via the Fab portion of the antibody and is responsible for the beneficial effects of the drug across the range of approved indications. Subsequent to the drug binding to HER2, various downstream processes occur, e.g. inhibition of dimerization and blocking of signal transduction pathways, inhibition of extracellular domain cleavage, endocytosis. Additionally, antibody dependent cellular cytotoxicity (ADCC), can occur, mediated by the binding of the Fc region of the antibody to an immune effector cell.

Figure 19: Key Steps in Trastuzumab's Mechanism of Action



Mylan's analytical similarity assessment included a battery of sensitive functional assays that reflect the key aspects of trastuzumab's pharmacology. Among these were:

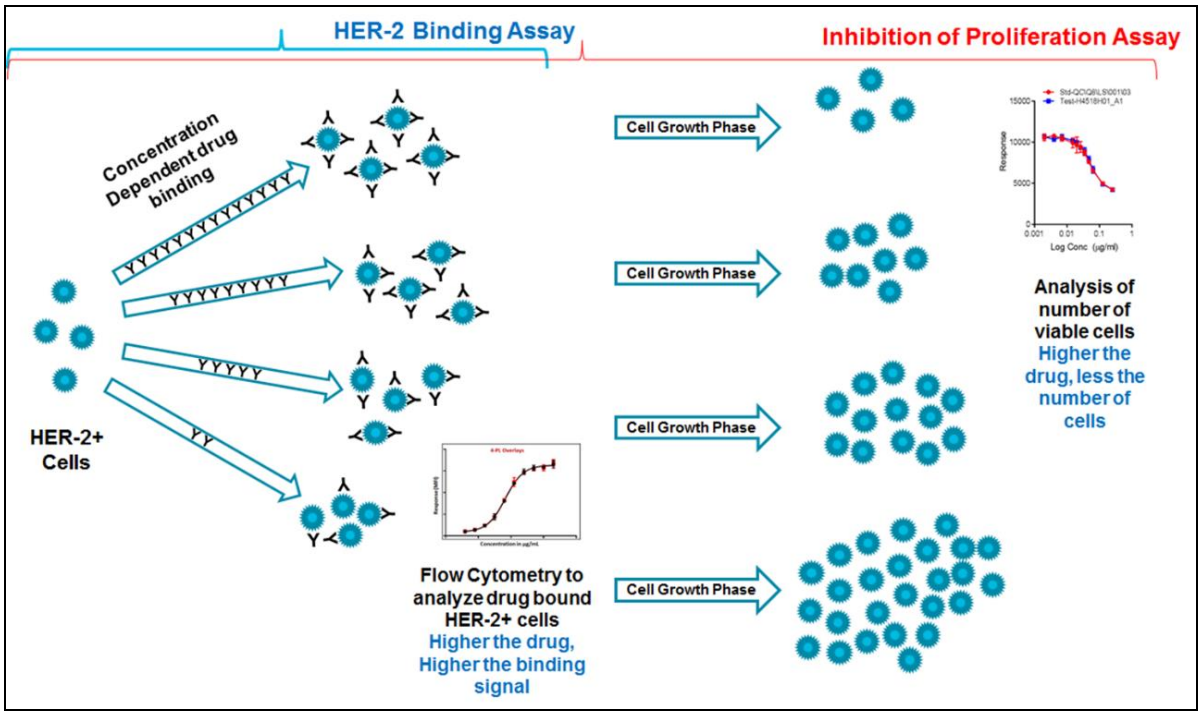
- Cell based assays involving Fab region of the antibody (i.e., binding to HER2 receptor and inhibition of proliferation of cells that overexpress HER2)
- Cell based assays involving Effector functions of immune cells through the constant region (Fc) of the antibody (i.e., ADCC measured *in vitro* using SK-BR3 breast cancer cells with human PBMCs as immune effector cells)
- Binding affinity to the FcγRIIIa receptor, which can directly impact effector function and ADCC, was monitored and compared using a surface plasma resonance (SPR)-based assay in kinetic mode.
- Binding of the antibody to the neonatal Fc receptor, FcRn, which can impact the antibody half-life
- Antibody binding to C1q that can affect the complement activation were also measured using SPR and enzyme-linked immunosorbent assays (ELISA), respectively.
- Binding affinity to a series of other Fc receptors (FcγRIa, FcγRIIa, FcγRIIb, and FcγRIIIb) were also measured using SPR-based assays.

6.2.3.1 *Fab-Mediated Functional Assays*

The mechanism of action of trastuzumab across all indications involves binding to the HER2 receptor. Receptor binding triggers suppression of the down-stream signaling cascade, thereby

inhibiting the proliferation of the tumor cells. As depicted in Figure 20, Mylan's analytical tools for evaluating HER2 binding and its associated biological effects comprised 2 cell-based assays, a binding assay using a flow cytometry and an inhibition of proliferation (IOP) assay.

Figure 20: Principles of the HER2 Binding and IOP Assays

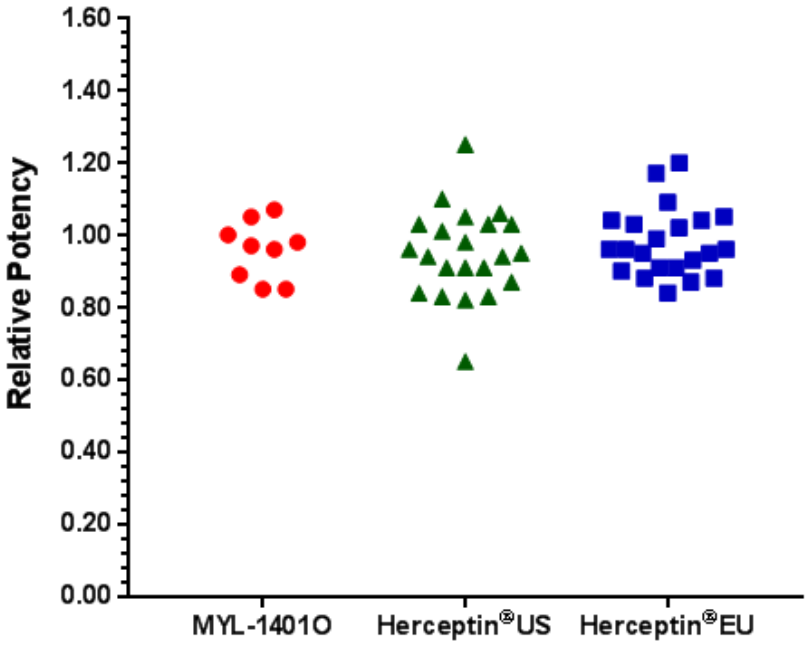


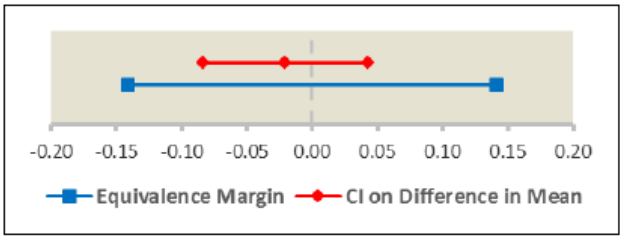
HER2 Target Binding Studies

Demonstrating that MYL-1401O binds to the HER2 receptor with similar affinity as Herceptin is a key element in establish biosimilarity. The immortalized breast cancer cell line SK-BR3, which overexpresses HER2 on its cell surface, was used to assess relative binding affinities. HER2 binding studies were conducted to compare MYL-1401O, US-Herceptin, and EU-Herceptin. In this assay, the dose-dependent response (cell binding) in the presence of trastuzumab test sample (MYL-1401O or Herceptin) as compared to a common reference standard was expressed as a relative potency value.

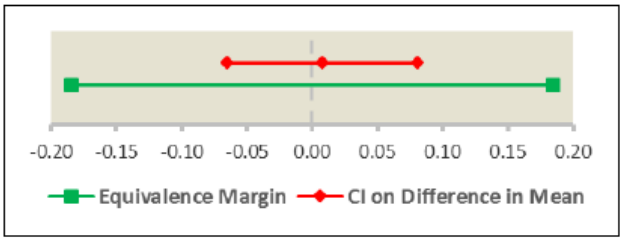
HER2 binding was a Tier 1 attribute and therefore was subjected to formal statistical equivalence analysis. Results are presented in Figure 21.

Figure 21: HER2 Binding and Statistical Analysis Results for MYL-1401O, US-Herceptin, and EU-Herceptin

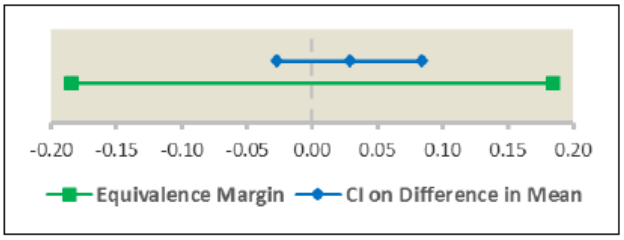




MYL-1401O vs. Herceptin EU



MYL-1401O vs. Herceptin US



Herceptin EU vs. Herceptin US

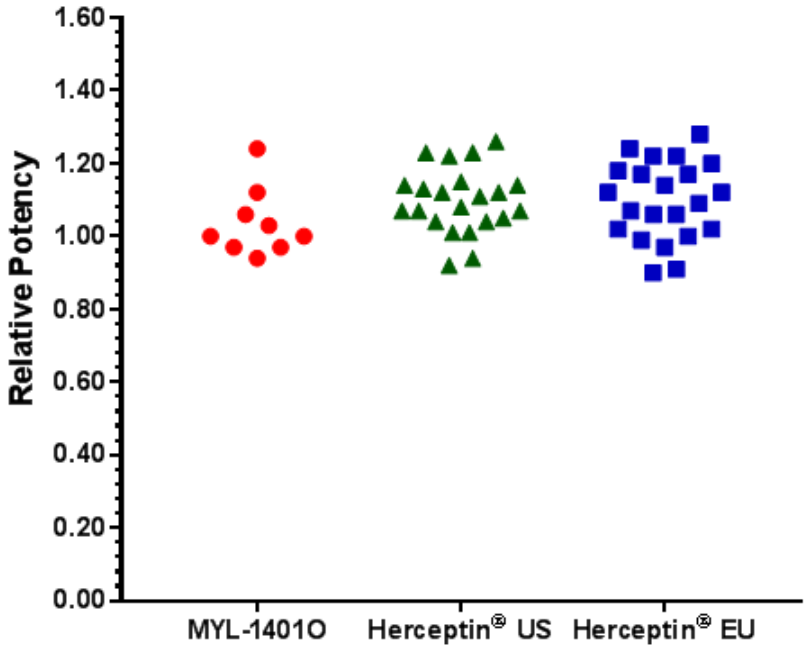
MYL-1401O met the statistical equivalence criteria and thus showed high similarity in HER2 binding to US- and EU-Herceptin. Also, the relative HER2 binding of EU-Herceptin was equivalent to US-Herceptin, thereby demonstrating a high similarity between the reference products from the US and the EU.

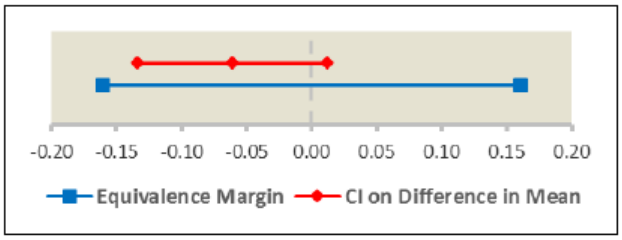
MYL-1401O Inhibition of Proliferation (IOP) Assay

As mentioned above, overexpression of the HER2 receptor promotes cell growth, proliferation, survival, and migration. Binding of trastuzumab to HER2 has a direct inhibitory effect on proliferation of HER2-overexpressing cells through multiple pathways. Evaluation of functional activity was measured *in vitro* for MYL-1401O, US-Herceptin, and EU-Herceptin using the HER2-overexpressing SK-BR3 cell line. As with the HER2 binding assay, the dose-dependent response or inhibition of proliferation in the presence of trastuzumab test sample (MYL-1401O or Herceptin) as compared to a common reference standard was expressed as a relative potency value.

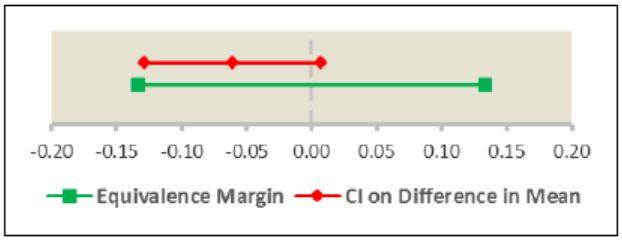
IOP was also a Tier 1 attribute and therefore was subjected to formal statistical equivalence analysis, the results of which are shown in Figure 22.

Figure 22: Inhibition of Cell Proliferation and Statistical Analysis Results for MYL-1401O, US-Herceptin, and EU-Herceptin

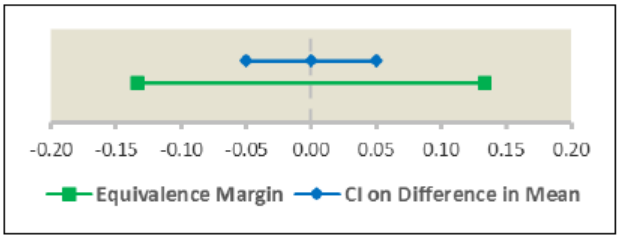




MYL-1401O vs. Herceptin EU



MYL-1401O vs. Herceptin US



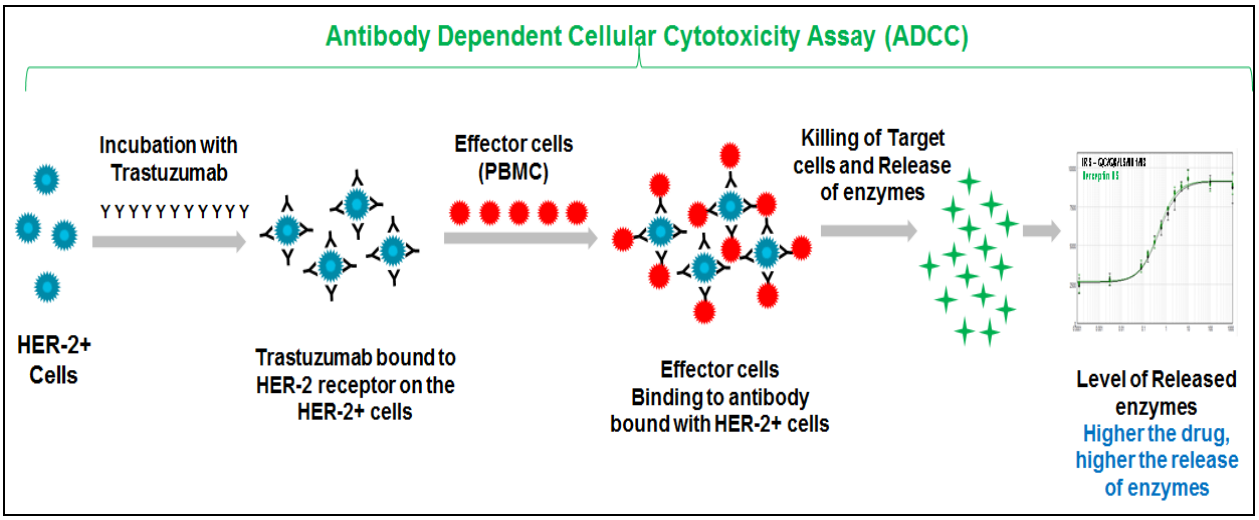
Herceptin EU vs. Herceptin US

MYL-1401O met the statistical equivalence criteria and therefore showed high similarity to US-Herceptin and EU-Herceptin lots with respect to IOP. Additionally, the relative IOP potency of EU-Herceptin was equivalent to US-Herceptin, thereby demonstrating high similarity of the reference products in a key biological activity of the molecules.

6.2.3.2 *Fab/Fc Mediated Antibody-Dependent Cell-Mediated Cytotoxicity Assay*

ADCC, one of trastuzumab's mechanisms or action, was evaluated using a cell-based assay that employed SK-BR3 breast cancer cells, peripheral blood mononuclear cells (PBMCs) as a source of immune effector cells, and a luminescence reader to detect the lysed (dead) cells. The assay principle is depicted in Figure 23.

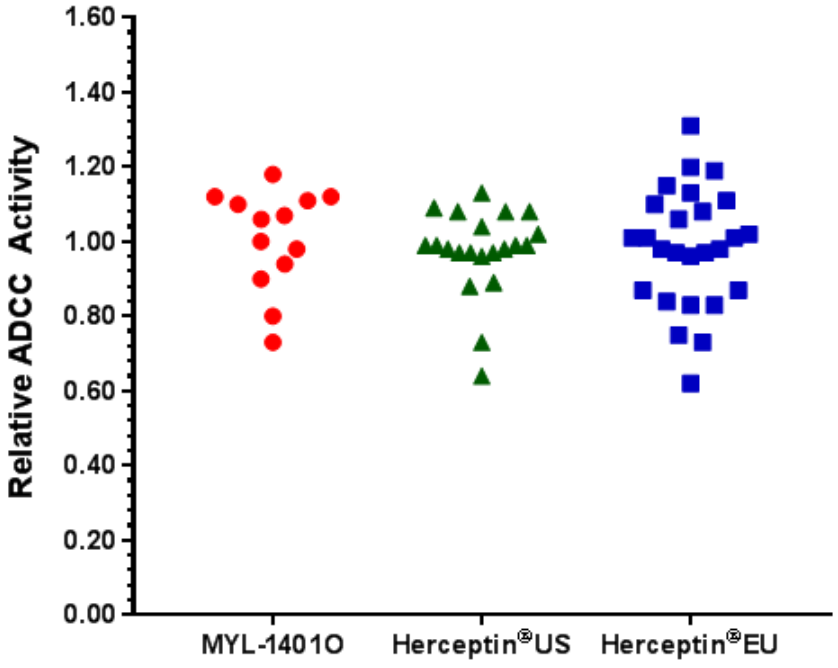
Figure 23: Principle of the Antibody-Dependent Cell-Mediated Cytotoxicity Assay

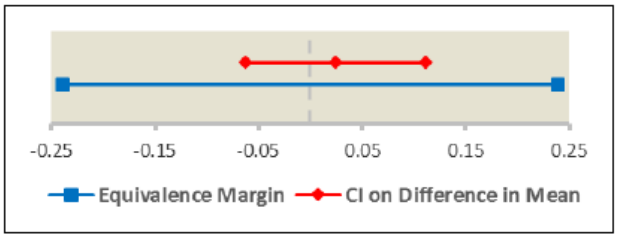


As with the HER2-binding and IOP assays, the dose-dependent response or inhibition of proliferation in the presence of trastuzumab test sample (MYL-1401O or Herceptin) as compared to a common reference standard was expressed as a relative potency value.

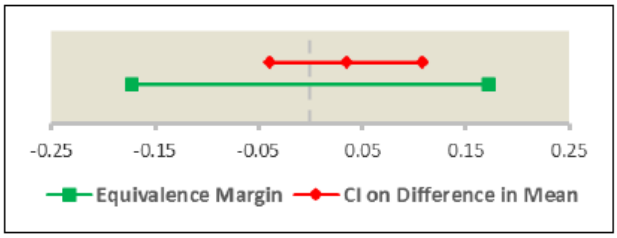
As shown in Figure 24, MYL-1401O met statistical equivalence criteria and showed high similarity to both US-Herceptin and EU-Herceptin. Likewise, the ADCC activity of EU-Herceptin was also equivalent to US-Herceptin, thereby establishing the high similarity of all 3 products respect to this key biological activity.

Figure 24: ADCC Activity and Statistical Analysis Results for MYL-1401O, US-Herceptin, and EU-Herceptin

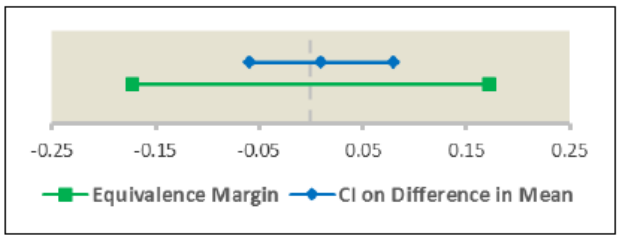




MYL-1401O vs. Herceptin EU



MYL-1401O vs. Herceptin US



Herceptin EU vs. Herceptin US

6.2.3.3 *Fc Domain Functional Characterization*

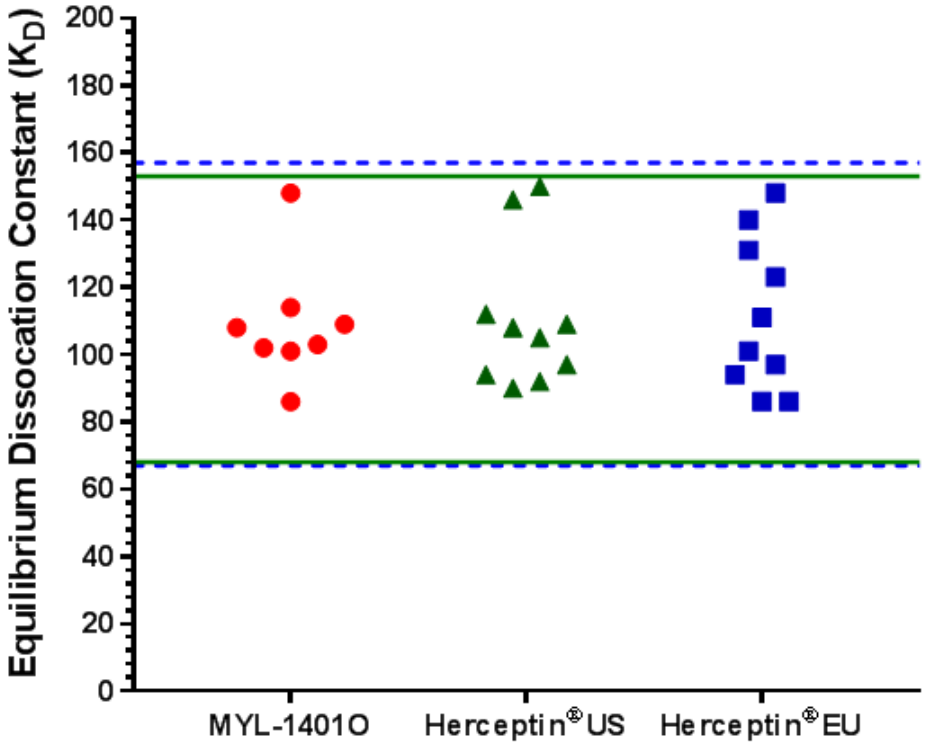
FcγRIIIa Binding Assay

As noted above, trastuzumab, like other IgG-based antibodies, mediates its effector functions of immune cells through the Fc region of the antibody. In particular, binding to the Fcγ receptor IIIa (FcγIIIa) is known to mediate ADCC effector function. Mylan utilized a surface plasmon resonance (SPR) method to determine and compare the binding kinetics of MYL-1401O, US-Herceptin, and EU-Herceptin to the V158 (high affinity) isoform of FcγRIIIa.

FcγRIIIa binding was classified as a Tier 2 attribute and accordingly was analyzed using Quality Ranges. Equilibrium dissociation constants (Kd) values determined for MYL-1401O, US-Herceptin, and EU-Herceptin, as well as the respective Quality Ranges are shown in Figure 25.

All products met the Quality Range criteria thus demonstrating high similarity of MYL-1401O, US-Herceptin, and EU-Herceptin respect to FcγRIIIa binding.

Figure 25: FcγRIIIa Binding Results for MYL-1401O, US-Herceptin and EU-Herceptin



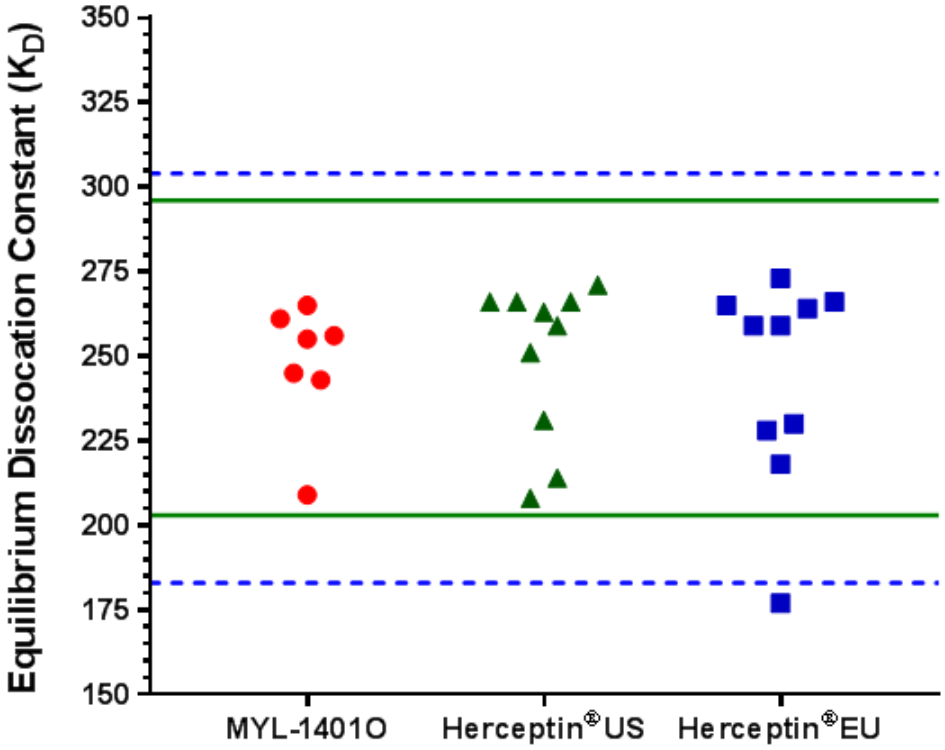
Solid Green Lines represent the Quality Range established for US-Herceptin; Dotted Blue Lines represent the Quality Range established for EU-Herceptin.

FcRn Kinetics Assay (Biacore Kinetics)

The neonatal Fc receptor (FcRn), unlike the other Fc receptors, is similar in structure to MHC Class I, consisting of 2 sub-units forming a heterodimer. FcRn is involved in recycling of IgG and regulates its serum half-life, maintaining its serum concentration and regulating IgG homeostasis. An SPR-based method was used to determine and compare the binding kinetics of MYL-1401O, US-Herceptin, and EU-Herceptin to FcRn.

FcγRn binding was classified as a Tier 2 attribute and accordingly was analyzed using Quality Ranges. Equilibrium dissociation constants (Kd) values determined for MYL-1401O, US-Herceptin, and EU-Herceptin, as well as the respective Quality Ranges are shown in Figure 26.

Figure 26: FcRn Binding Results for MYL-1401O, US-Herceptin and EU-Herceptin



Solid Green Lines represent the Quality Range established for US-Herceptin; Dotted Blue Lines represent the Quality Range established for EU-Herceptin.

All products met the Quality Range criteria, thus demonstrating high similarity of MYL-1401O, US-Herceptin, and EU-Herceptin respect to FcγRn binding.

Other Fc Domain-Binding Studies

In order to further characterize potential effector function activity of the products, binding affinity to other Fc receptors, FcγRIa, FcγRIIa, FcγRIIb, and FcγRIIIb was also assessed using

SPR-based assays. In addition to these analyses, binding to C1q, which can affect complement activation, was probed using an ELISA method. Data from all these studies demonstrated high similarity between MYL-1401O, US- Herceptin, and EU-Herceptin, adding to the overall body of data showing high similarity of the products with respect to functional activity.

6.3 Analytical Similarity Conclusion

Mylan's rigorous analytical similarity studies comprised a battery of sensitive, state-of-the art methods. As summarized in Table 4, MYL-1401O, US-Herceptin, EU-Herceptin were analyzed across an array of physicochemical attributes including primary, secondary, and higher order structure, product variants including variants in size, charge, and glycoforms. At the level of biological function, the products were analyzed in key cell-based assays that captured trastuzumab's mechanism of action (i.e., HER2 binding, inhibition of cell proliferation, and ADCC), as well as in a series of Fc receptor binding assays. This extensive body of data conclusively demonstrates that MYL-1401O, US-Herceptin, and EU-Herceptin are analytically highly similar.

Table 4: Overall Summary of the Analytical Similarity Assessment of MYL-1401O, US-Herceptin, and EU-Herceptin

PRODUCT CHARACTERISTICS		METHODS	MYL-1401O vs. HERCEPTIN
STRUCTURAL			
Protein content		UV 280 nm	Highly similar
Amino acid sequence/Primary Structure		Peptide Mapping/HPLC/MS/MS	Identical sequence
		Intact and LC/HC Mass by High Resolution MS	Highly similar
Secondary and Higher Order Structure		Far UV Circular Dichroism Spctroscopy	Highly similar
		Fourier Transform IR Spectroscopy	
		Free Cysteine by Ellman's Reagent/UV-VIS	
		Disulfide Bridging by HPLC-MS	
		Near UV Circular Dichroism	
		Differential Scanning Calorimetry	
		Intrinsic Fluorescence	
		Hydrophobic Interaction Chromatography	
Sub-visible Particles		Microflow Imaging (MFI)	Particle counts ≥ 5 µm Highly Similar*
Aggregates		Size Exclusion Chromatography – UV	Highly similar
		Analytical Ultra Centrifugation (AUC)	
		Size Exclusion Chromatography – MALS	
Fragments		CE-SDS (Non-Reduced)	Highly similar
Glycoform variants	Non-glycosylated	CE-SDS (Reduced)	Highly similar
	Afucosylated	Normal Phase HPLC	Highly similar

PRODUCT CHARACTERISTICS		METHODS	MYL-1401O vs. HERCEPTIN
	Terminal Galactose	Normal Phase HPLC	Highly similar
	High Mannose	Normal Phase HPLC	Minor quantitative differences
	Terminal Sialic acid	Reverse Phase HPLC	
Glycation		Boronate Affinity Chromatography	Highly similar
Methionine oxidation		Peptide Mapping/HPLC-MS	Highly similar
Charge variants		Cation Exchange Chromatography	Highly similar
Degradation Pathways		Thermal, Chemical, Mechanical and Photo Stress	Similar rates and pathways of degradation
FUNCTIONAL			
Target (HER2) binding		SK-Br3 Cell-Based Assay using Flow Cytometry	Equivalent
Inhibition of Cell Proliferation (IOP)		SK-Br3 Cell-Based Assay	Equivalent
ADCC		SKBr3 Cell-Based Assay using human PBMCs	Equivalent
FcγRIIIa Binding		Surface Plasmon Resonance (Kinetic Mode)	Highly Similar
FcRn Binding		Surface Plasmon Resonance (Kinetic Mode)	Highly Similar
FcγRI Binding		Surface Plasmon Resonance (Kinetic Mode)	Highly Similar
FcγRIIa Binding		Surface Plasmon Resonance (Kinetic Mode)	Highly Similar
FcγRIIb Binding		Surface Plasmon Resonance (Kinetic Mode)	Highly Similar
FcγRIIIb Binding		Surface Plasmon Resonance (Kinetic Mode)	Highly Similar
C1q Binding		ELISA	Highly Similar
CDC		CDC Cell Based Assay	Highly Similar

*Particle counts were separately assessed in the following size ranges: ≥2 µm, ≥5 µm, ≥10 µm, and ≥25 µm. MYL-1401O (n=12), US-Herceptin (n=6), and EU-Herceptin (n=6) were highly similar at 5 µm and above, however, in the 2 - 5 µm range, higher counts were observed for 4 lots of MYL-1401O lots. These particles were characterized and found to be non-proteinaceous and thus not of concern with respect to immunogenicity.

7 NONCLINICAL DEMONSTRATION OF BIOSIMILARITY

7.1 Nonclinical Development Program Overview

The nonclinical development program was developed in accordance with the FDA guidance on biosimilars and included 2 *in vitro* safety studies to compare the effects of MYL−1401O and Herceptin on cardiomyocytes, and *in vivo* single-dose pharmacokinetic and multi-dose toxicokinetic/toxicity studies in Cynomolugus monkeys. As Herceptin is known to be pharmacologically active in cynomolgus monkeys, this species was chosen for the pivotal nonclinical studies.

Table 5 presents an overview of the nonclinical development program.

Table 5: Overview of Nonclinical Development Program

Study No.	Type of Study; GLP Status	Species, Method or Cell line	Route of Administration	Comparator Product(s) Used
MYL-Her-PC-01	Pharmacology/ Safety Pharmacology Study; Non-GLP	Human cardiomyocytes	*In vitro*	EU-Herceptin
MYL-Her-PC-04	Pharmacology/ Safety Pharmacology; Non-GLP	Rat cardiomyocytes	*In vitro*	EU-Herceptin
MYL-Her-PC-02	Pharmacokinetics/ Other Pharmacokinetic Studies; Non-GLP	Cynomolgus Monkey (Macaca fascicularis) 2 parallel groups, 6 F/group	Intravenous infusion	EU-Herceptin
MYL-Her-PC-03	Toxicology/ Repeat-Dose Toxicity; GLP-compliant	Cynomolgus Monkey (Macaca fascicularis) 5 parallel groups 3M+3F/group	Intravenous infusion	EU-Herceptin

7.2 Safety Pharmacology

Cardiotoxicity has been observed with clinical use of Herceptin. Therefore, 2 safety pharmacology studies were performed to compare the effect of MYL−1401O and EU-Herceptin on mitochondrial function in human and rat cardiomyocytes as an indicator of relative cardiotoxicity potential. These studies demonstrated similar responses for MYL−1401O and EU-Herceptin for the cardiotoxicity endpoints evaluated.

MYL-HER-PC-01: Study in Human Adult Primary Cardiomyocytes

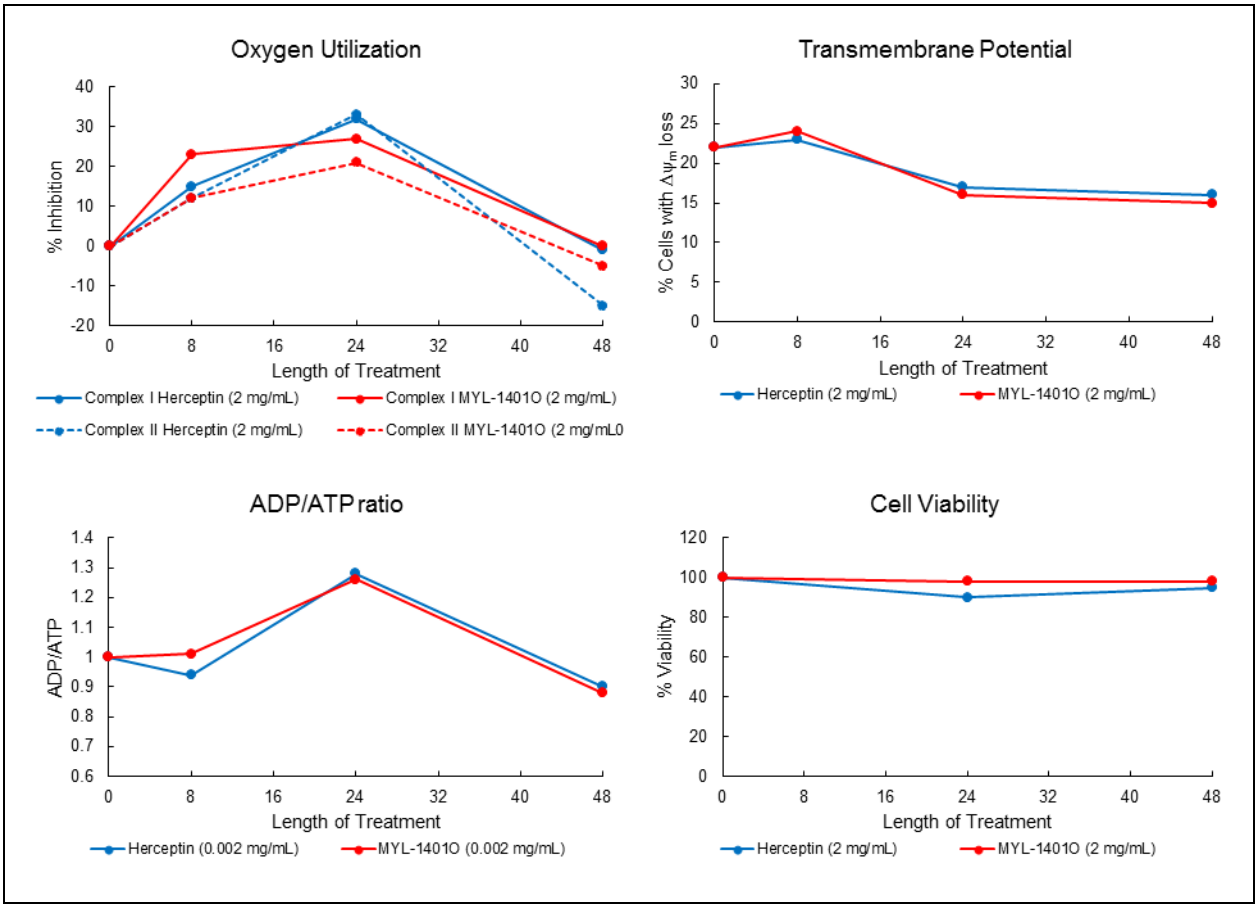
Human adult primary cardiomyocytes were obtained, seeded into cell culture plates, and incubated in growth medium for 24-hours prior to initiation of testing. The cardiomyocytes were treated with 5 log concentrations of Herceptin or MYL−1401O (0.0002; 0.002; 0.02; 0.2; 2 mg/mL) and for 8, 24, or 48 hours. Mitochondrial function was measured using the following parameters: 1) mitochondrial membrane delta potential, 2) respiratory complex I and II activity, 3) ADP/ATP ratio, and 4) cell viability. Specific positive and negative controls were used for each assay. Treatment concentrations, duration, and types of mitochondrial assay were determined by an initial pilot study using Herceptin alone.

The results demonstrated similar findings for both Herceptin and MYL−1401O:

- No observed or measurable effects on mitochondrial membrane delta potential or cell viability, indicating that neither product induced cellular toxicity.
- An increase in intracellular ADP at 24 hours led to an increase of ATP at 48 hours, indicating a transitory stress response.
- A transitory inhibition on the respiratory chain characterized by a decrease in oxygen consumption and changes in complex I and complex II activation at 24 hours with recovery at 48 hours. These changes were not sufficient to lead to cell death.
- None of the changes observed were dose-dependent; a nonparametric Mann-Whitney statistical analysis indicated no difference between Herceptin and MYL-1401O.

Representative graphs illustrating these changes over time are shown in Figure 27.

Figure 27: Changes in Human Cardiomyocyte Parameters in Response to Herceptin and MYL-1401O



The figure shows representative time lines for measurements conducted in adult human cardiomyocytes incubated with either Herceptin or MYL-1401O. Multiple doses were tested for each parameter; these graphs illustrate the data for the dose that demonstrated the greatest degree of change over time for each parameter.

MYL-HER-PC-04: Study in Neonatal Rat Cardiomyocytes

As summarized above, the study using human adult primary cardiomyocytes demonstrated a transient alteration in oxygen consumption and ADP/ATP ratios but no loss of cell viability in both Herceptin and MYL−1401O groups. A similar study was performed using neonatal rat cardiomyocytes, a potentially more sensitive model as these cells are primed to undergo apoptosis.

In concurrence with the results from human adult cardiomyocytes, the results using neonatal rat cardiomyocytes confirmed a transient stress response but no loss of cell viability in both Herceptin and MYL−1401O groups.

7.3 Nonclinical Pharmacology and Toxicology

A comparative single-dose PK study of MYL−1401O and EU-Herceptin was performed in Cynomolgus monkeys. This non GLP study (MYL-Her-PC-02) was performed to generate preliminary PK profiles and to determine appropriate sampling points for toxicokinetic (TK) evaluation in conjunction with the repeat-dose study (MYL-Her-PC-03). Neither of these studies were designed or powered for formal PK equivalence evaluation. Both studies utilized IV infusion for product administration, the same as the clinically indicated route. Table 6 provides a summary of the results of Studies MYL-Her-PC-02 and MYL-Her-PC-03.

Table 6: Summary Results of Nonclinical Pharmacology and Toxicology Studies

Study	Test System	Results / Summary
Pharmacokinetic Study MYL-Her-PC-02	Cynomolgus monkey (females) 2 parallel groups 6F/group	25 mg/kg MYL−1401O or EU-Herceptin given as a single dose IV infusion No relative differences in $AUC_{0\text{-}inf}$ and C_{max}, between MYL−1401O vs Herceptin Both treatments were well tolerated and did not cause any drug related clinical signs, changes in body weight or injection site skin reactions
Toxicokinetic Study MYL-Her-PC-03	Cynomolgus monkey (males and females) 5 parallel groups 3M+3F/group	25 or 50 mg/kg MYL−1401O or EU-Herceptin given as 5 weekly IV infusion doses Both treatments were well tolerated with no toxicity concerns; a NOEL of 50 mg/kg/week was assigned for both agents Comparisons of TK analysis following infusions on Day 1 and Day 22 demonstrated similar systemic availability

7.3.1 Nonclinical Pharmacokinetics

The objective of Study MYL-Her-PC-02 was to generate preliminary PK profiles of MYL-1401O and Herceptin following a single 30-minute IV infusion in female Cynomolgus Monkeys. Six female monkeys per treatment group were monitored for 6 weeks (3 to 4 serum half-lives) after dosing.

Single 25 mg/kg IV doses of MYL−1401O and Herceptin were well tolerated. No product-related clinical signs, or changes in body weight or injection site reactions were observed. There were no treatment-related effects on clinical signs or body weight for either test article. Effects were similar in frequency, appearance and duration in MYL−1401O and Herceptin treated animals. Serum concentrations of MYL−1401O and Herceptin declined in a bi-phasic manner with similar profiles. The exposures in both groups were similar with systemic availability of

MYL-1401O based on $AUC_{0-\infty}$ and C_{max} of 79.7% and 78.2%, respectively compared to Herceptin.

7.3.2 Nonclinical Toxicology

Study MYL-Her-PC-03 was a repeat-dose study designed to evaluate differences between MYL−1401O and Herceptin in terms of clinical signs, changes in weight, food consumption, blood pressure, electrocardiography (ECG), mortality, changes at the injection site (local tolerance), ophthalmology, TK, clinical pathology, and anatomical pathology following 5 weekly IV infusions in Cynomolgus monkeys.

Two parallel groups of 3 male and 3 female Cynomolgus monkeys received weekly doses of 25- or 50-mg per kilogram body weight MYL-1401O or EU-Herceptin for a total of 5 administrations. Test articles were administered by IV infusion over 30-minutes in a volume of 4.0 mL/kg. An additional group of animals received vehicle. The TK profile was compared after Dose 1 (Day 1) and Dose 4 (Day 22) to confirm exposure and compare TK profiles. Serum concentrations of Herceptin and MYL-1401O were measured using a validated ELISA using EU-Herceptin to generate calibration curves. The low dose (25 mg/kg) corresponded to an allometrically scaled human loading dose of 8 mg/kg used clinically.

There were no clinical signs observed in any of the monkeys on test that could be attributed to MYL-1401O or Herceptin. There were no local skin reactions at the injection site related to either treatment. Similarly, there were no drug-related changes on body weight, food consumption, ECG, blood pressure, hematology, clinical chemistry, urinalysis, or organ weights. At the terminal sacrifice (24 hours after Dose 5), organs and tissues were evaluated macroscopically or microscopically without any remarkable findings in monkeys dosed with either MYL-1401O or Herceptin. Based on the absence of findings, a NOEL of 50 mg/kg/week was assigned for both Herceptin and MYL-1401O.

Following single and repeated IV administration of Herceptin and MYL-1401O, systemic exposure based upon geometric mean AUC_{0-168} and C_{max} appeared to increase in a generally dose-proportional manner and to be sex independent over the 25 and 50 mg/kg dose range. Clearance on Day 22 (geometric mean in mL/hr/kg) was similar at the 25 mg/kg dose for Herceptin (0.282) and for MYL-1401O (0.261) and at the 50 mg/kg dose for Herceptin (0.266) and for MYL-1401O (0.274) with low geometric CV (range 1.7 to 9.8% for Herceptin and 9.9 and 11.8% for MYL-1401O). Upon repeated dosing, there was appreciable accumulation in both male and female animals, with mean accumulation ratios (RA_{AUC}) on Day 22 ranging from 2.0 to 2.5 for Herceptin and from 2.0 to 2.4 for MYL-1401O over the dose range studied. The relative bioavailability (Frel) of MYL-1401O based on geometric mean AUC_{0-168} ranged from 82.1 to 98.5%.

7.4 Nonclinical Conclusions

Cardiovascular pharmacology study results suggest that Herceptin and MYL-1401O mediated a comparable type and extent of mitochondrial stress, characterized by a transient increase in ADP/ATP ratio, but no effect on mitochondrial membrane potential or cellular viability. There were no significant differences observed between MYL-1401O and Herceptin.

Serum concentrations of Herceptin and MYL-1401O declined in a biphasic manner with similar geometric mean apparent half-lives. The systemic availability of MYL-1401O (vs. Herceptin) was in the similar range.

In the toxicology program for MYL-1401O, no adverse effects were associated with MYL-1401O or Herceptin at the highest dose tested, 50 mg/kg/week. This dose corresponds to approximately 6 times the indicated human loading dose (8 mg/kg) based on body weight and 2 times the human dose based on body surface area. There were no notable differences between MYL-1401O and Herceptin at the same dose levels for either TK or toxicological endpoints; significant accumulation was observed with repeated dosing for both the products. No gender difference in exposure was observed. The results from the non-clinical program demonstrated similarity between MYL-1401O and Herceptin and supported the safe use of MYL-1401O in the clinical program.

8 CLINICAL DEMONSTRATION OF BIOSIMILARITY

8.1 Clinical Development Program Overview

The MYL-1401O clinical program was developed in consultation with the FDA and EMA to support the global development of the product and included 786 subjects across 4 studies. Two of these studies were pivotal and two were supportive. The pivotal studies included:

- Study MYL-Her-1002 was a single-center, single-dose, randomized, double-blind, 3-arm parallel-group pivotal study investigating the bioequivalence of MYL-1401O versus EU-Herceptin and US-Herceptin as well as EU-Herceptin versus US-Herceptin after 8 mg/kg as single dose. This dose was administered as IV infusion over 90 minutes in healthy male subjects under fasting conditions. Other parameters included additional PK assessments for the similarity between MYL-1401O, EU-Herceptin, and US-Herceptin along with assessments of safety (including immunogenicity) and local tolerance. This 3-way parallel design along with analytical similarity studies allowed for bridging between US-Herceptin and EU-Herceptin and facilitated the use of a single sourced comparator reference product in the global confirmatory efficacy and safety study (HERITAGE).
- Study MYL-Her-3001 (HERITAGE) was a multicenter, double-blind, randomized, parallel-group, confirmatory study to compare the efficacy and safety of MYL-1401O plus docetaxel or paclitaxel (i.e., taxane) versus EU-Herceptin plus a taxane in patients

with HER2-positive metastatic breast cancer (documented by central laboratory results) for eight cycles. Following the eight cycles, patients who had at least stable disease received single-agent MYL-1401O or Herceptin, to evaluate continued safety and immunogenicity with monotherapy.

The study consisted of 2 parts: In Part 1 of the study (through Week 24), MYL-1401O plus a taxane or Herceptin plus a taxane was administered for a minimum of 8 treatment cycles (1 treatment cycle=3 weeks based on trastuzumab administration) unless the patient experienced unacceptable side effects, disease progression, or was prematurely withdrawn from treatment. The choice of taxane (docetaxel or paclitaxel) was made by the Investigator at each study site and applied to all patients enrolled by that site. Tumor assessments (based on a centralized oncologist review) were conducted every 6 weeks (±3 days).

In Part 2 of the study, after completing a minimum of 8 cycles of treatment in Part 1 of the study, all patients with at least stable disease continued to receive MYL-1401O or Herceptin as a single agent until disease progression, unacceptable toxicity, or death, whichever occurred first. Tumor assessments were conducted at every 12-week interval.

The study is ongoing and patients will be followed for OS every 3 months for 36 months or until 240 deaths occur (as observed from the time of randomization) in the study, whichever occurs first.

Ratio of best ORR at Week 24 was used to demonstrate equivalent efficacy between the products and was the primary endpoint of the study.

In addition to the pivotal studies, the following supportive studies were also conducted

- Study MYL-Her-1001 was a single-center, single-dose, 2-period, randomized, double-blind, crossover study in healthy male volunteers. The subjects either received the MYL-1401O or EU-Herceptin in Period I and the alternative treatment in Period II. The primary objective of this study was to confirm bioequivalence between MYL-1401O and Herceptin administered as a single IV infusion of 8 mg/kg, over 90 minutes in healthy male volunteers. This was the first study undertaken with MYL-1401O versus EU-Herceptin to assess the bioequivalence, safety, and tolerability in a 2-way crossover design.

Mylan's collaboration partner, Biocon Limited, conducted a clinical study in patients with MBC in India with a formulation that is identical to Herceptin and therefore differs from MYL-1401O in 2 excipients. This formulation is referred to as Bmab-200. A brief description of this supportive study is as follows:

- Study BM200-CT3-001-11 was a double-blind, randomized, parallel design, comparative PK, efficacy, safety, and immunogenicity study in which patients received either Bmab-200 or the reference product, EU-Herceptin, in combination with docetaxel. Both Bmab-200 and Herceptin were administered as an IV infusion of 8 mg/kg IV loading, followed by 6 mg/kg IV maintenance, every 3 weeks for 8 cycles. Overall treatment duration for each subject was up to 24 weeks. Study objectives included demonstration of

bioequivalence, comparative efficacy (overall response rate at 24 weeks), safety, and immunogenicity. Single-dose comparative PK was the primary endpoint of this study.

An overview of the design and objectives of the MYL-1401O clinical program is presented in Table 7, which also outlines the key data supporting approval of MYL-1401O.

Table 7: MYL−1401O Clinical Program Overview

Study	Study design / Reference drug	Study population and duration	Objective(s)/ Study Endpoints	Evidence Supporting MYL−1401O			
				PK	Efficacy	Safety	Immunogenicity
PIVOTAL STUDIES							
MYL-HER-1002	Randomized, double-blind, 3-way, parallel design; US-Herceptin and EU-Herceptin	Healthy Volunteers N=132 Up to 10 weeks	**Primary objectives** - Demonstrate pharmacokinetic bioequivalence of MYL-1401O and Herceptin (EU and US sourced) following a single dose based on primary pharmacokinetic parameters $AUC_{0-\infty}$, AUC_{0-last}, and C_{max}. - Demonstrate pharmacokinetic bioequivalence of US and EU-Herceptin following a single dose based on primary pharmacokinetic parameters $AUC_{0-\infty}$, AUC_{0-last}, and C_{max} to provide bridge. **Secondary Objectives** - Additional pharmacokinetic assessments (t_{max}, $t_{1/2}$, λz) - Assessment of safety, including immunogenicity and local tolerance	✓		✓	✓
MYL-HER-3001 (HERITAGE)	Randomized, double-blind, 2-way, parallel design: EU-Herceptin	HER2-positive metastatic breast cancer patients N=500 Up to 36 months	**Primary objectives** <u>Part 1</u>: - Best ORR at Week 24 Defined as a complete response or partial response according to RECIST 1.1 based on central independent tumor evaluation <u>Part 2:</u> - Safety, tolerability, immunogenicity, profile of single agent MYL-1401O and Herceptin **Secondary Objectives** <u>Part 1</u> - TTP, PFS, OS, at Week 24 - Safety, immunogenicity, tolerability of MYL-1401O & Herceptin with a taxane - PopPK profile of MYL-1401O & Herceptin including: AUC, C_{max}, C_{min} <u>Part 2</u> - PFS, OS and DR, and OS at week 48 - OS at 36 months or after 240 deaths (whichever occurs first) from time of randomization	✓	✓	✓	✓

Study	Study design / Reference drug	Study population and duration	Objective(s)/ Study Endpoints	Evidence Supporting MYL−1401O			
				PK	Efficacy	Safety	Immunogenicity
SUPPORTIVE STUDIES							
MYL-HER-1001	Randomized, double-blind, 2-way crossover; EU-Herceptin	Healthy Volunteers N=22 Up to 39 weeks	**Primary objective** - Demonstrate pharmacokinetic bioequivalence of MYL-1401O and Herceptin (EU sourced) following a single dose based on pharmacokinetic parameters $AUC_{0-\infty}$ and C_{max} **Secondary Objectives** - Additional pharmacokinetic measures (t_{max}, $t_{1/2}$, λz) Assess comparative systemic safety and tolerability including local tolerance, and to evaluate immunogenicity -Preliminary assessment of pharmacodynamics parameters as an exploratory analysis	✓		✓	✓
BM200-CT3-001-11	Randomized, double-blind, two-way, parallel design, Herceptin (EU)	HER2-positive metastatic breast cancer patients N=135 Up to 24 weeks	**Primary objective** - Single dose pharmacokinetic bioequivalence **Secondary Objectives** - Evaluate & compare efficacy as measured by best overall response rate (ORR) - Evaluate & compare safety profile - Evaluate & compare immunogenicity - Evaluate & compare multi-dose pharmacokinetics of Bmab 200 with Trastuzumab	✓	✓	✓	✓

8.2 Clinical Pharmacology

8.2.1 Pivotal PK Study MYL-Her-1002

8.2.1.1 *Study Design*

The study investigated the bioequivalence among MYL-1401O, US-Herceptin, and EU-Herceptin (i.e., MYL-1401O versus US-Herceptin, MYL-1401O versus EU-Herceptin, and EU-Herceptin versus US-Herceptin) administered at a dose of 8 mg/kg, infused as a single IV infusion over 90 minutes in healthy male volunteers under fasting conditions. Healthy volunteers were chosen for the comparative PK study because this study population is homogeneous and sensitive to detect meaningful differences, if any, in PK parameters. The primary objective of this study was to assess the PK similarity (C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$) of MYL-1401O with EU-Herceptin and US-Herceptin as well as the PK similarity of EU-Herceptin with US-Herceptin. Importantly, this 3-arm clinical PK study was also designed to establish a scientific bridge between EU-Herceptin and US-Herceptin.

The sample size for this study was based on blinded data from Period 1 of Study MYL-Her-1001. The blinded results of 16 subjects in a crossover PK study with MYL-1401O and EU-Herceptin showed CV% of AUC_{inf} ≤25% with other parameters being less variable. The sample size of 132, 44 subjects per treatment, in this 3-arm, parallel-group study provided at least 82% power overall, assuming inter-subject variability ≤25%, a true geometric mean ratio (GMR) between 0.92 and 1.08, and at least 90% of subjects complete. The power calculation was for a 90% CI (confidence interval, for 2 one-sided $\alpha = 0.05$ test) with the GMR to be in the 80%-125% range.

In each study period, blood samples were collected for PK analysis immediately prior to the dose administration (0 hour) and at 45 and 90 minutes (just prior to the end of infusion). Blood samples were collected after dosing at 3, 6, 9, 24, and 48 hours after dosing, relative to the start of infusion. Over a period of 10 weeks, blood samples were also collected on Days 5, 8, 11, 15, 22, 29, 43, 57, and 71. Serum samples were stored at -80°C ± 15°C until shipment for analysis. Serum samples were analyzed by a validated ELISA method.

A total of 132 subjects were randomized to the 3 treatment arms (1:1:1; MYL-1401O: EU-Herceptin: US-Herceptin) and on Day 1 were dosed a single IV infusion of either 8 mg/kg MYL-1401O, EU-Herceptin, or US-Herceptin. In total, 121 subjects completed the clinical portion of the study. 11 subjects (2 subjects in the MYL-1401O, 3 subjects in the Herceptin EU and 6 in the Herceptin US arm) withdrew consent or were lost to follow up prior to completion of this 10-week study. One subject in the Herceptin US group was excluded from the PK

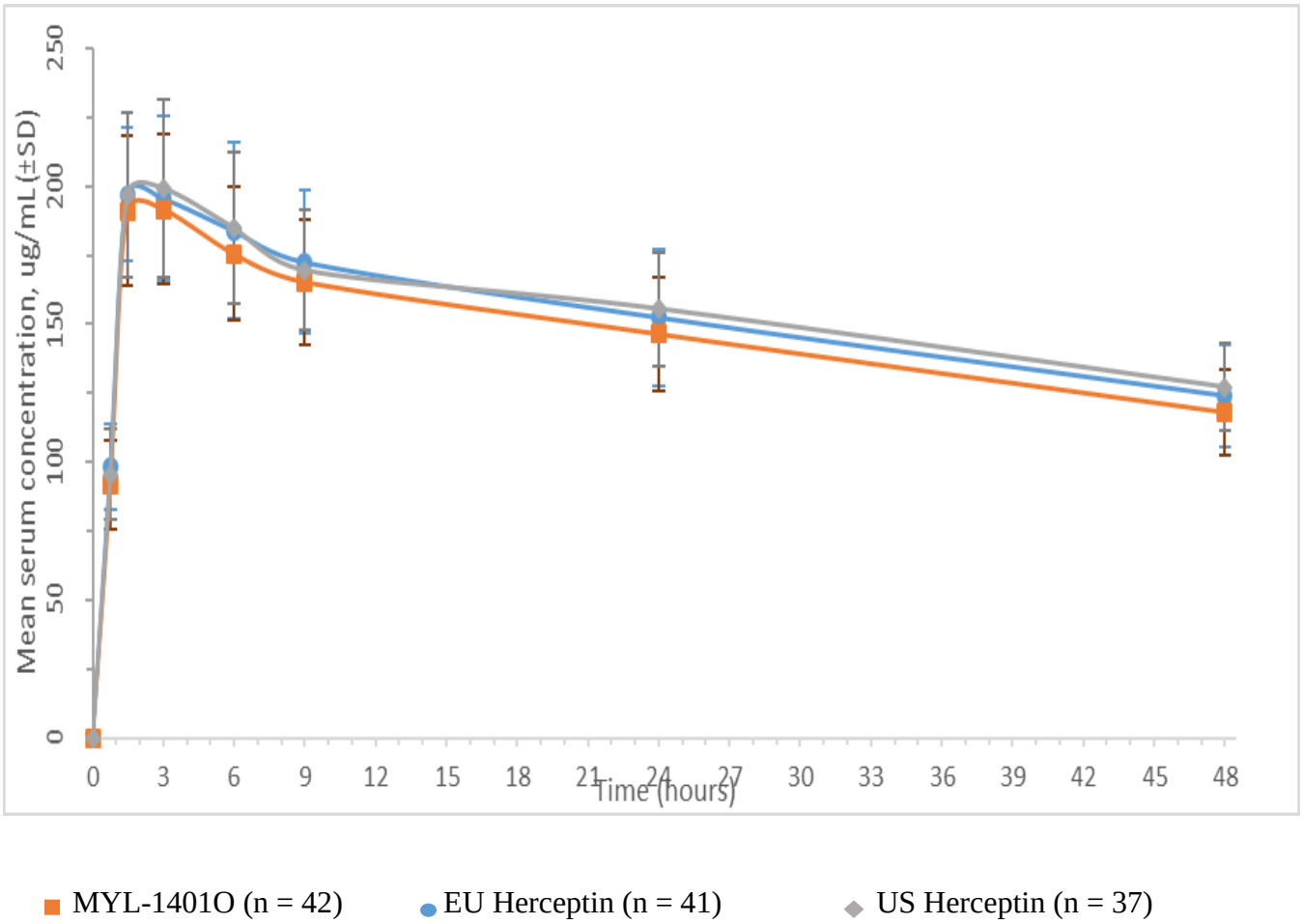
analysis as he received an incorrect dose of study medication due to dose preparation error. Thus a total of 120 subjects were included in the PK analysis.

To establish bioequivalence, it was required that the 90% CI for the LS Means ratio of natural log transformed C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}\infty}$ for the test and reference products should be between 80% and 125% of the natural log-transformed data.

8.2.1.2 *Pharmacokinetic Results*

The dose-normalized serum concentrations of MYL-1401O, EU-Herceptin, and US-Herceptin are graphically displayed in Figure 28. The mean serum concentration-time profile for the patients who received MYL-1401O and Herceptin appear superimposable.

Figure 28: Mean Graphical Presentation of Dose-Normalized Trastuzumab Serum Concentrations (Study MYL-Her-1002)



Dose-normalized PK results (mean [%CV]) of MYL-1401O and Herceptin are presented in Table 8. The least squares mean ratios and CI for the ratios are presented in Table 10. The 90%

CIs for the natural log-transformed parameters, $LNAUC_{0\text{-last}}$, $LNAUC_{0\text{-}\infty}$, and LNC_{max} for MYL-1401O, and US- and EU-Herceptin were within the 80%-125% for the test to reference ratio, and the following was concluded:

- MYL-1401O is bioequivalent to US-Herceptin
- MYL-1401O is bioequivalent to EU-Herceptin
- US-Herceptin is bioequivalent to EU-Herceptin

The 90% CI for most parameters were between 90% and 110% for MYL-1401O versus both EU- and US-Herceptin, indicating that MYL-1401O is highly similar to the reference product.

Table 8: Dose-Normalized Pharmacokinetic Parameters of MYL-1401O, EU-Herceptin, and US-Herceptin (Study MYL-Her-1002)

Parameter	Arithmetic Mean (%CV)		
	A = MYL-1401O N=42	B = EU-Herceptin N=41	C = US-Herceptin N=37
$AUC_{0\text{-last}}$ (ng*hr/mL)	48055 (15.92)	49823 (19.61)	49826 (13.98)
$AUC_{0\text{-}\infty}$ (ng*hr/mL)	48241 (16.19)	50075 (19.81)	50181 (13.86)
C_{max} (ng/mL)	200.4 (12.34)	192.6 (14.13)	197.9 (16.25)
λ_z (hr^{-1})	0.0046 (22.80)	0.0044 (27.14)	0.0042 (23.45)
$t_{½}$ (hr)	160.0 (28.39)	173.8 (32.92)	176.4 (29.85)
t_{max} (hr)	2.880 (54.83)	3.028 (118.2)	2.625 (53.37)

Treatment A: MYL-1401O 150 mg/vial, (Lot No.: DBBMPTV12-0003)
Treatment B: Herceptin (trastuzumab), 150 mg/vial, (Lot No.: H4078B02) – (EU-Herceptin)
Treatment C: Herceptin (trastuzumab) 440 mg/vial, (Lot No.: 516558) – (US-Herceptin)

Table 9: LS Mean Ratios and Confidence Intervals (Study MYL-Her-1002)

Parameter	LSMEANS Ratio*			90% Confidence Intervals**		
	A/B	A/C	C/B	A/B	A/C	C/B
$AUC_{0\text{-last}}$ (ng*hr/mL)	0.97	0.96	1.01	91.31% – 103.05%	90.34% – 102.29%	94.79% – 107.41%
$AUC_{0\text{-}\infty}$ (ng*hr/mL)	0.97	0.96	1.01	91.17% – 102.97%	89.96% – 101.94%	95.01% – 107.74%
C_{max} (ng/mL)	1.04	1.02	1.03	99.00% – 109.82%	96.42% – 107.26%	97.18% – 108.17%

Treatment A: MYL-1401O 150 mg/vial, (Lot No.: DBBMPTV12-0003)
Treatment B: Herceptin (trastuzumab), 150 mg/vial, (Lot No.: H4078B02) – (EU-Herceptin)
Treatment C: Herceptin (trastuzumab), 440 mg/vial, (Lot No.: 516558) – (US-Herceptin)
* Ratio (A/B) = $e^{[\text{LSMEANS of (LNA – LNB)}]}$
**Used Natural Log Transformed Parameter

8.2.2 Supportive PK Studies

In addition to the pivotal PK data generated from Study MYL-Her-1002 that demonstrated bioequivalence between MYL-1401O, US-Herceptin and EU-Herceptin, supportive PK data was also generated from healthy volunteers from Study MYL-Her-1001 and in patients with metastatic breast cancer from HERITAGE Study and Study BM200-CT3-001-11.

8.2.2.1 *MYL-Her-1001*

MYL-Her-1001 was the first clinical study conducted with MYL-1401O and EU-Herceptin to assess the bioequivalence, safety, and tolerability in a 2-way crossover design in healthy male subjects. Subjects either received MYL-1401O or EU-Herceptin in Period 1 and the alternative treatment in Period 2.

The primary objective of the study was to assess the bioequivalence of MYL-1401O and EU-Herceptin after infusing 8 mg/kg as a single IV dose over 90 minutes in healthy male subjects. Bioequivalence was established if the 90% confidence interval (CI) of the mean ratio of MYL-1401O to Herceptin met the standard bioequivalence criteria of 80% to 125% for the area under the serum concentration curve from 0 to infinity ($AUC_{0\text{-inf}}$) and maximum observed serum concentration (C_{max}). The sample size was based on 80% power ($\beta = 0.2$), 90% CI, at two 1-sided $\alpha = 0.05$, and an intra-subject variability of 20%. Based on these assumptions, a sample size of 19 subjects was required. All primary PK analyses were based on the PP set.

The results of MYL-Her-1001 showed that C_{max} and $AUC_{0\text{-}\infty}$, both normalized to a dose of 8.0 mg/kg, were similar for MYL-1401O and EU-Herceptin in the per protocol (PP) population

as demonstrated by the point estimates of the ratio of the geometric mean of MYL-1401O and Herceptin (0.92 and 0.94, respectively; Table 10). These point estimates were within the prespecified equivalence margins of 80% to 125% for both C_{max} and $AUC_{0\text{-}inf}$ indicating bioequivalence between MYL-1401O and EU-Herceptin. All secondary PK parameters were also similar for MYL-1401O relative to EU-Herceptin in the PP population.

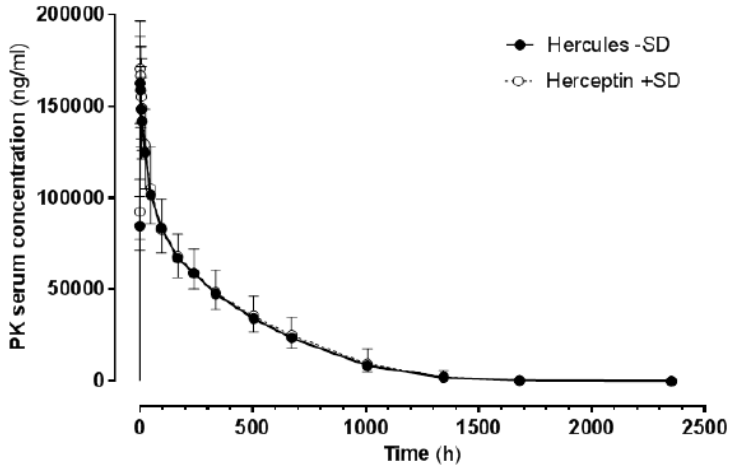
Table 10: Primary and Secondary PK Parameters (Study MYL-Her-1001; PP Population)

Parameter	MYL-1401O (N=19)	EU-Herceptin (N=19)	Geometric Mean Ratio (90% CI)
Primary parameters			
C_{max} normalized µg/mL	165 (15.7)	178 (15.6)	0.92 (87.60% - 96.99%)
$AUC_{0\text{-}\infty}$ normalized µg h/mL	45486 (22.7)	48350 (28.5)	0.94 (88.74% - 98.89%)
Secondary parameters			
C_{max} native µg/mL	167 (14.7)	175 (15.8)	0.94 (89.97% - 98.58%)
$AUC_{0\text{-}\infty}$ native µg.h/mL	45802 (23.0)	47547 (28.6)	0.96 (90.48% - 101.23%)
$AUC_{0\text{-}last}$ µg.h/mL	45747 (23.0)	47496 (28.5)	NA
T_{max} h (median [range])	1.5 (1.4-9.0)	1.5 (1.3-9.0)	NA
$t_{1/2}$ day	6.94 (22.6)	7.02 (26.3)	0.99 (94.28% - 103.53%)
V_z[a] L	2.96 (18.0)	2.81 (18.0)	1.05 (101.26% - 109.85%)
V_{ss}[a] L	4.38 (17.6)	4.30 (15.1)	1.02 (96.81% - 107.26%)
CL[a] L/day	0.296 (22.7)	0.278 (28.5)	1.07 (101.12% - 112.69%)

Data is presented as Geo Mean (Geo CV%) unless otherwise specified.
[a]Parameters adapted to 70 kg body weight.
Point estimate as a ratio of geometric means of MYL-1401O versus Herceptin (difference of adjusted means after back transformation).
Normalized $AUC_{0\text{-}\infty}$=area under the serum concentration-time curve from time zero to infinity (normalized to a dose of 8.0 mg/kg); Normalized C_{max}=maximum observed serum concentration (normalized to a dose of 8.0 mg/kg); CI=confidence interval; CL=total serum clearance; PK=pharmacokinetic; PP=per-protocol; NA=not applicable.

The concentration versus time plot of the geometric means for both MYL-1401O and EU-Herceptin averaged over all 19 subjects who received both formulations were superimposable (Figure 29).

Figure 29: Geometric Mean Serum Concentrations (Linear/Linear) ± GeoSD of MYL-1401O and Herceptin (PP Population; Study MYL-Her-1001)



geoSD: geometric standard deviation; PP: per-protocol; PK: pharmacokinetic.
Hercules= MYL-1401O (MYL-1401O was referred to as Hercules before the company code was generated).

In summary, MYL-1401O was shown to be bioequivalent to EU-Herceptin when administered as an 8.0 mg/kg IV infusion.

There are no validated PD markers to evaluate trastuzumab in a disease setting. However, in addition to the PK parameters, preliminary assessment was conducted including an *ex vivo* assessment of inhibition of proliferation using a BT-474 breast cancer cell line in this study. The inhibition of proliferation of BT-474 cells was similar with both MYL-1401O and EU-Herceptin.

8.2.2.2 *MYL-Her-3001 (HERITAGE Study)*

In the HERITAGE study, a PopPK model was developed using data from Study MYL-Her-1002, with consideration of previously published population analyses using a 2-compartment linear model. A stepwise modeling approach was undertaken, which included assessment of covariate effects on the inter-individual variability in pharmacokinetic parameters.

Trough (C_{min}) blood samples (pre-infusion) were collected for trastuzumab PK analysis for all patients in Part 1 of the study (8 cycles every 3 weeks apart). End of infusion (C_{max}) samples were collected from all patients in Cycle 1 and Cycle 6. A subset of patients provided additional blood samples in the first dosing interval and at approximate steady-state.

Two hundred and forty-five patients in the PK population received MYL-1401O, while 240 patients received Herceptin. The population PK dataset included 3172 concentration records with sufficient information to be included in the population PK analysis. Reported concentration

records that were below the lower limit of quantification, and samples before the first dose with values greater than zero, were excluded from the PopPK analysis. During the exploratory analysis, one sample was identified as an outlier with an implausibly high value (2632.811 µg/mL).

Population PK profiles of MYL-1401O versus Herceptin were not different in patients with HER2-positive metastatic breast cancer. Treatment was not a significant covariate of clearance (p=0.177) or volume of the central compartment (p=0.584) using the likelihood ratio Chi-square test. Model-based exposure measures were similar between treatments. In the C_{min} analysis, the test-to reference mean-ratios for Cycle 1 (end of first dose interval) and Cycle 6 C_{min} values were 103.11% and 104.16%, respectively, and their 90% CIs were 90.61% to 117.33% and 94.00% to 115.42%, respectively (Table 11). Thus, the observed trough concentrations were not different between treatments at the end of the first dosing interval nor at Cycle 6.

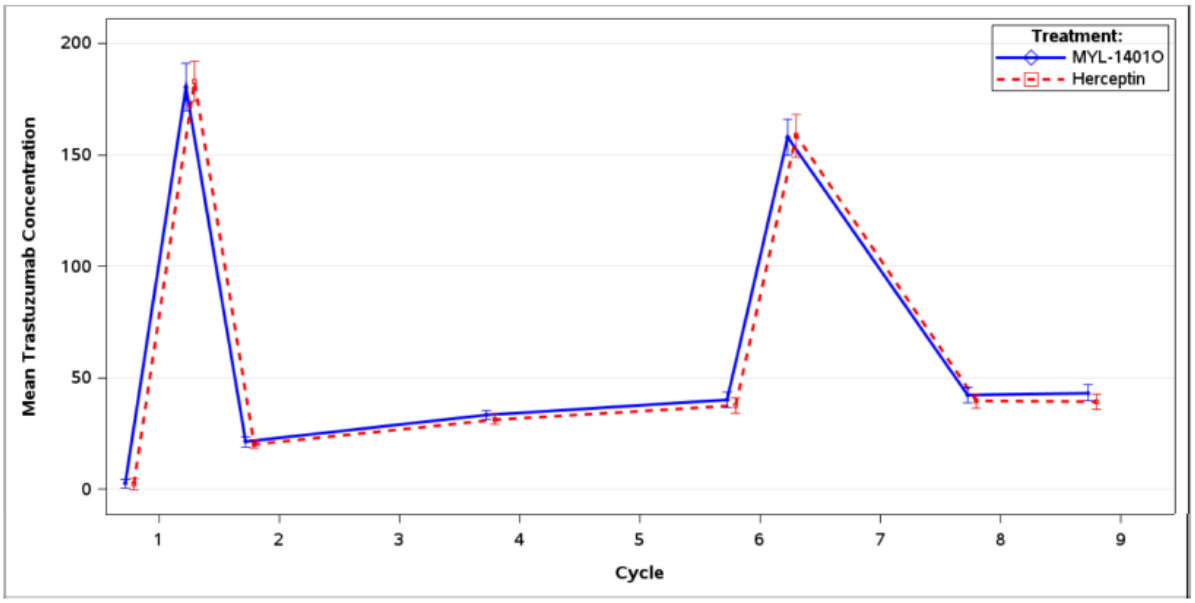
Table 11: Comparison of C_{min} (µg/mL) Between Treatment Groups in Cycle 1 and Cycle 6 (HERITAGE Study)

	Geometric LS Means			90% Confidence Interval	
C_{min} Timepoint	**MYL-1401O**	**Herceptin**	**Ratio**	**Lower Bound**	**Upper Bound**
Cycle 1	17.225	16.706	103.11	90.61	117.33
Cycle 6	34.098	32.735	104.16	94.00	115.42

Cmin=minimum serum concentration; LS=least squares
Analysis of variance model: Ln(C_{min}) = Treatment

As expected, HER2/ECD concentrations were a strong determinant of trastuzumab clearance but the drug clearance was not different between MYL-1401O and Herceptin. The Pop PK data from MBC patients, unlike the NHV PK studies, take into effect the role of target-mediated clearance and not just clearance by FcRn and hence demonstration of similar clearance between the two products is important. A mean concentration plot is presented in Figure 30, with mean concentrations given by treatment, along with the standard errors of the distribution of concentrations. The plot is limited to those nominal times that had at least 100 observations for each treatment. This plot demonstrates the similarity of concentrations from the 2 treatments.

Figure 30: Mean (Standard Error) Trastuzumab Concentrations (µg/mL) by Treatment (HERITAGE Study)



The data indicate that the estimates of exposure are comparable between MYL-1401O and EU-Herceptin in patients with metastatic breast cancer and that equivalence is demonstrated between products based on C_{min} values.

8.2.2.3 *BM200-CT3-001-11*

The primary objective of Study BM200-CT3-001-11 was to evaluate and compare the single-dose (first dose) PK parameters of Bmab-200 and EU-Herceptin in terms of C_{max} and AUC_{0-t}. For analysis of the primary objective, serum samples were collected at various pre-specified time points during the first treatment cycle after administering Bmab-200 or EU-Herceptin at loading dose of 8 mg/kg body weight. A validated ELISA was used for the quantification of Bmab-200 and Herceptin in patient serum samples.

The PK population consisted of 131 patients (n=64, Bmab-200; n=67, Herceptin). The primary PK parameters (in the PK population) C_{max} and AUC_{0-t} were similar for both Bmab-200 and Herceptin as demonstrated by the point estimates of the ratio (%) of geometric means of Bmab-200 versus Herceptin (97.58% and 88.44% for C_{max} and AUC_{0-t}, respectively). In addition, the 90% CIs were within the bioequivalence interval of 80% and 125% (C_{max}: 88.74% to 107.31%; AUC_{0-t}: 80.51% to 97.15%), thus confirming the similarity between Bmab-200 with EU-Herceptin.

The total subject variability was 33.45% for C_{max} and 33.05% for AUC_{0-t}. All primary and secondary single-dose PK parameters were comparable between Bmab-200 and Herceptin. A summary of the PK parameters is provided in Table 12. The time plot of geometric means averaged over the PK population showed that the concentration/time profiles after a single infusion of 8 mg/kg for the 2 study drugs were nearly superimposable.

Table 12: Bioequivalence Analysis of Bmab-200 Versus EU-Herceptin for Single-Dose PK Parameters (PK Population; Study BM200-CT3-001-11)

Measures	Primary PK Endpoints	
	Ln C_{max} (ng/mL)	Ln AUC_{0-t} (ng.hr/mL)
ANOVA p-value:	0.6705	0.0321
Geometric Mean		
Bmab-200	241880.690	26499087.198
Herceptin	247869.326	29964020.824
Ratio (%) of Geometric Means (Bmab-200 / Herceptin)	97.58	88.44
90% Confidence Interval (Bmab-200 / Herceptin)	(88.74 , 107.31)	(80.51 , 97.15)
Total Subject variability (%)	33.45	33.05
Power	98.64	98.78

Note: Two patients were excluded from the analysis, as the C_{max} was observed at 504 h (the cycle-2 pre-dose time point). The cycle-2 pre-dose concentration was several-fold higher than the post-dose concentrations.
ANOVA=analysis of variance; Ln AUC_{0-t}=log-transformed area under the plasma-drug concentration *vs*. time curve from time zero to the last measurable concentration of the first dose cycle; Ln C_{max}=log-transformed maximum measured plasma concentration of the first dose cycle.

8.2.3 Clinical Pharmacology Conclusions

The pivotal PK study for bioequivalence (Study MYL-Her-1002), demonstrated that MYL-1401O is bioequivalent to EU-Herceptin and US-Herceptin, and that EU-Herceptin is bioequivalent to US-Herceptin, thus establishing the bridge between the reference product sourced in 2 regions. The supportive PK study in healthy volunteers (Study MYL-Her-1001), also demonstrated that MYL-1401O was bioequivalent to EU-Herceptin. The mean serum concentration-time profile for MYL-1401O and Herceptin across these two studies in healthy volunteers was superimposable. Given that the number of confounding factors are limited, healthy volunteers is a sensitive and homogenous population for assessing potential differences in PK parameters.

The PK equivalence data seen in healthy volunteers was further supported by PK data from two studies in patients with metastatic breast cancer that were receiving concomitant taxane therapy.

The HERITAGE study demonstrated that ratio of trough levels after Cycle 1 and prior to Cycle 6, between MYL-1401O and Herceptin also met the 80%-125% equivalence criteria. The BM200-CT3-001-11 study demonstrated that Bmab 200 and EU-Herceptin were bioequivalent based on Cmax and AUC parameters. These consistent equivalence data across 4 studies in healthy volunteers and MBC patients demonstrate the robustness of PK results and further confirm that MYL-1401O is highly similar to Herceptin.

8.3 Clinical Efficacy

The purpose of clinical evaluation in the target patient population for a proposed biosimilar is to confirm the similarity established in the previous development steps and to demonstrate no clinically meaningful differences in comparison to the reference product. To that end, Mylan's HERITAGE study was designed to confirm comparable efficacy, safety, and immunogenicity of MYL-1401O with Herceptin in patients with MBC as well as demonstrate no clinically meaningful differences between the products. The results from this study have since been published in JAMA. In addition, supportive evidence has been obtained from Biocon's Study BM200-CT3-001-11, which was also conducted in patients with MBC.

Of the approved indications for Herceptin, MBC represents a sensitive population to evaluate any subtle differences in efficacy and safety between the products. The HERITAGE study included 2 parts, a 24-week treatment period with taxanes followed by a monotherapy treatment period, which allowed for the assessment of safety and immunogenicity in combination with taxanes as well as alone. Overall response rate (ORR) was chosen as the primary efficacy endpoint because it has been shown to strongly correlate with time to progression (TTP) and progression-free survival (PFS). The choices of primary endpoint and patient population were discussed and agreed upon with FDA and EMA as part of the global development program.

8.3.1 MYL-Her-3001 (HERITAGE Study)

8.3.1.1 *Patient Disposition and Study Population*

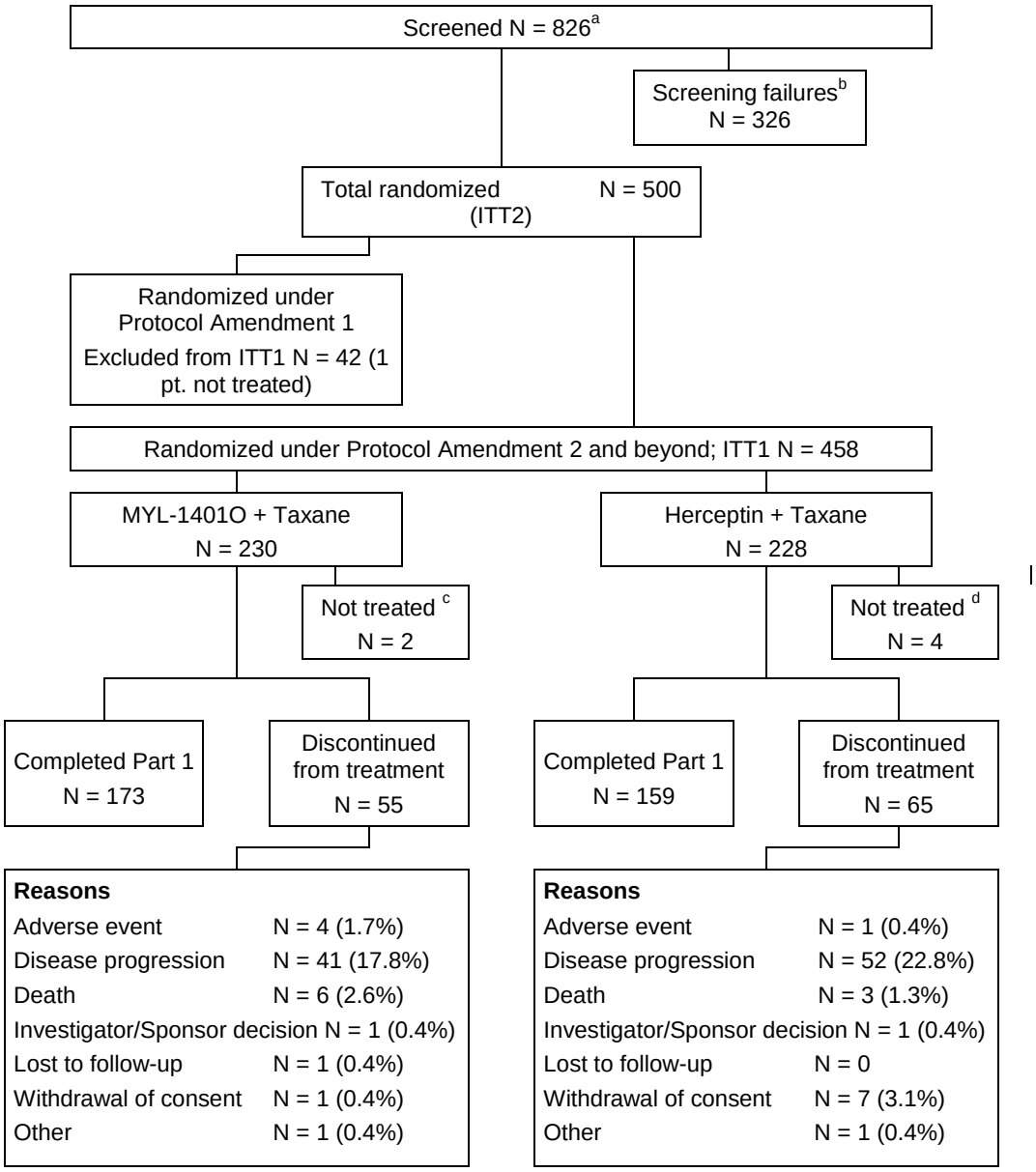
A total of 826 patients were screened for inclusion in the HERITAGE study. Before randomization to treatment, tumor tissue from each patient was sent to a central laboratory (PhenoPath, Seattle, WA) to confirm the HER2-positivity, and tumor images were checked for measurability by the central radiology review at Paraxel International, Berlin, Germany. Patients also underwent clinical laboratory testing as part of the screening procedures for study entry. Of the 826 patients screened for entry into the HERITAGE study, 326 (39.5%) patients did not meet the study's eligibility criteria. The most common reasons for screen failure were lack of confirmation of HER2 positivity, immeasurability of breast cancer according to the RECIST criteria, or clinical laboratory results that were outside the protocol's specified requirements.

For efficacy analyses, the Intent-to-treat (ITT) 1 Population (referred to as the ITT1 Population) consisted of all patients who were randomized into the study under Protocol Amendment 2 and beyond. The Protocol Amendment 2 excluded patients who had received a previous chemotherapy as first-line therapy for MBC (The original protocol had allowed for inclusion of these patients). ITT1 thus includes patients who received MYL-1401O or Herceptin as first line therapy for MBC and represents the primary population for the evaluation of efficacy. This approach was discussed and agreed with FDA.

The ITT1 Population consisted of 458 patients in the first-line treatment setting (230 patients were randomized to receive MYL-1401O and 228 patients were randomized to Herceptin group). The ITT2 population also includes 42 patients who were enrolled under Protocol Amendment 1 (which allowed 2nd line patients), and thus has a total of 500 patients who were randomized into the study. The Per Protocol Population (PP) was a subset of the ITT1 population that consisted of 438 patients (222 in the MYL-1401O group and 216 in the Herceptin group).

As shown in Figure 31, 500 patients were randomized to either MYL-1401O or Herceptin in the HERITAGE study. Of the 249 patients randomized to the MYL-1401O group, 185 completed Part 1 of the study (74.3%) including 173 patients per ITT1 population. In the Herceptin group, of the 251 patients randomized, 171 completed Part 1 of the study (68.1%) including 159 patients under ITT1. The most common reason for discontinuation was disease progression (MYL-1401O 18.9% versus Herceptin 23.1% for ITT2 population and MYL-1401O 17.8% versus Herceptin 22.8% for ITT1 population).

Figure 31: HERITAGE Study Patient Disposition (Part 1)



ITT: intent-to-treat, N: number of patients
Percentages are based on the number of patients randomized.
Note, the first 42 patients who were randomized under Protocol Amendment 1 were included in the ITT2 population (all randomized patients) but excluded from the ITT1 population used for the primary efficacy analysis, as Protocol Amendment 1 allowed randomization of patients who would receive second-line treatment for MBC. Of those 42 patients (MYL-1401O: 19, Herceptin: 23) 41 patients entered Part 1 (19/22) and 24 patients completed Part 1 (12/12). 17 patients (7/10) discontinued from treatment in Part 1. Reasons for discontinuation were: MYL-1401O: disease progression (6), withdrawal of consent (1); Herceptin: disease progression (6), Investigator/Sponsor decision (2), AE (1), other (1).
[a] 9 patients were re-screened.
[b] Screening failures patients were not randomized in the study.
[c] Reason: disease progression (2 patients).
[d] Reason: withdrawal of consent (2 patients), investigator/sponsor decision (2 patients).

After completing 8 treatment cycles of combination therapy in Part 1 of the study a total of 342 patients entered Part 2 of the study and continued with their originally assigned trastuzumab product. Although 32 patients still received taxane for 2-3 cycles (15 patients in MYL-1401O group and 17 patients in the Herceptin group). A total of 214 patients (116 patients in the MYL-1401O group and 98 patients in the Herceptin group) completed 48 weeks of the study. Patient disposition among patients who entered Part 2 of the HERITAGE study is provided in the following table.

Table 13: Disposition of Patients by Treatment Group During First 48 Weeks of Treatment – Randomized Patients/Patients Entering Part 2 (HERITAGE Study)

Part 2	MYL-1401O (N = 179) n (%)	Herceptin (N = 163) n (%)	Overall (N = 342) n (%)
Entered Part 2 of study	179 (100.0)	163 (100.0)	342 (100.0)
Completed 48 weeks in Part 2 of study	116 (64.8)	98 (60.1)	214 (62.6)
Discontinued treatment in Part 2	63 (35.2)	65 (39.9)	128 (37.4)
Continued taxane in Part 2	15 (8.4)	17 (10.4)	32 (9.4)
Reasons for treatment discontinuation between 25 and 48 weeks[a]			
Adverse event	2 (1.1)	4 (2.5)	6 (1.8)
Disease progression	56 (31.3)	52 (31.9)	108 (31.6)
Death[b, d]	1 (0.6)	0 (0.0)	1 (0.3)
Investigator/Sponsor decision	1 (0.6)	1 (0.6)	2 (0.6)
Lost to follow-up	1 (0.6)	2 (1.2)	3 (0.9)
Withdrawal of consent	1 (0.6)	3 (1.8)	4 (1.2)
Other[e]	1 (0.6)	3 (1.8)	4 (1.2)

N: number of patients in a treatment group, n: number of patients with data available
Percentages are based on the number of patients entering Part 2.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
a Reasons for treatment discontinuation as documented by the Investigator on the 'End of study treatment' page of the CRF.
b Death was noted as reason for treatment discontinuation and entered by the Investigator on the 'End of study treatment' page of the CRF. Numbers here do not indicate patients with fatal TEAEs.
c MYL-1401O group: alternative treatment of cancer (surgery); Herceptin group: from last investigational product dose more than 42 days lasted that required to discontinue the patient; patient missed more than 2 cycles due to family reason.
d Note this patient (163022) had a fatal TEAE. Patient 190524 had a fatal TEAE but the investigator recorded the reason for treatment discontinuation as 'adverse event' and not 'death'.
e MYL-1401O group: patient completed the study per Protocol Amendment 1 (which did not have survival follow-up); Herceptin group: surgery planned; due to patient's safety according to medical monitor; patient was unable to come to all planned procedures and treatment visits.

8.3.1.2 *Demographic Characteristics*

Table 14 summarizes the demographic profile of the 458 patients in the ITT1 population. All patients were female. The mean age of patients was slightly lower in the Herceptin arm: the mean age (± SD) of patients in the MYL-1401O arm was 54.3 ± 10.97 years with a range of 26 years to 79 years, and the mean age (± SD) of patients in the Herceptin arm was 52.9 ± 11.22 years with a range of 26 years to 82 years. The BSA (mean ± SD) of patients was very similar in both treatment groups (MYL-1401O 1.73 ± 0.206 m^2, range: 1.3 m^2 to 2.3 m^2; Herceptin 1.73 ± 0.220 m^2, range: 1.1 m^2 to 2.4 m^2). In both treatment groups, the majority of patients were Caucasian (MYL-1401O 69.1%, Herceptin 67.5%). A little less than one-third of patients were Asian (30.4% versus 31.6%, respectively).

Generally, the demographic profile was similar between treatment groups with respect to age, race, height, weight, and BSA.

Table 14: Demographic Characteristics by Treatment Group: ITT1 Population

	MYL-1401O + Taxane (N = 230)	Herceptin + Taxane (N = 228)
Age [years]		
N	230	228
Mean (SD)	54.3 (10.97)	52.9 (11.22)
Median	55.0	54.0
Range	26, 79	26, 82
Age category [n (%)]		
< 50 years	74 (32.2)	86 (37.7)
≥ 50 years	156 (67.8)	142 (62.3)
Race [n (%)]		
Asian	70 (30.4)	72 (31.6)
Black/African American	1 (0.4)	2 (0.9)
Caucasian	159 (69.1)	154 (67.5)
Height [cm]		
N	226	222
Mean (SD)	159.02 (7.073)	159.28 (7.560)
Median	160.00	160.00
Range	143.0, 177.0	131.0, 176.0
Weight [kg]		
N	230	228
Mean (SD)	68.39 (14.954)	68.86 (15.991)
Median	67.00	67.00
Range	41.0, 110.0	36.0, 120.0
Body surface area [m^2]		
N	230	228
Mean (SD)	1.73 (0.206)	1.73 (0.220)
Median	1.73	1.73
Range	1.3, 2.3	1.1, 2.4

ITT: intent-to-treat, N: number of patients in treatment group, n: number of patients with data available, SD: standard deviation
Percentages are based on the number of patients in the ITT1 population.

The demographic profile of the 342 patients in the safety population entering Part 2 are consistent with Part 1 population.

8.3.1.3 *Disease History and Baseline Characteristics*

Disease history and baseline characteristics of ITT1 population are presented in Table 15.

For more than 80% of patients in both treatment groups, the assigned taxane was docetaxel (MYL-1401O 83.9%, Herceptin 84.2%). At baseline, in 55.7% of patients in both treatment

groups the tumor was estrogen- and progesterone-receptor-negative. Most patients had an ECOG performance status of 0 or 1 at baseline. Slight differences between treatment groups were seen for the ECOG performance status and HER2/ECD status: A higher percentage of patients in the MYL-1401O group had an ECOG of 0 compared with the Herceptin group (51.4% versus 43.7%). Regarding HER2/ECD status, baseline values were slightly higher in the Herceptin group compared with the MYL-1401O group (HER2/ECD ≥ 15 ng/mL: MYL-1401O 73.1%, Herceptin 78.8%). The majority of patients in both treatment arms were IHC positive (MYL-1401O 81.3%, Herceptin 89.0%). A total of 18.3% of patients in the MYL-1401O and 10.5% of patients in the Herceptin group were FISH positive. FISH confirmation was only required for patients with IHC2+ status.

Disease history including tumor progression into metastatic phase and previous disease treatment were very similar in both treatment groups.

Generally, disease history and baseline characteristics were comparable in both treatment groups and no clinically relevant differences were observed.

Table 15: Disease History and Baseline Characteristics by Treatment Group (HERITAGE Study)

	MYL-1401O + Taxane	Herceptin + Taxane
	n (%)	n (%)
ECOG performance status (Safety population)	**(N = 247)**	**(N = 246)**
0	127 (51.4)	107 (43.7)
1	115 (46.6)	132 (53.9)
2	5 (2.0)	6 (2.4)
Missing	0	1
ITT1 population	**(N = 230)**	**(N = 228)**
Assigned taxane		
Docetaxel	193 (83.9)	192 (84.2)
Paclitaxel	35 (15.2)	32 (14.0)
No treatment	2 (0.9)	4 (1.8)
Tumor endocrine status		
Estrogen- and progesterone-receptor-negative	128 (55.7)	127 (55.7)
Estrogen- or progesterone-receptor-positive	102 (44.3)	101 (44.3)
HER2/ECD status		
< 15 ng/mL	60 (26.9)	47 (21.2)
≥ 15 ng/mL	163 (73.1)	175 (78.8)
Missing	7	6
IHC status		
Equivocal	41 (17.8)	24 (10.5)
Positive	187 (81.3)	203 (89.0)
Negative	2 (0.9)	1 (0.4)
FISH status		
Positive	42 (18.3)	24 (10.5)
Equivocal	0	1 (0.4)
Negative	0	0
Missing	188 (81.7)	203 (89.0)
Tumor progression into metastatic phase		
< 2 years	146 (63.5)	153 (67.1)
≥ 2 years	75 (32.6)	71 (31.1)
Missing	9 (3.9)	4 (1.8)
Previous trastuzumab treatment		
Yes	22 (9.6)	16 (7.0)
No	207 (90.0)	212 (93.0)
Missing	1 (0.4)	0 (0.0)
Previous taxane treatment		
Yes	46 (20.0)	42 (18.4)
No	183 (79.6)	186 (81.6)
Missing	1 (0.4)	0 (0.0)
Previous lapatinib treatment		
Yes	2 (0.9)	1 (0.4)
No	228 (99.1)	227 (99.6)

	MYL-1401O + Taxane	Herceptin + Taxane
	n (%)	n (%)
Previous hormonal treatment		
Yes	47 (20.4)	43 (18.9)
No	182 (79.1)	185 (81.1)
Missing	1 (0.4)	0 (0.0)
Previous bone disease treatment		
Yes	18 (7.8)	20 (8.8)
No	211 (91.7)	208 (91.2)
Missing	1 (0.4)	0 (0.0)
Previous CNS disease treatment		
Yes	4 (1.7)	3 (1.3)
No	225 (97.8)	225 (98.7)
Missing	1 (0.4)	0 (0.0)

CNS: central nervous system, ECOG: Eastern Cooperative Oncology Group, FISH: fluorescent in situ hybridization, HER2/ECD: human epidermal growth factor receptor 2 extracellular domain, IHC: immunohistochemistry, ITT: intent-to-treat, N: number of patients in treatment group, n: number of patients with data available
Percentages are based on the number of patients in the ITT1 population, except for ECOG performance status where percentages are based on the number of patients in the safety population.

Generally, in the 342 patients of the safety population entering Part 2 of the study, disease history and baseline characteristics were comparable in both treatment groups with no clinically relevant differences observed and were consistent with Part 1 of the study.

8.3.1.4 *Primary Efficacy Results*

In the HERITAGE study, the efficacy assessments based on tumor scans were performed twice, first by the investigator at the investigative site and independently in parallel by a central evaluation center. The central evaluation included 2 independent radiologist assessments and a final assessment by a board-certified oncologist, who considered the assessments made by the independent radiologists as well as evaluated clinical data available for each patient. The primary objective of Part 1 of the study was to compare the best ORR at Week 24 as determined by the central oncologist assessment in patients treated with MYL-1401O plus taxane compared with patients treated with Herceptin plus taxane.

ORR at 24 weeks was selected as the primary endpoint, as this objective response is a sensitive early efficacy endpoint to detect differences between a proposed biosimilar and the reference product.

ORR is highly correlated with progression-free survival (PFS) and time to tumor progression (TTP) in patients with MBC receiving trastuzumab. To demonstrate this correlation, Mylan plotted ORR data against TTP/PFS data from 9 relevant treatment groups from 5 studies. A weighted least squares (WLS) model was fitted and a strong R^2 of 0.889 was observed based on

this analysis. The analysis conducted by Mylan was consistent with the data presented by Burzykowski et al (2008) where a tight association was shown between ORR and PFS in patients with MBC. In that publication, the treatment effect for ORR and that for PFS were highly correlated with correlation coefficient of 0.96 in MBC patients treated with an anthracycline (alone or in combination) or with a taxane (alone or in combination with an anthracycline).

Twenty-four weeks was considered the appropriate time point for assessment of ORR for this treatment combination as it allows the delivery of up to 8 cycles of combination treatment. In the pivotal study of the reference product, significant difference in the ORR was observed between Herceptin plus docetaxel and docetaxel alone at 24 weeks.

Per the FDA's recommendation, to establish therapeutic equivalence between the treatments, the primary efficacy endpoint analysis should demonstrate that the 2-sided 90% CI for the ratio of best ORRs at Week 24 is entirely within a pre-defined equivalence margin. The equivalence margin of 0.81-1.24 was chosen for this study. This equivalence margins was determined by first performing a fixed-effects meta-analysis of IHC3+ and/or fluorescent in situ hybridization (FISH)-positive patients from 3 historical randomized Herceptin trials to estimate the treatment effect (and 95% CI) of Herceptin plus chemotherapy versus chemotherapy alone. From this meta-analysis, the estimate for risk ratio (trastuzumab + taxane versus taxane alone) and its 95% CI were 1.92 and (1.544, 2.386), respectively. The lower bound of the 95% CI (i.e. 1.544) was then used as the conservative estimate of the treatment effect, and 50% of that effect was retained as the basis for the equivalence margin.

A sample size of 410 patients (205 per treatment group) was required to provide at least 80% power to declare MYL-1401O equivalent to Herceptin in the analysis of ORR at Week 24. This sample size assumed that both treatment groups would exhibit an ORR of 69% at Week 24 and that the ratio of MYL-1401O to Herceptin was analyzed with a 2-sided 90% CI. If the 90% CI fell wholly within an equivalence region defined as (0.81, 1.24), then equivalence was to be declared. To arrive at the planned number of patients, the required sample size of 410 was increased to 456 to reflect an approximate 10% attrition rate.

The results of the primary efficacy analysis are summarized in Table 16. The central ORR assessment by the central review at Week 24 was 69.6% in the MYL-1401O group and 64.0% in the Herceptin group. The ratio of the ORRs of MYL-1401O: Herceptin was 1.09 with a 90% CI of (0.974, 1.211). As this CI is entirely within the pre-defined equivalence boundaries of 0.81 and 1.24, therapeutic equivalence of MYL-1401O and Herceptin was statistically confirmed per FDA's recommendation for this study.

The mean difference in best ORR between treatment groups (MYL-1401O minus Herceptin, ITT1 population) was 5.5% (95% CI: -3.08%, 14.04%). This difference entirely fell within the

predefined equivalence interval of (-15%, 15%) that was required by EMA to demonstrate equivalence in efficacy.

Table 16: Best Overall Response Rate (ORR) by the Central Oncologist's Assessment at Week 24 and Ratio of Best ORR (HERITAGE Study; ITT1 Population)

Response		MYL-1401O + Taxane (N = 230)	Herceptin + Taxane (N = 228)
Complete response	n (%)	3 (1.3)	0 (0.0)
Partial response	n (%)	157 (68.3)	146 (64.0)
Stable disease	n (%)	48 (20.9)	49 (21.5)
Progressive disease	n (%)	9 (3.9)	20 (8.8)
N/A	n (%)	13 (5.7)	13 (5.7)
Overall response rate	n (%)	160 (69.6)	146 (64.0)
90% CI		(64.57, 74.56)	(58.81, 69.26)
Ratio MYL-1401O:Herceptin		1.09	
90% CI		(0.974, 1.211)	

CI: confidence interval, ITT: intent-to-treat, N: number of patients in treatment group, n: number of patients with data available, N/A: not applicable
Percentages are based on the number of patients in the ITT1 population.
Overall response was defined as confirmed complete response or partial response according to RECIST Version 1.1 based on central tumor evaluation. Equivalence was declared if the 90% CI of the ratio is completely within the equivalence range of (0.81, 1.24). The 90% CI was calculated on the natural log scale and back transformed using the exponential function to the original scale.

As sensitivity analyses, the centrally evaluated ORR was analyzed using the PP population and the ITT2 population.

- In the PP population, the ratio between both treatment arms (MYL-1401O: Herceptin) was 1.06 with a 90% CI of (0.954, 1.178).
- In the ITT2 population, the ratio (MYL-1401O:Herceptin) was 1.06 with a 90% CI of (0.957, 1.184).

Another set of sensitivity analyses were conducted based on the ORR assessed by the Investigator.

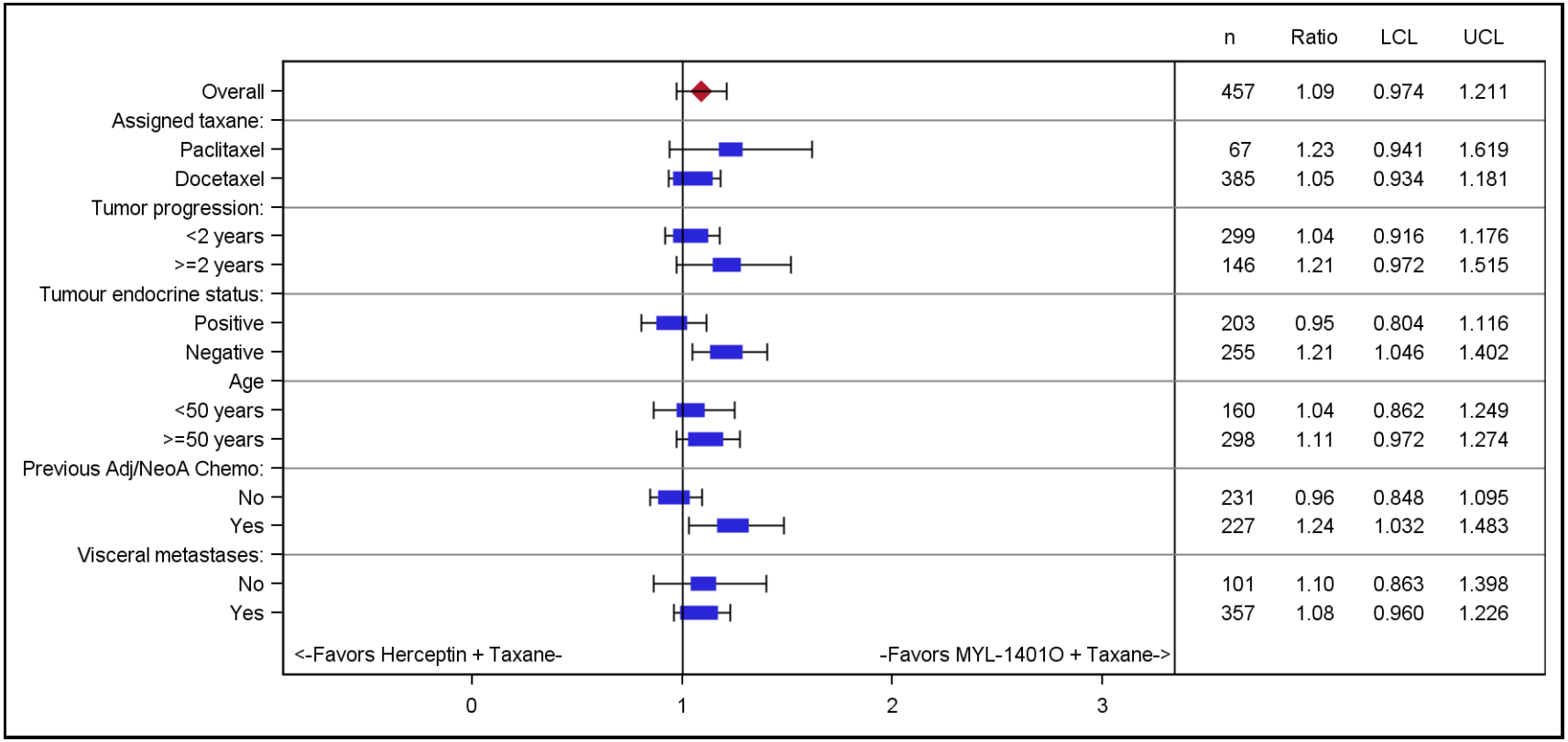
- For the ITT1 population based on investigator assessment, the ratio between both treatment groups (MYL-1401O: Herceptin) was 1.10, 90% CI: 0.988, 1.223
- In the PP population based on investigator assessment, the ratio between both treatment groups (MYL-1401O: Herceptin) was 1.07, 90% CI: 0.961, 1.183
- For the ITT2 population based on investigator assessment, the ratio between both treatment groups (MYL-1401O: Herceptin) was 1.08, 90% CI: 0.976, 1.202

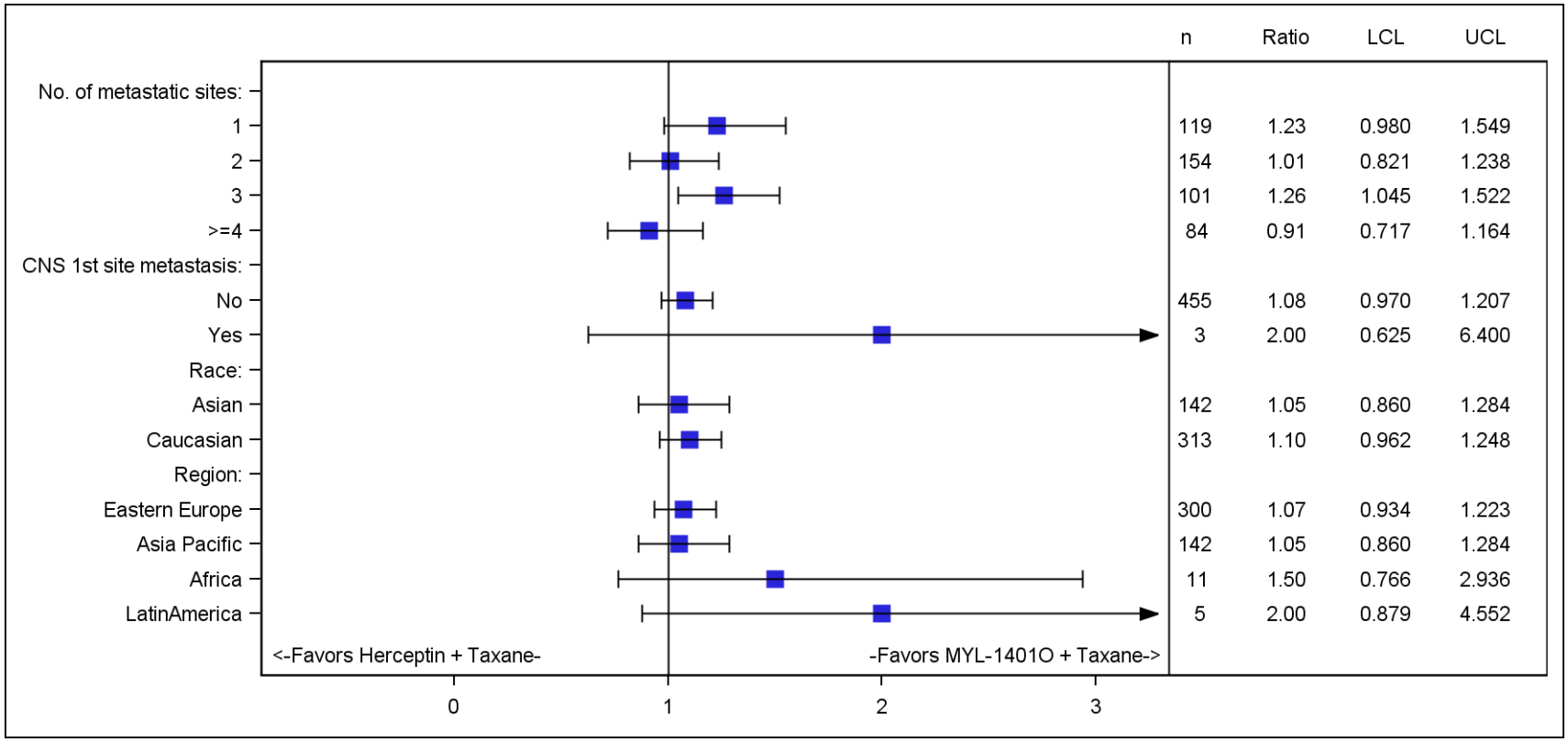
The sensitivity analyses performed using investigator assessment, PP population, and ITT2 population, all fell within the 0.81-1.24 equivalence margin and were consistent with the primary analysis (ITT1 population with central oncologist assessment). These analyses demonstrate the robustness of efficacy data and support the therapeutic equivalence between MYL-1401O and Herceptin.

8.3.1.5 *Subgroup Analyses of Efficacy*

Subgroup analyses of best ORR were performed by stratification factors (assigned taxane, tumor progression, tumor endocrine status), age, previous adjuvant/neoadjuvant chemotherapy or HER2 targeted treatment, visceral metastases, number of metastatic sites, CNS as first site of metastasis, race, and geographic region (Eastern Europe, Asia Pacific, Africa, Latin America). As shown in Figure 32, for majority of these subgroup analyses, the 90% CI of the ORR ratio (MYL-1401O: Herceptin) included 1. For the following three subgroups, tumor endocrine status negative, previous adjuvant/neoadjuvant chemotherapy, subgroup of patients with 3 metastatic sites, the 90% CI did not include 1. There was no clinical explanation and the observation was possibly attributed to relatively small number of patients per subgroup and was not considered to be of clinical or statistical significance.

Figure 32: Ratio of Best Overall Response Rate (ORR) by the Central Oncologist's Assessment at Week 24 Overall and by Subgroup (HERITAGE Study; ITT1 Population)




n
Ratio
LCL
UCL
No. of metastatic sites:
1 119 1.23 0.980 1.549
2 154 1.01 0.821 1.238
3 101 1.26 1.045 1.522
>=4 84 0.91 0.717 1.164
CNS 1st site metastasis:
No 455 1.08 0.970 1.207
Yes 3 2.00 0.625 6.400
Race:
Asian 142 1.05 0.860 1.284
Caucasian 313 1.10 0.962 1.248
Region:
Eastern Europe 300 1.07 0.934 1.223
Asia Pacific 142 1.05 0.860 1.284
Africa 11 1.50 0.766 2.936
LatinAmerica 5 2.00 0.879 4.552
<-Favors Herceptin + Taxane-
-Favors MYL-1401O + Taxane->
0
1
2
3

8.3.1.6 *Secondary Efficacy Results*

In the HERITAGE study, secondary analyses for TTP, PFS, and OS were evaluated at Week 24 and Week 48 for the ITT1 population. Also, DR was analyzed at Week 48. Results from Week 48 for all secondary efficacy parameters are presented in this document.

Time to Tumor Progression for ITT1 Population

TTP was defined as the time from randomization to the date of first documentation of objective progression.

Through Week 48 (Table 17), 95 patients (41.3%) in the MYL-1401O group had tumor progression compared with 98 patients (43.0%) in the Herceptin group. According to the log-rank test, the time-to-event curves for both treatment groups were not statistically significantly different (p = 0.684). Median time to tumor progression (Kaplan-Meier estimates) was 11.1 months in both treatment arms. Note that for more than 50% of events, data were censored at the Week 48 cut-off (i.e., more than 50% of patients in both treatment arms did not have tumor progression until Week 48). At 48 weeks, still more than 50% of the population in both arms did not shown progressive disease, so a longer TTP is likely to be observed at the end of the study.

The hazard ratios MYL-1401O: Herceptin obtained from the Cox proportional hazard model were 0.74 (unstratified) and 0.70 (stratified) at Week 24 and 0.94 (unstratified) and 0.92 (stratified) at Week 48. The difference was not statistically significant for the unstratified and stratified hazard.

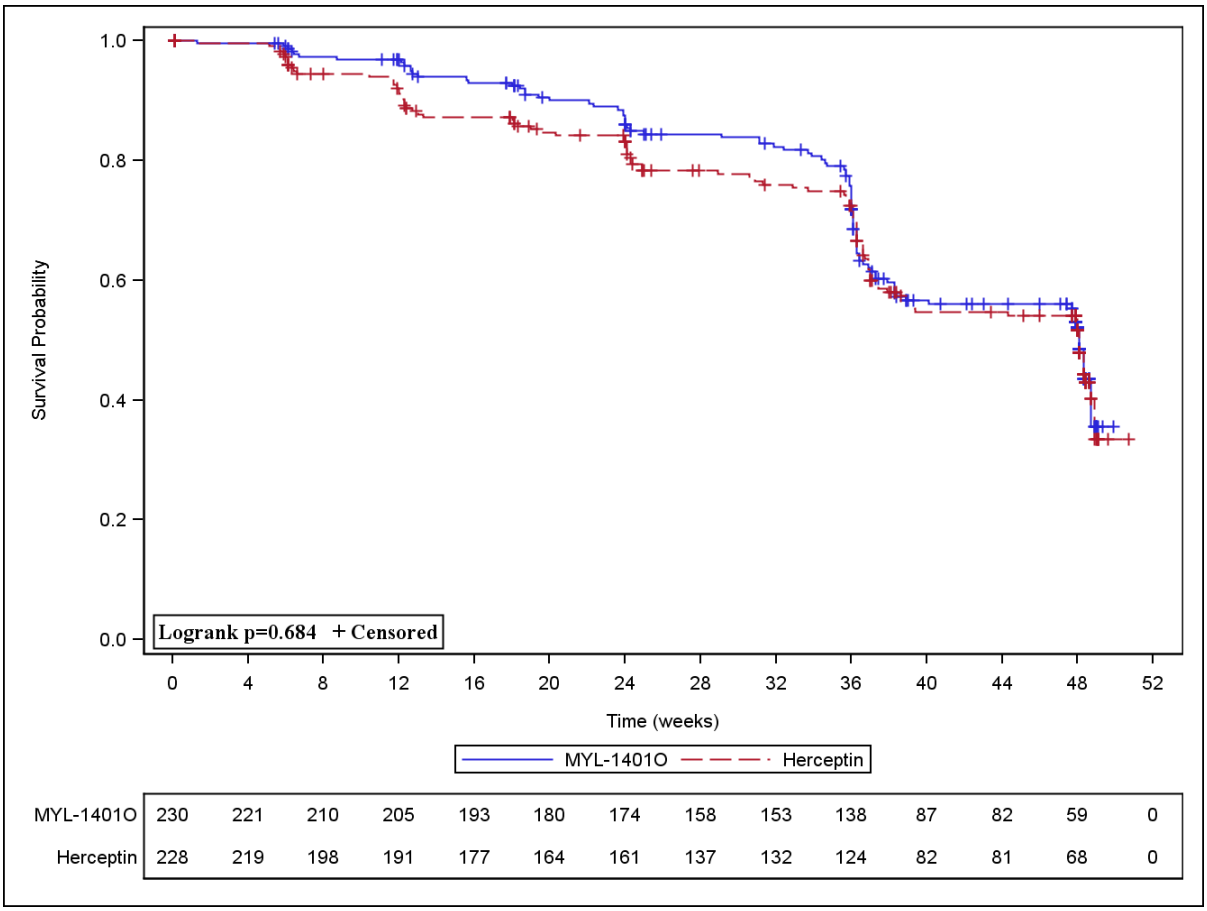
Table 17: Time to Tumor Progression (TTP) at Week 48 (HERITAGE Study; ITT1 Population)

	MYL-1401O (N = 230)	Herceptin (N = 228)
Patient status		
Number of patients	230	228
Events, n (%)	95 (41.3)	98 (43.0)
Censored,[a] n (%)	135 (58.7)	130 (57.0)
Log-rank test: p-value	0.684	
Kaplan-Meier estimates [months]		
N	230	228
Median (95% CI)	11.1 (8.83, 11.20)	11.1 (8.88, 11.20)
Q1, Q3	8.3, NE	7.8, NE
Min, Max	0.0, 11.5	0.0, 11.7
Cox proportional hazard[b]		
Unstratified hazard (95% CI)		
N	230	228
Hazard ratio (95% CI)	0.94 (0.712, 1.254)	
p-value	0.694	
Stratified hazard[c] (95% CI)		
N	220	220
Hazard ratio (95% CI)	0.92 (0.692, 1.231)	
p-value	0.584	

CI: confidence interval, ITT: intent-to-treat, Max: maximum, Min: minimum, N: number of patients in treatment group, n: number of patients with data available, NE: not estimable, Q: quartile, SE: standard error, TTP: time to tumor progression defined as the time from randomization to date of first documentation of objective progression, divided by (365.25/12)
Percentages are based on the number of patients in the ITT1 population.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
a Events occurring after the data cut-off were censored at the date of cut-off.
b The hazard and hazard ratio estimates were obtained from the Cox proportional hazard model. A hazard ratio < 1.0 indicates a lower average hazard rate and a longer TTP for MYL-1401O relative to Herceptin.
c Stratified by assigned taxane, tumor progression, and tumor endocrine status.

Figure 33 shows a Kaplan-Meier plot of TTP at Week 48 based on central tumor evaluation. As described above, time-to-event curves were very similar in both treatment arms with no statistically significant difference (p = 0.684, log-rank test).

Figure 33: Kaplan-Meier Plot of Time to Tumor Progression at Week 48: ITT1 Population



ITT: intent-to-treat
Numbers of patients at risk are displayed at the bottom of figure.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.

Progression-Free Survival for ITT1 Population

Through Week 48 of the HERITAGE study (Table 18), 128 patients (55.7%) in the MYL-1401O group and 126 patients (55.3%) in the Herceptin group still did not have progression of the disease, while 102 patients in both treatment arms had an event. Per the log-rank test, the time-to-event curves for both treatment groups were also not statistically significantly different ($p = 0.842$) at Week 48. The median time for PFS (Kaplan-Meier estimates) was 11.1 months in both treatment arms. Note that for more than 50% of events, data were censored at the Week 48 cut-off (i.e., more than 50% of patients in both treatment arms did not have tumor progression until Week 48).

The hazard ratios of MYL-1401O: Herceptin obtained from the Cox proportional hazard model were 0.80 (unstratified) and 0.75 (stratified) at Week 24 and 0.97 (unstratified) and 0.95

(stratified) at Week 48. At both cut-off times, the difference was not statistically significant for both the unstratified and stratified hazard.

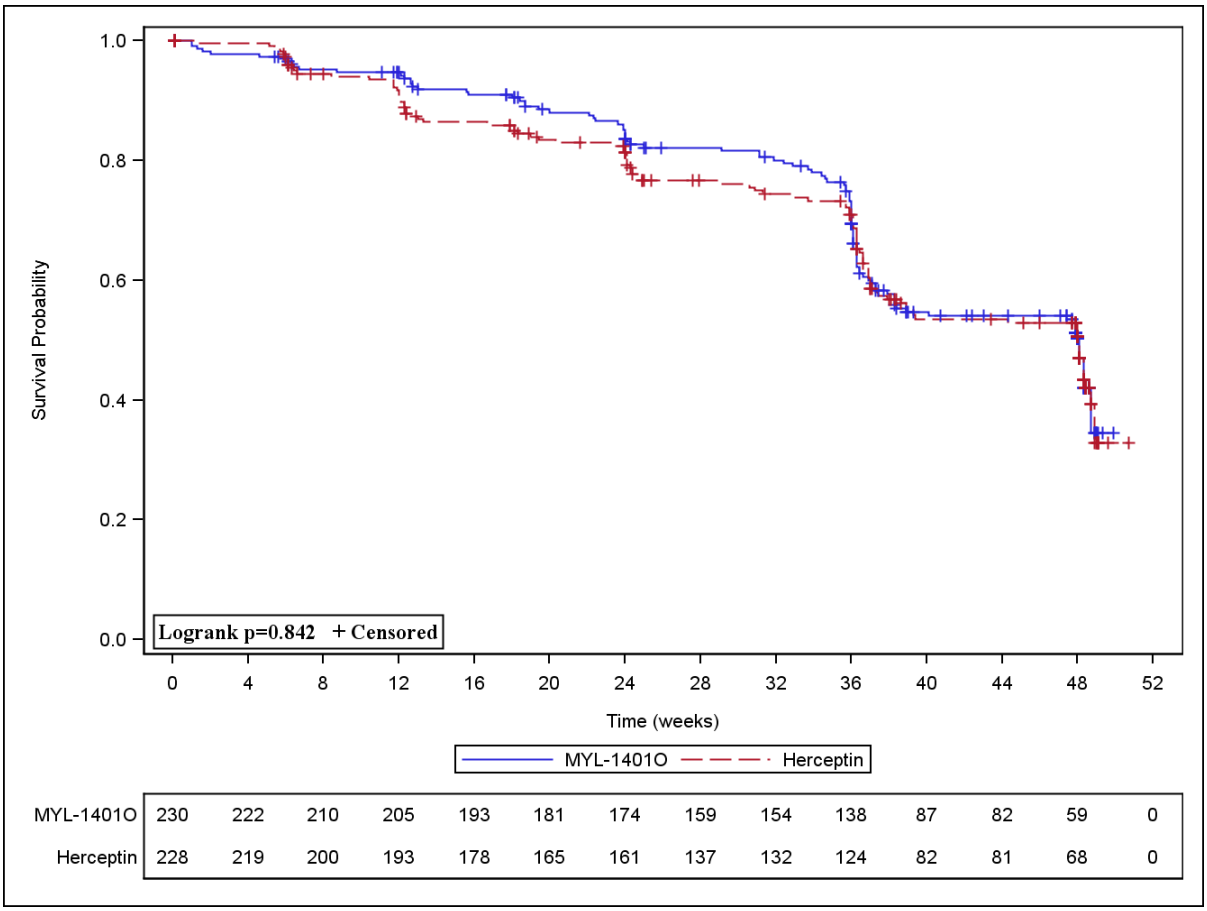
Table 18: Progression-Free Survival (PFS) at Week 48 (HERITAGE Study; ITT1 Population)

	MYL-1401O (N = 230)	Herceptin (N = 228)
Patient status		
Number of patients	230	228
Events, n (%)	102 (44.3)	102 (44.7)
Censored,[a] n (%)	128 (55.7)	126 (55.3)
Log-rank test: p-value	0.842	
Kaplan-Meier estimates [months]		
N	230	228
Median (95% CI)	11.1 (8.81, 11.20)	11.1 (8.60, 11.20)
Q1, Q3	8.2, NE	7.1, NE
Min, Max	0.0, 11.5	0.0, 11.7
Cox proportional hazard[b]		
Unstratified hazard (95% CI)		
N	230	228
Hazard ratio (95% CI)	0.97 (0.740, 1.282)	
p-value	0.851	
Stratified hazard[c] (95% CI)		
N	220	220
Hazard ratio (95% CI)	0.95 (0.714, 1.251)	
p-value	0.694	

CI: confidence interval, ITT: intent-to-treat, Max: maximum, Min: minimum, N: number of patients in treatment group, n: number of patients with data available, NE: not estimable, PFS: progression-free survival defined as the time from randomization to first documentation of objective progression or to death due to any cause, divided by (365.25/12), Q: quartile, SE: standard error
Percentages are based on the number of patients in the ITT1 population.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
a Events occurring after the data cut-off were censored at the date of cut-off.
b The hazard and hazard ratio estimates were obtained from the Cox proportional hazard model. A hazard ratio < 1.0 indicates a lower average hazard rate and a longer PFS for MYL-1401O relative to Herceptin.
c Stratified by assigned taxane, tumor progression, and tumor endocrine status.

Figure 34 shows a Kaplan-Meier plot of PFS at Week 48 based on central tumor evaluation. As described above, time-to-event curves were very similar in both treatment arms with no statistically significant difference (p = 0.842, log-rank test).

Figure 34: Kaplan-Meier Plot of Progression-Free Survival at Week 48 (HERITAGE Study; ITT1 Population)



ITT Numbers at risk are displayed at the bottom of the figure.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.

Overall Survival for ITT1 Population

OS was defined as the time from randomization to date of death due to any cause.

Through Week 48 of the HERITAGE study (Table 19), 205 patients (89.1%) survived in the MYL-1401O group compared with 194 patients (85.1%) in the Herceptin group. According to the log-rank test, the survival curves for both treatment groups were not statistically significantly different (p = 0.131).

Note that for the Kaplan-Meier estimates for OS, the median was not reached due to the relatively small number of patients in the ITT1 population who died prior to Week 24 and Week 48. Due to the data-cut that occurred at 24 and 48 weeks, all Kaplan-Meier estimates are of limited value at this point of time.

The hazard ratio of MYL-1401O: Herceptin obtained from the Cox proportional hazard model was 0.68 (unstratified) and 0.57 (stratified) at Week 24 and 0.67 (unstratified) and 0.61 (stratified) at Week 48. At both cut-off times the difference was not statistically significant for both the unstratified and stratified hazard.

Table 19: Overall Survival (OS) at Week 48: ITT1 Population

	MYL-1401O (N = 230)	Herceptin (N = 228)
Patient status		
Number of patients	230	228
Events, n (%)	25 (10.9)	34 (14.9)
Censored,[a] n (%)	205 (89.1)	194 (85.1)
Log-rank test: p-value	0.131	
Kaplan-Meier estimates [months]		
N	230	228
Median (95% CI)	NE (NE,NE)	NE (NE,NE)
Q1, Q3	NE, NE	NE, NE
Min, Max	0.1, 11.5	0.0, 11.7
Cox proportional hazard[b]		
Unstratified hazard (95% CI)		
N	230	228
Hazard ratio (95% CI)	0.67 (0.402, 1.129)	
p-value	0.134	

CI: confidence interval, ITT: intent-to-treat, Max: maximum, Min: minimum, N: number of patients in treatment group, n: number of patients with data available, NE: not estimable, OS: overall survival defined as the time from date of randomization to date of death due to any cause, divided by (365.25/12), Q: quartile, SE: standard error
Percentages are based on the number of patients in the ITT1 population.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
a Events occurring after the data cut-off were censored at the date of cut-off.
b The hazard and hazard ratio estimates were obtained from the Cox proportional hazard model. A hazard ratio < 1.0 indicates a lower average hazard rate and a longer OS for MYL-1401O relative to Herceptin.
c Stratified by assigned taxane, tumor progression, and tumor endocrine status.

Duration of Response

DR was defined as the time from the first documentation of objective tumor response (complete response or partial response) to the date of first documentation of objective tumor progression or to death due to any cause, whichever occurred first. Table 20 shows DR for the ITT1 population at Week 48. Only patients with an overall response of complete response or partial response were included in the analysis.

In the MYL-1401O group, 81 patients (42.4%) out of the 191 patients with objective response had tumor progression or died before the 48-week cut-off compared with 81 patients (44.5%) out of the 182 patients in the Herceptin group. According to the log-rank test, the time-to-event

curves for both treatment groups were not statistically significantly different (p = 0.790). Median time (Kaplan-Meier estimates) to tumor progression or death after objective tumor response was 9.7 months in both treatment arms. Note that for more than 50% of events, data were censored at the Week 48 cut-off (i.e., more than 50% of patients in both treatment arms did not have tumor progression or did not die until Week 48). Therefore, the median duration of response might still change when applying a later data cut-off.

The hazard ratios MYL-1401O: Herceptin obtained from the Cox proportional hazard model were 0.96 (unstratified) and 0.97 (stratified) at Week 48 with p-values >0.05 for both hazard ratios. Thus, the average hazard rate for tumor progression or death after the tumor response as well as DR were not statistically significantly different in both treatment groups.

Table 20: Duration of Response (DR) at Week 48 (HERITAGE Study; ITT1 Population)

	MYL-1401O (N = 230)	Herceptin (N = 228)
Patient status		
Number of patients	191	182
Events, n (%)	81 (42.4)	81 (44.5)
Censored,[a] n (%)	110 (57.6)	101 (55.5)
Log-rank test: p-value	0.790	
Kaplan-Meier estimates [months]		
N	191	182
Median (95% CI)	9.7 (7.38, 9.89)	9.7 (7.68, 9.87)
Q1, Q3	6.5, NE	6.2, NE
Min, Max	0.0, 9.9	0.0, 10.1
Cox proportional hazard[b]		
Unstratified hazard (95% CI)		
N	191	182
Hazard ratio (95% CI)	0.96 (0.705, 1.306)	
p-value	0.795	
Stratified hazard[c] (95% CI)		
N	183	180
Hazard ratio (95% CI)	0.97 (0.706, 1.329)	
p-value	0.846	

CI: confidence interval, DR: duration of response defined as the time from the first documentation of objective tumor response (complete response [CR] or partial response [PR]) to the date of first documentation of objective tumor progression or to death due to any cause, whichever occurred first, divided by (365.25/12). Only patients with objective response (CR or PR) were included in the analysis. ITT: intent-to-treat, Max: maximum, Min: minimum, N: number of patients in treatment group, n: number of patients with data available, NE: not estimable, Q: quartile, SE: standard error
Percentages are based on the number of patients in the ITT1 population.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
[a] Events occurring after the data cut-off were censored at the date of cut-off.
[b] The hazard and hazard ratio estimates were obtained from the Cox proportional hazard model. A hazard ratio < 1.0 indicates a better outcome for MYL-1401O relative to Herceptin.
[c] Stratified by assigned taxane, tumor progression, and tumor endocrine status.

8.3.1.7 *Clinical Efficacy Conclusions for HERITAGE Study*

This pivotal confirmatory study confirmed that MYL-1401O and EU-Herceptin are therapeutically equivalent in the treatment of HER2-positive metastatic breast cancer patients. The ORR based on central oncologist assessment was 69.6% in the MYL-1401O group compared with 64.0% in the Herceptin group.

The MYL-1401O to Herceptin ratio between treatment groups was 1.09 (90% CI: 0.974, 1.211), entirely within the pre-defined equivalence interval of 0.81 to 1.24. Multiple sensitivity analyses including analysis using PP and ITT2 population (with oncologist assessment) and ITT1, ITT2

and PP population (with investigator assessment), each fell within the pre-defined equivalence margin demonstrating the robustness of data and confirming the therapeutic equivalence of MYL-1401O and Herceptin.

At Week 48, progression event was noted in 102 patients in each treatment arm. PFS rate at Week 48 was 55.7% in the MYL-1401O group compared with 55.3% in the Herceptin group, with a HR: 0.97 (0.740, 1.282). Although the median time to progression has not been reached, it was 11.1 months in both treatment arms based on Week 48 cut-off and will likely exceed this duration. At Week 48 the OS rate was 89.1% in the MYL-1401O group compared with 85.1% in the Herceptin group, with a HR 0.67 (0.402, 1.129). The time to event results at 48 weeks are also supporting similar efficacy.

The efficacy data generated from this study including the ORR at Week 24 of 64-69.6% and median time to progression of at least 11.1 months is similar to the recent data published from the CLEOPATRA study, where the ORR in the Herceptin arm with taxane was 69.3% and the median time to progression was 12.4 months (Baselga et al. 2012). These data are also consistent with the data from the MARIANNE study, where the ORR in the Herceptin plus taxane arm was 67.9% with median time to progression of 13.7 months (Ellis et al 2015).

8.3.2 Supportive Efficacy Data - Study BM200-CT3-001-11

In Study BM200-CT3-001-11, efficacy assessment was a secondary endpoint and included ORR (complete response + partial response) at 24 weeks. Additionally, the correlation of ORR with shed HER2 ECD was also evaluated as an exploratory endpoint. The tumor assessment for evaluating best ORR was conducted at 12-week intervals. There was a single central radiologist involved in assessment of response. However, since efficacy was a secondary endpoint, more robust evaluation like a second radiologist assessment, an adjudication mechanism and central oncologist's assessment of response was not conducted.

A total of 135 patients were included in the intent-to-treat full analysis set (ITT-FAS) population (67 in the Bmab-200 group and 68 in the Herceptin group). One patient withdrew consent before the first dosing; this patient was also excluded from the efficacy evaluations.

The ORR was 65.15% in the Bmab-200 group and 75.00% in the Herceptin group. The clinical benefit rate (complete response + partial response + stable disease) was 86.36% in the Bmab-200 group and 89.71% in the Herceptin group. Analysis of the maximum change in target lesion size revealed similar mean reductions between the 2 groups (66.1% decline from baseline to Week 24 for MYL-1401O vs 66.0% decline for EU-Herceptin).

Although efficacy assessment was not the primary objective of this study, efficacy data from this study supports the conclusion of equivalence in the pivotal confirmatory study. The observed ORR is in line with the historical ORR observed for EU-Herceptin.

8.3.3 Overall Clinical Efficacy Conclusions

Therapeutic equivalence of MYL-1401O and Herceptin was statistically confirmed by the primary efficacy analysis of the HERITAGE study. All secondary efficacy analyses at Week 24 and Week 48 supported the conclusion of therapeutic equivalence.

The primary endpoint of the HERITAGE study was to evaluate the therapeutic equivalence of MYL-1401O and Herceptin when administered in combination with a taxane for best ORR at Week 24. At Week 24, the ORR was 69.6% in the MYL-1401O group and 64.0% in the Herceptin group. Therapeutic equivalence of MYL-1401O and Herceptin was statistically confirmed. Additionally, the ORR data were consistent with the published data for trastuzumab.

All secondary efficacy analyses in the HERITAGE study at both Week 24 (TTP, PFS, OS) and Week 48 (TTP, PFS, OS, DR) supported the conclusion of therapeutic efficacy. Only relatively few patients had tumor progression or died during Part 1. Therefore, for the time-to-event analyses, the median of the Kaplan-Meier estimates was not reached. At Week 48, data for all secondary endpoints (TTP, PFS, OS, DR) were censored for more than 50% of events, as more than half of all patients in both treatment groups did not have tumor progression and were still alive. The TTP and PFS data available at Week 48 indicated no differences between treatment groups. For OS, the median was not met for the Kaplan-Meier estimate.

8.4 Clinical Safety and Immunogenicity

Safety assessments included treatment-emergent adverse events, clinical laboratory testing, immunogenicity, vital signs, physical examinations, and electrocardiograms.

Based on differences in study design, patient population, treatment duration, data collection, and overall objectives, no integrated analysis of the safety results was performed. Overall, MYL-1401O was well tolerated, and the overall safety profile of MYL-1401O was comparable with Herceptin. No new safety concerns were reported during the studies.

8.4.1 Common Treatment-Emergent Adverse Events

8.4.1.1 *Study MYL-Her-1001*

In Study MYL-HER-1001, the most frequently reported treatment-emergent adverse events (TEAEs) among healthy volunteers in the MYL-1401O group were headache (47.4% subjects), nasopharyngitis (26.3%), and the most frequently reported TEAEs for the Herceptin group were

nasopharyngitis (54.5%), headache (45.5%), and rhinitis (36.4%). Most TEAEs were mild. There was a single severe TEAE of streptococcal pharyngitis, which was considered possibly related to the administration of MYL-1401O.

8.4.1.2 *Study MYL-Her-1002*

In Study MYL-Her-1002, the most frequently reported TEAE among healthy volunteers following administration of MYL-1401O, EU-Herceptin, and US-Herceptin was headache, which was reported by 12 of 44 subjects (27.3%), 13 of 44 subjects (29.5%), and 10 of 44 subjects (22.7%), respectively. All TEAEs were mild or moderate in severity.

8.4.1.3 *Study MYL-Her-3001 (HERITAGE Study)*

This study had 2 parts: a 24-week treatment period where patients received MYL-1401O or Herceptin concomitantly with either docetaxel or paclitaxel. After 24 weeks, patients who had not progressed could enter the monotherapy part of the study, where they continued to receive MYL-1401O or Herceptin until disease progression. Thus, the safety assessment of this study had two distinct parts, where many of the TEAEs during Part 1 of the study could be attributed to concomitant taxane therapy. The safety data through Week 48 were included as part of Mylan's BLA.

An overview of the cumulative safety events during the entire 48-week treatment for the safety population is presented in Figure 35. The safety events during the monotherapy part of the study (Weeks 24 through 48) are presented in Figure 36.

Figure 35: Overall Cumulative Safety Events Until Week 48 (Safety Population)

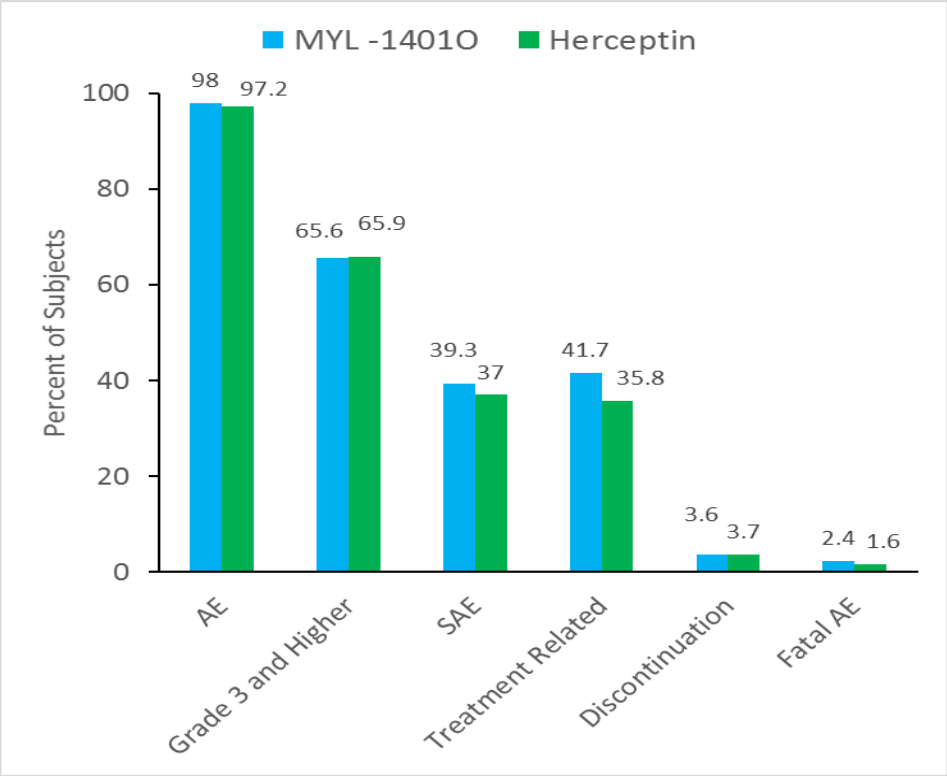
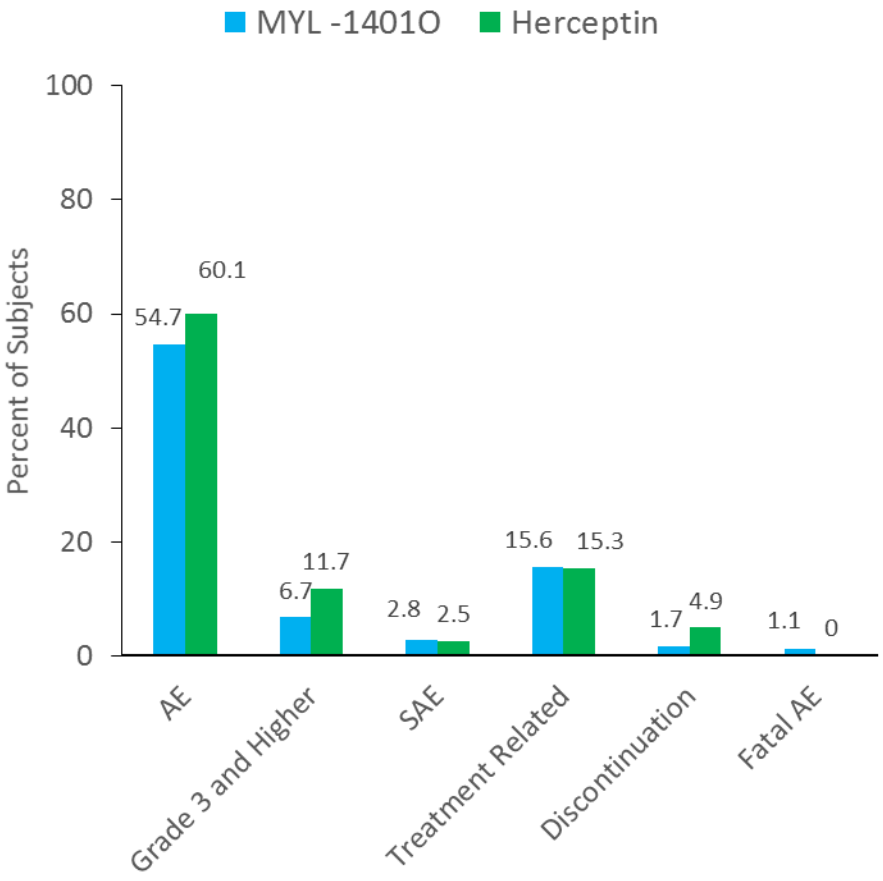


Figure 36: Cumulative Safety Events From Weeks 24 Through 48 (HERITAGE Study: Safety Population)



As is evident from Figure 35 and Figure 36, the overall incidence of TEAE, Grade 3 or higher TEAE, serious adverse events, treatment related adverse events, AEs leading to discontinuation and fatal AEs are similar in both treatment arms. As expected the incidence of these events is much lower during the monotherapy period versus cumulative incidence through Week 48, which are primarily driven by concomitant taxane therapy.

Table 21 presents the TEAEs that occurred in >5% of patients in either treatment group through Week 48 of the HERITAGE study.

Table 21: Treatment-Emergent Adverse Events Occurring in >5% of Patients in Either Treatment Group by Preferred Term Through Week 48 (HERITAGE Study Parts 1 and 2; Safety Population)

System Organ Class Preferred Term	MYL-1401O (N = 247) n (%)	Herceptin (N = 246) n (%)	Overall (N = 493) n (%)
Number of patients with at least 1 TEAE	242 (98.0)	239 (97.2)	481 (97.6)
Blood and lymphatic system disorders	168 (68.0)	162 (65.9)	330 (66.9)
Anaemia	41 (16.6)	44 (17.9)	85 (17.2)
Leukopenia	43 (17.4)	53 (21.5)	96 (19.5)
Neutropenia	143 (57.9)	133 (54.1)	276 (56.0)
Gastrointestinal disorders	105 (42.5)	93 (37.8)	198 (40.2)
Diarrhoea	52 (21.1)	51 (20.7)	103 (20.9)
Nausea	52 (21.1)	38 (15.4)	90 (18.3)
Vomiting	27 (10.9)	24 (9.8)	51 (10.3)
General disorders and administration site conditions	131 (53.0)	134 (54.5)	265 (53.8)
Asthenia	57 (23.1)	41 (16.7)	98 (19.9)
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)
Infections and infestations	82 (33.2)	72 (29.3)	154 (31.2)
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)
Injury, poisoning and procedural complications	22 (8.9)	19 (7.7)	41 (8.3)
Infusion related reaction	17 (6.9)	12 (4.9)	29 (5.9)
Investigations	75 (30.4)	69 (28.0)	144 (29.2)
Alanine aminotransferase increased	22 (8.9)	22 (8.9)	44 (8.9)
Aspartate aminotransferase increased	16 (6.5)	24 (9.8)	40 (8.1)
Metabolism and nutrition disorders	60 (24.3)	75 (30.5)	135 (27.4)
Decreased appetite	23 (9.3)	25 (10.2)	48 (9.7)
Hyperglycaemia	15 (6.1)	19 (7.7)	34 (6.9)

System Organ Class Preferred Term	MYL-1401O (N = 247) n (%)	Herceptin (N = 246) n (%)	Overall (N = 493) n (%)
Musculoskeletal and connective tissue disorders	84 (34.0)	66 (26.8)	150 (30.4)
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)
Nervous system disorders	98 (39.7)	108 (43.9)	206 (41.8)
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)
Respiratory, thoracic and mediastinal disorders	72 (29.1)	54 (22.0)	126 (25.6)
Cough	19 (7.7)	18 (7.3)	37 (7.5)
Dyspnoea	17 (6.9)	18 (7.3)	35 (7.1)
Skin and subcutaneous disorders	163 (66.0)	162 (65.9)	325 (65.9)
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)

n: number of patients with events, TEAE: treatment-emergent adverse event.
Percentages were based on the number of patients in the safety population (N).
Adverse events were coded using Medical Dictionary for Regulatory Activities Version 18.0. System organ class and preferred term are ordered alphabetically.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.

Through Week 48 of the HERITAGE study, the most frequently reported TEAEs were alopecia (56.4%), neutropenia (56.0%), and diarrhea (20.9%).

Overall the incidence of TEAE were similar between both treatment arms. There were few noted differences (>5%) in the incidence of TEAEs between the treatment groups (MYL-1401O versus Herceptin) including nausea (21.1% versus 15.4%), asthenia (23.1% versus 16.7%), arthralgia (13.4% versus 5.7%), and upper respiratory tract infection (7.3% versus 2.0%). Generally, no explanation for these differences was found; they were considered to occur by chance or were related to confounding factors such as previous medical conditions and unbalanced use of some medications. Of note, most of these differences were driven by Part 1 of the study, during which patients received combination therapy with taxanes. In Part 2 of the study when patients were on trastuzumab monotherapy, the incidence of these events were similar between MYL-1401O and Herceptin: nausea 2.2% versus 2.5%, asthenia 2.8% versus 1.8%, arthralgia 2.8% versus 1.2%, and upper respiratory tract infection 2.2% versus 1.2%.

Approximately 80% of patients who had TEAEs had events that were Grade 1 or Grade 2 in severity. There were no notable differences in the severity of TEAEs between the treatment groups.

During Part 2 of the study when patients received trastuzumab monotherapy, the most frequently reported TEAEs were headache (7.3% [MYL-1401O 6.7% versus Herceptin 8.0%]), anemia (5.0% [MYL-1401O 2.8% versus Herceptin 7.4%]), and alopecia (3.2% [MYL-1401O 3.4% versus 3.1%]). Generally, there were few numerical differences in the incidence of TEAEs between the treatment groups. No infusion reactions were reported in Part 2 of the study in the MYL-1401O arm.

Of the total 5015 TEAEs through Week 48, only 513 TEAEs had on onset while patients were receiving trastuzumab monotherapy, clearly suggesting that most of the TEAEs that occurred over 48 weeks were driven by data collected through Week 24 and most likely attributable to the background taxane therapy.

8.4.1.4 *Study BM200-CT3-001-11*

In Study BM200-CT3-001-11, the most common TEAEs in both groups were pyrexia (18.18% for the Bmab-200 group, 22.06% for the Herceptin group) and diarrhea (16.67% for the Bmab-200 group and 14.71% for the Herceptin group). Most the TEAEs were mild in intensity. Three severe TEAEs in the Herceptin group were possibly or probable/likely related to the study drug: generalized swelling, fatigue, and hyperglycemia. Two severe TEAEs in the Bmab-200 group were probably/likely related to the study drug: rash pustular and skin reaction. All other severe TEAEs were either unlikely related or unrelated to the study drugs.

8.4.2 Deaths, Nonserious Adverse Events, and Discontinuations From Study Drug

8.4.2.1 *Deaths*

There were no deaths reported in the healthy volunteer PK studies, MYL-Her-1001 and MYL-Her-1002.

Through Week 48 of the HERITAGE study, 65 patients died during the study, 24 patients in the MYL-1401O group and 39 patients in the Herceptin group. In addition, 2 patients died untreated. Most patients died from primary disease. Seven patients in the MYL-1401O group and 5 patients in the Herceptin group died within 28 days of their last dose, indicating that most patients did not die while on study treatment.

Of the patients who died through Week 48, 10 patients had fatal TEAEs, 6 in the MYL-1401O group and 4 in the Herceptin group. A listing of all patients with fatal TEAEs is presented in Table 22.

Table 22: Listing of Patients with Fatal Treatment-Emergent Adverse Events Through Week 48 (HERITAGE Study Parts 1 and 2; Safety Population)

Patient Number	TEAE System Organ Class	TEAE Preferred Term	Study Day Onset	Study Drug Relationship T: trastuzumab P: paclitaxel D: docetaxel
MYL-1401O + Taxane Group				
131846	Respiratory, thoracic and mediastinal disorders	Respiratory failure	7	T: Possible D: Not related
140422	Blood and lymphatic system disorder	Pancytopenia	7	T: Not related D: Definite
	Hepatobiliary disorders	Hepatic failure	7	T: Not related D: Not related
140535	Cardiac disorders	Cardiac failure	157	T: Unlikely D: Unlikely
	Respiratory, thoracic and mediastinal disorders	Respiratory failure	157	T: Unlikely D: Unlikely
160322 (monotherapy in Part 2)	Respiratory, thoracic and mediastinal disorders	Dyspnea	229	T: Not related D: Not applicable
190225	General disorders and administrative site conditions	Multi-organ failure	13	T: Not related D: Not related
190524 (monotherapy in Part 2)	Cardiac disorders	Carditis	340	T: Unlikely D: Not applicable
Herceptin + Taxane Group				
150123	General disorders and administrative site conditions	Death	59	T: Unlikely D: Probable
160922	Respiratory, thoracic and mediastinal disorders	Respiratory failure	76	T: Possible P: Not related
161824	Infections and infestations	Pneumonia	160	T: Unlikely D: Unlikely
	Infections and infestations	Sepsis	160	T: Unlikely D: Unlikely
170402	Hepatobiliary disorders	Hepatic failure	4	T: Not related D: Definite
	Metabolism and nutrition disorders	Tumor lysis syndrome	4	T: Not related D: Not related

TEAE: treatment-emergent adverse events
Adverse events were coded using Medical Dictionary for Regulatory Activities Version 18.0.

Four deaths occurred in Study BM200-CT3-001-11 (2 in each treatment group). Table 23 presents the TEAEs with fatal outcomes in Study BM200-CT3-001-11.

Table 23: Listing of Patients with Treatment-Emergent Adverse Events with Fatal Outcome (Study BM200-CT3-001-11; Safety Population)

Patient Number	TEAE System Organ Class	TEAE Preferred Term	Study Drug Relationship
Bmab-200			
14001	General disorders and administration site conditions	Disease progression	Unrelated
16040	General disorders and administration site conditions	Multi-organ failure	Unrelated
Herceptin			
02013	Blood and lymphatic system disorders	Disseminated intravascular coagulation	Possible
15005	Infections and infestations	Sepsis	Unlikely

8.4.2.2 *Serious Adverse Events*

There were no treatment-emergent SAEs reported in the healthy volunteer studies.

HERITAGE Study

Through 48 weeks in the HERITAGE study, 330 SAEs were reported in 188 patients. The incidence of SAEs was similar between treatment groups: 97 patients (39.3%) in the MYL-1401O group and 91 patients (37.0%) in the Herceptin group. Neutropenia was the most frequent SAE and the incidence of Grade 4 neutropenia was similar between the treatment arms. The majority of neutropenic events were asymptomatic without complications such as infection or fever and most recovered without treatment with GCSF or antibiotics.

Most SAEs that began in Part 1 resolved or resolved with sequelae, and all SAEs that began in Part 2 resolved or resolved with sequelae. There was 1 SAE of quadriplegia in the Herceptin arm with an unknown outcome; the SAE began on Day 206, about 25 days after the last dose of study drug. Alternative etiology was progression of disease, and the patient withdrew consent on Day 210.

In general, the number and type of SAEs were expected for this patient population, and there were no notable differences in SAEs between the treatment groups.

Table 24: Serious Treatment-Emergent Adverse Events Through Week 48 Occurring in At Least 2 Patients Overall (HERITAGE Study Parts 1 and 2; Safety Population)

System Organ Class Preferred Term	MYL-1401O (N = 247) n (%)	Herceptin (N = 246) n (%)	Overall (N = 493) n (%)
Number of patients with at least 1 serious TEAE	97 (39.3)	91 (37.0)	188 (38.1)
Blood and lymphatic system disorders	79 (32.0)	70 (28.5)	149 (30.2)
Febrile neutropenia	11 (4.5)	10 (4.1)	21 (4.3)
Leukopenia	5 (2.0)	12 (4.9)	17 (3.4)
Neutropenia	68 (27.5)	62 (25.2)	130 (26.4)
Cardiac disorders	4 (1.6)	0	4 (0.8)
Cardiac failure	2 (0.8)	0	2 (0.4)
Gastrointestinal disorders	6 (2.4)	9 (3.7)	15 (3.0)
Diarrhoea	3 (1.2)	4 (1.6)	7 (1.4)
Nausea	2 (0.8)	1 (0.4)	3 (0.6)
Vomiting	1 (0.4)	3 (1.2)	4 (0.8)
General disorders and administration site conditions	2 (0.8)	5 (2.0)	7 (1.4)
Pyrexia	0	2 (0.8)	2 (0.4)
Hepatobiliary disorders	2 (0.8)	2 (0.8)	4 (0.8)
Hepatic failure	1 (0.4)	1 (0.4)	2 (0.4)
Immune system disorders	3 (1.2)	2 (0.8)	5 (1.0)
Anaphylactic reaction	2 (0.8)	0	2 (0.4)
Hypersensitivity	0	2 (0.8)	2 (0.4)
Infections and infestations	13 (5.3)	16 (6.5)	29 (5.9)
Bronchitis	0	2 (0.8)	2 (0.4)
Gastroenteritis	3 (1.2)	1 (0.4)	4 (0.8)
Pneumonia	6 (2.4)	5 (2.0)	11 (2.2)
Sepsis	0	3 (1.2)	3 (0.6)
Urinary tract infection	2 (0.8)	1 (0.4)	3 (0.6)

System Organ Class Preferred Term	MYL-1401O (N = 247) n (%)	Herceptin (N = 246) n (%)	Overall (N = 493) n (%)
Investigations	3 (1.2)	1 (0.4)	4 (0.8)
Blood uric acid increased	1 (0.4)	1 (0.4)	2 (0.4)
Metabolism and nutrition disorders	3 (1.2)	8 (3.3)	11 (2.2)
Hypernatraemia	0	2 (0.8)	2 (0.4)
Hyperuricaemia	2 (0.8)	2 (0.8)	4 (0.8)
Hypokalaemia	1 (0.4)	1 (0.4)	2 (0.4)
Hyponatraemia	0	2 (0.8)	2 (0.4)
Renal and urinary disorders	1 (0.4)	1 (0.4)	2 (0.4)
Acute kidney injury	1 (0.4)	1 (0.4)	2 (0.4)
Respiratory, thoracic and mediastinal disorders	7 (2.8)	6 (2.4)	13 (2.6)
Dyspnoea	2 (0.8)	0	2 (0.4)
Pleural effusion	1 (0.4)	1 (0.4)	2 (0.4)
Pneumonitis	1 (0.4)	2 (0.8)	3 (0.6)
Respiratory failure	2 (0.8)	1 (0.4)	3 (0.6)

n: number of patients with TEAEs, TEAE: treatment-emergent adverse event.
Percentages were based on the number of patients in the safety population (N)
Adverse events were coded using Medical Dictionary for Regulatory Activities Version 18.0. System organ class and preferred term are ordered alphabetically.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.

Among patients receiving monotherapy in Part 2 of the HERITAGE study, 11 SAEs were reported in 9 patients. The incidence of SAEs was similar between treatment groups: 5 patients (2.8%) in the MYL-1401O group and 4 patients (2.5%) in the Herceptin group. One patient in each treatment group experienced an SAE that was attributed by the Investigators to the study drug, 1 SAE of dyspnea in the MYL-1401O group and 1 SAE of pneumonitis in the Herceptin group. Most of these related events had other possible etiology, including underlying disease and exposure to concomitant medication.

Generally, the clear majority of SAEs occurred in Part 1 of the study while patients were receiving combination therapy with taxanes. In Part 2, there were no SAEs of blood and lymphatic disorders (and thus no neutropenia SAEs) and no SAEs of immune disorders. There was 1 cardiac disorder SAE, carditis, in 1 patient treated with MYL-1401O, the diagnosis was not confirmed.

Study BM200-CT3-001-11

Overall, in study BM200-CT3-001-11, 44 SAEs were reported in 31 patients. The Bmab-200 group reported fewer treatment-emergent SAEs in comparison with the Herceptin group (16 treatment-emergent SAEs in 11 patients versus 28 treatment-emergent SAEs in 20 patients,

respectively). Table 25 summarizes the treatment-emergent SAEs that occurred in at least 2 patients overall in Study BM200-CT3-001-11.

Table 25: Summary of Treatment-Emergent Serious Adverse Events That Occurred in at Least 2 Patients Overall (Study BM200-CT3-001-11)

System Organ Class Preferred Term	Bmab-200 (N=66) n (%)	Herceptin (N=68) n (%)
Gastrointestinal disorders	1 (1.52)	3 (4.41)
Diarrhea	1 (1.52)	1 (1.47)
General disorders and administration site conditions	6 (9.09)	4 (5.88)
Disease progression	1 (1.52)	1 (1.47)
Pyrexia	2 (3.03)	3 (4.41)
Infections and infestations	1 (1.52)	5 (7.35)
Gastroenteritis	0 (0)	3 (4.41)
Injury, poisoning and procedural complications	2 (3.03)	2 (2.94)
Infusion-related reaction	0 (0)	2 (2.94)
Respiratory, thoracic, and mediastinal disorders	1 (1.52)	3 (4.41)
Pneumonitis	0 (0)	2 (2.94)

In the Bmab-200 group, most frequently reported treatment-emergent SAEs by SOC was general disorders and administration site conditions (9.09%). The specific events reported included disease progression and pyrexia. In the Herceptin group, the most frequently reported treatment-emergent SAEs by SOC were infections and infestations (7.35%). The specific events reported were lower respiratory tract infection and sepsis; and gastroenteritis (4 events in 3 patients). There were two events of infusion related reactions in the Herceptin arm and none in the Bmab-200 arm.

8.4.2.3 *Discontinuation From Study Drug*

In the healthy volunteer PK study, MYL-Her-1001, 1 subject was withdrawn as a precaution due to raised values for liver function tests (transaminases) following administration of Herceptin in Period I. The mild and reversible increases in liver function tests were considered as possibly related to study drug administration (Herceptin). In PK Study MYL-Her-1002, no patient was withdrawn due to safety reasons.

In the HERITAGE study, the incidence of TEAEs that led to treatment discontinuation was low: 41 TEAEs leading to treatment discontinuation were reported among 26 patients. The incidence

of TEAEs leading to study drug discontinuation was slightly higher in the Herceptin group (16 patients, 6.5%) than in the MYL-1401O group (10 patients, 4.0%).

Only 5 TEAEs resulted in treatment discontinuation for more than 1 patient each as follows: cardiac failure (3 patients in the MYL-1401O group), ejection fraction decreased (2 patients in the MYL-1401O group and 1 patient in the Herceptin group), dizziness, pneumonitis and pneumonia (2 patients each in the Herceptin group), dyspnea (1 patient in the MYL-1401O group and 2 patients in the Herceptin group), and respiratory failure (1 patient in each group).

In Part 2, 3 patients (1.7%) in the MYL-1401O group and 8 patients (4.9%) in the Herceptin group experienced TEAEs leading to treatment discontinuation. Cardiac events leading to treatment discontinuation were cardiac failure in 1 patient of the MYL-1401O group and cardiomyopathy in 1 patient of the Herceptin group.

In Study BM200-CT3-001-11, excluding TEAEs related to disease progression, 1 patient who received Herceptin had a TEAE of ejection fraction decreased that resulted in the patient's withdrawal from the study. The event was considered related to study drug by the investigator.

8.4.2.4 *Adverse Events of Special Interest*

Adverse events of special interest from the HERITAGE study are presented in the following section.

Infusion Reactions, Allergic-like Reactions, and Hypersensitivity

Treatment-emergent AESIs of infusion reactions, allergic-like reactions, and hypersensitivity, including PTs of infusion related reactions (IRRs), anaphylactic reaction, drug hypersensitivity, and hypersensitivity are summarized in Table 26 for Part 1 and 2 through Week 48. A total of 67 events were documented for the above mentioned 4 preferred terms. In both treatment groups the majority of the events were unrelated to treatment (MYL-1401O 66.7% [26 unrelated events out of 39 events], Herceptin 71.4% [20/28]).

Infusion-related reaction (preferred term) was reported in 29 patients (5.9%) overall. Fifteen patients (3.0%) had IRRs that were considered related to trastuzumab, 9 in the MYL-1401O arm and 6 in the Herceptin arm. The majority of these occurred in the first cycle, and all of the IRRs resolved the same day of onset with interruption of the infusion and/or conservative treatment. One IRR in the Herceptin arm was serious, resulting in hospitalization; this subject received subsequent cycles at a reduced infusion rate with no further IRR reported. Most patients continued treatment in subsequent cycles without reporting further trastuzumab-related infusion reactions. The nature and severity of these reactions were consistent with known trastuzumab and taxane infusion reactions and do not yield any new safety concerns.

According to the Herceptin European SmPC it is estimated that approximately 40% of patients who are treated with Herceptin will experience some form of infusion-related reaction. The observed incidence of the preferred term "infusion-related reaction" in this study was lower. It should be noted that the SmPC refers to a broader term of infusion-related reaction that includes chills, fever, dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, respiratory distress, rash, nausea, vomiting, and headache.

The other most frequently reported significant TEAE was hypersensitivity in 12 patients (2.4%), where the incidence was similar between treatment arms. Most of these events were Grade 1 or 2 in intensity. Two events of hypersensitivity were reported as SAEs in 2 patients in the Herceptin arm, 1 was Grade 3 and 1 was Grade 2 in intensity; both events resolved and were considered unrelated to study drug or taxane. Majority of TEAEs hypersensitivity was considered not related to study drug.

Two anaphylactic reaction events were reported in 2 patients in the MYL-1401O arm. Both were reported as SAEs of Grade 3 intensity, and both events resolved; 1 event was considered related to MYL-1401O and resolved on the same day, the other event was unrelated to MYL-1401O but was considered related to concomitant medication (piperacillin/tazobactam).

Of note, except for one event, all of these 67 events of IRRs, anaphylactic reaction, drug hypersensitivity, and hypersensitivity occurred in Part 1 of the study. Only 1 patient in the Herceptin group experienced an IRR during Part 2.

Table 26: Significant Treatment-Emergent Adverse Events – Infusion-related Reactions, Allergic-like Reactions, and Hypersensitivity (HERITAGE Study Through Week 48; Safety Population)

TEAE Category Preferred Term	MYL-1401O (N = 247) n (%)	Herceptin (N = 246) n (%)	Overall (N = 493) n (%)
Total TEAE			
Infusion related reaction	17 (6.9)	12 (4.9)	29 (5.9)
Anaphylactic reaction	2 (0.8)	0	2 (0.4)
Drug hypersensitivity	1 (0.4)	1 (0.4)	2 (0.4)
Hypersensitivity	5 (2.0)	7 (2.8)	12 (2.4)
Grade 3 or greater			
Infusion related reaction	1 (0.4)	1 (0.4)	2 (0.4)
Anaphylactic reaction	2 (0.8)	0	2 (0.4)
Drug hypersensitivity	1 (0.4)	0	1 (0.2)
Hypersensitivity	0	1 (0.4)	1 (0.2)
Serious adverse event			
Infusion related reaction	0	1 (0.4)	1 (0.2)
Anaphylactic reaction	2 (0.8)	0	2 (0.4)
Drug hypersensitivity	1 (0.4)	0	1 (0.2)
Hypersensitivity	0	2 (0.8)	2 (0.4)

n: number of patients with TEAEs, TEAE: treatment-related adverse event
Percentages were based on the number of patients in the safety population (N).
Adverse events were coded using Medical Dictionary for Regulatory Activities Version 18.0.
AE with missing severity grade were considered Grade 3.
Treatment-related included TEAEs that were possibly, probably, or definitely related to trastuzumab or whose causal relationship was reported as "unknown".

Pulmonary Toxicity

Significant TEAEs of pulmonary toxicity across the study, including preferred terms of pneumonitis, pneumonia, dyspnea, dyspnea exertional, pulmonary congestion, pulmonary fibrosis, and respiratory failure, are summarized in Table 27 for Part 1 and 2 through Week 48.

Of the pulmonary TEAEs, dyspnea (7.1%), pneumonia (3.4%), and pneumonitis (1.2%) were reported most frequently overall, and the frequency of the events varied between treatment arms. Most of the TEAEs were Grade 1 or 2 in intensity. The majority of pulmonary toxicity TEAEs were considered not related to study drug and related to the taxane.

Most common Grade 3 or higher TEAE were dyspnea and pneumonia and the overall incidence was similar in both treatment arms. The overall incidence of SAEs was also similar in both treatment arms with pneumonia being the most common SAE.

Table 27: Significant Treatment-Emergent Adverse Events – Pulmonary Toxicity (HERITAGE Study Through Week 48; Safety Population)

TEAE Category Preferred Term	MYL-1401O (N = 247) n (%)	Herceptin (N = 246) n (%)	Overall (N = 493) n (%)
Total TEAE Respiratory Events	32 (13)	30 (12.2)	62 (12.6)
Dyspnea	17 (6.9)	18 (7.3)	35 (7.1)
Dyspnea exertional	3 (1.2)	2 (0.8)	5 (1.0)
Pneumonia	7 (2.8)	10 (4.1)	17 (3.4)
Pneumonitis	4 (1.6)	2 (0.8)	6 (1.2)
Pulmonary congestion	0	1 (0.4)	1 (0.2)
Pulmonary fibrosis	1 (0.4)	0	1 (0.2)
Respiratory failure	2 (0.8)	1 (0.4)	3 (0.6)
Grade 3 or greater			
Dyspnea	3 (1.2)	2 (0.8)	5 (1.0)
Pneumonia	3 (1.2)	5 (2.0)	8 (1.6)
Pneumonitis	0	2 (0.8)	2 (0.4)
Respiratory failure	2 (0.8)	1 (0.4)	3 (0.6)
Serious adverse event			
Dyspnea	2 (0.8)	0	2 (0.4)
Pneumonia	6 (2.4)	5 (2.0)	11 (2.2)
Pneumonitis	1 (0.4)	2 (0.8)	3 (0.6)
Respiratory failure	2 (0.8)	1 (0.4)	3 (0.6)

n: number of patients with TEAEs, TEAE: treatment-related adverse event
Percentages were based on the number of patients in the safety population (N).
Adverse events were coded using Medical Dictionary for Regulatory Activities Version 18.0.
AE with missing severity grade were considered Grade 3.
Treatment-related included TEAEs that were possibly, probably, or definitely related to trastuzumab or whose causal relationship was reported as unknown.

Cardiac Toxicity

Significant TEAEs of cardiac toxicity across the study, including preferred terms of cardiac failure, cardiotoxicity, left ventricular dysfunction, and metabolic cardiomyopathy are summarized in Table 28 for Part 1 and 2 through Week 48. These adverse events are known and well documented for trastuzumab. In addition to assessment of AEs related to cardiac function, a systematic objective evaluation of cardiac function was also conducted.

Most of these TEAEs were Grade 1 or 2 in intensity. Two events of cardiac failure in the MYL-1401O arm were reported as SAEs; 1 was a Grade 3 SAE that resolved, and the other was fatal (Grade 5). Three left ventricular dysfunction events were reported as Grade 3 in intensity, two in the MYL-1401O arm and one in the Herceptin arm.

The majority of cardiac toxicity TEAEs were considered related to study drug. But cardiac toxicities related with trastuzumab are known to be triggered by a second hit, most of these patients were previously treated with anthracyclines or had a medical condition like previous and concomitant cardiovascular disorders, diabetes mellitus, and hypertension.

Most of the cardiac events occurred during Part 1 while patients received combination therapy. While on monotherapy in Part 2, 17 cardiac events occurred: 6 patients (3.4%) in the MYL-1401O group and 4 patients (2.5%, 5 events) in the Herceptin group experienced ejection fraction decreased. Cardiomyopathy and congestive cardiomyopathy for 1 patient each was noted in the Herceptin group while cardiac failure, cardiotoxicity, carditis and left ventricular dysfunction were reported for 1 patient each in the MYL-1401O group. No events of left ventricular failure or metabolic cardiomyopathy occurred during Part 2.

Table 28: Significant Treatment-Emergent Adverse Events – Cardiac Toxicity (HERITAGE Study Through Week 48; Safety Population)

TEAE Category Preferred Term	MYL-1401O (N = 247) n (%)	Herceptin (N = 246) n (%)	Overall (N = 493) n (%)
Total TEAE cardiac disorders	12 (4.9)	10 (4.1)	22 (4.5)
Cardiac failure	6 (2.4)	1 (0.4)	7 (1.4)
Cardiomyopathy	1 (0.4)	1 (0.4)	2 (0.4)
Cardiotoxicity	2 (0.8)	0	2 (0.4)
Carditis	1 (0.4)	0	1 (0.2)
Congestive cardiomyopathy	0	1 (0.4)	1 (0.2)
Left ventricular dysfunction	2 (0.8)	3 (1.2)	5 (1.0)
Left ventricular failure	0	1 (0.4)	1 (0.2)
Metabolic cardiomyopathy	1 (0.4)	3 (1.2)	4 (0.8)
Grade 3 or greater			
Cardiac failure	3 (1.2)	0	3 (0.6)
Carditis	1 (0.4)	0	1 (0.2)
Left ventricular dysfunction	2 (0.8)	1 (0.4)	3 (0.6)
Serious adverse event			
Cardiac failure	2 (0.8)	0	2 (0.4)
Carditis	1 (0.4)	0	1 (0.2)

n: number of patients with TEAEs, TEAE: treatment-related adverse event
Percentages were based on the number of patients in the safety population (N).
Adverse events were coded using Medical Dictionary for Regulatory Activities Version 18.0.
AE with missing severity grade are considered to be Grade 3.
Treatment-related includes TEAEs possibly, probably, or definitely related to trastuzumab or relationship unknown.

Overall the adverse events on special interest were similar in both treatment arms and the isolated differences in events could be attributed to preferred terms used. The overall incidence was similar to that available in literature with trastuzumab in combination with taxane.

8.4.2.5 *Assessment of Left Ventricular Function*

An objective and systematic assessment of left ventricular function was conducted during the study using ECHO cardiography or MUGA scan at 12-week intervals during Part 1 and 2 of the study.

Table 29 presents descriptive statistics for LVEF results over the course of the study through Cycle 17 Week 48. Mean and median LVEF values did not change appreciably from Baseline to Week 48 for either treatment arm and were similar between treatment arms. Change from Baseline at Cycle 9 Week 24 and Cycle 17 Week 36 was minimal for both treatment arms.

Table 29: Descriptive Statistics of LVEF (%) Values by Visit (HERITAGE Study; Safety Population)

		MYL-1401O (N = 247)		Herceptin (N = 246)	
Visit	**Statistic**	**Observed**	**Change from Baseline**	**Observed**	**Change from Baseline**
Baseline	n	246		244	
	Mean (SD)	64.0 (5.79)		64.1 (5.71)	
	Median	64.0		63.0	
Week 12	n	212	212	209	207
	Mean (SD)	63.3 (6.11)	-1.0 (5.55)	63.4 (5.78)	-0.8 (4.59)
	Median	63.0	-1.0	63.0	0.0
Week 24	n	182	182	168	166
	Mean (SD)	63.1 (5.10)	-0.9 (5.18)	63.1 (6.30)	-1.2 (5.41)
	Median	63.0	-1.0	62.0	-1.0
Week 36	n	139	139	128	127
	Mean (SD)	62.3 (5.08)	-1.6 (5.02)	63.1 (5.81)	-1.1 (5.05)
	Median	62.0	-1.0	62.0	-1.0
Week 48	n	84	84	68	68
	Mean (SD)	63.1 (4.99)	-1.3 (5.38)	63.3 (4.92)	-1.2 (4.95)
	Median	63.0	-1.0	63.0	-1.5
EOT	n	86	85	84	83
	Mean (SD)	61.8 (7.32)	-2.4 (6.80)	62.8 (7.90)	-1.4 (7.10)
	Median	62.0	-2.0	62.0	-1.0

EOT: end of treatment, LVEF: left ventricular ejection fraction, N: number of patient in treatment group, n: number of patients with available data, SD: standard deviation. Baseline was the screening visit, prior to first dose of study drug.

In addition to mean LVEF data, the per-patient incidence of new-onset myocardial dysfunction based on LVEF (%) is summarized in the following table for the safety population of the HERITAGE study. Only a few patients had an LVEF value of <50% at least once post-baseline, with similar incidence observed in both treatment groups (MYL-1401O 4.0%, Herceptin 3.3%).

The incidence of patients with an LVEF value of <50% at least once post-baseline and a reduction of more than 10 percentage points from baseline were also similar in both groups (MYL-1401O 3.6%, Herceptin 2.8%). There are multiple predisposing factors for cardiotoxicity in this patient population including anthracycline use, radiotherapy to chest wall, diabetes and hypertension.

The overall incidence of clinically relevant LVEF changes seen in this study (2.8%-3.6%) are consistent with the published literature for Herceptin and recently conducted clinical studies, wherein it was 6.6% in the Cleopatra study and 4.5% in the Marianne study in the arms with trastuzumab plus taxane (Baselga et al. 2012, Perez et al. 2017).

Table 30: Per-Patient Incidence of New Onset Myocardial Dysfunction Through Week 48 by LVEF ([%] (HERITAGE Study; Safety Population)

	MYL-1401O (N = 247)	Herceptin (N = 246)
	n (%)	n (%)
LVEF < 50% at least once post-baseline		
Yes	10 (4.0)	8 (3.3)
No	237 (96.0)	238 (96.7)
p-value	0.637	
LVEF post-baseline and LEVF decrease		
LVEF <50% post-baseline and decrease <10 percentage points	1 (0.4)	1 (0.4)
LVEF <50% post-baseline and decrease ≥10 percentage points	9 (3.6)	7 (2.8)

LVEF: left ventricular ejection fraction, N: number of patient in treatment group, n: number of patients with available data

8.4.3 Immunogenicity

The presence of antibodies (ADA) against MYL-1401O/Bmab-200 and Herceptin in clinical study samples was assessed using validated assays in a multi-tiered approach that included screening, confirmation, titer assessment, and neutralizing antibody (NAb) assay.

In the screening tier, sample response was compared to a statistically determined cut-point to identify potentially positive responders. In the confirmatory tier, the screened positive samples were incubated in the presence and absence of excess drug, and the sample responses were used to calculate the percent inhibition due to the drug. The percent inhibition was compared with a statistically determined confirmatory cut-point to identify drug-specific responders (confirmed positive samples). Cross-reactivity of the ADA-positive samples was also evaluated in the confirmatory tier via incubation with excess Herceptin. The relative titer of confirmed ADA-positive samples was measured by performing serial dilutions until the sample response dropped below the titer cut-point.

8.4.3.1 *Study MYL-Her-1001*

In Study MYL-HER-1001, the immunogenicity of MYL-1401O and Herceptin was assessed by analyzing samples collected at baseline (pre-infusion at 0 hours) and at 2 weeks and 10 weeks during each treatment period. Of the 123 samples tested, 1 sample (Subject 102, Herceptin group) was ADA-positive at baseline. The subsequent samples for this subject (at 2 weeks and 10 weeks) were negative. Therefore, all post-baseline samples tested negative for ADA in this study of healthy volunteers.

8.4.3.2 *Study MYL-Her-1002*

In Study MYL-Her-1002, the immunogenicity of MYL-1401O, US-Herceptin, and EU-Herceptin was assessed by analyzing samples collected at pre-dose (Day 1) and Day 71 (or at early termination). All 126 subjects dosed had evaluable post-dose immunogenicity samples. The occurrence of ADA-positive samples was low for each of the products. Four subjects were confirmed ADA-positive at pre-dose (2 in MYL-1401O group, 1 in US-Herceptin group, 1 in EU-Herceptin group); of these, 2 remained ADA-positive at Day 71 (1 in MYL-1401O group, 1 in US-Herceptin group). There were no instances of treatment-emergent ADAs in the study, as no subject seroconverted after study drug administration.

8.4.3.3 *HERITAGE Study*

In the HERITAGE study, the immunogenicity of MYL-1401O and Herceptin was assessed by analyzing samples collected pre-infusion at baseline (Cycle 1, Week 0) and at Weeks 6, 12, 18, 24, 36, and 48 (Cycles 3, 5, 7, 9, 13, and 17). The confirmation of ADA positivity was based on a 0.1% false-positive error rate (FPER). The samples that were identified as ADA positive were further subjected to assessment of titers and for determining if the samples were also positive for neutralizing antibodies.

Immunogenicity Data Based on 0.1% FPER

Prior to dosing (baseline), 14 of the 237 patients (5.9%) with results available were ADA-positive in MYL-1401O group and 22 of the 240 patients (9.2%) were ADA-positive in the Herceptin group. A similar baseline ADA-positive rate was observed in previous clinical studies with the originator product. Baseline positivity may be due to presence of pre-existing antibodies or ADA assay interference with high levels of extracellular domain of HER2 receptor (HER2 ECD).

As the number of patients continuing in the study decreased over time, the number of samples available for immunogenicity assessment also decreased over time. The number of ADA-positive samples and proportion at each time point were calculated. As shown in Table 31, the number of ADA-positive patients declined over time. The overall incidence of ADA-positive samples was

low and in most cases, it was isolated with no consistent trend noted over time. The maximum proportion of ADA-positive patients post-baseline was seen at Week 6 (2.5% in the MYL-1401O group and 3.0% in the Herceptin group). At the Week 48 timepoint, none of the patients in either treatment group were ADA-positive.

Nine patients in the MYL-1401O group (3.9%) and 10 patients (4.4%) in the Herceptin group were ADA-positive at least once at any timepoint post-baseline, regardless of the ADA result at baseline.

Table 31: Summary of ADA Results by Visit and Treatment Through Week 48 (HERITAGE Study; Safety Population)

		MYL-1401O (N = 247)	Herceptin (N = 246)
Visit	**ADA result**	**n (%)**	**n (%)**
Baseline (Cycle 1 Week 0)	ADA result available	237	240
	ADA positive	14 (5.9)	22 (9.2)
	ADA negative	223 (94.1)	218 (90.8)
	Missing	8	5
Cycle 3 Week 6	ADA result available	201	200
	ADA positive	5 (2.5)	6 (3.0)
	ADA negative	196 (97.5)	194 (97.0)
	Missing	5	5
Cycle 5 Week 12	ADA result available	213	205
	ADA positive	2 (0.9)	2 (1.0)
	ADA negative	211 (99.1)	203 (99.0)
	Missing	5	1
Cycle 7 Week 18	ADA result available	190	174
	ADA positive	2 (1.1)	1 (0.6)
	ADA negative	188 (99.9)	173 (99.4)
	Missing	1	2
Cycle 9 Week 24	ADA result available	179	166
	ADA positive	2 (1.1)	1 (0.6)
	ADA negative	177 (98.9)	165 (99.4)
	Missing	0	1

		MYL-1401O (N = 247)	Herceptin (N = 246)
Visit	**ADA result**	**n (%)**	**n (%)**
Cycle 13 Week 36 [a]	ADA result available	140	130
	ADA positive	3 (2.1)	1 (0.8)
	ADA negative	137 (97.9)	129 (99.2)
	Missing	0	0
Cycle 17 Week 48 [a,b]	ADA result available	103	93
	ADA positive	0	0
	ADA negative	103 (100.0)	93 (100.0)
	Missing	3	2
Last non-missing result post-baseline [c]	ADA positive	3 (1.3)	3 (1.3)
	ADA negative	225 (98.7)	224 (98.7)
At least one positive ADA sample post-baseline regardless of baseline result [c,d]		9 (3.9)	10 (4.4)

ADA: antidrug antibody, n: number of patients
Baseline was Cycle 1 Day 1, prior to first dose of study treatment.
Samples were taken before administration of study drug since study drug levels can interfere with the detection of antidrug antibody.
Percentages are based on the number of patients in the safety population (N) with an ADA assessment performed at the respective cycle. Missing are the number of patients who attended the visit but did not have an ADA sample collected.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
[a] Five patients at Cycle 13 Week 36 (3 in the MYL-1401O group and 2 in the Herceptin group) and 1 patient at Cycle 17 Week 48 in the Herceptin group continued to receive taxane, but these patients are included in Cycle 13 Week 36 and Cycle 17 Week 48 of Part 2.
[b] Cycle 17 Week 48 data include results occurring after the Week 48 cut-off.
[c] Post-baseline includes only on treatment samples until Week 48 and excludes EOT/EOS samples.
[d] The denominator for this calculation is the number of non-missing post-baseline samples available in each group, which include 228 patients in the MYL-1401O group and 227 patients in the Herceptin group.

Confirmed ADA-positive samples were further tested using a validated cell based neutralizing antibody (NAb) assay. Table 32 presents a summary of the NAb results by visit and treatment. ADA-positive samples through Week 48 were isolated, had a very low incidence in both treatment arms, and was thus consistent with the low immunogenic potential of Herceptin.

At baseline, of the patients who were ADA-positive, NAbs were detected in 1 patient in the MYL-1401O group and 2 patients in the Herceptin group. One patient in the MYL-1401O group and 3 patients in the Herceptin group were tested positive for NAb at least once at any timepoint post-baseline, regardless of the ADA results at baseline.

With regards to treatment-emergent NAb data (i.e., patients that were NAb negative at baseline but were positive post-baseline), 2 patients in the Herceptin group who were ADA-positive at

baseline but were NAb-negative, became NAb-positive post-baseline. The patient in the MYL-1401O group who was NAb-positive at Week 36 did not have a baseline result (thus was considered treatment-emergent NAb-positive).

The NAb-positivity was isolated and in this small group of patients, none of them had positivity at more than 1 post-baseline timepoint. These data are consistent with the literature with Herceptin, where the incidence of ADA and NAb positivity is very low. Given the very low treatment-induced NAb positivity, any correlation to efficacy is of limited value.

Table 32: Summary of NAb Results by Visit and Treatment Through Week 48 (HERITAGE Study; Safety Population)

Visit			MYL-1401O (N = 247)	Herceptin (N = 246)
Baseline (Cycle 1 Week 0)	ADA result available	n	237	240
	ADA positive	n	14	22
	NAb negative	n	13	20
	NAb positive	n (%)	1 (0.4)	2 (0.8)
Cycle 3 Week 6	ADA result available		201	200
	ADA positive	n	5	6
	NAb negative	n	5	3
	NAb positive	n (%)	0	3 (1.5)
Cycle 5 Week 12	ADA result available		213	205
	ADA positive	n	2	2
	NAb negative	n	2	2
	NAb positive	n (%)	0	0
Cycle 7 Week 18	ADA result available		190	174
	ADA positive	n	2	1
	NAb negative	n	2	1
	NAb positive	n (%)	0	0
Cycle 9 Week 24	ADA result available		179	166
	ADA positive	n	2	1
	NAb negative	n	2	1
	NAb positive	n (%)	0	0
Cycle 13 Week 36[a]	ADA result available		140	130
	ADA positive	n	3	1
	NAb negative	n	2	1
	NAb positive	n (%)	1 (0.7)	0
Cycle 17 Week 48 [a,b]	ADA result available		103	93
	ADA positive	n	0	0
At least one positive NAb sample post-baseline regardless of baseline result [c,d]		n (%)	1 (0.4)	3 (1.3)

ADA: antidrug antibody, n: number of patients, NAb: neutralizing antibodies
Baseline was Cycle 1 Day 1, prior to first dose of study treatment.
Samples were taken before administration of study drug since study drug levels can interfere with the detection of antidrug antibody. Confirmed positive ADA samples were further tested using a validated cell based NAb assay.
Percentages are based on the number of patients in the safety population (N) with available ADA results.
Note, during Part 1 of the study patients received study drug (MYL-1401O or Herceptin) plus taxane treatment and during Part 2 patients received study drug (MYL-1401O or Herceptin) alone.
[a] Five patients at Cycle 13 Week 36 (3 in the MYL-1401O group and 2 in the Herceptin group) and 1 patient at Cycle 17 Week 48 in the Herceptin group continued to receive taxane, but these patients are included in Cycle 13 Week 36 and Cycle 17 Week 48 of Part 2.
[b] Cycle 17 Week 48 data include results occurring after the Week 48 cut-off.
[c] Post-baseline includes only on treatment samples until Week 48 and excludes end of treatment/end of study samples.
[d] The denominator for this calculation is the number of non-missing post-baseline samples available in each group, which include 228 patients in the MYL-1401O group and 227 patients in the Herceptin group.

The overall ADA and NAb rate was calculated using a conservative approach, which considers all patients who tested positive for ADA or NAb at least once at any time point post-baseline regardless of the ADA result at baseline. The overall ADA rate was 3.9% in the MYL-1401O group and 4.4% in the Herceptin group. The overall NAb rate was very low with 1 patient (0.4%) and 3 patients (1.3%) in the MYL-1401O and Herceptin groups, respectively.

The treatment-induced ADA rate was calculated based on baseline ADA-negative patients (or patients with no baseline results) who tested positive for ADA at least once at any time point post-baseline. The treatment-induced NAb rate was calculated based on baseline NAb-negative patients (or patients with no baseline results) who tested positive for NAb at least once at any time point post-baseline. For the treatment-induced NAb rate also patients were included who were ADA-positive (but NAb-negative) at baseline. These results are presented in Table 33. The treatment-induced ADA rate in the MYL-1401O group was 1.7% and 1.8% in the Herceptin group. The treatment-induced NAb rate was 0.4% and 0.9 % in the MYL-1401O and Herceptin groups, respectively.

Table 33: Summary of Treatment-Induced ADA and NAb Rate Through 48 Weeks (HERITAGE Study; Safety Population)

	MYL-1401O (N = 233)	Herceptin (N = 224)
Visit	**n (%)**	**n (%)**
Treatment-induced ADA rate	4 (1.7)	4 (1.8)
Treatment-induced NAb rate	1 (0.4)	2 (0.9)

ADA: antidrug antibody, NAb: neutralizing antibody
Percentages were based on the number of patients in the safety population (N) with available ADA post-baseline results and include 229 patients in the MYL-1401O group and 227 patients in the Herceptin group.
Note, post-baseline includes only on treatment samples until Week 48 and excludes end of treatment/end of study samples.
For the treatment-induced NAb rate also patients were included who were ADA-positive but NAb-negative at baseline.

Overall, ADA titers were low in both treatment groups across all timepoints. The highest pre-dose ADA titers obtained were 7.1 and 6.9, respectively, in the MYL-1401O and Herceptin groups. The highest post-dose ADA titers obtained were 11.5 and 5.5, respectively, in the MYL-1401O and Herceptin groups. Consistent with ADA and NAb results, the titers were low and there was no consistent trend. These data are also consistent with literature for Herceptin.

Immunogenicity Based on 1% FPER

During the review of the BLA, the FDA asked Mylan to provide an analysis of the ADA data based on a 1% FPER (20.8% inhibition).

Table 34 presents a summary of the ADA results by visit and treatment and includes the original analysis (using a confirmatory cut-point at the 0.1% false positive error rate) presented earlier, side-by-side with the revised analysis (using a confirmatory cut-point at the 1.0% false positive error rate). Changes in the results based on the revised analysis are highlighted in green font.

In the revised analysis based on a confirmatory cut-point with a 1% false-positive error rate, 13 additional patients were considered ADA-positive at baseline compared with the original analysis using a confirmatory cut-point with a 0.1% false-positive error rate. In the revised analysis, 20 of the 237 patients (8.4%) in MYL-1401O arm and 29 of the 240 patients (12.1%) in the Herceptin arm were ADA-positive prior to dosing. As noted earlier, baseline positivity may be due to presence of pre-existing antibodies or ADA assay interference with high levels of extracellular domain of the HER2 receptor.

Consistent with the original analysis, the proportions of ADA-positive patients in the revised analysis were similar between the treatment arms and declined over time. The overall incidence of ADA-positive patients was low in both treatment arms and in most cases, it was isolated with no consistent trend noted over time. In both the original and revised analyses, the highest proportions of ADA-positive patients post-baseline occurred at Week 6. In the revised analysis, the proportions of ADA-positive patients at Week 6 were 3.0% in the MYL-1401O arm and 4.0% in the Herceptin arm.

In the original analysis, 3.9% of patients in the MYL-1401O treatment arm and 4.4% of patients in the Herceptin treatment arm were ADA-positive at least once at any timepoint post-baseline, regardless of their ADA result at baseline. The results of the revised analysis also showed that the proportions of patients who were ADA-positive at least once at any timepoint post-baseline were similar between treatment arms, as 5.9% of patients in the MYL-1401O treatment arm and 6.8% of patients in the Herceptin treatment arm were ADA-positive at least once at any timepoint post-baseline, regardless of their ADA result at baseline.

The proportions of ADA-positive patients at the end of treatment are also shown in Table 34. These values were low and similar between the treatment arms (3.3% in the MYL-1401O arm and 2.6% in the Herceptin arm).

Table 34: Original Analysis and Revised Analysis Based on a Confirmatory Cut-Point with a 1% False-Positive Error Rate of ADA Samples by Visit and Treatment Through Week 48 (HERITAGE Study; Safety Population)

		Original Analysis Based on CCP with 0.1% FPER*		Revised Analysis Based on CCP with 1% FPER*	
		MYL-1401O (N = 247)	Herceptin (N = 246)	MYL-1401O (N = 247)	Herceptin (N = 246)
Visit	**ADA result**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Cycle 1 Week 0	ADA result available	237	240	237	240
	ADA positive	14 (5.9)	22 (9.2)	20 (8.4)	29 (12.1)
	ADA negative	223 (94.1)	218 (90.8)	217 (91.6)	211 (87.9)
	Missing	8	5	8	5
Cycle 3 Week 6	ADA result available	201	200	201	200
	ADA positive	5 (2.5)	6 (3.0)	6 (3.0)	8 (4.0)
	ADA negative	196 (97.5)	194 (97.0)	195 (97.0)	192 (96.0)
	Missing	5	5	5	5
Cycle 5 Week 12	ADA result available	213	205	213	205
	ADA positive	2 (0.9)	2 (1.0)	2 (0.9)	3 (1.5)
	ADA negative	211 (99.1)	203 (99.0)	211 (99.1)	202 (98.5)
	Missing	5	1	5	1
Cycle 7 Week 18	ADA result available	190	174	190	174
	ADA positive	2 (1.1)	1 (0.6)	3 (1.6)	2 (1.1)
	ADA negative	188 (99.9)	173 (99.4)	187 (98.4)	172 (98.9)
	Missing	1	2	1	2
Cycle 9 Week 24	ADA result available	179	166	179	166
	ADA positive	2 (1.1)	1 (0.6)	2 (1.1)	2 (1.2)
	ADA negative	177 (98.9)	165 (99.4)	177 (98.9)	164 (98.8)
	Missing	0	1	0	1
Cycle 13 Week 36	ADA result available	140	130	140	130
	ADA positive	3 (2.1)	1 (0.8)	3 (2.1)	2 (1.5)
	ADA negative	137 (97.9)	129 (99.2)	137 (97.9)	128 (98.5)
	Missing	0	0	0	0
Cycle 17 Week 48	ADA result available	103	93	103	93
	ADA positive	0	0	1 (1.0)	0
	ADA negative	103 (100.0)	93 (100.0)	102 (99.0)	93 (100.0)
	Missing	3	2	3	2
End of Treatment	ADA positive	3 (1.3)	3 (1.3)	8 (3.3)	6 (2.6)
	ADA negative	225 (98.7)	224 (98.7)	231 (96.7)	229 (97.4)
At least 1 positive ADA sample post-baseline regardless of baseline result		9 (3.9)	10 (4.4)	14 (5.9)	16 (6.8)

Changes in results based on the revised analysis are indicated in green font.

To assess the treatment-emergent ADA response, an analysis that excluded baseline-positive patients was conducted. Table 35 presents a summary of the treatment-induced ADA-positive patients by visit and treatment. As shown in the table, the treatment-induced ADA rates remained similar between the treatment arms after the revised analysis was conducted. Per the original analysis, the treatment-induced ADA rates were 1.7% in the MYL-1401O arm compared with 1.8% in the Herceptin arm. In the revised analysis, the treatment-induced ADA rates were 3.2% in the MYL-1401O arm compared with 3.3% in the Herceptin arm.

Table 35: Original Analysis and Revised Analysis Based on a Confirmatory Cut-Point with a 1% False-Positive Error Rate of Treatment-Emergent ADA Results by Visit and Treatment Through Week 48 (HERITAGE Study; Safety Population)

Visit		Original Analysis Based on CCP with 0.1% FPER		Revised Analysis Based on CCP with 1% FPER	
		MYL-1401O (N = 233)	Herceptin (N = 224)	MYL-1401O (N = 227)	Herceptin (N = 217)
		n (%)	n (%)	n (%)	n (%)
Cycle 3 Week 6	ADA results available	192	180	188	176
	ADA positive	3 (1.6)	1 (0.6)	3 (1.6)	0
Cycle 5 Week 12	ADA results available	206	186	201	183
	ADA positive	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
Cycle 7 Week 18	ADA results available	184	158	180	155
	ADA positive	1 (0.5)	0	1 (0.6)	0
Cycle 9 Week 24	ADA results available	174	152	170	149
	ADA positive	2 (1.1)	1 (0.7)	2 (1.2)	1 (0.7)
Cycle 13 Week 36	ADA results available	137	119	133	116
	ADA positive	2 (1.5)	1 (0.8)	2 (1.5)	1 (0.9)
Cycle 17 Week 48	ADA results available	101	83	98	81
	ADA positive	0	0	0	0
End of Treatment	ADA results available	Not determined		222	210
	ADA positive	Not determined		4 (1.8)	4 (1.9)
At least 1 positive ADA sample post-baseline		4 (1.7)	4 (1.8)	7 (3.2)	7 (3.3)

Changes in results based on the revised analysis are indicated in green font.

Since the cell-based neutralizing antibody assay and titers are run only for ADA-positive samples, the sponsor has requested the CRO to conduct the assay for the newly identified ADA-positive samples based on the confirmatory cut-point with a 1.0% false-positive error rate.

In summary, although the ADA positive rate using a 1% FPER are slightly higher compared to 0.1% FPER, the data is very consistent with the earlier analysis in that the proportion of patients that are ADA positive at each timepoint or have at least 1 post baseline ADA positive sample are similar in both treatment arms. Similarly, the proportion of patients that are treatment emergent positive post baseline are also similar between both treatment arms. These data are also consistent with the relatively low immunogenic potential of trastuzumab.

8.4.3.4 *Study BM200-CT3-001-11*

In Study BM200-CT3-001-11, immunogenicity samples were collected at baseline (Week 0), Week 12, and Week 24 for the detection of ADAs. A total of 134 patients (66 in the Bmab-200 group and 68 in the Herceptin group) were evaluated for immunogenicity. Table 36 displays the incidence of ADA at baseline, Week 12, and Week 24.

Table 36: Summary of ADA Results by Visit and Treatment Through Week 24 (Study BM200-CT3-001-11)

Time Point	Bmab-200 (N=66) n (%)	Herceptin (N=68) n (%)
Baseline	4 (6.06)	4 (5.88
Week 12	2 (3.03)	0 (0)
Week 24	1 (1.52)	0 (0)

Note: Increased dilution indicates higher titer (i.e., nondiluted sample has the lowest titer, followed by the 1:4 and 1dilutions).

Overall, the prevalence of ADA was similar in the two treatment groups at baseline (4 patients were seropositive in each group); however, all these patients became seronegative while on treatment. In the Bmab-200 group, 2 patients were seropositive at Week 12; 1 patient continued to be ADA-positive until the end of the treatment, while the other discontinued due to disease progression after Week 12. The titers dropped from Week 12 to Week 24 (4-fold to 1-fold) in the patient who continued through Week 24.

In conclusion, the immunogenicity results across the 4 clinical studies showed that MYL-1401O/Bmab-200 and Herceptin have a similar and low immunogenic potential. No clear association was observed between the presence of ADAs and pharmacokinetics, efficacy, or to infusion reactions.

8.4.4 Post-Marketing Experience

Biocon Limited (co-development partner of Mylan) received marketing authorization for Bmab-200 (which was used in Study BM200 CT3-001-11) in India in October 2013. This

formulation has been available on the Indian market since January 2014. Sales data indicate a patient exposure of more than 14,000-patient treatment courses since launch of the product. Safety information received from the post approval exposure is being continuously evaluated and analyzed for inclusion in the Periodic Safety Update Reports as per local (Indian) regulations. Periodic review of this safety data does not indicate any new safety signals from the post-approval experience of more than 2 years. None of the articles screened during the worldwide literature review contained safety information indicating a newly identified or potential risk with trastuzumab.

8.5 Clinical Conclusions

Studies MYL-Her-1001 and MYL-Her-1002, the healthy volunteer PK studies, indicate that all prespecified bioequivalence criteria were met, i.e. 90% CIs of the T/R ratios of the primary PK parameters were within the pre-specified bioequivalence acceptance limit of 80.00% to 125.00%. There were no instances of either treatment-induced or treatment-boosted ADA-positive subjects in the study.

The results of Study MYL-Her-1002 demonstrated bioequivalence between MYL-1401O and US-Herceptin, MYL-1401O and EU-Herceptin, and EU-Herceptin and US-Herceptin. Thus, a scientific “bridge” was clinically established among US-Herceptin, EU-Herceptin, and MYL-1401O and results obtained in studies using EU-Herceptin can be inferred to results obtained with US-Herceptin. Additionally in this study, the safety profile of MYL-1401O was found to be similar to Herceptin with no new safety signals identified.

The HERITAGE study was the main confirmatory safety and efficacy study in patients with MBC and conclusively established the therapeutic equivalence of MYL-1401O and Herceptin by comparing the independently assessed best ORR at Week 24. Secondary analyses also demonstrated therapeutic equivalence confirming the robustness of the finding. The descriptive comparison of safety, immunogenicity, and tolerability of MYL-1401O and Herceptin given in combination with a taxane also did not reveal any clinically meaningful differences between the treatments. Furthermore, there was no impact on cardiac function or the clinical pharmacology parameters evaluated.

These findings are supported by data from Study BM200-CT3-001-11, which used a slightly different formulation representing the Herceptin Reference Product formulation (Bmab-200). This study demonstrated equivalent PK, safety, and efficacy between Bmab-200 and EU-Herceptin.

In conclusion, the clinical data confirm the high similarity established from the physicochemical, analytical, biological, and nonclinical studies, and demonstrate bioequivalence, therapeutic

equivalence, and no clinically meaningful differences between MYL-1401O and Herceptin, thus contributing to the totality of the data in support of the biosimilarity between MYL-1401O and Herceptin.

9 OVERALL CONCLUSION

In summary, the comprehensive analytical, nonclinical, and clinical data presented in Mylan's dossier establish high similarity and demonstrate no clinically meaningful differences between MYL-1401O and Herceptin in terms of purity, efficacy, safety, pharmacokinetics, immunogenicity, and potency. Residual uncertainties were addressed in a stepwise fashion and the totality of evidence supports the proposed clinical use of MYL-1401O as a biosimilar to Herceptin. The extrapolation to all Herceptin approved indications was scientifically justified based on the demonstration of biosimilarity (MYL-1401O shown to be essentially the same molecule as Herceptin), a common mechanism of action across indications, high similarity between MYL-1401O and Herceptin in functional studies, and common conditions of use of trastuzumab in all approved indications.

In conclusion, Mylan therefore proposes MYL-1401O to be approved as a biosimilar to Herceptin and in all indications approved for the reference product.

10 REFERENCES

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