APPLICATION NUMBER:

761074Orig1s000

NON-CLINICAL REVIEW(S)
MEMORANDUM

Date: August 1, 2017
From: Todd Palmby, PhD
Pharmacology/Toxicology Supervisor
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)
To: File for 351(k) BLA 761074 for Ogivri (MYL-1401O)
Re: Approvability for Pharmacology and Toxicology

The nonclinical data submitted to this BLA were reviewed by Haw-Jyh Chiu, PhD. The nonclinical findings are summarized in the “Executive Summary” section of the Pharmacology/Toxicology BLA review. Based on the determination of similarity of Ogivri to US-Herceptin, the nonclinical sections of the labeling should be comparable to those in the labeling for US-Herceptin.

I concur with Dr. Chiu’s conclusion that the submitted pharmacology and toxicology data were adequate to demonstrate similarity in the safety and PK profiles of MYL-1401O and EU-Herceptin in cynomolgus monkeys, and that the relevance of the results of animal studies with EU-Herceptin to the determination of biosimilarity of MYL-1401O to US-Herceptin was justified by an appropriate scientific bridge comprised of comparative analytic data for MYL-1401O, EU-Herceptin and US-Herceptin. I concur that these Pharmacology and Toxicology data support approval of BLA 761074 for Ogivri.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TODD R PALMBY
08/01/2017
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number: 761074
Supporting document: 1
Applicant's letter date: November 3, 2016
CDER stamp date: November 3, 2016
Product: MYL-1401O (Ogivri)
Indication: Treatment of patients with HER2-overexpressing breast cancer
Applicant: Mylan GmbH
Thurgauerstrasse 40
Zurich CH-8050, Switzerland
Review Division: Division of Hematology Oncology Toxicology (DHOT) for Division of Oncology Products 1 (DOP1)
Reviewer: Haw-Jyh Chiu, PhD
Supervisor: Todd R Palmby, PhD
Division Director: John K Leighton, PhD, DABT (DHOT)
Julia Beaver, MD (acting, DOP1)
Project Manager: Charlene Wheeler, MSHS
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1 Executive Summary

1.1 Introduction

On November 3, 2016, Mylan GmbH (the Applicant) submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for MYL-1401O, a proposed biosimilar to US-Herceptin (trastuzumab). Nonclinical in vitro pharmacology, as well as animal pharmacokinetic and toxicology studies in cynomolgus monkeys were submitted in support of this BLA.

1.2 Brief Discussion of Nonclinical Findings

*In vitro*, treatment of cultured rat neonatal and human cardiomyocytes resulted in transient changes in ADP/ATP ratios and oxygen consumption following treatment with MYL-1401O or Herceptin; however, there were no significant differences in these values when comparing cells treated with either antibody.

The Applicant submitted two nonclinical animal studies 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-1401O 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 (relative exposure of MYL1401O to Herceptin ranged from 82.1 to 98.5%, based on geometric mean AUC$_{0-168}$).

In summary, the animal studies provided in the BLA submission did not identify differences in the PK or toxicity profile of MYL-1401O compared to EU-Herceptin in cynomolgus monkeys. Since the Applicant used a non-US-licensed comparator (EU-Herceptin) in nonclinical studies, the Applicant provided a bridge to demonstrate the similarity between EU-Herceptin and US-Herceptin. Results from comparative analytic data provided the necessary bridge between MYL-1401O, EU-Herceptin and US-Herceptin to justify the relevance of the results of the animal studies conducted using EU-Herceptin to a demonstration of biosimilarity of MYL-1401O to US-Herceptin. From the perspective of the Pharmacology and Toxicology discipline, the results of these animal studies were adequate to demonstrate similarity in the safety and PK profiles of MYL-1401O to EU-Herceptin in cynomolgus monkeys. No residual uncertainties were identified by the Pharmacology and Toxicology discipline.
1.3 Recommendations

1.3.1 Approvability
Based on the nonclinical pharmacology and toxicology studies submitted in this BLA, the application is recommended for approval from the perspective of the Pharmacology and Toxicology discipline.

1.3.2 Additional Nonclinical Recommendations
None

1.3.3 Labeling
Refer to the final approved Prescribing Information for the final labeling. Overall, based on the overall determination of similarity of Ogivri to US-licensed Herceptin, the nonclinical sections of the labeling were comparable to those in the label for US-licensed Herceptin.

2 Drug Information

2.1 Drug
Generic Name: Trastuzumab-dkst
Code Name: MYL-1401O (Bmab-200)
Chemical Name: Immunoglobulin G1, anti-(human p185neu receptor) (human-mouse monoclonal r-hu-Mab HER2 g1-chain), disulfide with human-mouse monoclonal rhu0Mab HER2 light γ-chain, dimer
Molecular Formula: Heavy chain: C_{2198}H_{3399}N_{585}O_{672}S_{16}
Light chain: C_{1032}H_{1603}N_{277}O_{335}S_{6}
Molecular Weight: 148 kDa
Structure: MYL-1401O is composed of two identical heavy chains and two identical light chains, which are cross-linked by disulfide bonds. The two heavy chains are further cross-linked by two disulfide bonds. Four intrachain disulfide bonds are also found in each heavy chain, while light chains have each two intrachain disulfide bonds. The heavy chain sequence is made of 450 amino acids and the light chain sequence is made of 214 amino acids. N-glycosylation of trastuzumab occurs at the consensus asparagine found at amino acid 300 in the heavy chain sequence.
Pharmacologic class: HER2/neu receptor antagonist

2.2 Relevant IND/s, NDA/s, and DMF/s
IND 113682

2.3 Drug Formulation
MYL-1401O (440 mg) is a sterile, off-white to pale yellow preservative-free lyophilized powder for intravenous infusion.

Table 1: Composition of MYL-1401O (440 mg) drug product.

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity per Vial (in mg)</th>
<th>Function</th>
<th>Reference to Standards</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>[b][4]</td>
<td>Drug substance</td>
<td>In-house specification</td>
</tr>
<tr>
<td>L-Histidine</td>
<td></td>
<td></td>
<td>USP, Ph. Eur.</td>
</tr>
<tr>
<td>L-Histidine hydrochloride</td>
<td></td>
<td></td>
<td>Ph. Eur.</td>
</tr>
<tr>
<td>monohydrate</td>
<td></td>
<td></td>
<td>USP, Ph. Eur.</td>
</tr>
<tr>
<td>Polyethylene glycol 3350/Macrogol 3350</td>
<td></td>
<td></td>
<td>USP, Ph. Eur.</td>
</tr>
<tr>
<td>D-Sorbitol</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Excerpted from Applicant’s submission)

2.4 Comments on Novel Excipients
None

2.5 Comments on Impurities/Degradants of Concern
The Pharmacology and Toxicology discipline reviewed a literature-based risk assessment for the proposed limit for residual [b][4] in the final drug substance (DS) for Ogivri. [b][4] Potential residual [b][4] level is tested and is quantified by ELISA with a limit of quantification (LOQ) of [b][4] ng/mL and a limit of detection (LOD) of [b][4] ng/mL. The Applicant proposed to set the limit for residual [b][4] in the final DS at NMT [b][4] ng/mL.
2.6 Proposed Clinical Population and Dosing Regimen

- Proposed clinical population: patients with HER2-overexpressing breast cancer.
- Dosing regimen
  - Adjuvant treatment of HER2-overexpressing breast cancer
    - Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel/carboplatin). One week after the last dose of Ogivri, administer 6 mg/kg as an IV infusion over 30 to 90 minutes over three weeks to complete a total of 52 weeks of therapy, or
    - Initial dose of 8 mg/kg over 90 minute IV infusion, then 6 mg/kg over 30 to 90 minute IV infusion every three weeks for 52 weeks.
  - Metastatic HER2-overexpressing breast cancer
    - Initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusion.

2.7 Regulatory Background

FDA held a pre-IND meeting with the Applicant on April 5, 2012 and subsequently received the initial IND 113682 submission for MYL-1401O on November 7, 2012. On November 2, 2016, Mylan submitted this original 351(k) BLA for MYL1401O.

3 Studies Submitted

3.1 Studies Reviewed

<table>
<thead>
<tr>
<th>Pharmacology</th>
<th>Study Number</th>
<th>Study Title</th>
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<tbody>
<tr>
<td>MYL-Her-PC-01</td>
<td>Mitochondrial impact of trastuzumab monoclonal antibodies on cultured human cardiomyocytes.</td>
<td></td>
</tr>
<tr>
<td>MYL-Her-PC-04</td>
<td>The impact of trastuzumab on mitochondrial in cultured primary neonatal rat cardiomyocytes.</td>
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</tr>
</tbody>
</table>
Pharmacokinetics

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Study Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYL-Her-PC-02</td>
<td>Comparative pharmacokinetic profile of Hercules vs. Herceptin® after intravenous infusion of a single dose to cynomolgus monkeys with long term follow-up.</td>
</tr>
</tbody>
</table>

Toxicology

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Study Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYL-Her-PC-03</td>
<td>Compare toxicity and toxicokinetic profile of Hercules vs. Herceptin after weekly intravenous infusion doses to cynomolgus monkeys.</td>
</tr>
</tbody>
</table>

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

The Applicant did not submit any pharmacology studies in the primary pharmacology section of the BLA submission in support of this BLA.

4.2 Secondary Pharmacology

The Applicant did not submit any pharmacology studies in the secondary pharmacology section of the BLA submission in support of this BLA.
4.3 Safety Pharmacology

Study title: Mitochondrial impact of trastuzumab monoclonal antibodies on cultured human cardiomyocytes.

- Study no.: MYL-Her-PC-01
- Study report location: eCTD Section 4.2.1.3.
- Conducting laboratory and location: [redacted]
- Date of study initiation: September 2010
- GLP compliance: No
- QA statement: No
- Drug, lot #, and % purity: Hercules, Batch # DEVBV10-0001
  Herceptin® (EU-sourced), Batch # H0696B01 and H7013B01

Methods and Key Study Findings

- Cultured human cardiomyocytes were treated with 0.0002 – 2 mg/mL MYL-1401O or Herceptin for 8, 24, or 48 hours at 37°C in 24-well plates.
- Parameters evaluated included membrane delta potential, cytochrome c release, respiratory complex I and II activities, production of reactive oxygen species, ADP/ATP ratio and MTT-based viability assay.
- Statistically significant increased ADP/ATP ratio (24 h) and oxygen consumption (all timepoints) were observed in cells treated with Hercules and EU-Herceptin; however, there were no statistically significant differences in any parameters between Hercules- and EU-Herceptin-treated cells.
- No changes in viability were observed.
Study title: The impact of trastuzumab on mitochondrial in cultured primary neonatal rat cardiomyocytes.

Study no.: MYL-Her-PC-04
Study report location: eCTD Section 4.2.1.3.
Conducting laboratory and location: 

Date of study initiation: July 19, 2011
GLP compliance: No
QA statement: No
Drug, lot #, and % purity: Hercules, Batch # V10DEVB-0005 Herceptin® (EU-sourced), Batch # H0745B01

Methods and Key Study Findings

- Cultured primary neonatal rat cardiomyocytes were treated with 0.0002, 0.002, or 2 mg/mL MYL1401O or Herceptin for 8, 24, and 48 h.
- Parameters evaluated included membrane delta potential, oxygen consumption, intracellular ADP, ATP, and ADP/ATP ratio, in the presence of 1% serum.
- A transient mitochondrial stress with partially reversible inhibition of oxygen consumption and an increase in the ADP/ATP ration at 8 h, however, there were no significant differences between MYL-1401O- and Herceptin-treated groups in any of the parameters.
5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study title: Comparative pharmacokinetic profile of Hercules vs. Herceptin® after intravenous infusion of a single dose to cynomolgus monkeys with long term follow-up.

Study no.: MYL-Her-PC-02 (Study Number 8230210)
Study report location: eCTD Section 4.2.2.7.
Conducting laboratory and location: ...
Date of study initiation: September 23, 2010
GLP compliance: No
QA statement: Yes
Drug, lot #, and % purity: Hercules, Batch # DEVB-V10-0001 Herceptin® (EU-sourced), Batch # H0702B01

Key Study Findings

- No significant test article-related toxicity findings were noted in animals administered either MYL1401O or EU-Herceptin.
- Following intravenous infusion administration the systemic availability of Hercules based on \( \text{AUC}_{0-\infty} \) and \( C_{\text{max}} \) was 79.7 and 78.2%, respectively, relative to that of Herceptin.

Methods

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doses:</td>
<td>25 mg/kg</td>
</tr>
<tr>
<td>Frequency of dosing:</td>
<td>Single dose</td>
</tr>
<tr>
<td>Route of administration:</td>
<td>Intravenous infusion (30 min)</td>
</tr>
<tr>
<td>Dose volume:</td>
<td>4 mL/kg</td>
</tr>
<tr>
<td>Formulation/Vehicle:</td>
<td>Sterile water for powder dissolution and 3% saline for final formulation</td>
</tr>
<tr>
<td>Species/Strain:</td>
<td>Cynomolgus monkey/ Macaca fascicularis</td>
</tr>
<tr>
<td>Number/Sex/Group:</td>
<td>6 females/group</td>
</tr>
<tr>
<td>Age:</td>
<td>28 to 31 months old</td>
</tr>
<tr>
<td>Weight:</td>
<td>2.89 to 3.78 kg</td>
</tr>
<tr>
<td>Satellite groups:</td>
<td>None</td>
</tr>
<tr>
<td>Unique study design:</td>
<td>None</td>
</tr>
<tr>
<td>Deviation from study protocol:</td>
<td>None were considered to have had a significant impact on the study results.</td>
</tr>
</tbody>
</table>
Observations and Results

Mortality
There were no early decedents.

Clinical Signs
No remarkable clinical signs were noted.

Skin Observations
- Erythema (grade 1 or 2) was observed in five out of six animals administered Herceptin or MYL1401O 8 hours after IV administration. Erythema (grade 1) was observed 48 hours post-dose in three or one animals administered Herceptin or MYL-1401O, respectively.
- Desquamation was observed 72 hours post-dose in one animal administered Herceptin and one animal administered MYL-1401O.

Body Weights
No remarkable body weight changes were noted.

Hematology
No remarkable findings were noted.

Clinical Chemistry
No remarkable changes in clinical chemistry parameters were noted.

Gross Pathology
No remarkable changes in gross pathology were noted.

Histopathology
Adequate Battery: Yes
Peer Review: No
Histological Findings: No remarkable changes in histopathology were noted.

Toxicokinetics
- One animal (# 10) was excluded from PK analysis due to suspected under-dosing.
- Following intravenous infusion administration the systemic availability of
MYL-1401O based on AUC$_{0-\infty}$ and C$_{\text{max}}$ was 79.7 and 78.2%, respectively, relative to that of Herceptin. The Applicant attributed the differences to the parallel design and low power of this exploratory study which was mostly intended to aid in the design of the subsequent GLP-compliant toxicology study.

Table 2. Summary of toxicokinetics parameters following a single intravenous infusion administration of EU-Herceptin and MYL01401O (Hercules) in cynomolgus monkeys.

(Excerpted from Applicant’s submission)

Anti-Drug Antibody (ADA) Analysis
No ADA was detected in either treatment groups.

Dosing Formulation Analysis
The dosing formulations for EU-Herceptin and MYL-1401O were 102 and 101% of the nominal concentrations.

5.2 Toxicokinetics
See discussion within the review of the toxicology study.
6 General Toxicology

6.1 Single-Dose Toxicity

The Applicant did not submit any single-dose toxicity study reports in support of this BLA.

6.2 Repeat-Dose Toxicity

Study title: Compare toxicity and toxicokinetic profile of Hercules vs. Herceptin® after weekly intravenous infusion doses to cynomolgus monkeys.

Study no.: MYL-Her-PC-03 (Study Number 8230211)
Study report location: eCTD Section 4.2.3.2.
Conducting laboratory and location: (b) (4)
Date of study initiation: October 20, 2010
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Bmab-200 (Hercules), Batch # DEVBV10-0001
Herceptin®, Batch # H0713B01 (EU-sourced)

Key Study Findings

- No remarkable test article-related toxicity findings were noted in animals administered either MYL-1401O or EU-Herceptin.
- Based on geometric mean AUC$_{0-168}$, the relative exposure of MYL-1401O to EU-Herceptin ranged from 82.1 to 98.5% in cynomolgus monkeys.
Methods

Doses: 0 (3% saline), 25, 50 mg/kg/week
Frequency of dosing: Weekly (on Days 1, 8, 15, 22, and 29)
Route of administration: Intravenous infusion
Dose volume: 4 mL/kg
Formulation/Vehicle: Sterile water for powder dissolution and 3% saline for final formulation
Species/Strain: Cynomolgus monkey/ *Macaca fascicularis*
Number/Sex/Group: 3
  Age: 102 to 115 weeks old
  Weight: 2.22 to 2.97 kg
Satellite groups: None
Unique study design: None
Deviation from study protocol: None reported

Observations and Results

Mortality

There were no early decedents.

Clinical Signs

No remarkable clinical signs were noted.

Skin Observations

- Skin observations were performed according to a modified Draize index (as per [SOP](#)). Observations of the dosing sites were carried out pre-dose, on return to the home cage and 1, 2, 3, and 4 hours post-end of infusion.
- No remarkable erythema, edema, atonia, desquamation, or fissuring were noted.

Body Weights

No remarkable body weight changes were noted.

ECG and Blood Pressure

No test article-related changes in ECG traces and blood pressure were noted.

Hematology

No test article-related changes in hematology parameters were noted.
Clinical Chemistry
No remarkable changes in clinical chemistry parameters were noted.

Urinalysis
No remarkable changes in urine volume and specific gravity were noted.

Gross Pathology
No remarkable changes in gross pathology were noted.

Organ Weights
No remarkable changes in organ weight were noted.

Histopathology
Adequate Battery: Yes
Peer Review: No
Histological Findings: No remarkable histopathology findings were noted.

Toxicokinetics
- On Days 1 and 22, systemic exposure to EU-Herceptin and MYL-1401O increased in a generally dose-dependent manner over the 25 to 50 mg/kg/week dose range.
- Following repeated dosing, accumulation of EU-Herceptin and MYL-1401O was noted. Mean accumulation ratios ranged from 2.0 to 2.5 and 1.9 to 2.4 in EU Herceptin- and MYL-1401O-treated animals, respectively.
- There were no sex-dependent differences in PK parameters.
- Based on geometric mean AUC$_{0-168}$, the relative exposure of MYL-1401O relative to EU-Herceptin ranged from 82.1 to 98.5% in cynomolgus monkeys.
Table 3. Summary of AUC$_{0-168}$ and $C_{\text{max}}$ following once weekly administration of EU-Herceptin or MYL-1401O (Hercules) in cynomolgus monkeys.

<table>
<thead>
<tr>
<th>Weekly Dose (mg/kg)</th>
<th>0 (Control)</th>
<th>25 (Herceptin®)</th>
<th>25 (Hercules)</th>
<th>50 (Herceptin®)</th>
<th>50 (Hercules)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Animals</td>
<td>M: 3</td>
<td>F: 3</td>
<td>M: 3</td>
<td>F: 3</td>
<td>M: 3</td>
</tr>
</tbody>
</table>

### Toxicokinetics:

#### AUC$_{0-168}$ (µg.h/mL)

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Arithmetic Mean</th>
<th>NA</th>
<th>NA</th>
<th>49600</th>
<th>47700</th>
<th>43400</th>
<th>36300</th>
<th>89800</th>
<th>80900</th>
<th>84300</th>
<th>85100</th>
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<tbody>
<tr>
<td></td>
<td>CV%</td>
<td>4.3</td>
<td>12.0</td>
<td>4.8</td>
<td>NC</td>
<td>10.8</td>
<td>9.1</td>
<td>17.0</td>
<td>12.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Geometric Mean</td>
<td>NA</td>
<td>NA</td>
<td>49500</td>
<td>47500</td>
<td>43400</td>
<td>36300</td>
<td>89400</td>
<td>80700</td>
<td>83500</td>
<td>84700</td>
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<tr>
<td></td>
<td>Geometric CV%</td>
<td>NA</td>
<td>NA</td>
<td>4.3</td>
<td>11.9</td>
<td>4.8</td>
<td>NC</td>
<td>10.7</td>
<td>9.0</td>
<td>16.9</td>
<td>12.3</td>
</tr>
<tr>
<td>Day 22</td>
<td>Arithmetic Mean</td>
<td>NA</td>
<td>NA</td>
<td>126000</td>
<td>93600</td>
<td>89100</td>
<td>90800</td>
<td>190000</td>
<td>193000</td>
<td>162000</td>
<td>196000</td>
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<tr>
<td></td>
<td>CV%</td>
<td>14.0</td>
<td>1.7</td>
<td>9.5</td>
<td>11.5</td>
<td>18.7</td>
<td>9.8</td>
<td>4.3</td>
<td>22.6</td>
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<tr>
<td></td>
<td>Geometric Mean</td>
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<td>NA</td>
<td>125000</td>
<td>93600</td>
<td>88800</td>
<td>90400</td>
<td>188000</td>
<td>192200</td>
<td>162000</td>
<td>192200</td>
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<tr>
<td></td>
<td>Geometric CV%</td>
<td>NA</td>
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<td>14.2</td>
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<td>19.1</td>
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#### AUC$_{0-168}$ (norm)

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Arithmetic Mean</th>
<th>NA</th>
<th>NA</th>
<th>1970</th>
<th>1860</th>
<th>1700</th>
<th>1400</th>
<th>1780</th>
<th>1530</th>
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<th>1620</th>
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<td>4.3</td>
<td>22.6</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Geometric Mean</td>
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#### C$_{\text{max}}$

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<th>0 (Control)</th>
<th>25 (Herceptin®)</th>
<th>25 (Hercules)</th>
<th>50 (Herceptin®)</th>
<th>50 (Hercules)</th>
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<td>F: 3</td>
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### Toxicokinetics (cont.):

#### C$_{\text{max}}$ (µg/mL)

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<th>NA</th>
<th>723</th>
<th>573</th>
<th>692</th>
<th>456</th>
<th>1270</th>
<th>1150</th>
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<th>1210</th>
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<tr>
<td></td>
<td>Geometric Mean</td>
<td>NA</td>
<td>NA</td>
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<td>573</td>
<td>692</td>
<td>456</td>
<td>1270</td>
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<td>1150</td>
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<td>NA</td>
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<td>NA</td>
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<td>1600</td>
<td>1110</td>
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<td>2000</td>
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<td>1660</td>
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<td>19.1</td>
<td>9.0</td>
<td>14.9</td>
<td>17.6</td>
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<tr>
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<td>959</td>
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#### C$_{\text{max}}$ (norm)

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<th>NA</th>
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<th>23.0</th>
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<tr>
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<td>NA</td>
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<td>27.0</td>
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<td>22.4</td>
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<td>Geometric CV%</td>
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<td>NA</td>
<td>9.6</td>
<td>6.3</td>
<td>1.1</td>
<td>NC</td>
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<td>4.8</td>
<td>11.2</td>
<td>7.7</td>
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<td>NA</td>
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<td>9.0</td>
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<tr>
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#### $t_{\text{max}}$ (h)

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<th>0.520</th>
<th>0.500</th>
<th>2.04</th>
<th>0.500</th>
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</thead>
<tbody>
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<td>Day 22</td>
<td>Median</td>
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<td>NA</td>
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<td>0.520</td>
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<td>0.500</td>
<td>0.500</td>
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</table>

#### CL (mL/hr/kg)

<table>
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<tr>
<th>Day 22</th>
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<th>NA</th>
<th>0.203</th>
<th>0.282</th>
<th>0.262</th>
<th>0.276</th>
<th>0.265</th>
<th>0.267</th>
<th>0.302</th>
<th>0.250</th>
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</thead>
<tbody>
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<td></td>
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<td>14.2</td>
<td>1.7</td>
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<td></td>
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<tr>
<td></td>
<td>Geometric Mean</td>
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<td>NA</td>
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<td>0.282</td>
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<td>0.266</td>
<td>0.302</td>
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NA - Not applicable, NC - Not calculable

(Excerpted from Applicant’s submission)
Table 4. Summary of relative exposure to MYL-1401O and EU-Herceptin in cynomolgus monkeys.

<table>
<thead>
<tr>
<th>Occasion</th>
<th>Dose Level (mg/kg/week)</th>
<th>Gender</th>
<th>Fw (%) (Based on Geometric Mean AUC(0-168))</th>
<th>Fw (%) (Based on Geometric Mean Cmax)</th>
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</thead>
<tbody>
<tr>
<td>Day 1</td>
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<td>Male</td>
<td>86.3</td>
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<td>75.2</td>
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<tr>
<td></td>
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<td>Male</td>
<td>91.8</td>
<td>89.1</td>
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<tr>
<td></td>
<td></td>
<td>Female</td>
<td>105.7</td>
<td>105.9</td>
</tr>
<tr>
<td>Day 22</td>
<td>25</td>
<td>Male</td>
<td>77.3</td>
<td>68.7</td>
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<td>Female</td>
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<td>85.6</td>
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<td>Female</td>
<td>108.5</td>
<td>107.3</td>
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</tbody>
</table>

(Excerpted from Applicant’s submission)

Dosing Formulation Analysis
The dosing formulation for EU-Herceptin and MYL-1401O ranged from 92.8 to 104.8%, which was within the acceptance criteria of %.

7 Genetic Toxicology
The Applicant did not submit any genetic toxicology study reports in support of this BLA submission.

8 Carcinogenicity
The Applicant did not submit any carcinogenicity study reports in support of this BLA submission.

9 Reproductive and Developmental Toxicology
The Applicant did not submit any reproductive and developmental toxicology study reports in support of this BLA submission.
10 Special Toxicology Studies
None

11 Integrated Summary and Safety Evaluation
Refer to Executive Summary.

12 Appendix/Attachments
References
1. [b] (4)
2. [b] (4)
3. [b] (4)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HAW-JYH CHIU
08/01/2017

TODD R PALMBY
08/01/2017