CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761074Orig1s000

CLINICAL REVIEW(S)

Date	*Electronic Stamp Date*
From	Suparna Wedam, M.D.
Subject	Addendum to Clinical/Stats Review
NDA/BLA #	351(k) BLA 761074
Applicant	Mylan GmbH
Date of Submission	11/3/2016
BsUFA Goal Date	12/3/2017
Proprietary Name / Established (USAN) names	OGIVRI/Trastuzumab-dkst MYL-1401O Lyophilized Powder for Intravenous Infusion
Dosage forms / Strength	for injection/420 mg per vial
Proposed Indication(s)	OGIVRI is a HER2/neu receptor antagonist indicated for: • the treatment of HER2-overexpressing breast cancer • the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma
Recommended Indication(s)	OGIVRI is a HER2/neu receptor antagonist indicated for: • the treatment of HER2-overexpressing breast cancer • the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma

BLA 761074 for MYL-1401O (Herceptin biosimilar) was submitted November 3, 2016 with an original Biosimilar User Fee Amendments (BsUFA) goal date of September 3, 2017. A major amendment was issued for this BLA extending the BsUFA goal date to December 3, 2017.

The applicant is seeking indications that are the same as those for US-Herceptin. The applicant is seeking licensure for the indication studied in its clinical program – metastatic breast cancer – as well as for the adjuvant breast cancer and metastatic gastric cancer indications, which have not been directly studied in the MYL-1401O clinical program. The data submitted to the BLA from the clinical development program of MYL-1401O support a demonstration of no clinically meaningful differences between MYL-1401O and US-licensed Herceptin. In addition, the Applicant provided adequate scientific justification for extrapolation of data to support biosimilarity in the adjuvant breast cancer and metastatic gastric cancer indications. The Applicant demonstrated that MYL-1401O is highly similar to US-Herceptin based on extensive analytical data and that MYL-1401O has similar pharmacokinetics effects, immunogenicity, efficacy, and safety which support extrapolating the data to other indications (adjuvant breast cancer and metastatic gastric cancer). The mechanism of action of trastuzumab is the same across the indications. However, since the original BsUFA goal date was earlier than the date on which the orphan drug exclusivity for Herceptin's gastric cancer indication expired (October 20, 2017), a decision was made not to grant the gastric cancer indication at the time that the clinical/statistical review was entered to DARRTS. The new BsUFA goal date is now past the exclusivity expiration date and therefore the clinical team recommends also granting the gastric cancer indication for MYL-14010. Based on this, appropriate changes are recommended to sections 1 and 14 of the OGIVRI labeling.

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/s/

SUPARNA B WEDAM
11/17/2017

LALEH AMIRI KORDESTANI
11/17/2017

CLINICAL REVIEW

Application Type	BLA, Original 351(k)
Application Number(s)	761074
Priority or Standard	Standard
Submit Date(s)	11/3/2016
Received Date(s)	11/3/2016
PDUFA Goal Date	9/3/2017
Division / Office	DOP1/OHOP
Reviewer Name(s)	Suparna Wedam, MD Jennifer Gao, MD Lijun Zhang, PhD
Review Completion Date	8/1/2017
Established Name	Trastuzumab-dkst
(Proposed) Trade Name	OGIVRI*
Therapeutic Class	HER2-binding humanized monoclonal antibody
Applicant	Mylan
Formulation(s)	IV
Dosing Regimen	8 mg/kg IV loading dose, then 6 mg/kg IV q3 wks
Proposed Indication(s)	OGIVRI is a HER2/neu receptor antagonist indicated for: • the treatment of HER2-overexpressing breast cancer • the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma
Recommended Indication	OGIVRI is a HER2/neu receptor antagonist indicated for: • the treatment of HER2-overexpressing breast cancer Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

*In this document, FDA generally refers to the Applicant's proposed product by the Applicant descriptor "MYL-1401O".

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1. Recommendations/Risk Benefit Assessment

1.1. Recommendation on Regulatory Action

The biosimilar licensure pathway under section 351(k) of the Public Health Service Act (PHS Act) requires that the proposed biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the proposed biosimilar and reference products in terms of safety, purity and potency. Both parts of the statutory definition need to be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a demonstration that the products are highly similar.

From a clinical standpoint, the data submitted to the 351(k) BLA from the clinical development program of MYL-1401O support a demonstration of no clinically meaningful differences between MYL-1401O and US-licensed Herceptin. A demonstration that MYL-1401O is highly similar to US-licensed Herceptin, notwithstanding minor differences in clinically inactive components together with the clinical data discussed in this review, will support licensure of MYL-1401O as a biosimilar to US-licensed Herceptin under section 351(k) of the PHS Act.

1.2. Risk Benefit Assessment

Breast cancer is the number one cancer in women, with more than 200,000 women newly diagnosed in the United States and about 40,000 women dying of breast cancer annually. (1) HER2 is a tyrosine kinase transmembrane receptor that is amplified in about 20-30% of breast cancers. HER2-positive breast cancer is associated with a more aggressive phenotype.

Gastric cancer is much more common in less-developed countries than it is in the United States today. In 2017, about 28,000 new cases of gastric cancer and 11,000 deaths due to it are estimated in the United States, with about 7-34% of them overexpressing HER2. (2, 3) Known risk factors for gastric cancer are male sex, increasing age, ethnicity, geography, Helicobacter pylori infection, diet, and smoking to name a few. As in breast cancer, HER2 positive gastric cancer has been associated with a more aggressive phenotype and resulting poorer prognosis. (3)

Treatment of HER2 positive breast and gastric cancer with targeted therapy such as trastuzumab has led to significant increases in response rates compared to chemotherapy alone. It is one of the key agents used to target these tumor subtypes throughout the world and thus plays a central role in treatment of patients with breast and gastric cancer.

Testing for HER2 status is commonly performed in all new diagnoses of invasive breast cancer and frequently also tested at the time of recurrence. Targeted therapy such as trastuzumab has led to significant increases in response rates compared to chemotherapy alone. Trastuzumab is FDA approved for the treatment of HER2-overexpressing breast cancer. For the adjuvant treatment of HER2 positive breast cancer, trastuzumab is given for 1 year, in combination with 4-6 cycles of taxane-based chemotherapy. For the treatment of HER2 positive MBC, trastuzumab is FDA approved in combination with paclitaxel for first-line treatment and as single agent for treatment in patients who have received prior chemotherapy for metastatic disease. Pertuzumab (Perjeta) is FDA approved as a front line treatment of HER2 positive MBC in combination with trastuzumab and docetaxel, which was shown to have both a progression free survival (PFS) and overall survival (OS) benefit over trastuzumab and docetaxel alone. (11, 12) For patients who progress on first line treatment, subsequent HER2 targeted treatment options include ado-trastuzumab emtansine (T-DM1, Kadcyla) and lapatinib (Tykerb). For the treatment of metastatic HER2 positive gastric adenocarcinoma, trastuzumab is FDA approved to be used in the first-line setting in addition to chemotherapy with fluoropyrimidine (capecitabine or 5-fluorouracil) and cisplatin.

MYL-1401O is a proposed biosimilar to US-Herceptin (trastuzumab). The Applicant has submitted a BLA for MYL-1401O with proposed indications the same as for US-Herceptin:

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

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

3. Metastatic gastric cancer[1]:

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

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

The clinical team recommends approval of MYL-1401O for the following indications:

Adjuvant Breast Cancer
For adjuvant treatment of HER2-overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer

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

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

Metastatic Breast Cancer

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

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

The results of the clinical development program support a demonstration of no clinically meaningful differences between MYL-1401O and US-Herceptin. The Applicant submitted data from a study assessing MYL-1401O when used as first line treatment in patients with HER2 positive metastatic breast cancer (MBC) in comparison to EU-Herceptin. In the comparative clinical trial, Study 3001 (MYL-Her-3001), the primary endpoint of overall response rate (ORR) ratio as assessed by central review of 1.09 (90% CI: 0.98, 1.22) was within the pre-specified equivalence margin of 0.81 to 1.24.

The Applicant is seeking indications that are the same as those for US-Herceptin. The Applicant has provided the following justification for extrapolation from MBC to adjuvant breast cancer and metastatic gastric cancer:

- The mechanism of action of trastuzumab is the same across all indications as the target receptor involved (HER2) is the same across indications
- The available safety data of US-Herceptin does not indicate that there are any significant differences in expected toxicities for each condition of use and patient population
- There are no toxicities that are related to off-target activities in MBC compared with adjuvant breast cancer or metastatic gastric cancer
- The dose of trastuzumab and route of administration is similar across all indications

- PK results support a demonstration of no clinically meaningful differences between MYL-1401O and US-Herceptin
- Immunogenicity was low and similar between MYL-1401O and EU-Herceptin

The Applicant has provided adequate justification for extrapolation. The Applicant has demonstrated that MYL-1401O is highly similar to US-Herceptin based on extensive analytical data and that MYL-1401O has similar pharmacokinetics effects, immunogenicity, efficacy, and safety which supports extrapolating the data to other indications (adjuvant breast cancer and metastatic gastric cancer). The mechanism of action of trastuzumab is the same across the indications. Therefore, the reviewers consider extrapolation across all indications to be scientifically justified. However, as the gastric cancer indication is protected by orphan drug exclusivity until October 20, 2017, the indication for gastric cancer will not be granted at this time.

The Applicant conducted the following clinical studies to support the application:

- MYL-Her-1002 (PK similarity study)
  Study 1002 (MYL-Her-1002) was a single-center, single-dose, randomized, double-blind, 3-arm parallel-group study investigating the pharmacokinetics of MYL-1401O versus EU-approved
  Herceptin and US-licensed Herceptin as well as EU-approved Herceptin versus US-licensed Herceptin after 8 mg/kg as single dose administered as IV infusion over 90 minutes in healthy male subjects under fasting conditions.

  Other parameters assessed included additional PK assessments for the similarity among MYL-1401O, EU-approved Herceptin, and US-licensed Herceptin along with assessments of safety (including immunogenicity) and local tolerance. The study was conducted in the US and was completed (last subject's last visit) on 27 February 2014.

- MYL-Her-3001 (comparative clinical study)
  Study 3001 (MYL-Her-3001) was a randomized, double-blinded, parallel group two part trial in which patients received either MYL-1401O or EU-Herceptin with either docetaxel or paclitaxel by physician choice every 3 weeks in Part 1. Patients with at least stable disease after Part 1 could continue in Part 2 with maintenance monotherapy therapy every 3 weeks until disease progression or death. Study 3001 was designed as an equivalence trial, with the primary endpoint of overall response rate (ORR) ratio as assessed by central review of 1.09 was within the pre-specified equivalence margin of 0.81 to 1.24 . The ratio of ORR between the two treatment arms was 1.09 with a 90% CI of (0.98, 1.22), which was within the pre-defined equivalence margins of 0.81 and 1.24. Secondary endpoints of time to treatment progression (TTP) and progression free survival (PFS) were similar between both treatment arms (11.1 months in both arms for both endpoints). The OS results are immature at this time as the median as not yet been reached.

The safety findings of 3001 were reviewed, with special focus on cardiac, pulmonary, infusion reaction, and embryo-fetal toxicities. Overall no meaningful differences were found in the safety population.

A scientific bridge between EU-Herceptin, US-Herceptin, and MYL-1401O has been established, based in part on the pharmacokinetic (PK) evaluation in Study MYL-HER-1002 which evaluated the pharmacokinetic (PK) similarities of MYL-1401O, EU-Herceptin and US-Herceptin. The totality of the analytical data supports a demonstration that MYL-1401O and US-Herceptin are highly similar, notwithstanding minor differences in clinically inactive components. The clinical data which includes pharmacokinetics, efficacy, safety, and immunogenicity, supports the finding of no clinically meaningful differences between MYL-1401O and US-Herceptin. Extrapolation for use in all of the proposed indications is justified by the totality of the evidence. Thus, the totality of the evidence supports biosimilarity of MYL-1401O and US-Herceptin.

1.3. Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No clinical postmarket risk evaluation and mitigation strategies are anticipated at this time.

1.4. Recommendations for Postmarket Requirements and Commitments

No PMRs were requested. The clinical team recommends the following Postmarketing Commitment (PMC):

- Submit the overall survival (OS) data and results from Study MYL-Her 3001 "A Multicenter, Double-Blind, Randomized, Parallel-Group, Phase III Study of the Efficacy and Safety of Hercules Plus Taxane Versus Herceptin® Plus Taxane as First Line Therapy in Patients With HER2-Positive Metastatic Breast Cancer"

Rationale: The OS data is important information to follow the long term outcomes with MYL-1401O.

2. Introduction and Regulatory Background

2.1. Product Information

MYL-1401O (proposed trade name Ogivri) is a proposed biosimilar to US-licensed Herceptin (trastuzumab). Trastuzumab is a humanized IgG1 monoclonal antibody of the kappa isotype consisting of two identical glycosylated heavy chains and two identical light chains. The target of trastuzumab is the cell surface human epidermal growth factor receptor 2. HER2 is part of the HER family of transmembrane tyrosine kinases that have been shown to play a role in the regulation of cellular survival, proliferation, adhesion and differentiation.

2.2. Tables of Currently Available Treatments for Proposed Indications

Table 1 below lists the current treatment options for HER2 positive breast and gastric cancer.

Table 1: Summary of FDA Approved Treatments for HER2 Positive Breast and Gastric Cancer

Name	Indication	Approval	Dosing	Efficacy	Safety and Tolerability
Trastuzumab (IV)	HER2 overexpressing breast cancer HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma	1998	Adjuvant breast cancer (52 weeks total): 1) 4 mg/kg load, then 2 mg/kg weekly with taxane, then 6 mg/kg every 3 weeks; 2) after anthracycline-based chemotherapy 8 mg/kg load, then 6 mg/kg every 3 weeks Metastatic breast cancer: 4 mg/kg load, then 2 mg/kg weekly Metastatic gastric cancer: 8 mg/kg load, then 6 mg/kg every 3 weeks	Adjuvant breast cancer: 4 studies showing benefit in DFS and OS with addition of trastuzumab to chemotherapy Metastatic breast cancer: 2 studies showing benefit in TTP and ORR Metastatic gastric cancer: 1 study showing benefit in OS	Cardiomyopathy Infusion reactions Embryo-fetal toxicity Pulmonary toxicity Exacerbation of chemotherapy-induced neutropenia
Pertuzumab (IV)	With trastuzumab and docetaxel for	2012	840 mg load, then 420 mg every 3 weeks	Metastatic breast cancer: 1 study	Left ventricular dysfunction Infusion reaction Diarrhea

	first-line treatment of HER2 positive metastatic breast cancer With trastuzumab and docetaxel as neoadjuvant treatment of HER2 positive, locally advanced, inflammatory, or early breast cancer			showing improvement in PFS and OS Neoadjuvant breast cancer: 2 studies showing improvement in pCR	Embryo-fetal toxicity
Ado-trastuzumab emtansine (IV)	HER2 positive metastatic breast cancer after treatment with trastuzumab and a taxane	2013	3.6 mg/kg every 3 weeks	1 study showing benefit in PFS and OS compared to patients treated with lapatinib and capecitabine	Pulmonary toxicity Infusion reaction Hemorrhage Thrombocytopenia Neurotoxicity Hepatotoxicity Left ventricular dysfunction Embryo-fetal toxicity
Lapatinib (PO)	With capecitabine in patients with advanced/metastatic HER2	2007	Lapatinib 1250 mg daily on days 1-21 in combination with capecitabine	With capecitabine: 1 study showing benefit in TTP	Decreased LVEF Hepatotoxicity Diarrhea Pulmonary toxicity QT prolongation Skin reaction

	positive breast cancer who previously received an anthracycline, a taxane, and trastuzumab With letrozole for postmenopausal women with hormone receptor and HER2 metastatic breast cancer when hormonal therapy indicated		2000 mg/m2/day on days 1-14 in 21 day cycles Lapatinib 1500 mg daily continuously with letrozole 2.5 mg daily	when lapatinib added Hormone receptor positive/ HER2 positive breast cancer: 1 study showing benefit in PFS and ORR	

2.3. Availability of Proposed Active Ingredient in the United States

MYL-1401O is not currently marketed in the United States.

Reference Product:
Herceptin was initially licensed in the United States in September 25, 1998. Subsequently, two additional indications were approved based on supplements to the BLA. The indications for which trastuzumab are licensed are:

- The treatment of HER2 overexpressing breast cancer.
- The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

2.4. Important Safety Issues With Consideration to Related Drugs

Black box warnings from the FDA label for US-Herceptin include cardiomyopathy, infusion reactions, embryo-fetal toxicity, and pulmonary toxicity. Additional warnings and precautions from the FDA label include exacerbation of chemotherapy-induced neutropenia.

2.5. Summary of Presubmission Regulatory Activity Related to Submission

The major clinical regulatory activity with the FDA was as follows:

April 25, 2012: Pre-IND meeting for IND 113682, product Bmab-200, Type B Meeting
- Discussed presentation, data for biosimilarity, evaluation of activity for biosimilarity assessment, viral safety, CMC development and control strategy, and various non-clinical topics.

October 21, 2015: Biologics Product Development, Type 2 Meeting
- Discussed results of MYL-HER-1002 (PK and safety), clinical development plan for MYL-HER-3001, extrapolating results for all FDA approved indications of Herceptin, and that immunogenicity needs to be tested in MYL-HER-3001.

September 1, 2016: Biologics Product Development, Type 2 and 4 Meeting
- Discussed what should be provided in the BLA, the need to include an analytical similarity assessment between MYL-1401O and EU-Herceptin and bridging data to US-Herceptin, quality standards for manufacturing.

November 3, 2016: BLA 761074 submitted to FDA.

2.6. Other Relevant Background Information

None

3. Ethics and Good Clinical Practices

3.1. Submission Quality and Integrity

The overall data quality and integrity are acceptable to the reviewers. The submitted datasets are generally consistent and variables are clearly labeled and or explained. The tumor response datasets included all assessment values and time points. In addition, the Applicant responded to numerous information inquiries in a timely manner and resolved identified issues and/or review questions satisfactorily. Based on the submitted data and reports, the reviewers believe that analyses and results are reliable for regulatory decision making.

3.2. Compliance with Good Clinical Practices

The Applicant stated study 3001 was conducted in compliance with the April 1996 International Council for Harmonisation (ICH) Guidance for Industry E6 Good Clinical Practice (GCP) (including archiving of essential study documents), the 2008 version of the Declaration of Helsinki, the applicable regulations of the countries in which the study was conducted, and with the Commission Directives 2001/20/EC and 2005/28/EC.

The Applicant stated that it and its designees performed quality control checks on this clinical study to assure the accuracy and reliability of study-related data including the selection of qualified Principal Investigators and appropriate study centers, review of protocol procedures with the Principal Investigators and associated personnel, and periodic monitoring visits conducted by the Applicant or Applicant Representative. The Applicant stated a valid Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and relevant regulatory authorities (RA) had to review and approve the protocol before study initiation.

This study was subject to audit by the Applicant or designee at intervals to ensure that the clinical study was conducted and data were generated, documented (recorded), and reported in compliance with the study protocol, ICH GCP E6 consolidated guidelines, and other applicable regulations.

3.3. Financial Disclosures

All investigators were assessed for equity interest, significant payments of other sorts, and other compensation by the Applicant and propriety interest. Financial disclosure information is provided for covered studies MYL-Her-1001, MYL-Her-1002 and MYL-Her-3001. The Applicant has stated that none of the clinical investigators involved with the MYL-1401O studies have financial interests or arrangements to disclose as defined in 21 CFR 54.2(f).

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1. Product Quality

The analytical similarity program consisted of two parts: 1) an analytical comparison between the proposed biosimilar and US-Herceptin to support the demonstration that the products are highly similar, and 2) analytical comparisons between MYL-1401O, US-Herceptin and EU-Herceptin to establish the analytical portion of the scientific bridge to justify the use of clinical and animal data generated using EU-Herceptin as the comparator. The results of the analytical similarity comparison show that for the critical functional assays [binding to human epidermal growth factor receptor 2 (HER2), inhibition of target cell proliferation, and antibody-dependent cellular cytotoxicity (ADCC) activity] MYL-1401O, US-Herceptin, and EU-Herceptin met the pre-defined statistical criteria for analytical similarity. These results support that MYL-1401O and US-Herceptin are highly similar. Minor differences observed in other quality attributes do not preclude a demonstration that MYL-1401O is highly similar to US-Herceptin, as the differences were determined not to have clinical impact. Therefore, the data presented supported both a demonstration that US-Herceptin and MYL-1401O are highly similar and the analytical portion of the scientific bridge between MYL-1401O, US-Herceptin and EU-Herceptin.

Please refer to Dr. Kristen Nickens's review for BLA 761074 for further details.

4.2. Clinical Microbiology

The manufacturing process of MYL-1401O bulk drug substance and drug product aspects were assessed and recommended for approval from a microbial control and microbiology product quality perspective.

Please refer to Dr. Lakshmi Narasimhan's and Maria Candauchacon's review for BLA 761074 for further details.

4.3. Immunogenicity

The incidence of immunogenicity for MYL-1401O and EU-Herceptin was compared in a multiple-dose, parallel-arm study in 493 patients with breast cancer (MYL-HER-3001). The results indicate similar incidence and titers of anti-drug antibodies (ADA) for both products. No apparent impact of ADA on safety, efficacy, or pharmacokinetic endpoints was observed. Therefore, the data indicates that there is no increase in immunogenicity risk for MYL-1401O as compared to EU-Herceptin, which supports the demonstration of no clinically meaningful differences to US-Herceptin.

Please refer to Dr. Brian Janelsins's review for BLA 761074 for further details.

4.4. Preclinical Pharmacology/Toxicology

Two nonclinical animal studies were submitted in support of this BLA: (1) a single-dose comparative pharmacokinetic (PK) study in cynomolgus monkeys comparing MYL-1401O to EU-Herceptin and (2) a 4-week, repeat-dose toxicity and toxicokinetic study in cynomolgus monkeys comparing MYL-14010 to EU-Herceptin. Overall, based on the nonclinical studies provided in this BLA submission, there was no evidence to indicate potential clinical safety concerns associated with MYL-1401O administration. There were no toxicity findings in animals treated with either MYL-1401O or EU-Herceptin. The toxicokinetic profile of MYL-1401O was comparable to that of EU-Herceptin.

Please refer to Dr. Haw-Jyh Chiu's review for BLA 761074 for further details.

4.5. Clinical Pharmacology

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

Please refer to Dr. Brian Furmanski's review for BLA 761074 for further details.

4.5.1. Mechanism of Action

Trastuzumab is a humanized $IgG_1κ$ monoclonal antibody directed against an epitope on the extracellular juxtamembrane domain of HER2. Multiple mechanisms of action have been proposed for trastuzumab, including inhibition of HER2 receptor dimerization, increased destruction of the endocytic portion of the HER2 receptor, inhibition of extracellular domain shedding, and activation of cell-mediated immune defenses such as ADCC activity. Trastuzumab has not been shown to inhibit the dimerization of HER2 with the other isoforms; therefore, signaling through the other three receptor isoforms is maintained in the presence of the antibody. Studies have supported a mechanism by which trastuzumab is bound to the HER2 receptor and taken up by the target cell through endocytosis and subsequently degrades the receptor leading to a downregulation of downstream survival signaling, cell cycle arrest and apoptosis. Trastuzumab has also been shown to block the cleavage/shedding of the HER2 receptor extracellular domain thereby preventing the formation of the activated truncated p95, which has been correlated with a poor prognosis based on the detection of the released extracellular domain of HER2 in the serum of metastatic breast cancer patients. (4, 5, 6)

Please refer to Dr. Brian Furmanski's review for BLA 761074 for further details.

4.5.2. Pharmacodynamics

No pharmacodynamics studies were conducted for this BLA.

4.5.3. Pharmacokinetics

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

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

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

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

Please refer to Dr. Brian Furmanski's review for BLA 761074 for further details.

4.6. Devices and Companion Diagnostic Issues

CDRH was consulted on May 23, 2017 for the product label for BLA 761074 under sections 1.1, 1.2, and 1.3 regarding the statement for the companion diagnostic. The agreed-upon wording regarding a companion diagnostic was "Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product." The Applicant provided an adequate rationale for why the approved companion diagnostics for trastuzumab could serve as a companion diagnostic for MYL-1401O.

5. Sources of Clinical Data

5.1. Tables of Studies/Clinical Trials

A listing of clinical trials applicable to this BLA is provided below in Table 2.

Table 2: Listing of Clinical Trials

Trial	Trial Design	Dosing	Endpoints	Study Duration	Number Patients	Patient Population	Sites
Controlled Studies to Support Efficacy and Safety							
MYL-Her-3001	Randomized Parallel-group	Part 1: MYL-1401O or Herceptin 8 mg/kg IV load, then 6 mg/kg IV q3wks Part 2: monotherapy 6 mg/kg q3wks	Primary endpoint: ORR by central review at week 24	Part 1: 24 weeks Part 2: ongoing After study discontinuation: patients followed for OS every 3 months for 36 months or 240 study deaths	ITT1: 458 (protocol amendment 2) ITT2: 42+458 =500 (protocol amendment 1) Safety: 493	Untreated HER2+ MBC (ultimately no male patients enrolled)	95 sites in 15 countries where pertuzumab was not approved or part of the standard of care
Other pertinent studies							
MYL-Her-1001	Single-center Single-dose Randomized Double-blind, Crossover	8 mg/kg single IV infusion	Primary objective: PK bioequivalence of Bmab-200 and EU-Herceptin	39 weeks	22	Healthy male volunteers	Single center
MYL-Her-1002	Single-center Single-dose Randomized Double-blind 3-arm Parallel-group	8 mg/kg single IV infusion MYL-1401O	Primary objective: PK similarity of MYL-1401O, EU-Herceptin and US-Herceptin	Aug 8, 2013 – Feb 24, 2014	132	Healthy fasting male volunteers	Single center

5.2. Review Strategy

The efficacy review was conducted by Dr. Suparna Wedam, the safety review by Dr. Jennifer Gao and the statistical review was conducted by Dr. Lijun Zhang. The clinical review included the following:

1. Literature review of HER2-positive breast and gastric cancer
2. Research of the FDA data base for regulatory history of the MYL-1401O IND 113682 and review of meeting minutes conducted during drug development
3. Review of Applicant submitted CSR, protocol, protocol amendments, and selected datasets for Study MYL-Her-3001
4. Review of selected case report forms (CRFs) for MYL-Her-3001
5. Review of selected patient narratives for serious adverse events and deaths in MYL-HER-3001
6. Review of response to clinical and biostatistical queries sent to the Applicant
7. Review of consultation reports from the Office of Scientific Investigations
8. Consultation with other disciplines, including CDRH.
9. Review of Herceptin label

5.3. Discussion of Individual Studies/Clinical Trials

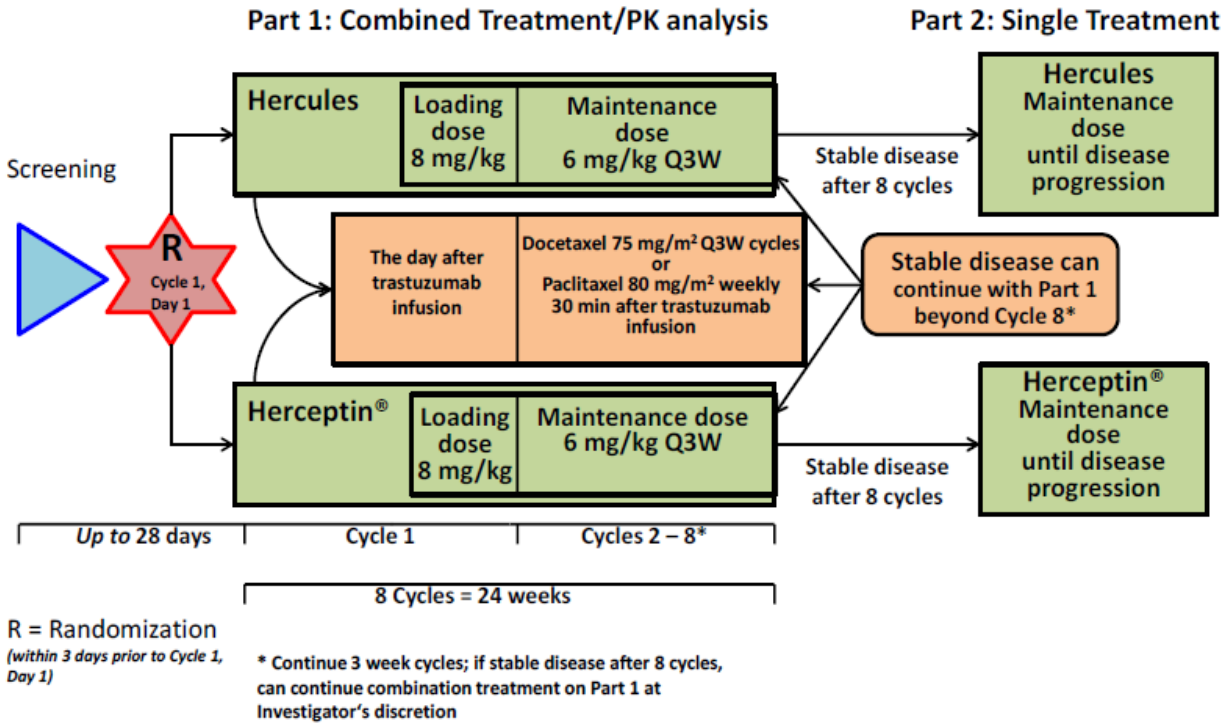
MYL-Her-3001 is a two-part multicenter, double-blind, randomized, parallel-group, confirmatory study. Part 1 looks at the efficacy and safety of MYL-1401O plus docetaxel or paclitaxel versus EU-Herceptin plus docetaxel or paclitaxel in patients with untreated HER2-positive metastatic breast cancer. Patients were randomized 1:1 and stratified by time of tumor progression to metastatic disease from primary diagnosis, ER and PR status, and type of taxane received. Patients with at least stable disease in Part 1 were allowed to continue trastuzumab monotherapy in Part 2.

Part 1: MYL-1401O or EU-Herceptin plus a taxane was given for a minimum of 8 cycles (1 cycle = 3 weeks based on trastuzumab administration). Patients with at least stable disease would progress onto Part 2, where the same single agent trastuzumab was to be administered.

Part 2: All patients who had at least stable disease in Part 1 were to continue with the original trastuzumab agent alone.

The study design is shown in Figure 1 below.

Figure 1: Study 3001 Design



Hercules= MYL-1401O
Source: MYL-Her-3001 Protocol Amendment 6

***Reviewer comment**: The design of the comparative clinical study is acceptable. The metastatic breast cancer population studied and the efficacy endpoint of ORR ratio at 24 weeks is appropriate.*

The schedule of activities for Part 1 is shown in Figure 2 below.

Figure 2: Study 3001 Schedule of Activities for Part 1

Table 1 Schedule of Activities Part 1

GREY FIELDS: To be done PRIOR to dosing at specified time point	Screen.	Part 1 - Combined Treatment: Herceptin® and Taxane[a,d,e]														
		Cycle 1			Cycle 2 W3 Day 22	Cycle 3 W6 Day 43	Cycle 4 W9 Day 64	Cycle 5 W12 Day 85	Cycle 6 W16 Day 106	Cycle 7 W18 Day 127	Cycle 8[12] W21 Day 148	Cycle 9 SD W24[13] Day 169	Cycle XS[14] Every 3 weeks	EOT[c]	EOS[16]	Every 3 mo follow-up to 36 mo
	≤28 days	Day 1	Day 2	Day 8												
Informed consent	X															
Demographic data	X															
Medical and breast cancer history	X															
Physical examination including vital signs	X	X			X	X	X	X	X	X	X	X	X	X	X	
Weight (plus height on W0 only)	X	X			X	X	X	X	X	X	X	X	X			
ECOG performance status	X				X	X	X	X	X	X	X	X	X	X	X	
Tumor burden (RECIST)[1]	X					X		X		X		X	X[15]	X[17]		
CT/MRI of chest and upper abdomen[2]	X					X		X		X		X	X[15]	X[17]		
ECG	X							X				X	X[15]		X	
Left Ventricle Ejection Fraction (LVEF) by ECHO[3] or MUGA	X							X[3]				X[3]	X[15]	X[17]		X[3]
Immunohistochemistry (IHC) and/or fluorescent *in situ* hybridization (FISH)	X															

GREY FIELDS: To be done PRIOR to dosing at specified time point	Screen.	Part 1 - Combined Treatment: Herceptin® and Taxane[a,d,e]														
		Cycle 1			Cycle 2 W3 Day 22	Cycle 3 W6 Day 43	Cycle 4 W9 Day 64	Cycle 5 W12 Day 85	Cycle 6 W16 Day 106	Cycle 7 W18 Day 127	Cycle 8[12] W21 Day 148	Cycle 9 SD W24[13] Day 169	Cycle XS[14] Every 3 weeks	EOT[c]	EOS[16]	Every 3 mo follow-up to 36 mo
	≤28 days	Day 1	Day 2	Day 8												
ER/PgR Determination	X															
Hematology	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation (PT/PTT/INR)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Immunogenicity[4]		X				X		X		X		X	X[15]	X	X	
Dipstick urine analysis	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test (from serum on screening and from urine thereafter)	X	X			X	X	X	X	X	X	X	X	X	X		
Randomization within 3 days prior to Day 1[b]	X															
Samples for C_{min} for all patients[5]		X			X		X		X		X	X				
Samples for C_{max} for all patients[5]		X							X							
Additional samples for PopPK for patients in the PopPK subset[6]			X	X			X									
Sample for exploratory analysis		X														
Samples for soluble ECD fragments		X				X		X		X		X	X[15]	X	X	
Taxane premed according to local SOC[7]		X	X		X	X	X	X	X	X	X	X	X			
Dosing of Herceptin®		X			X	X	X	X	X	X	X	X	X			

GREY FIELDS: To be done PRIOR to dosing at specified time point	Screen.	Part 1 - Combined Treatment: Herceptin® and Taxane[a,d,e]														
	≤28 days	Cycle 1			Cycle 2 W3 Day 22	Cycle 3 W6 Day 43	Cycle 4 W9 Day 64	Cycle 5 W12 Day 85	Cycle 6 W15 Day 106	Cycle 7 W18 Day 127	Cycle 8[12] W21 Day 148	Cycle 9 SD W24[13] Day 169	Cycle XS[14] Every 3 weeks	EOT[c]	EOS[15]	Every 3 mo follow-up to 36 mo
		Day 1	- Day 2	Day 8												
Administration of docetaxel Day 1 or weekly paclitaxel[8]			X		X	X	X	X	X	X	X	X	X			
Adverse events[9]		throughout the study														
Concomitant medication and procedures[10]	throughout the study															
Survival follow-up upon discontinuation of study treatment[11]	throughout the study															X

C_{max} = maximum drug concentration; C_{min} = minimum drug concentration; CT = computed tomography; ECD = extracellular domain (of HER2); ECG = electrocardiogram; ECHO = echocardiogram; EOS = end of study; EOT = end of treatment; ER/PgR = estrogen receptor/progesterone receptor; INR = international normalized ratio; mo = month; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scan; SD= stable disease; SOC = standard of care; PopPK = population pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; Screen. = screening; W = week.

[a] *For all cycle visits there is a grace period of +/- 3 days for scheduling these visits. Study treatment cycles should be scheduled with respect to the previous cycle.*

[b] *Randomization will only be performed upon written informed consent and fulfilling all eligibility criteria and no more than 3 days prior to Cycle 1, Day 1.*

[c] *Do not perform EOT visit at end of Part 1 for patients continuing onto Part 2. EOT should be performed at the time patients discontinue treatment.*

[d] *The following procedures are performed locally throughout the study – hematology, chemistry, coagulation, urinalysis, pregnancy testing.*

[e] *The following procedures are performed centrally throughout the study – Her2, ER/PgR, PK, ECD, immunogenicity, exploratory analysis, ECG.*

1: At baseline, central confirmation of imaging is required prior to randomization. The imaging method used at baseline to assess a specific lesion must be used throughout the study to consistently assess the lesion according to RECIST 1.1 criteria. Activities associated with tumor burden (including bone scan) must be completed within 28 days prior to dosing on Cycle 1, Day 1. If patient screen fails, rescreen must be completed within 42 days of original screening visit date, tumor burden must be completed within 28 days of randomization. Tumor assessments are to be conducted every 6 weeks (± 3 days) independent of delays in treatment administration in Part 1 (up to Cycle 8) and conducted every 12 weeks (± 3 days) independent of delays in treatment administration Cycle 9 and beyond.

2: Except for baseline imaging, to be performed earlier if clinically indicated. CT/MRI of brain for patients with brain involvement and bone scans if bone involvement and can be repeated during the study, if clinically indicated. Contact the Medical Monitor if baseline bone scan has been performed outside the 28 day screening window. Bone scan must be repeated if beyond 42 days from projected Cycle 1, Day 1 visit. Confirmatory x-rays should be obtained at baseline and at each tumor assessment thereafter of lesions on bone scan that are consistent with metastatic disease.

3: ECHO is preferred; same methodology is to be used throughout study. Repeat at least every 3 weeks if 16% absolute decrease in LVEF from pre-treatment levels or LVEF below institutional level of normal and a 10% absolute decrease in LVEF, and also consult with Medical Monitor. ECHO or MUGA to be performed every 6 months after the EOT visit for 24 months.

4: Immunogenicity blood sample collection includes: anti-drug antibody (ADA). If patient develops hypersensitivity reaction, obtain ADA and PK blood sample at the time of reaction.

5: One pre-dose sample (C_{min}) in all patients Cycles 1, 2, 4, 6, 8 and 9; 1 post dose sample Cycle 1 and Cycle 6. If unable to obtain at Cycle 6 sample may be obtained at any Cycle 7 - 9.

6: One post-dose sample (C_{max}) at Cycle 4. In addition to the two random samples at Day 2 and Day 8, two more random samples should be taken at any two unscheduled visits during Cycles 2 - 8. Samples should be taken prior to taxane administration.

7: Premedication according to the local SOC for taxane (see appropriate SmPC for guidance). If to be administered Cycle 1, Day 1 should be administered after Herceptin® infusion is completed.

8: Beginning with Cycle 2, Day 1 and on Day 1 for every cycle thereafter in Part 1; docetaxel or paclitaxel should be administered 30 minutes (± 10 minutes) after completion of the Herceptin or Herceptin® infusion; paclitaxel is given weekly; docetaxel is given on Day 1 only of each cycle. At the discretion of the Investigator, 1 dose of paclitaxel may be omitted every 4 weeks.

9: All SAEs will be recorded from time ICF is signed until EOS visit and should be followed until resolution or deemed stable. Should an Investigator be made aware of any SAE occurring any time after the active reporting period, the SAE (in case of reasonable causality) must be reported to Mylan within 24 hours. AEs will be collected from the first dose of study drug administration until the EOS visit.

10: All medication given within 3 weeks prior to screening and until EOS. All pharmacological and radiological therapy for breast cancer at any time until EOS.

11: Survival follow-up every 3 months by telephone call until death or 36 months from the date of randomization have elapsed. Confirm continued use of contraception at the first 2 contacts for survival follow-up, i.e. 7 months after last dose of blinded trastuzumab.

12. At Cycle 9 patients with at least SD will proceed to Part 2. Patients with disease progression or unacceptable toxicity should proceed to EOT assessments. This decision is based on clinician's decision of local assessments.

13: End of Part 1 assessment Visit.

14: In Cycle XS; X denotes next consecutive numerical cycle, e.g., 10, 11, etc.

15: Perform EOS assessments 28 days (+/- 7 days) after last dose of study treatment.

16: Obtain tumor assessments (RECIST, CT/MRI scan), cardiac function, immunogenicity, and ECD samples at Cycle 13 and every 4 cycles thereafter.

17: Obtain if not performed within prior 6 weeks (2 cycles).

Source: MYL-Her-3001 Protocol Amendment 6

<u>Reviewer Comment:</u> The schedule of activities is appropriate. Cardiac assessment was formed at baseline and every 12 weeks as is the standard of care. Laboratory, EKG, AE, and PK assessments are also appropriate.

<u>Primary Objective</u>

Part 1:

- To compare the independently assessed best overall response rate (ORR) (according to Response Evaluation Criteria in Solid Tumor [RECIST] 1.1 criteria) at Week 24 with MYL-1401O plus taxane versus EU-Herceptin plus taxane in patients who have not received previous first line treatment for HER2+ MBC.

Part 2:

- To descriptively compare the safety, immunogenicity, and tolerability profile of single agent MYL-1401O and EU-Herceptin and; to compare the immunogenicity of MYL-1401O and EU-Herceptin by examining clinical immunogenic response.

Secondary Objectives

Part 1:

- To compare independently assessed clinical activity at Week 24 between treatment arms by measuring: time to tumor progression (TTP), progression-free survival (PFS), and overall survival;
- To descriptively compare the safety, immunogenicity, and tolerability profile of MYL-1401O and EU-Herceptin given in combination with a taxane;
- To compare the populations pharmacokinetic (PopPK) AUC, Cmax, minimum drug concentration (Cmin), clearance, volume of distribution (Vd), and T1/2, profiles of MYL-1401O and EU-Herceptin.

Part 2:

- To compare the clinical activity at Week 48 between treatment arms by measuring: PFS, OS, and duration of response, and OS at 36 months or after 240 deaths, whichever occurs first, as observed from the time of randomization.

Reviewer comment: The objectives are appropriate, with ORR ratio at 24 weeks an appropriate endpoint and agreed upon by the FDA.

Inclusion Criteria

1. ≥18 years of age.
2. Histologically confirmed diagnosis of breast cancer.
3. Locally recurrent or MBC that is not amenable to curative surgery and/or radiation.
4. Documentation of HER2 gene amplification by fluorescent *in situ* hybridization (FISH); as defined by a ratio >2.0) or documentation of HER2-overexpression by immunohistochemistry (IHC) (defined as IHC3+, or IHC2+ with FISH confirmation) based on Applicant-identified central laboratory prior to randomization. Archival tumor tissue samples can be used.
5. Documentation of estrogen receptor/progesterone receptor (ER/PgR) status (positive or negative) based on either a local or central laboratory report must be available before randomization.
6. Pathologically confirmed breast cancer with at least one measurable metastatic target lesion (based on RECIST criteria, Version 1.1). Bone, central nervous system (CNS), and skin lesions, as well as lesions that were irradiated, biopsied or had any form of local intervention or surgical manipulation are only to be assessed as non-target lesions. Baseline imaging studies and submitted for central confirmation of target lesions must have been performed in the 4 weeks preceding randomization.
7. Patients with a history of CNS metastases or cord compression are eligible if they have been successfully treated and are off steroids for at least 4 weeks before first dose of

investigational product. Patients with newly detected CNS metastases must be successfully treated (e.g., radiotherapy, stereotactic radiosurgery) before being considered for the trial. Patients with known or suspected brain metastases must undergo a baseline brain computed tomography (CT) or magnetic resonance imaging (MRI).

8. Patients previously treated with trastuzumab or lapatinib in the adjuvant setting are allowed if metastatic disease was diagnosed at least one year after the last dose of treatment.
9. Prior treatment with hormonal agents or bisphosphonates/denosumab is allowed. Bisphosphonates/denosumab can be given simultaneously with study treatment but cannot start after randomization and is considered an indication of progressive disease (PD). Hormonal agents must be discontinued prior to beginning study therapy.
10. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 - 2.
11. Screening laboratory values within the following parameters:
    - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L (1500/mm^3).
    - Platelet count ≥100 x 10^9/L (100,000/mm^3).
    - Hemoglobin ≥9.0 g/dL (90 g/L), without a prior transfusion in the last 2 weeks.
    - Serum creatinine ≤1.5 x upper limit of normal (ULN).
    - Total bilirubin ≤1.0 x ULN (>1 ULN if documented Gilbert's disease).
    - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤2.5 x ULN.
    - AST and/or ALT <1.5 x ULN, if alkaline phosphatase > 2.5 x ULN.
    - Alkaline phosphatase >2.5 x ULN, if bone metastases present and no liver dysfunction present.
12. Left ventricular ejection fraction (LVEF) within institutional range of normal as measured by multiple gated acquisition scan (MUGA) or echocardiogram (ECHO).
13. The patient is willing to comply with the protocol and procedures for the duration of the study, including all scheduled visits and examinations.
14. The patient is either not of childbearing potential or is willing to practice birth control by using two different highly effective methods of contraception, or abstain from sexual intercourse for the duration of the study and follow-up. In particular, patients of childbearing potential must:
    - Female patients are to use a method which results in less than 1% failure rate per year when used consistently and correctly such as implants, injectables, combined oral contraceptives, intrauterine devices, sexual abstinence, or vasectomized partner. Have a negative human chorionic abstinence, or vasectomized partner. Have a negative human chorionic on Day 1.
    - Male patients without vasectomy are required to use a condom with spermicide and their female partner to use another form of contraception.
15. Written informed consent signed by the patient or her legal representative (if patient is unable to provide) prior to any study-related procedures not standard of care.

Exclusion Criteria

1. Prior systemic therapy in the metastatic disease setting. This includes: chemotherapy, signal transduction inhibitors (e.g., lapatinib), HER2 targeted therapy (e.g., trastuzumab), or other investigational anticancer therapy.
2. Prior treatment with neoadjuvant or adjuvant anthracyclines with a cumulative dose of doxorubicin of >400 mg/m^2, epirubicin dose >800 mg/m^2.
3. Participation in the active treatment phase of an investigational drug study ≤28 days prior to randomization.
4. Patients with bone or skin as the only site of disease. Patients with skin lesions measurable by CT scans or MRI as only site of measurable disease are allowed.
5. Surgery or radiotherapy ≤2 weeks preceding Day 1. Target lesions have to be outside the irradiated fields and the patient has fully recovered from surgery or radiotherapy.
6. Association criteria, history of myocardial infarction <1 year from randomization, clinically significant valvular disease, serious cardiac arrhythmia requiring treatment, uncontrolled hypertension or known pulmonary hypertension.
7. Peripheral sensory or motor neuropathy Grade 2 or higher according to the National Cancer Institute-Common Terminology Criteria (NCI-CTC) Version 4.03.
8. Any other cancer, including contralateral breast cancer, within 5 years prior to screening with the exception of adequately treated ductal carcinoma *in situ*, adequately treated cervical carcinoma *in situ*, or adequately treated basal or squamous cell carcinoma of the skin.
9. Immunocompromised patients, including known seropositivity for human immunodeficiency virus, or current or chronic hepatitis B and/or hepatitis C infection (as detected by positive testing for hepatitis B surface antigen or antibody to hepatitis C virus with confirmatory testing).
10. Patients with documented severe hypersensitivity reaction to trastuzumab, paclitaxel, docetaxel or excipients used in their formulations, including murine protein remnants and patients with heredity fructose intolerance.
11. Evidence of significant medical illness or abnormal laboratory finding (including dyspnea at rest or serious pulmonary illness) that, in the Investigator's judgment, will substantially increase the risk associated with the patient's participation in, and completion of, the study, or could preclude the evaluation of the patient's response.

Reviewer Comment: ***The inclusion and exclusion criteria are appropriate. Of note, including patients with HER2 positive MBC for first line therapy only occurred after adopting Amendment 2 to the protocol.***

Drug Administration

Part 1: Trastuzumab was to be given at a loading dose of 8 mg/kg IV over 90 min, followed by 6 mg/kg IV over 30 min every 3 weeks for 8 cycles (24 weeks). If a patient missed a dose of study treatment by more than 1 week, a re-loading dose of 8 mg/kg was to be given over 90 minutes,

unless cardiotoxicity was the reason for dose delay. For patients receiving docetaxel, it was to be given at 75 mg/m2 of BSA IV over 1 hour on day 1 of a 3 week cycle for 8 cycles, except for cycle 1 when docetaxel was to be administered on day 2 of the cycle. For patients receiving paclitaxel, it was to be given at 80 mg/m2 weekly over 1 hour except for week 1 when paclitaxel to be administered 24 hours after trastuzumab infusion has completed. The investigator had the discretion to omit 1 administration of paclitaxel every 4 weeks.

Part 2: All patients with at least stable disease in Part 1 were to continue with the trastuzumab product they were originally allocated to until disease progression, discontinuation, or death. Tumor assessments were to be conducted every 12 weeks independent of treatment delays.

Dose Modifications

Trastuzumab: for infusion reactions, the infusion rate should be decreased or the infusion should be temporarily interrupted. For cardiac dysfunction, trastuzumab might either be held or discontinued and consultation with a cardiologist might be warranted.
Docetaxel: only one dose reduction to 60 mg/m2 is allowed for any reason.
Paclitaxel: only one dose reduction to 70 mg/m2 is allowed for any reason.

Statistical Analysis Plan

Sample Size: The primary efficacy endpoint was ORR at Week 24 (Part 1). To provide at least 80% power to demonstrate equivalence between MYL-1401O and EU-Herceptin on the primary ORR analysis (ratio of ORR) with the pre-defined equivalence margin of (0.81, 1.24), a sample size of 410 patients (205 per treatment group) was required. Accounting for a 10% attrition rate, the sample size was increased to 456. This sample size calculation assumed that the ORR would be approximately 69% in both treatment arms and the ORR ratio of MYL-1401O to EU-Herceptin was to be analyzed with a two-sided 90% CI (i.e., alpha controlled ≤ 0.05). If the 90% CI completely falls in an equivalence region defined as 0.81-1.24, then equivalence would be declared. The equivalence region was derived using a fixed-effect meta-analysis of historical trastuzumab trials to estimate the treatment effect of trastuzumab with taxane versus taxane alone.

Equivalence Margin: Fifteen relevant trials were reviewed, from which 3 trials proved to be appropriate as randomized trials comparing taxane and trastuzumab combination versus taxane alone. The meta-analysis was conducted using only the IHC3+ and/or FISH positive patient populations in order to be consistent with the current study population. The p-value for the heterogeneity test among the three selected trials was 0.297, indicating that the heterogeneity among the three studies in the meta-analysis was not significant. Hence, a fixed-effects approach was used for the meta-analysis which included only the IHC3+ and/or FISH positive patient populations in the selected trials. The treatment effect of trastuzumab in each historical trial and the results of meta-analysis are summarized in Table 3.

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

Trial[a]	Trastuzumab + Taxane	Taxane	ORR Ratio[b]
	ORR (n/N)	ORR (n/N)	95% CI
Gasparini (9)	85% (33/39)	48% (20/42)	1.78 (1.26, 2.51)
Marty (10)	61% (56/92)	34% (32/94)	1.79 (1.29, 2.48)
Slamon (11)	49% (33/68)	17% (13/77)	2.87 (1.65, 5.00)
Meta-Analysis (Fixed-effect model)			1.92 (1.54, 2.39)

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

From the meta-analysis, the estimated treatment effect (ORR ratio, trastuzumab + taxane vs. taxane) and its 95% CI was 1.92 (1.54, 2.39). Fifty percent of the lower bound of the 95% CI (i.e., 1.54) in natural log scale was calculated as 1.24. This value was used as the upper bound of the equivalence region in study MYL-HER3001. The lower bound of the equivalence region was set as 0.81 (i.e., 1/1.24=0.81). The equivalence region (0.81, 1.24) is symmetrical on the natural log scale.

***Reviewer comment*: In deriving the margin for an equivalence trial, several general points need to be considered. First, as per the FDA guidance for industry titled Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, a comparative clinical trial would be needed to resolve any residual uncertainties rather than demonstrating efficacy. Second, the equivalence margin is to assess whether there are clinically meaningful differences between the two products. Third, the equivalence trial needs to be feasible and the sample size is not based on establishing efficacy. The equivalence margin of 0.81-1.24 has been agreed upon by the FDA.**

Analysis Population: The intention to treat (ITT) population included all randomized patients. The safety population (SAF) was all patients who received at least 1 dose of MYL-1401O or EU-Herceptin. The pharmacokinetic population (PK) was all randomized patients who received at least one dose of MYL-1401O or EU-Herceptin and provided at least one post-dose sample for PK analysis. Primary efficacy analysis was based on the ITT population of patients who were randomized into the study under Amendment 2 and beyond and was called the ITT population #1 (ITT1). The ITT population #2 (ITT2) included all randomized patients and also was referred as the full ITT set. Primary safety analysis was based on the safety population. The per-protocol population was a supportive analysis population for efficacy, and it was defined as a subset of ITT1 who met the following additional criteria:

- Received the treatment to which they were randomized,
- The absence of any major protocol violations in Part 1 which precluded the evaluation of the patient

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

Primary efficacy analysis: The ratio of the best ORR at Week 24 was to be compared using H0: RT / RC ≤0.81% or RT / RC ≥1.24 and H1: 0.81 <RT / RC <1.24 (RT= ORR of MYL-1401O, RC= ORR of EU-Herceptin). Equivalence would be declared if the two-sided 90% CI for the ratio of the ORR is completely within the equivalence range of 0.81-1.24.

Secondary efficacy analyses:

- TTP: TTP was defined as time from randomization to the date of first documentation of objective progression. Patients last known to be 1) alive, 2) on treatment or within 28 days after discontinuation of treatment, and 3) progression-free were to be censored at the date of the last objective disease assessment that verified lack of disease progression. Patients with no disease assessments or inadequate baseline disease assessments were to be censored at the start date. Patients who died prior to objective progression while on treatment were to be censored at the date of last objective tumor assessment prior to death. Patients with at least one on-study disease assessment who discontinued treatment without disease progression were to be censored at the date of the last objective disease assessment. Patients with documentation of progression after an unacceptably long interval (2 or more missed or indeterminate assessments) since the last tumor assessment were to be censored at the time of last objective assessment without progression before the missing assessments. TTP was to be compared using a log-rank test, and the estimation of TTP curves for the two treatment groups was to be generated using the Kaplan-Meier method. The hazard ratio with a two-sided 95% confidence interval was derived from a Cox proportional hazards model adjusted for stratification. The analysis was to be performed at weeks 24 and 48 for Parts 1 and 2 of the ITT1 population.

- PFS: PFS was defined as time from randomization to first documentation of objective progression or death due to any cause. Patients last known to be 1) alive; 2) on treatment or within 28 days of discontinuation of treatment; and 3) progression-free were to be censored at the date of the last objective disease assessment that verified lack of disease progression. Patients with inadequate baseline disease assessment were to be censored at the start date. Patients with no on-study disease assessments were to be censored at the start date unless death occurred prior to the first planned assessment, in which case the death was an event. Patients with at least one on-study disease assessment who discontinued treatment without documented disease progression and without death were to be censored at the date of the last objective disease assessment (with objective status CR, PR or Stable). Patients with documentation of progression or death after an unacceptably long interval (2 or more

missed or indeterminate assessments) since the last tumor assessment were to be censored at the time of last objective assessment without progression. PFS was to be analyzed the same way as TTP.

- OS: OS was defined as the time from date of randomization to date of death due to any cause. Patients last known to be alive were censored at date of last contact. OS was to be analyzed the same way as TTP. OS was to be analyzed at weeks 24 and 48 for Parts 1 and 2, and the final analysis of OS will be performed at 36 months or after 240 deaths, whichever occurs first.

- DR: DR was defined as the time from the first documentation of objective response until the date of first documentation of objection progression or death due to any cause. DR was to be analyzed the same way as PFS at week 48 only and only responders were included in the analysis.

Sensitivity analyses: Sensitivity analyses were to performed on the primary endpoint of ORR based on investigator assessments, Cochran-Mantel-Haenszel analysis, logistic regression, and in the PP and full ITT populations.

Population pharmacokinetics: The similarity of the PKs of MYL-1401O and EU-Herceptin was to be analyzed using graphical exploration, structural pharmacokinetic model, models for inter-individual and residual variability random effects, covariate model, and maximum likelihood parameter estimation.

Independent Review Charter

(b) (4) is a subsidiary of (b) (4) and has a contractual agreement with (b) (4) to provide the independent assessment of imaging studies and clinical data for MYL-Her-3001 (3001). A minimum of 3 qualified, board-eligible radiologists and 1 board-eligible oncologist were assigned to independently review imaging and clinical data to assess the overall tumor response at each time point using RECIST 1.1. A summary of how each independent review was conducted is as follows:

1. Radiology Review:
    a. Primary review: an independent radiologist assesses the images for any given patient at any given time point to determine overall tumor response per RECIST 1.1. The radiologist will be blinded. Each imaging will be reviewed by two radiologists.
    b. Global review: after the primary radiologist has completed their review, the same primary radiologist will look at all images from all time points for the subject and has the option of updating their previous time point overall tumor assessment per RECIST 1.1
    c. Adjudication review: adjudication is required if the radiologists disagree on the results of the global review. The adjudicator is a radiologist who did not participate

in the primary or global review for the patient. This adjudicator will choose the radiologist with whose global review they agree the most and provide justification for this. The adjudicator's assessment will then be considered the final radiology assessment for the patient.

2. Oncology Review: 1 independent oncologist will review the results of the RECIST 1.1 radiology review as well as all clinical data and provide a global determination of best overall response, date of first documentation of response, type of first response, and date of progression.

Protocol Amendments

The following protocols were available for review:

- Original protocol, V1.0, Feb 7, 2012
- Amendment 1, V2.0, July 2, 2012 – initially allowed recruitment of patients receiving trastuzumab as first and second line treatment for MBC, 42 patients randomized
- Amendment 2, V5.0, October 11, 2013 – after meeting with regulatory agencies, amendment 2 limited recruitment to patients receiving trastuzumab as first-line treatment to increase the homogeneity of the study population and reliability of the study results and to more closely reflect the standard of care. These patients who are treated first-line are in the ITT1 population and primary efficacy analysis was performed on this population. The ITT2 population consists of all randomized patients including the 42 patients enrolled under amendment 1. The SAP also includes sensitivity analyses on ITT2.
- Amendment 3, V6.0, May 28, 2014: France only
- Amendment 4, V7.0, July 15, 2014: Greece only
- Amendment 5, V8.0, Aug 19, 2014: France only
- Amendment 6, V9.0, April 10, 2015: Global Amendment

6. Review of Efficacy

Efficacy Summary

The results of Study 3001 support the determination of no clinically meaningful differences between MYL-1401O and US-Herceptin. The results of the clinical development program (including Study 3001) indicate that the Applicant's data support a determination of no clinically meaningful differences between MYL-1401O and US-Herceptin in terms of efficacy in the indication studied. Specifically, the 90% confidence intervals for the overall response rate ratio between MYL-1401O and EU-Herceptin in Study 3001 are within the equivalence margins. A scientific bridge between EU-Herceptin, US-Herceptin, and MYL-1401O has been established based in part on pharmacokinetic (PK) evaluation.

6.1. Indication

The Applicant proposed indications are the same as those for US-licensed Herceptin.

6.2. Methods

Similarity in clinical efficacy was assessed in Study 3001 comparing MYL-1401O with EU-Herceptin in patients with MBC. The primary efficacy analysis was based on the ratio of objective response rate by week 24 per central review in the ITT1 population. Sensitivity analyses were performed as appropriate. Recalculating of the primary and secondary efficacy endpoints was conducted from the submitted datasets. Analyses of the primary endpoint, secondary endpoints, and safety are included in this review.

6.3. Demographics

This was an international study with patients enrolled from 15 countries in the ITT1 population as seen in Table 4.

Table 4: Study 3001 Enrollment by Country for ITT1 Population

Country	MYL-1401O + Taxane N=230 n (%)	EU-Herceptin + Taxane N=228 n (%)
Russia	73 (31.7)	71 (31.1)
India	31 (13.5)	24 (10.5)
Ukraine	28 (12.2)	24 (10.5)
Georgia	23 (10)	26 (11.4)
Philippines	18 (7.8)	30 (13.2)
Thailand	23 (10)	16 (7.0)
Poland	6 (2.6)	13 (5.7)
Hungary	8 (3.5)	5 (2.2)
South Africa	3 (1.3)	8 (3.5)
Romania	5 (2.2)	3 (1.3)
Latvia	2 (0.9)	4 (1.8)
Chile	4 (1.7)	1 (0.4)
Serbia	2 (0.9)	3 (1.3)
Slovakia	1 (0.4)	2 (0.9)
Czech Republic	1 (0.4)	0 (0)

Source: Study 3001 adsl.xpt

Reviewer Comment: ***Patients were enrolled from 16 countries in the ITT2 population (there were two patients enrolled in Bulgaria that were not part of the ITT1 population). The top five countries for enrollment were Russia, India, Ukraine, Georgia and Philippines. There were no patients enrolled from the United States as this study was conducted in countries where trastuzumab+taxane was considered an acceptable first line treatment in patients with HER2+ MBC. First line treatment for patients with HER2+ MBC in the United States is considered to be trastuzumab+pertuzumab+taxane therapy based on the overall survival***

benefit seen in the CLEOPATRA study.

Table 5: Demographic Characteristics for Study 3001 in ITT1 Population

Demographic Parameters	MYL-1401O + Taxane N = 230 n (%)	EU-Herceptin + Taxane N = 228 n (%)
Sex		
Female	230 (100)	228 (100)
Age		
Mean (SD)	54.3 (10.97)	52.9 (11.22)
Median (years)	55	54
Age Group		
≥ 17 - < 65 years	186 (80.9)	195 (85.5)
≥ 65 - < 75 years	37 (16.1)	26 (11.4)
≥ 75 years	7 (3.0)	7 (3.1)
Race		
Caucasian	159 (69.1)	154 (67.5)
Asian	70 (30.4)	72 (31.6)
Black	1 (0.4)	2 (0.9)
Geographic region:		
Africa	5 (2.2)	5 (2.2)
Asia pacific	45 (23.9)	45 (23.9)
Latin America	1 (0.4)	1 (0.4)
North America	0	0
Eastern Europe	77 (33.5)	77 (33.5)
Western Europe	0	0

Source: Study 3001 adsl.xpt, abdh.xpt; Study MYL-HER-3001 CSR page 102

Reviewer Comment: ***Baseline patient demographics were well balanced between the two arms. All patients were female and a majority of patients were Caucasian.***

Table 6: Baseline Disease Characteristics for Study 3001 in ITT1 Population

	MYL-1401O + Taxane N = 230 n (%)	EU-Herceptin + Taxane N = 228 n (%)	Total N=458 n (%)
Measurable disease (by investigator)			
Yes	230 (100)	228 (100)	458 (100)
ER Status			
Positive	102 (44.3)	101 (44.3)	203 (44.3)
Negative	128 (55.7)	127 (55.7)	255 (55.7)
HER2 status			
Positive	229 (99.6)	227 (99.6)	456 (99.6)
Negative	1 (0.4)	0	1 (0.2)
Equivocal	0	1 (0.4)	1 (0.2)
Time to metastatic disease			
< 2 years	146 (63.5)	153 (67.1)	299 (65.3)
≥ 2 years	75 (32.6)	71 (31.1)	146 (31.9)
Missing	9 (3.9)	4 (1.8)	13 (2.8)
ECOG Performance Status			
0	112 (48.7)	97 (42.5)	209 (45.6)
1	113 (49.1)	127 (55.7)	240 (52.4)
2+	5 (2.2)	3 (1.3)	8 (1.7)
Missing	0	1 (0.4)	1 (0.2)
Visceral disease			
Yes	172 (74.8)	185 (81.1)	357 (77.9)
Number of metastatic sites			
1	58 (25.2)	61 (26.8)	119 (26)
2	87 (37.8)	67 (29.4)	154 (33.6)
3	44 (19.1)	57 (25)	101 (22.1)
≥4	41 (17.8)	43 (18.9)	84 (18.3)

Source: Study 3001 abdh.xpt and adsl.xpt

***Reviewer Comment:** There was a difference (≥5%) in baseline characteristics between treatment arms regarding ECOG performance status, presence of baseline visceral disease and number of baseline metastatic sites. This difference is unlikely to have affected the efficacy results.*

Table 7: Prior Anti-Neoplastic Therapy

	MYL-1401O + Taxane N = 230 n (%)	**EU-Herceptin + Taxane N = 228 n (%)**
Previous trastuzumab therapy: Yes	22 (9.6)	16 (7)
Previous taxane therapy: Yes	46 (20)	42 (18.4)
Previous lapatinib therapy: Yes	2 (0.9)	1 (0.4)
Prior hormonal therapy: Yes	47 (20.4)	43 (18.9)

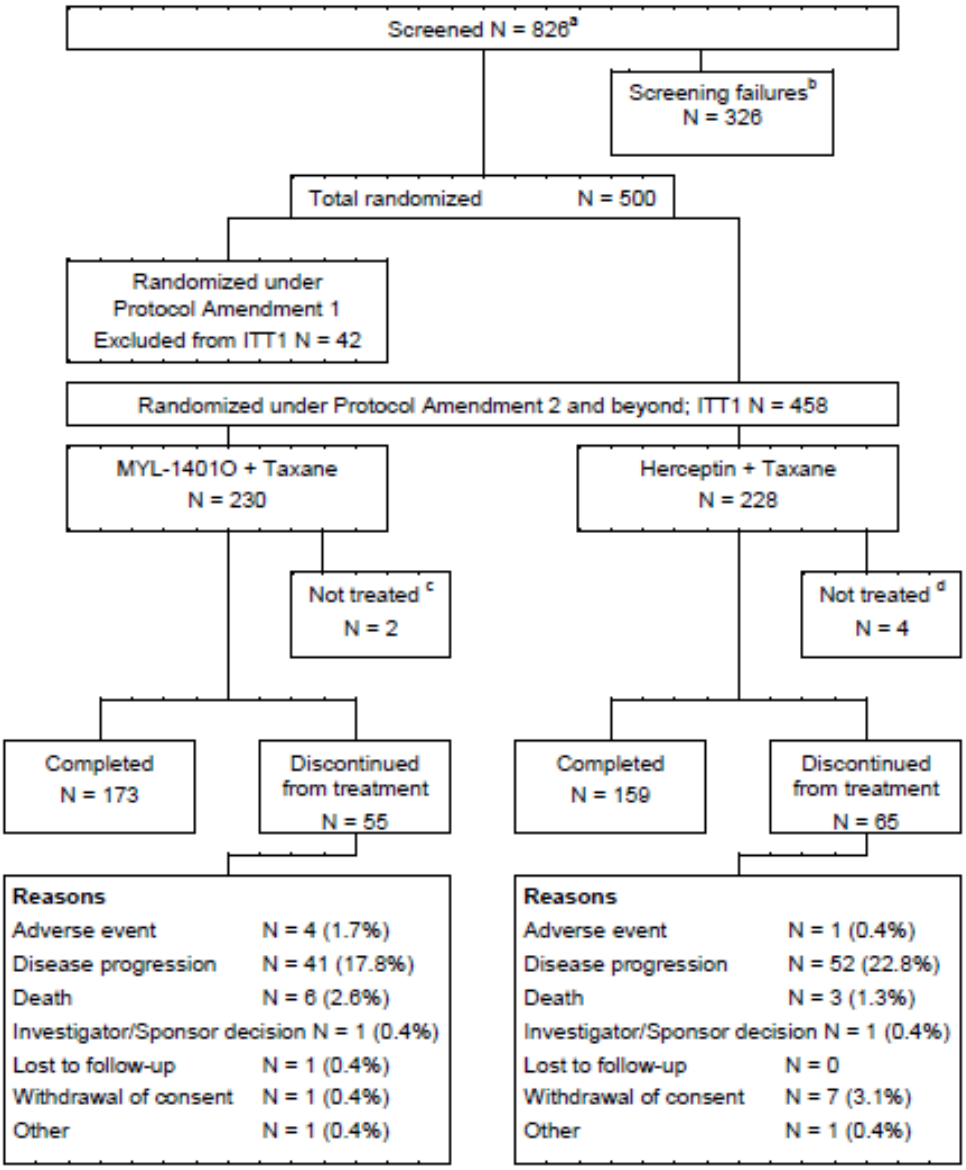
Source: Study 3001 abdh.xpt

Reviewer Comment: ***Prior therapy was similar between the two treatment arms.***

6.4. Subject Disposition

The most common reasons for failing screening included: lack of confirmation of HER2 positivity, lack of measurable disease according to the RECIST criteria and violation of laboratory parameters at screening. In total, 500 women were randomized onto study from 95 sites in 16 countries. Two hundred forty nine patients were randomized to the MYL 1401O arm and 251 patients were randomized to the EU-Herceptin arm.

Figure 3: Patient Disposition Study 3001



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.
[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).
Source: Table 14.1.1.1a, Table 14.1.1.3a, Listing 16.2.1.3a

Source: Study 3001 CSR page 97

Reviewer Comment: ***Although 500 patients were enrolled onto study, the ITT1 population consisted of a total of 458 patients (230 in the MYL-1401O arm and 228 in the EU-Herceptin arm) who were randomized into the study under Protocol Amendment 2 and beyond. Thus, only patients who received trastuzumab (MYI-1401O or EU-Herceptin) as first-line treatment were included in the primary ITT1 analysis. All analysis populations are shown in Table 8. Treatment was discontinued in 18.9% of patients in the MYL-1401O arm and in 23.1% of patients in the EU-Herceptin arm, with disease progression being the most common reason.***

Table 8: Analysis Populations for Study 3001

	MYL-1401O+taxane N=249 (%)	**EU-Herceptin+taxane N=251 (%)**
All Randomized patients	249 (100)	251 (100)
ITT1 population	230 (92.4)	228 (90.8)
ITT2 population	249 (100)	251 (100)
FDA's PP population	223 (89.6)	216 (86.1)
Safety population	247 (99.2)	246 (98)

Source: Edited from Table 12 Study 3001 CSR page 102
ITT=intent-to-treat; PP=per protocol

Reviewer Comment: The patients included in the per protocol (PP) population are slightly different between the Applicant's analysis and FDA's analysis (see Table 9). The FDA's analysis followed the pre-specified rules of PP population definition. In the efficacy results section, all analyses in the PP population are based on the FDA's PP population.

Protocol Violations/Deviations

The most common major protocol deviation reported for both treatment arms in the ITT1 population was "Failure to comply with Protocol Schedule of Activities and/or processes".

Table 9 lists the protocol deviations leading to exclusion from the PP population.

Table 9: Protocol Deviations Leading to Exclusion from the PP Population, FDA's Analysis

	MYL-1401O+taxane N=7	EU-Herceptin+taxane N=12
No measurable disease at baseline	1	0
HER2 negative at randomization	1[1]	0
Baseline CT scan 6 days after C1D1	1	0
With contralateral breast cancer	1	0
With >42 days between doses	0	1
Received prior chemo for breast cancer	0	1
Received prohibited medication	1	1
Received radiotherapy	0	1
No post-baseline tumor assessment[2]	3	8

[1] The patient with Her2 negative MBC also had no post-baseline tumor assessment; therefore, this patient is included in both categories.
[2] Includes patients randomized but not treated.
Source dataset: Study 3001 adrs.xpt

Reviewer Comments: ***Protocol deviations leading to exclusion from the PP population were few and unlikely to have a meaningful impact on the efficacy analysis. ORR results observed from the PP population in which patients with major protocol deviations were excluded are consistent to those from the primary analysis population.***

6.5. Analysis of Primary Endpoint(s)

Overall response rate (ORR) per central review at week 24 was the primary efficacy endpoint of Study 3001. The primary analysis of ORR was based on the ratio of ORRs between the MYL-1401O and EU-Herceptin in the ITT1 population. The results of the primary analysis are summarized in Table 10.

Table 10: Study 3001 ORR per Central Review at Week 24, ITT1 Population

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

**N/A=Not applicable; Includes patients that died before assessment, patients with no measurable disease, and patients with data not adequate for assessment per central review*
Source: Response to Information Request dated 4/27/2017 and study 3001 dataset adrs.xpt

Reviewer Comments: ***The ratio of ORR between the two treatment arms was 1.09 with a 90% CI of (0.98, 1.22), which was within the pre-defined equivalence margins of 0.81 and 1.24. The difference in ORR between the two arms was 6.0% (95% CI: -1.3%, 13.2%). ORR per central review at week 24 was also evaluated in the PP population. The ORR was 71% in the MYL-1401O arm and 67% in the EU-Herceptin arm. The ratio of ORR is 1.06 (90% CI: 0.96, 1.18). The ratio was within the pre-defined equivalence margins. Results from the PP population are consistent with those from the ITT1 population.***

One patient in the MYL-1401O arm with no measurable disease at baseline was determined as a complete responder per central review of non-target lesions. This patient was considered as a complete responder in the FDA's analysis (as shown in the Table above) but not in the Applicant's primary analysis as shown in Study 3001 CSR. This has been communicated with the Applicant during the BLA review.

Sensitivity Analyses for ORR

Results of ORR sensitivity analyses conducted by the FDA are shown in Table 11.

Table 11: Study 3001 Sensitivity Analyses of ORR at Week 24

	MYL-1401O + Taxane	EU-Herceptin + Taxane	ORR RR (90% CI)
	#of responders/# of pts (ORR%)	#of responders/# of pts (ORR%)	
ORR per central review, PP population	159/223 (71%)	145/216 (67%)	1.06 (0.96, 1.18)
ORR per central review, ITT2 population	170/249 (68%)	160/251 (64%)	1.07 (0.96, 1.19)
ORR per INV, ITT1 population	163/230 (71%)	147/228 (64%)	1.10 (0.99, 1.22)
ORR per INV, PP population	160/223 (72%)	146/216 (68%)	1.06 (0.96, 1.18)
ORR per INV, ITT2 population	173/249 (70%)	161/251 (64%)	1.08 (0.98, 1.20)

Note: The PP population analyses are based on FDA's PP population
Source: Study 3001 dataset adrs.xpt

Reviewer Comment: ***Results of ORR sensitivity analyses per central review or investigator assessment in different analysis populations are consistent with the primary findings.***

6.6. Analysis of Secondary Endpoints(s)

Secondary endpoints included TTP, PFS, and OS at Week 24 and Week 48 and duration of response at Week 48 for the ITT1 population.

Time to Progression (TTP)

Time to progression was analyzed twice: at week 24 cutoff and at week 48 cutoff. Table 12 shows TTP per central review at Week 24 and Week 48 for the ITT1 population. As of Week 48 cutoff time, 95 patients (41%) in the MYL-1401O arm and 98 patients (43%) in the EU-Herceptin arm had tumor progression. The Kaplan-Meier plot for TTP at Week 48 is shown in Figure 4. The hazard ratios of MYL-1401O vs. EU-Herceptin were 0.94 (unstratified) and 0.92 (stratified) in the Week 48 analysis.

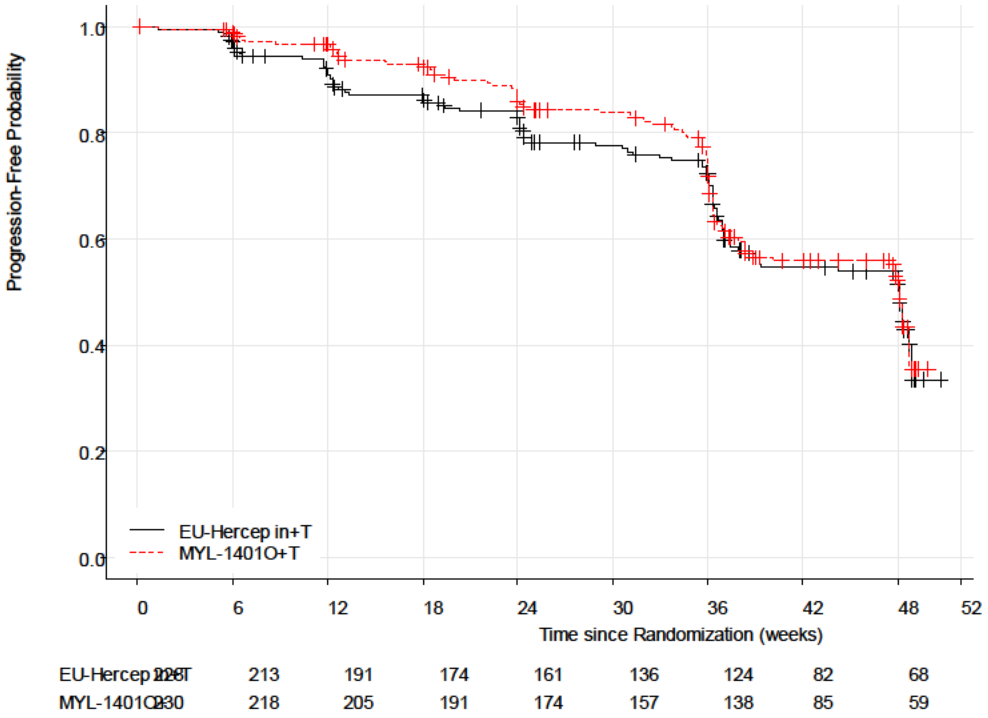
Table 12: Study 3001 Results of TTP per Central Review, ITT1 Population

PFS	**MYL-1401O + Taxane (N=230)**	**EU-Herceptin + Taxane (N=228)**
Part 1 (week 24)		
Number of Progression	35 (15%)	44 (19%)
Median (95% CI), months	NR	NR
Unstratified HR (95% CI)	0.74 (0.48, 1.16)	
Stratified HR (95% CI)*	0.70 (0.45, 1.11)	
Part 2 (week 48)		
Number of Progression	95 (41%)	98 (43%)
Median (95% CI), months	11.1 (8.8, 11.2)	11.1 (8.9, 11.2)
Unstratified HR (95% CI)	0.94 (0.71, 1.25)	
Stratified HR (95% CI)*	0.92 (0.69, 1.23)	

*Stratified by assigned taxane, time of tumor progression to metastatic disease from primary diagnosis, and tumor endocrine status. Eighteen patients with one or more stratification factor data missing in CRFs were not included in the stratified analysis.
NR=Not Reached
Source: Study 3001 CSR Table 21 and Week 48 CSR update Table 22; study 3001 dataset adtte.xpt

Reviewer Comment: ***At Week 48 cutoff, hazard ratio of TTP was close to 1. There was no apparent difference in TTP between the two arms.***

Figure 4: Kaplan-Meier Curves of TTP per Central Review by Week 48, in the ITT1 Population



Source: Study 3001 Week 48 CSR update Figure 5 and study 3001 week 48 update dataset adtte.xpt

Progression-Free Survival (PFS)

Progression-free survival was analyzed twice: at week 24 cutoff and at week 48 cutoff. Table 13 shows PFS per central review at Week 24 and Week 48 for the ITT1 population. As of Week 48 cutoff time, 102 patients in each arm had either progression or died. Kaplan-Meier plot for PFS at Week 48 is shown in Figure 5. The hazard ratios of MYL-1401O vs. EU-Herceptin were 0.97 (unstratified) and 0.95 (stratified) at Week 48.

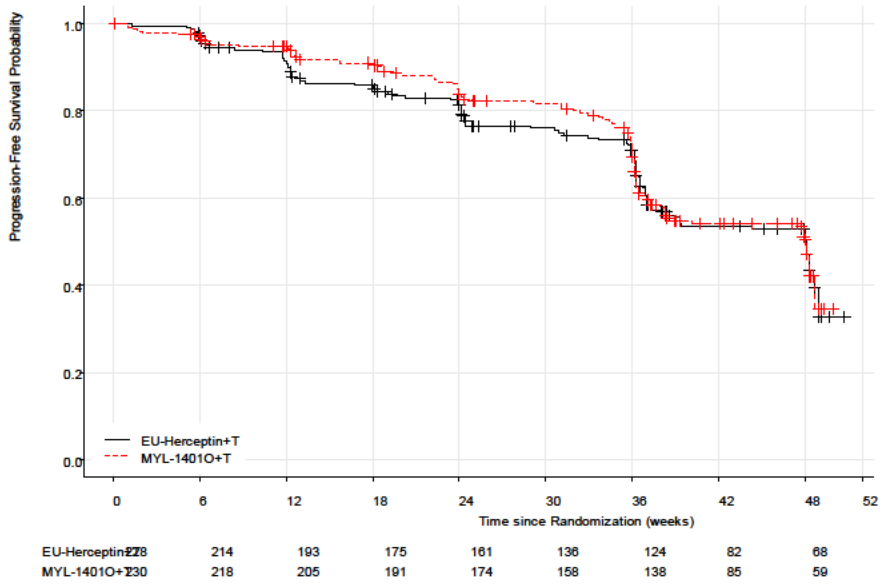
Table 13: Study 3001 Results of PFS per Central Review, ITT1 Population

PFS	MYL-1401O + Taxane (N=230)	EU-Herceptin + Taxane (N=228)
Part 1 (Week 24)		
Number of PFS events	41 (18%)	48 (21%)
Median (95% CI), months	NR	NR
Unstratified HR (95% CI)	0.80 (0.53, 1.22)	
Stratified HR (95% CI)*	0.75 (0.49, 1.14)	
Part 2 (Week 48)		
Number of PFS events	102 (44%)	102 (45%)
Median (95% CI), months	11.1 (8.8, 11.2)	11.1 (8.6, 11.2)
Unstratified HR (95% CI)	0.97 (0.74, 1.28)	
Stratified HR (95% CI)*	0.95 (0.71, 1.25)	

*Stratified by assigned taxane, time of tumor progression to metastatic disease from primary diagnosis, and tumor endocrine status. Eighteen patients with one or more stratification factor data missing in CRFs were not included in the stratified analysis.

Source: Study 3001 CSR Table 22 and Week 48 CSR update Table 24; Study 3001 dataset adtte.xpt

Figure 5: Kaplan-Meier Curves of PFS per Central Review by Week 48, in the ITT1 Population



Source: Study 3001 Week48 CSR update Figure 7 and study 3001 week 48 update dataset adtte.xpt

Reviewer Comment: ***PFS HR was close to 1 at Week 48 cutoff. There was no apparent***

difference in PFS between the two arms.

Overall Survival

Overall survival was analyzed twice: at week 24 cutoff and at week 48 cutoff. Table 14 shows OS at Week 24 and Week 48 for the ITT1 population. As of Week 48 cutoff time, 25 patients (11%) in the MYL-1401O arm and 34 patients (15%) in the EU-Herceptin arm had died. Kaplan-Meier plot for OS at Week 48 is shown in Figure 6. The hazard ratios of MYL-1401O vs. EU-Herceptin were 0.67 (unstratified) and 0.61 (stratified) at Week 48.

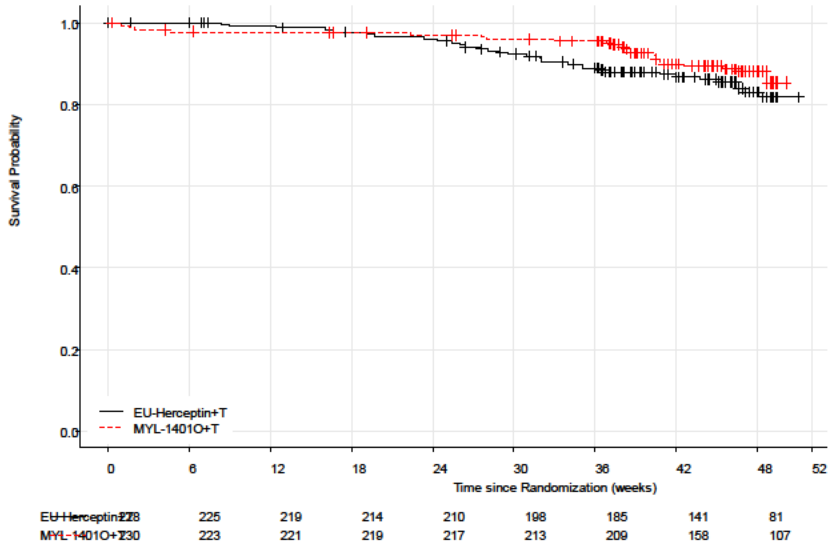
Table 14: Study 3001 Results of OS, ITT1 Population

OS	**MYL-1401O + Taxane (N=230)**	**EU-Herceptin + Taxane (N=228)**
Part 1 (Week 24)		
Number of deaths	7 (3%)	10 (4%)
Median (95% CI), months	NR	NR
Unstratified HR (95% CI)	0.68 (0.26, 1.78)	
Stratified HR (95% CI)*	0.57 (0.21, 1.58)	
Part 2 (Week 48)		
Number of deaths	25 (11%)	34 (15%)
Median (95% CI), months	NR	NR
Unstratified HR (95% CI)	0.67 (0.40, 1.13)	
Stratified HR (95% CI)*	0.61 (0.36, 1.04)	

*Stratified by assigned taxane, time of tumor progression to metastatic disease from primary diagnosis, and tumor endocrine status. Eighteen patients with one or more stratification factor data missing in CRFs were not included in the stratified analysis.

Source: Study 3001 CSR Table 23 and Week 48 CSR update Table 26; Study 3001 dataset adtte.xpt

Figure 6: Kaplan-Meier Curves of OS, in the ITT1 Population



Source: Study 3001 Week48 CSR update Figure 9 and study 3001 week 48 update dataset adtte.xpt

Reviewer Comment: ***The OS results are immature as the median has not been reached in either treatment arm at Week 48.***

Duration of Response

Duration of response was planned to be evaluated at Week 48 cutoff time only. As of Week 48 cutoff, 81 patients (42%) out of the 191 responders in the MYL-1401O arm and 81 patients (45%) out of the 182 responders in the EU-Herceptin arm had either progressed or died. The median time of response duration was 9.7 months in both arms.

Reviewer Comment: ***In this duration of response analysis, both Part 1 responders and Part 2 responders were included. If limiting the analysis among the Part 1 responders only, 41% and 42% of responders in the MYL-1401O arm and EU-Herceptin arm had progression or died, respectively. The median time of response duration was approximately 9.7 months in both arms.***

6.7. Other Endpoints

There were no other endpoints for study 3001 other than those discussed above.

6.8. Subpopulations

Subgroup analyses of ORR

Subgroup analyses of ORR per central review in the ITT1 population were performed by stratification factors (assigned taxane, tumor progression, and tumor endocrine status), age, ECOG status, race, and geographic region. As shown in Table 15, in all subgroups the 90% CI of the ORR ratio (MYL-1401O: EU-Herceptin) included "1" except the subgroup of patients with tumor endocrine status negative.

Table 15: FDA Subgroup Analyses of ORR per Central Review, in the ITT1 Population

	MYL-1401O + Taxane n/N (ORR%)	EU-Herceptin + Taxane n/N (ORR%)	ORR Ratio (90% CI)
Overall	161/230 (70%)	146/228 (64%)	1.09 (0.98, 1.22)
Age			
<65	129/186 (69%)	128/195 (66%)	1.05 (0.94, 1.19)
≥65	32/44 (73%)	18/33 (55%)	1.33 (0.99, 1.80)
Region			
EU	104/151 (69%)	96/149 (64%)	1.07 (0.93, 1.22)
Asia	48/70 (69%)	46/72 (64%)	1.07 (0.88, 1.31)
Race			
Caucasian	112/159 (70%)	99/154 (64%)	1.10 (0.96, 1.25)
Asian	48/70 (69%)	46/72 (64%)	1.07 (0.88, 1.31)
Assigned taxane			
Paclitaxel	27/35 (77%)	20/32 (63%)	1.23 (0.94, 1.62)
Docetaxel	134/193 (69%)	126/192 (66%)	1.06 (0.94, 1.19)
Tumor progression into metastatic phase			
<2 yrs	105/146 (72%)	105/153 (69%)	1.05 (0.93, 1.19)
≥2 yrs	50/75 (67%)	39/71 (55%)	1.21 (0.97, 1.52)
Tumor endocrine status			
Positive	67/102 (66%)	69/101 (68%)	0.96 (0.82, 1.13)
Negative	94/128 (73%)	77/127 (61%)	1.21 (1.05, 1.40)
ECOG PS			
0	85/112 (76%)	71/97 (73%)	1.04 (0.91, 1.19)
1	73/113 (65%)	72/127 (57%)	1.14 (0.96, 1.35)

Source: Study 3001 adsl.xpt and adrs.xpt

6.9. Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable to this application.

6.10. Discussion of Persistence of Efficacy and/or Tolerance Effects

See duration of response results described in the section of secondary endpoints. The median of response duration was 9.7 months in both treatment arms as of Week 48 cutoff. Persistence of effect is addressed by the secondary endpoints of duration of response and PFS which are time to event endpoints.

6.11. Additional Efficacy Issues/Analyses

Treatment Compliance
Study treatment was delivered in the clinic by site personnel; therefore, no measurement of treatment compliance was required.

Concomitant Medications
Nearly all patients used concomitant medications (99.6% in the MYL-1401O arm and 100.0% in the EU-Herceptin arm). The most commonly used concomitant medications in both treatment groups were part of pre- or post-chemotherapy treatment: corticosteroids for systemic use (MYL-1401O 96.4%, EU-Herceptin 99.6%), antiemetics (70.9% versus 75.2%), drugs for acid-related disorders (61.9% versus 61.4%), and antihistamines for systemic use (56.3% versus 54.9%).

7. Review of Safety

Safety Summary

The results of the clinical development program indicate that the Applicant's data support a determination of no clinically meaningful differences between MYL-1401O and US-Herceptin in terms of safety in the indication studied. The safety analyses in MYL-Her-3001, which compared MYL-1401O and EU-Herceptin in HER2 positive metastatic breast cancer patients, did not show any meaningful differences in safety between arms.

7.1. Methods

7.1.1. Studies/Clinical Trials Used to Evaluate Safety

The safety evaluation for this application is based off Parts 1 and 2 of study 3001. Details of the design for 3001 are presented in Section 5 above. Key features of two additional pivotal PK similarity studies utilizing MYL-1401O (MYL-Her-1001 and MYL-Her-1002), as well as a supportive study utilizing Bmab-200 (BM200-CT3-01-11) are summarized in Section 5.1. Efficacy results for 3001 are presented in Section 6. Results from Part 2 of the study were submitted during the 120-Day Safety update.

For the remainder of this safety review, study MYL-Her-3001 will be referred to as 3001, study

MYL-Her-1001 will be referred to as 1001, MYL-Her-1002 will be referred to as 1002, and BM200-CT3-01-11 will be referred to as BM200.

The Applicant proposed that MYL-1401O have the same indications as US-Herceptin: 1) adjuvant and metastatic treatment of patients with HER2 positive breast cancer and 2) HER2 positive metastatic gastric adenocarcinoma (Herceptin's gastric cancer indication is protected by orphan drug exclusivity until October 2017). Given studies 1001 and 1002 were conducted in a different patient population of healthy volunteers than the intended population of cancer patients, these two studies are not included in the overall safety assessment of MYL-1401O. BM200 is also not included given Bmab-200, and not MYL-1401O, was used in the study.

Study 3001 was the only study conducted using the product MYL-1401O with the intended patient population in the United States and is the primary study used for the overall safety assessment of MYL-1401O. There is no pooling of safety data as agreed upon with the FDA during a previous Type 4 meeting.

The safety assessments for 3001 are adequate. There was particular attention to assessment of cardiac adverse events (AEs) due to the known cardiac effects of trastuzumab. A dedicated case report form (CRF) was used to collect data from electrocardiograms (ECGs) at screening, cycles 5, 9, 13, and every 4 cycles thereafter, and at end of study, and left ventricular ejection fraction (LVEF) by echo or multi-gated acquisition scan (MUGA) at screening, cycle 5, cycle 9, cycle 13, and every 4 cycles thereafter, at end of treatment, and every 6 after the end of treatment for 24 months. Echocardiogram (echo) was preferred over MUGA, but the same methodology was to be used throughout the study. Imaging was repeated at least every 3 weeks if there was a 16% absolute decrease in LVEF from pre-treatment levels or LVEF below institutional level of normal and a 10% absolute decrease in LVEF.

7.1.2. Categorization of Adverse Events

The applicant defined an adverse event as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with the product. The definition included exacerbation of pre-existing diseases or conditions.

A serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose resulted in death, is life-threatening, resulted in persistent or significant disability/incapacity, is a congenital anomaly, is an important medical event, or requires inpatient hospitalization or prolongation of existing hospitalization.

Treatment emergent adverse events (TEAE) were defined as any AE which started or deteriorated at or after treatment with a trastuzumab product on or within 28 days following the last dose of the drug.

AEs and SAEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) v.18.0. AEs were graded for severity using the National Cancer Institute Common Terminology criteria for Adverse Events (NCI CTCAE) version 4.03. AEs were summarized by MedDRA primary system organ class (SOC) and preferred term (PT).

7.1.3. Pooling of Data Across Studies to Estimate and Compare Incidence

There was no pooling as there was only one comparative study.

7.2. Adequacy of Safety Assessments

7.2.1. Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety population consisted of 493 total patients, 247 in the MYL-1401O arm and 246 in the EU-Herceptin arm and is defined as all patients who received at least 1 dose of study drug in any amount. This is the primary population for the overall safety analysis in this safety assessment.

Table 16 and Table 17 below list the mean number of cycles, mean duration of exposure, and mean loading dose for MYL-1401O, EU-Herceptin, and docetaxel or paclitaxel in Part 1 of the study.

Table 16: Safety Population Exposure to Trastuzumab Product During Part 1

	MYL-1401O (n=247)	EU-Herceptin (n=246)
Mean number of cycles (SD)	7.76 (2.13)	7.54 (2.27)
Mean duration of exposure in weeks (SD)	21.04 (6.43)	20.33 (6.82)
Mean loading dose in mg/kg	8.0	8.0

Source dataset: ADEX.xpt

Table 17: Safety Population Exposure to Taxanes During Part 1

	MYL-1401O (n=247)		EU-Herceptin (n=246)	
	Docetaxel (n=212)	Paclitaxel (n=35)	Docetaxel (n=214)	Paclitaxel (n=32)
Mean dose intensity in mg/m^2/wk	24.75	69.36	24.62	68.43
Mean total exposure duration in weeks	18.70	21.19	18.45	17.91
Mean cycles received	7.06	7.34	7.00	6.22

Source dataset: ADEX.xpt

Of the 342 patients who entered Part 2 monotherapy, the median and median trastuzumab exposure was similar in both arms. The median number of cycles during Part 2 was 16 in both groups.

***Reviewer Comments*: The exposure was well balanced between the two arms in Parts 1 and 2.**

The safety population consisted of all patients who received at least 1 dose of MYL-1401O or EU-Herceptin in any amount. This is a subset of the intention to treat population 1 (ITT1 – all patients who entered the study under Protocol Amendment 2 and later which limited recruitment to patients receiving trastuzumab as first-line treatment to help increase the homogeneity of the study population, increase the reliability of study results, and more closely reflect the standard of care). The trial was conducted at 95 sites in 16 countries (Bulgaria, Chile, Czech Republic, Georgia, Hungary, India, Latvia, Philippines, Poland, Romania, Russia, Serbia, Slovakia, South Africa, Thailand, and Ukraine). These countries were chosen because the study protocol did not allow the use of pertuzumab in combination with trastuzumab and thus, the study sites were limited to countries where pertuzumab was not approved or part of the standard of care. Table 18 below provides an overview of the demographic characteristics of the safety population.

Table 18: Overview of the Safety Population Demographic Characteristics of 3001

	MYL-1401O N=247 N (%)	**EU-Herceptin N=246 N (%)**
Age		
Mean	52.4	53.6
SD	15.3	15.9
Median	52.5	53.5
Range	24-79	26-82
Age Range		
< 50	79 (32.0)	90 (36.6)
≥ 50	168 (68.0)	156 (63.4)
ECOG		
0	127 (51.4)	107 (43.5)
1	115 (46.6)	132 (53.7)
2	5 (2.0)	5 (2.0)
3	0 (0.0)	1 (0.4)
Unknown	0 (0.0)	1 (0.4)
Race		
Asian	73 (29.6)	76 (30.9)
Black/African American	1 (0.4)	2 (0.8)
Caucasian	172 (69.6)	167 (67.9)

Other	1 (0.4)	1 (0.4)
Country		
BGR (Bulgaria)	0 (0.0)	2 (0.8)
CHL (Chile)	1 (0.4)	4 (1.6)
CZE (Czech Republic)	1 (0.4)	1 (0.4)
GEO (Georgia)	32 (13.0)	29 (11.8)
HUN (Hungary)	6 (2.4)	8 (3.3)
IND (India)	24 (9.7)	29 (11.8)
LVA (Latvia)	4 (1.6)	2 (0.8)
PHL (Philippines)	30 (12.1)	19 (7.7)
POL (Poland)	13 (5.3)	6 (2.4)
ROU (Romania)	3 (1.2)	5 (2.0)
RUS (Russia)	74 (30.0)	77 (31.3)
SRB (Serbia)	3 (1.2)	2 (0.8)
SVK (Slovakia)	2 (0.8)	1 (0.4)
THA (Thailand)	19 (7.7)	28 (11.4)
UKR (Ukraine)	25 (10.1)	28 (11.4)
ZAF (South Africa)	10 (4.0)	5 (2.0)
Previous Treatment		
Taxane	49 (19.8)	49 (19.9)
Anthracycline	105 (42.5)	122 (49.6)
Trastuzumab	23 (9.3)	19 (7.7)
Primary Metastatic Site		
Adrenal gland	0 (0.0)	3 (1.2)
Bone	4 (1.6)	6 (2.4)
Brain	1 (0.4)	2 (0.8)
Breast	4 (1.6)	5 (2.0)
Chest wall	2 (0.8)	1 (0.4)
Liver	82 (33.2)	75 (30.5)
Lung	56 (22.7)	81 (32.9)
Mediastinum	0 (0.0)	1 (0.4)
Neck	0 (0.0)	1 (0.4)
Other	22 (8.9)	18 (7.3)
Pleura	2 (0.8)	2 (0.8)
Thorax/axillary	8 (3.2)	4 (1.6)
Unknown	66 (26.7)	47 (19.1)
Number Metastatic Sites at Screening		
1	64 (25.9)	65 (26.4)
2	91 (36.8)	72 (29.3)
3	49 (19.8)	63 (25.6)
≥4	43 (17.4)	46 (18.7)
ER		

Negative	137 (55.5)	138 (56.1)
Positive	109 (44.1)	108 (43.9)
Unknown	1 (0.4)	0 (0.0)
PR		
Negative	2 (0.8)	2 (0.8)
Positive	37 (15.0)	55 (22.4)
Unknown	208 (84.2)	189 (76.8)
HER2		
1+	2 (0.8)	0 (0.0)
2+ and FISH unknown	17 (6.9)	13 (5.3)
2+ and FISH positive	13 (5.3)	29 (11.8)
3+	209 (84.6)	195 (79.3)
Unknown	6 (2.4)	9 (3.7)

Source dataset: ADSL.xpt, ADBH.xpt

Reviewer Comments: ***The demographics, previous treatment exposure, and breast tumor characteristics are well balanced between the two arms. More patients in the MYL-1401O arm had a baseline ECOG 0 and over the age of 50 compared to those in the EU-Herceptin arm. However, this is unlikely to impact the safety profile of the study. The majority of patients were Caucasian and Asian. African Americans are underrepresented in this study, with only 1 patient per arm. However, this is unlikely to impact the safety profile of MYL-1401O, as MYL-1401O is expected to act the same regardless of race.***

7.2.2. Explorations for Dose Response

Not applicable.

7.2.3. Special Animal and/or In Vitro Testing

Not applicable.

7.2.4. Routine Clinical Testing

The schedule of safety evaluations for 3001 was described in Section 7 Table 1 of the study protocol (refer to Figure 2 above). The frequency of monitoring was considered adequate within the context of the study. ECG and left ventricle ejection fraction monitoring were adequate.

7.2.5. Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6. Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable.

7.3. Major Safety Results

7.3.1. Deaths

The number of deaths in each treatment group is shown in Table 19 below.

Table 19: Treatment-Emergent Deaths During Parts 1 and 2

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

Source: ADAE.xpt, ADSL.xpt

Two additional patients died in Part 1 of the study. Patient (b) (6) received MYL-1401O plus paclitaxel and per investigator died of disease progression. Patient (b) (6) received EU-Herceptin plus docetaxel and per investigator died of disease progression.

MYL-1401O Deaths

- Patient (b) (6) was a 54 year old Caucasian woman treated in Russia with liver as the first site of metastasis. On day 7 of study, after receiving MYL-1401O 8 mg/kg loading dose on day 1 and docetaxel 75 mg/m2 on day 2, she experienced weakness, loss of consciousness, stupor, and shortness of breath. The patient died from respiratory failure within 2-3 hours. No autopsy was performed and no death certificate was available. No treatment was recorded and it is not known if any examination was performed.
- Patient (b) (6) was a 46 year old Caucasian woman treated in Georgia with liver as the first site of metastasis. On day 1 she received MYL-1401O 8 mg/kg loading dose and on day 2 she received docetaxel 75 mg/m2. On day 7 she was diagnosed with grade 5 pancytopenia and hepatic failure after being hospitalized with diarrhea and general weakness. Cause of death was reported as pancytopenia and liver metastatic damage and autopsy was not performed. The Investigator felt pancytopenia was due to docetaxel and liver failure due to progressive disease.
- Patient (b) (6) was a 64 year old Caucasian woman treated in Georgia with lung as the first site of metastasis. On day 157 (week 22), after receiving 8 cycles of treatment, the patient experienced cardiac and respiratory failure. Her day 85 ECG and LVEF of 64% were normal (baseline LVEF 61%). The patient presented with weakness, nausea, vomiting, abdominal pain, hypotension, and increased intestinal peristalsis. On admission, her temperature was 36.0, pulse 120, blood pressure 85/55, with dull heart tones, decreased breath sounds, and

abdominal pain. Her lower extremity ultrasound revealed a right femoral popliteal vein thrombosis. Results of other laboratory and diagnostic tests were otherwise not reported. She died the same day of heart and respiratory failure. An autopsy was not performed. Her last tumor assessment a month prior had shown partial response and therefore progression of disease was not felt to be cause of death.

- Patient (b) (6) was a 53 year old Asian woman. She completed Part 1 of the study with docetaxel and started Part 2 with MYL-1401O monotherapy on study day 190. Her last dose of study medication was study day 212. On study day 178 imaging showed partial response on central review. On Study day 229 she had dyspnea with an SpO2 of 74% with bilateral crepitations and decreased breath sounds. EKG was normal. She died on study day 230 and no other AEs were ongoing at the time of death. EF was 76% on (b) (6) and normal prior to death (DOD (b) (6)).
- Patient (b) (6) was a 43 year old Asian woman treated in the Philippines with multiple metastatic sites at screening. She received MYL-1401O 8 mg/kg loading dose on day 1 and docetaxel 75 mg/m2 on day 2. On study day 11 the patient had grade 4 pneumonia and febrile neutropenia and was admitted to the hospital. On study day 12 the patient had grade 3 anaphylactic reaction (resolved same day), grade 4 septic shock, grade 3 peripheral ischemia, and grade 4 acute MI. On study day 13, the patient had multi-organ failure leading to death on day 14. On day 11, the patient presented with febrile neutropenia and chills, which resulted in the development of pneumonia and subsequent hospitalization. She received IV piperacillin/tazobactam. On day 12, the patient had an anaphylactic reaction (hives and respiratory difficulty) to the second infusion of IV antibiotics. Her pneumonia progressed and she eventually required intubation. She remained highly febrile and had progressive respiratory difficulty. She also experienced an ST elevation MI and acute right arm peripheral ischemia and septic shock. On day 13, the patient experienced multi-organ failure and died on day 14. An autopsy was not performed. The Investigator felt pneumonia, febrile neutropenia, multi-organ failure, acute myocardial infarction, peripheral ischemia, and septic shock were due to underlying disease.
- Patient (b) (6) was a 56 year old Asian woman. She completed Part 1 of the study with docetaxel and started Part 2 with MYL-1401O monotherapy on study day 169. Her last dose of study medication was study day 319. She died on study day 340. A week prior she had experienced low grade fevers, chills, sweats, with a normal Echo and EKG, with EF 65% (change from baseline -2%). On study day 340 she presented with hypotension and tachycardia. Chest x-ray post intubation showed cardiomegaly. Laboratory tests showed increased bands and elevated liver enzymes. She had no other ongoing AEs at the time of death.

<u>EU-Herceptin Deaths</u>

- Patient (b) (6) was a 45 year old Black/African American woman treated in South Africa with lung as the first site of metastasis. She died on day 59 of unknown causes at home after completing 3 cycles of treatment with Herceptin and docetaxel. No autopsy was performed. Her tumor assessment on day 43 showed partial response. Due to her husband reporting symptoms of chills and shortness of breath, the investigators felt the cause of

death may have been related to docetaxel.

- Patient (b) (6) was a 37 year old Asian woman treated in India with thoracic metastases at screening. On day 160, the patient presented with pneumonia (Acinetobacter baumannii) and sepsis and had completed 8 cycles on EU-Herceptin and docetaxel. She was not neutropenia on admission and tumor assessments on day 125 showed partial response. Her death on day 164 was felt to be due to breast cancer.
- Patient (b) (6) was a 60 year old Asian woman treated in India with lung as the first site of metastasis. On day 76, after 4 cycles of EU-Herceptin and paclitaxel (80 mg/m2), the patient was admitted with respiratory distress and hypotension. CT imaging showed pneumonia and progressive disease in the pulmonary and lymphatic system. Her LVEF was 55% on admission, same as baseline. The patient died on day 87 and autopsy was not performed. The cause of death was felt to be disease progression.
- Patient (b) (6) was a 63 year old Asian woman treated in Thailand with liver as the first site of metastasis. On day 2, the patient developed grade 3 diarrhea. On day 4, the patient was admitted with tumor lysis syndrome and acute liver failure, with elevated creatinine and uric acid. Diarrhea was grade 2 on admission. She was intubated on day 6 and died the same day with tumor lysis syndrome and hepatic failure as the primary causes of death. No autopsy was performed and no tumor assessment data was available. Docetaxel was felt to be the primary cause.

Reviewer Comments: ***Narratives were reviewed for the patients who died. Pulmonary embolism, infection, and disease progression are high on the differential for likely cause of death. These causes of death are well balanced between the two arms and unlikely to have a meaningful safety impact.***

MYL-1401O:
For patients (b) (6) ***and*** (b) (6) ***who died after receiving only 1 dose of study drug, disease progression and PE are possible causes of death.***
For patients (b) (6) ***and*** (b) (6) ***PE are high on the differential for cause of death.***
For patients (b) (6) ***and*** (b) (6) ***infection are high on the differential for cause of death.***

EU-Herceptin:
For patients (b) (6) ***and*** (b) (6) ***infection is on the differential for cause of death.***
For patients ***and*** ***progressive disease is high on the differential for cause of death.***

7.3.2. Nonfatal Serious Adverse Events

Serious TEAEs from Parts 1 and 2 of 3001 are listed in Table 20 below. These were predominantly seen in less than 2% of patients. Neutropenia, leukopenia, febrile neutropenia, and pneumonia were most common, likely related to taxanes, and well balanced between the two arms.

Table 20: Serious Safety Population Treatment-Emergent Adverse Events in Parts 1 and 2

MedDRA Term	MYL-1401O N=247 N (%)	EU-Herceptin N=246 N (%)	TOTAL N=493 N (%)
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 failure	2 (0.8)	0 (0.0)	2 (0.4)
Diarrhoea	3 (1.2)	5 (2.0)	8 (1.6)
Nausea	2 (0.8)	1 (0.4)	3 (0.6)
Vomiting	1 (0.4)	3 (1.2)	4 (0.8)
Pyrexia	0 (0.0)	2 (0.8)	2 (0.4)
Hepatic failure	1 (0.4)	1 (0.4)	2 (0.4)
Anaphylactic reaction	2 (0.8)	0 (0.0)	2 (0.4)
Hypersensitivity	0 (0.0)	2 (0.8)	2 (0.4)
Bronchitis	0 (0.0)	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 (0.0)	3 (1.2)	3 (0.6)
Urinary tract infection	2 (0.8)	2 (0.8)	4 (0.8)
Blood uric acid increased	2 (0.8)	1 (0.4)	3 (0.6)
Hypernatraemia	1 (0.4)	2 (0.8)	3 (0.6)
Hyperuricaemia	2 (0.8)	2 (0.8)	4 (0.8)
Hypokalaemia	1 (0.4)	1 (0.4)	2 (0.4)
Hyponatraemia	0 (0.0)	2 (0.8)	2 (0.4)
Acute kidney injury	1 (0.4)	1 (0.4)	2 (0.4)
Dyspnoea	2 (0.8)	0 (0.0)	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)

Source dataset: ADAE.xpt

Reviewer Comments: ***Overall the serious TEAEs are well balanced between the two arms with no safety concerns. Neutropenia, leukopenia, and febrile neutropenia are likely due to taxanes and balanced between the two arms.***

7.3.3. Dropouts and/or Discontinuations

The pre-specified safety withdrawal criteria are reasonable and included cardiac symptoms related to the study drug (symptomatic cardiac failure, symptomatic decrease of LVEF below institutional lower limit of normal, symptomatic LVEF decrease > 10% lasting more than 8 weeks, suspension of EU-Herceptin for more than 3 episodes of cardiomyopathy) or the taxane (severe hypersensitivity reaction or requiring more than 1 dose reduction). Table 22 below lists the number of patients in each study arm who was withdrawn from the study due to TEAEs.

Reviewer Comments: ***TEAEs leading to withdrawal from study occurred infrequently in both arms and was well-balanced.***

Significant Adverse Events Table 21 below lists patients on each treatment arm who had TEAEs leading to withdrawal from the study and the associated AE and grade.

Table 21: TEAEs Leading to Withdrawal From Study 3001 During Parts 1 and 2

Patient	Treatment	MedDRA Term(s)	Grade
(b) (6)	EU-Herceptin	Cerebral infarction	2
	EU-Herceptin	Ejection fraction decreased	3
	EU-Herceptin	Headache	3
	EU-Herceptin	Pneumonitis	4
	EU-Herceptin	Pneumonitis	4
	EU-Herceptin	Death	5
	EU-Herceptin	Pneumonia/sepsis	5/5
	EU-Herceptin	Hepatic failure/tumour lysis syndrome	5/5
	EU-Herceptin	Pneumonia/respiratory failure	4/5
	MYL-1401O	Ejection fraction decreased	2
	MYL-1401O	Cardiac failure	3
	MYL-1401O	Cardiac failure	3
	MYL-1401O	Respiratory failure	5
	MYL-1401O	Hepatic failure/pancytopenia	5/5
	MYL-1401O	Cardiac failure/respiratory failure	5/5
	MYL-1401O	Dyspnoea	5
	MYL-1401O	Multi-organ failure	5
	MYL-1401O	Carditis	5

Source dataset: ADAE.xpt

Reviewer Comments: ***There were relatively few patients who withdrew from the study (9 patients from each arm or 3.6% of the total patients). These were well balanced between the two arms. Please refer to Section 7.3.1 for details regarding the patients who experienced died. Overall there were no concerning safety findings.***

7.3.4. Submission Specific Primary Safety Concerns

Treatment emergent adverse events were assessed through 28 days after the last dose of study drug. The TEAEs were well balanced between the arms overall with a slightly higher percentage of patients on the MYL-1401O arm experiencing treatment-related TEAEs (Table 22).

Table 22: Summary of TEAEs in Parts 1 and 2

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

Source dataset: ADAE.xpt

More patients who received MYL-1401O experienced treatment-related TEAEs compared to those who received EU-Herceptin. The majority of these were grade 1-2 and occurred in Part 1 of the study. Table 23 below lists the patients who experienced treatment-related TEAEs during monotherapy Part 2 of the study.

Table 23: Treatment-Related TEAEs from 3001 Part 2

Patient ID	Treatment Arm	MedDRA Term	Grade	Withdrawn from study?
(b) (6)	EU-Herceptin	Pneumonitis	4	Y
	MYL-1401O	Cardiac failure	3	Y
	MYL-1401O	Dyspnoea	3	N
	MYL-1401O	Ejection fraction decreased	3	N
	MYL-1401O	Left ventricular dysfunction	3	N
	MYL-1401O	Leukopenia and Neutropenia	3	N
	MYL-1401O	Neutropenia	3	N

Source dataset: ADAE.xpt

(b) (6): This patient was hospitalized for grade 4 pneumonitis on study day 211, after having received EU-Herceptin alone for 1 cycle in Part 2. On day 220 her symptoms resolved. Her last dose of study drug was on day 192.

(b) (6): This patient had grade 3 symptomatic cardiac failure with LVEF 49% (baseline 60%) on study day 277, after having received MYL-1401O for 5 cycles in Part 2. Her symptoms were resolving at the last report. Her last dose of study drug was on day 255.

(b) (6): This patient had grade 3 dyspnea on study day 268 after having received MYL-1401O alone for 5 cycles in Part 2. She also experienced slurred speech and weakness. Brain MRI showed metastatic lesions with surrounding edema. She was reported as having disease progression on this day. Her dyspnea resolved on day 271. Her last dose of study drug was on day 267.

(b) (6) This patient had a LVEF decrease from 78% at baseline to 61% on study days 85 (Part 1) and 196 (end of treatment, Part 2). Her LVEF had returned to institutional level of normal on study day 172 with LVEF 65%.

(b) (6) This patient had a screening LVEF of 59% and a grade 3 10% decrease in LVEF on study day 341 (Part 2 Cycle 17, LVEF 49%). The AE is reported as resolved on day 362.

Reviewer comments: ***Patients (b) (6) and (b) (6) experienced leukopenia and neutropenia. While these can be seen with trastuzumab, this is unlikely to have a meaningful safety impact, especially as both these patients had resolution of their TEAEs. Patients (b) (6) and (b) (6) had asymptomatic decreases in LVEF, both of which resolved. Patient (b) (6) had disease progression and new brain metastases at the same time as dyspnea, which could have contributed to her symptoms. Patient (b) (6) had symptomatic heart failure and was taken off study with an LVEF absolute decrease of 11%. Her symptoms are resolving at the last report. Patient (b) (6) had resolution of her symptoms after EU-Herceptin was stopped. Overall these treatment-related TEAEs are expected based on prior experience with US-Herceptin and unlikely to impact the overall safety of MYL-1401O.***

Adverse Events of Special Interest

Major events of interest which are listed as Black Box Warnings in the prescribing information for US-Herceptin include cardiomyopathy, pulmonary toxicity, infusion reactions, and embryo-fetal toxicity. There were no pregnancies reported in 3001. Cardiac toxicities, pulmonary toxicities, and infusion reactions are discussed below.

Cardiac Toxicity

Table 24 below lists the cardiac TEAEs during Parts 1 and 2 of the study. More patients who received MYL-1401O experienced cardiac failure and ejection fraction decrease. Two of the 3 patients who received MYL-1401O and had grade 3 or higher cardiac failure had resolution of their adverse event and the third patient died from cardiac and respiratory failure with lower extremity ultrasound showing deep vein thromboses (DVTs). Of the patients who experienced ejection fraction decrease, the majority of patients in both arms had resolution of their TEAEs and only one patient in each arm had grade 3 or higher ejection fraction decrease; the patient who received MYL-1401O had resolution of their AE and the outcome of the patient who received EU-Herceptin is unknown.

Table 24: Cardiac TEAEs During Parts 1 and 2

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

Source dataset: ADAE.xpt

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

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

[c] Of the patients with grade 3 or higher ejection fraction decrease, the patient who received MYL-1401O had resolution of their adverse event and the adverse event outcome of patient who received EU-Herceptin is unknown.

Reviewer Comments:
More patients in the MYL-1401O arm experienced cardiac failure and ejection fraction decrease, but both are within the up to 11% expected cardiotoxicity as listed in the US-Herceptin label. The majority of all cardiac TEAEs were grade 1-2 and most patients had resolution of their TEAEs. Three clinical IRs involving cardiac toxicities were sent to the Applicant on 6/9/17, 5/24/17, and 1/5/17 with satisfactory responses by the Applicant. Overall the cardiac TEAEs are within the expected level based on previous experience with US-Herceptin and likely not meaningful.

Pulmonary Toxicity and Infusion Reactions
Table 25 below lists the frequency of treatment-emergent pulmonary toxicities and infusion reactions. These were infrequent overall and balanced between the two arms.

Table 25: Pulmonary Toxicities and Infusion Reactions During Parts 1 and 2

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

Source dataset: ADAE.xpt

Reviewer Comments: ***There are no safety concerns noted for pulmonary toxicities and infusion reactions.***

7.4. Supportive Safety Results

7.4.1. Common Adverse Events

Common TEAEs seen in ≥5% of patients in any group are shown in Table 26 below.

Table 26: Frequency of common treatment-emergent adverse events (≥5% in any group) During Parts 1 and 2

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

Source dataset: ADAE.xpt

Reviewer Comments: ***TEAEs seen in ≥5% in any arm are well balanced with no meaningful differences. Differences in nausea, asthenia, upper respiratory tract infection, and arthralgia are likely taxane related rather than due to the study drug. Narratives were reviewed for the patients who died. Pulmonary embolism, infection, and disease progression are high on the differential for likely cause of death. These causes of death are well balanced between the two arms and unlikely to have a meaningful safety impact.***

MYL-1401O:
For patients (b) (6) and (b) (6) who died after receiving only 1 dose of study drug, disease progression and PE are possible causes of death.
For patients (b) (6) and (b) (6) PE are high on the differential for cause of death.
For patients and infection are high on the differential for cause of death.

EU-Herceptin:
For patients (b) (6) and (b) (6) , infection is on the differential for cause of death.
For patients and , progressive disease is high on the differential for cause of death.

7.4.2. Laboratory Findings

Trastuzumab is not known to cause significant laboratory abnormalities, but docetaxel and paclitaxel are. The reported changes in laboratory values in the Week 48 CSR were reviewed and overall well balanced between the treatment arms in hematology labs and chemistries for the safety population in Parts 1 and 2 of the study.

Reviewer Comments: No safety concerns noted. Trastuzumab is not known to cause significant laboratory findings.

7.4.3. Vital Signs

Changes in vital signs for the safety population reported in Week 48 CSR were reviewed and overall well balanced between the treatment arms for temperature, blood pressure, heart rate, and respiratory rate for Parts 1 and 2.

Reviewer Comments: No safety concerns noted.

7.4.4. Electrocardiograms (ECGs)

The ECG data was compared between the MYL-1401O and EU-Herceptin arms at baseline, C5 (week 12) and C9 (week 24) (Table 27). The HR, PR, QRS, QT, and QTcB intervals were comparable between the two arms with no concerning safety concerns.

Table 27: Safety Population ECG Changes During Part 1

			MYL-1401O (n=247)		EU-HERCEPTIN (n=246)	
			Observed	Change from Baseline	Observed	Change from Baseline
PR	Baseline	N	227.0		220.0	
		Mean	153.9		154.6	
		SD	21.6		22.2	
		95% CI	151.1-156.7		151.6-157.6	
		Median	155.0		154.0	
		Range	79-220		96-228	
	Cycle 5 Week 12	N	202.0		195.0	
		Mean	154.1	0.2	152.9	-1.7
		SD	21.8	0.2	22.0	-0.2
		95% CI	151.0-157.2		149.7-156.2	
		Median	154.5	-0.5	151.0	-3.0
		Range	70-220		96-212	
	Cycle 9 Week 24	N	166.0		163.0	
		Mean	153.9	0	154.6	0
		SD	21.0	-0.6	21.4	-0.8
		95% CI	150.6-157.2		151.1-158.1	
		Median	156.0	1.0	155.0	1.0
		Range	79-199		96-212	
HR	Baseline	N	236.0		232	
		Mean	80.8		83.4	
		SD	13.2		15.5	
		95% CI	79.1-82.5		81.4-85.5	
		Median	80.0		82.5	
		Range	50-125		48-147	
	Cycle 5 Week 12	N	211.0		205.0	
		Mean	81.0	0.2	83.6	0.2
		SD	13.1	-0.1	15.8	0.3
		95% CI	79.1-82.8		81.3-85.8	
		Median	80.0	0.0	83.0	0.5
		Range	50-125		48-147	
	Cycle 9 Week 24	N	171.0		172.0	
		Mean	81.0	0.2	82.9	-0.5
		SD	12.7	-0.5	15.8	0.3
		95% CI	79.0-82.9		80.4-85.4	
		Median	81.0	1.0	83.0	0.5
		Range	50-125		53-147	

QRS	Baseline	N	227.0		222	
		Mean	86.1		83.3	
		SD	10.9		9.5	
		95% CI	84.7-87.5		82.0-84.5	
		Median	84.0		82.0	
		Range	59-140		58-124	
	Cycle 5 Week 12	N	202.0		197.0	
		Mean	86.4	0.3	83.0	-0.3
		SD	11.3	0.4	9.4	-0.1
		95% CI	84.8-88.0		81.6-84.4	
		Median	84.0	0.0	82.0	0.0
		Range	59-140		58-124	
	Cycle 9 Week 24	N	166.0		165.0	
		Mean	86.3	0.2	82.9	-0.4
		SD	11.2	0.3	8.4	-1.1
		95% CI	84.5-88.0		81.5-84.2	
		Median	84.0	0	82.0	0
		Range	59-140		58-110	
QT	Baseline	N	227.0		222.0	
		Mean	370.6		366.5	
		SD	29.0		34.7	
		95% CI	366.9-374.4		361.9-371.1	
		Median	372.0		362.0	
		Range	285-438		270-470	
	Cycle 5 Week 12	N	202.0		197.0	
		Mean	371.1	0.5	365.6	-0.9
		SD	28.3	-0.7	34.7	0.0
		95% CI	367.1-375.1		360.5-370.7	
		Median	370.0	-2.0	360.0	-2.0
		Range	285-438		270-468	
	Cycle 9 Week 24	N	166.0		165.0	
		Mean	370.0	-0.6	366.2	-0.3
		SD	27.6	-1.4	35.8	1.1
		95% CI	365.6-374.3		360.4-372.0	
		Median	370.0	-2.0	360.0	-2.0
		Range	294-428		270-468	
QTcb	Baseline	N	247.0		242.0	
		Mean	424.3		424.9	
		SD	27.2		25.7	
		95% CI	420.7-427.8		421.5-428.3	
		Median	423.0		425.0	
		Range	337-524		352-504	

	Cycle 5 Week 12	N	225.0		215.0	
		Mean	424.9	0.6	424.0	-0.9
		SD	27.1	-0.1	25.5	-0.2
		95% CI	421.5-428.6		420.4-427.6	
		Median	423.0	0.0	425.0	0.0
		Range	337-524		352-504	
	Cycle 9 Week 24	N	184.0		173.0	
		Mean	424.1	-0.2	423.0	-1.9
		SD	26.4	-0.8	26.0	0.3
		95% CI	420.1-428.0		418.8-427.1	
		Median	423.0	0.0	423.5	-1.5
		Range	337-495		352-504	

Source dataset: ADEG.xpt

The Week 48 Safety Update CSR was reviewed for Part 2 monotherapy (Tables 14.3.4.3.1.2b, 14.3.4.3.2.1b, and 14.3.4.3.2.2b). New clinically significant ECG findings at cycle 13 week 36 (1 patient MYL-1401O and 2 patients EU-Herceptin) and cycle 17 week 48 (1 patient MYL-1401O and 1 patient EU-Herceptin) were seen in both arms and in very few patients.

***Reviewer Comments*: No safety concerns.**

7.4.5. Special Safety Studies/Clinical Trials

No special safety studies were conducted.

7.4.6. Immunogenicity

Table 28 below lists the immunogenicity findings during Part 1 of 3001. At baseline (Cycle 1 Week 0), 14 patients in the MYL-1401O and 22 patients in the EU-Herceptin arm had a positive anti-drug antibody assay. Of these, 1 patient in the MYL-1401O and 2 patients in the EU-Herceptin arms had positive neutralizing antibodies. The number of patients with positive neutralizing antibodies in each arm eventually declined to 0 in both groups. A small number of patients in each arm continued to have a positive anti-drug antibody assay throughout Part 1 of the study, although this was balanced between the two arms.

Table 28: Safety Population Immunogenicity During Part 1

Visit	Result	MYL-1401O (n=247)		EU-Herceptin (n=246)	
		n	%	n	%
Cycle 1 Week 0	Anti-Drug Antibody Assay	13	5.3%	20	8.1%
	Neutralizing Antibody Positive	1	0.4%	2	0.8%
Cycle 3 Week 6	Anti-Drug Antibody Assay	5	2.0%	6	2.4%
	Neutralizing Antibody Positive	0	0.0%	3	1.2%
Cycle 5 Week 12	Anti-Drug Antibody Assay	2	0.8%	2	0.8%
	Neutralizing Antibody Positive	0	0.0%	0	0.0%
Cycle 7 Week 18	Anti-Drug Antibody Assay	2	0.8%	1	0.4%
	Neutralizing Antibody Positive	0	0.0%	0	0.0%
Cycle 9 Week 24	Anti-Drug Antibody Assay	2	0.8%	1	0.4%
	Neutralizing Antibody Positive	0	0.0%	0	0.0%

Source dataset: ADIMM.xpt

Immunogenicity data was reviewed for Parts 1 and 2 combined in the Applicant's Week 48 CSR Table 41 with anti-drug antibody positivity occurring infrequently overall and balanced between the two arms. Neutralizing antibodies (Week 48 CSR Table 42) were also infrequent and balanced between the two arms. Overall the anti-drug antibody and neutralizing antibody rates were low and balanced between the two arms (Week 48 CSR Table 43).

Please also refer to Dr. Brian Furmanski's review for BLA 761074 for further details regarding immunogenicity.

Reviewer Comments: ***Table 14.3.4.1.4.2a in the Week 24 CSR reported in the EU-Herceptin arm at Cycle 9 Week 24, there were no patients with positive ADA. FDA review of the ADIMM dataset showed 1 patient with positive ADA in the EU-Herceptin arm at Week 24. However this discrepancy is unlikely to have a significant clinical safety impact. Mylan Week 48 CSR Tables 41-45 were reviewed with no meaningful differences for ADA and Nab and low positivity overall.***

7.5. Other Safety Explorations

None

7.6. Additional Safety Evaluations

7.6.1. Human Carcinogenicity

Trastuzumab is not known to cause secondary malignancies. An evaluation of second primary malignancies found one patient on the EU-Herceptin arm that developed lymphangiosis carcinomatosis.

Reviewer Comments: ***No safety concerns noted.***

7.6.2. Human Reproduction and Pregnancy Data

There has been no reported MYL-1401O exposure in pregnant women in 3001. There have been no reported embryo-fetal toxicities.

Reviewer Comments: ***No safety concerns noted.***

7.6.3. Pediatrics and Assessment of Effects on Growth

There has been no MYL-1401O exposure in pediatric patients in 3001.

Reviewer Comments: ***No safety concerns noted.***

7.6.4. Overdose, Drug Abuse Potential, Withdrawal and Rebound

There was no experience of overdose in 3001. The highest dose given was 8 mg/kg, which is the same as the loading dose.

Reviewer Comments: ***No safety concerns noted.***

7.7. Additional Submissions / Safety Issues

There are no additional safety issues that were not presented elsewhere in this review.

8. Postmarket Experience

MYL-1401O is not marketed in any country. There is no postmarket safety data.

9. Appendices

9.1. Literature Review/References

1: NCI: SEER, Cancer Stat Facts: Breast Cancer, https://seer.cancer.gov/statfacts/html/breast.html, Accessed June 30, 2017.

2: NCI: SEER, Cancer Stat Facts: Stomach Cancer, https://seer.cancer.gov/statfacts/html/stomach.html, Accessed June 30, 2017.

3: Bang, et al., The Lancet, 2010, 376, 687-697

4: Nahta, et al., Oncogene, 2007, 26, 3637-3643

5: Pupa, et al., Oncogene, 1993, 8, 2917-2923

6: Hayes, et al., Clinical Cancer Research, 2001, 7, 2701-2711

7: Arnould, et al., British Journal of Cancer, 2006, 94, 2559-2267

8: Wen, et al., Oncogene, 2006, 25, 6986-6996

9: Gasparini, et al., Breast Cancer Research and Treatment, 2007, 101, 355-365

10: Marty, et al., Journal of Clinical Oncology, 2005, 4265-4274

11: Slamon, et al., New England Journal of Medicine, 2001, 365, 783-792

12: Baselga, et al., New England Journal of Medicine, 2012, 366, 109-119

13: Swain, et al., New England Journal of Medicine, 2015, 372, 724-734

9.2. Labeling Recommendations

The following changes were made to the US-Herceptin label:

1. References specific to gastric cancer, including Study 7, were removed from the label given orphan drug exclusivity expiring October 20, 2017
2. Per guidance for biosimilars, throughout the label:
    a. “trastuzumab” refers to US-Herceptin
    b. “trastuzumab product(s)” refers to US-Herceptin and biosimilars
    c. “Ogivri” refers to MYL-1401O
3. Highlights of Prescribing Information
    a. Product name changed to “OGIVRI”

   b. Full product title changed to "OGIVRI (trastuzumab-dkst)"
   c. Added description of biosimilar and biosimilarity of Ogivri
4. Section 1 Indications and Usage
   a. CDRH was consulted regarding the companion diagnostic language and the following agreed upon: *"Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product."*
5. Section 3 Dosage Forms and Strength
   a. Identifying characteristics of the dosage were added

9.3. Advisory Committee Meeting

This application was presented at the ODAC meeting on July 13, 2017. The committee discussed the totality of evidence for analytical similarity, clinical similarity, and extrapolation to support licensure for all proposed indications (HER2 positive breast cancer in the adjuvant and metastatic settings and metastatic HER2 positive gastric cancer). All 16 members of the voting committee voted yes to the voting question "Does the totality of the evidence support licensure of MYL-1401O as a biosimilar product to US-Herceptin for the following indications for which US-Herceptin is licensed and for which the Applicant is eligible for licensure (HER2 positive breast cancer in the metastatic and adjuvant settings)?"

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/s/

SUPARNA B WEDAM
08/01/2017

JENNIFER J GAO
08/01/2017

LIJUN ZHANG
08/01/2017

SHENGHUI TANG
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RAJESHWARI SRIDHARA
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08/02/2017