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APPLICATION NUMBER:

761074Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology
351(k) Biosimilar Review

351(k) BLA Number	761074
Applicant	Mylan GmbH
Submission Date	November 11, 2016
Submission Type	Standard
Link to EDR	Application 761074 - 0000 -0000 (ORIG-1)
Brand (Generic) Name	Ogivri (MYL-1401O)
Dosage Form and Strength	(b) (4) of lyophilized drug product in a (b) (4) sterile glass vial
Route of Administration	Intravenous infusion
Proposed Indication(s)	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 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
Associated IND	113682
Reference Product Information (U.S.-licensed)	
Brand (Generic) Name	Herceptin (Trastuzumab)
Dosage Form and Strength	440 mg of lyophilized drug product in a (b) (4) sterile glass vial
OCP Review Team Signers	
OCP Review Team	Brian D. Furmanski., Ph.D. Sarah J. Schrieber., Pharm.D.
OCP Final Signatory	Nam Atiqur Rahman., Ph.D.

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1. EXECUTIVE SUMMARY

This Biologic License Application (BLA) for MYL-1401O has been submitted under Section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)). The applicant is seeking approval for MYL-1401O as a proposed biosimilar to US-licensed Herceptin licensed under BLA 103792 by Genentech. The applicant is seeking licensure for the treatment of adjuvant or metastatic breast cancer indications for which US-licensed Herceptin is currently approved. The applicant submitted pharmacokinetic (PK) similarity data and a comparative clinical study to support a demonstration of no clinical meaningful difference between MYL-1401O and US-licensed Herceptin. Study MYL-HER-1002 was a single-dose, randomized, double-blind, 3-arm, parallel group study in 120 healthy male subjects designed to determine the PK similarity of MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin following a single 8 mg/kg intravenous (IV) dose. The 90% confidence intervals (CI) for all three pairwise comparisons of the pre-specified PK endpoints were within the pre-specified limits of 80 to 125%. The results of the study established the PK similarity between MYL-1401O and US-licensed Herceptin based on the primary PK endpoint of $AUC_{0\text{-inf}}$. The study also established the PK portion of the scientific bridge between MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin, which supports the use of EU-approved Herceptin in the comparative clinical Study MYL-HER-3001.

Overall, Study MYL-HER-1002 supports a demonstration of PK similarity between MYL-1401O and US-licensed Herceptin, as well as the PK portion of the scientific bridge between MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin. The scientific bridge along with the analytical similarity allows for relying on data from the study using EU-approved Herceptin as a comparator product for the overall biosimilarity assessment. In conclusion, the PK results support a demonstration of no clinically meaningful difference between MYL-1401O and US-licensed Herceptin and add to the totality of the evidence to support a demonstration of biosimilarity MYL-1401O and US-licensed Herceptin.

The incidence of immunogenicity for MYL-1401O and EU-approved 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 PK endpoints was observed. Therefore, the data indicates that there is no increase in immunogenicity risk for MYL-1401O as compared to EU-approved Herceptin, which supports the demonstration that there are no clinically meaningful differences between MYL1401O and US-licensed Herceptin.

1.1 Recommendations

The Office of Clinical Pharmacology recommends approval of MYL-1401O based on demonstration of PK similarity between MYL-1401O and US-licensed Herceptin.

Review Issue	Recommendations and Comments
Pivotal evidence of PK similarity	PK similarity was demonstrated between MYL-1401O and US-licensed Herceptin, as well as the PK portion of the scientific bridge between MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin. The 90% CI of the geometric mean ratio for each product pairwise comparison for the primary pre-specified PK endpoint of $AUC_{0\text{-}inf}$ fell within the pre-specified margin of 80 to 125%.
Evidence of immunogenicity comparability	The results of Study MYL-HER3001 indicate similar incidence of anti-drug antibodies (ADA) for MYL-1401O to EU-approved Herceptin.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Clinical Pharmacology and Pharmacokinetics

MYL-1401O is a proposed biosimilar to US-licensed Herceptin. US-licensed Herceptin (trastuzumab) is a humanized $IgG_1\kappa$ monoclonal antibody directed against an epitope on the extracellular juxtamembrane domain of HER2. Multiple mechanisms of action have been proposed for trastuzumab, including inhibition of HER2 receptor dimerization, increased destruction of the endocytic portion of the HER2 receptor, inhibition of extracellular domain shedding, and activation of cell-mediated immune defenses such as ADCC activity. MYL-1401O is produced using a mammalian cell line expanded in bioreactor cultures followed by a drug substance purification process that includes various steps designed to isolate and purify the protein product. Details on the clinical pharmacology of US-licensed Herceptin can be found in the product label (USPI).

In Study MYL-HER-1002, the 90% confidence intervals (CI) for the geometric mean ratios of the primary PK endpoint of $AUC_{0\text{-}inf}$ and secondary PK endpoint of C_{Max} were within the pre-specified limits of 80% to 125% in the pairwise comparisons between MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin, as summarized in **Table 1**.

Table 1. Summary statistical analyses for PK similarity (Study MYL-HER-1002)

Comparison	Geometric Mean Ratio* (90% CI)	
	$AUC_{0\text{-}inf}$	C_{Max}
MYL-1401O vs US-licensed Herceptin	95.2 (89.3-101.5)	101.1 (95.8-106.4)
MYL-1401O vs EU-approved Herceptin	96.6 (90.7-102.8)	104.0 (98.8-109.4)
EU-approved Herceptin vs US-licensed Herceptin	98.5 (92.4-105.1)	97.1 (92.2-102.4)

*Presented as percent

Overall, the submitted clinical pharmacology study adequately demonstrated similarity of PK among MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin. The PK results support a demonstration of no clinically meaningful differences between MYL-1401O and US-licensed Herceptin, and add to the totality of the evidence to support a demonstration of biosimilarity of MYL-1401O and US-licensed Herceptin.

The incidence of immunogenicity for MYL-1401O and EU-approved Herceptin was compared in a multiple-dose, parallel-arm study in 493 patients with metastatic 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 PK endpoints was observed. Therefore, the data indicates that there is no increase in immunogenicity risk for MYL-1401O as compared to EU-approved Herceptin, which supports the demonstration that there are no clinically meaningful differences between MYL-1401O and US-licensed Herceptin.

2.2 Outstanding Issues

None

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Regulatory Background

3.1.1 Describe relevant regulatory history for the review of this 351(k) BLA.

MYL-1401O is a proposed biosimilar to US-licensed Herceptin. The applicant is seeking licensure for the treatment of adjuvant or metastatic breast cancer indications for which US-licensed Herceptin is currently approved. The applicant is also seeking approval for metastatic gastric or gastroesophageal junction adenocarcinoma; however it is currently protected by orphan drug exclusivity expiring on October 20, 2017.

3.2 Clinical Pharmacology Review Questions

3.2.1 What are the design features of the clinical pharmacology and/or clinical studies to support biosimilarity?

The applicant conducted one clinical pharmacology study and one comparative clinical study, as is described in **Table 2**.

Table 2. **Summary of relevant clinical studies**

Protocol	Title	Subjects	Objectives	Route/Dose/Duration
PK Similarity Study				
MYL-HER-1002	A single-dose, randomized, double-blind, 3-arm, parallel-group study designed to compare the pharmacokinetic profiles of MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin in healthy subjects.	Healthy (N=120)	PK similarity	Single IV 8 mg/kg
Comparative Clinical Study				
MYL-HER-3001	A multicenter, randomized, double-blinded, parallel group design to assess the efficacy and safety of MYL-1401O compared to EU-approved Herceptin plus docetaxel or paclitaxel in patients with HER2-positive MBC	MBC (N=642)	Efficacy, safety, immuno-genicity	Loading dose 8 mg/kg IV followed by a maintenance dose 6 mg/kg Q3W with docetaxel 75 mg/m^2 or paclitaxel 80 mg/m^2 Q3W

PK: pharmacokinetics; IV, intravenous; MBC: metastatic breast cancer

Study MYL-HER-1002 was used to support PK similarity. This study was a single-dose, randomized, double-blind, 3-arm, parallel-group study designed to compare the pharmacokinetic profiles of MYL-1401O (n = 42), US-licensed Herceptin (n = 37), and EU-approved Herceptin (n = 41) administered as a single 8 mg/kg IV infusion over 90 minutes to healthy male volunteers (N=120). The pre-specified PK endpoints evaluated were $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{Max}. PK similarity was concluded if the 90% CI of the geometric mean ratio for each pairwise comparison between MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin were within the pre-specified limits of 80% to 125%.

The study design of Study MYL-HER-1002 is considered adequate due to the following reasons:

1. 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.
2. 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.
3. Considering PK assay sensitivity, dose-exposure linearity, and tolerability, a single IV dose of 8 mg/kg trastuzumab is considered appropriate for a PK similarity study.

MYL-HER-3001 was a comparative clinical study in patients with HER2-positive MBC. Refer to Clinical review for further details.

3.2.2 What are the endpoints in the clinical pharmacology and/or clinical studies to support biosimilarity?

In Study MYL-HER-1002, the pre-specified PK similarity criteria for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{Max} were that the 90% CI of the geometric mean ratio should lie within 80-125%. This margin proposed by the applicant was acceptable.

- PK serum samples were collected on Day 1 at predose 0.75, 1.5, 3, 6, 9, 24, 48, 96, 168, 240, 336, 504, 672, 1008, 1344, and 1680 hours post dose.

3.2.3 Are the pharmacologically active moieties of the proposed biosimilar and the reference product in plasma (or other biological matrix) appropriately identified and measured to assess the PK parameters?

Yes. See **Section 4.1** for details. Trastuzumab levels were measured in serum by a validated enzyme-linked immunosorbent assay (ELISA).

3.2.4 Is PK similarity met?

Yes, PK similarity between MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin was demonstrated, where the 90% confidence intervals of geometric mean ratios of PK endpoints for each product pairwise comparison were contained within prospectively defined criteria of 80 to 125% (**Table 3**). Also, as shown in **Figure 1**, the PK profiles of MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin overlay each other. A summary of the 8 mg/kg IV single dose PK parameters from Study MYL-HER-1002 for each product is shown in **Table 4**.

Table 3. Summary statistical analyses for PK similarity (Study MYL-HER-1002)

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

*Presented as percent

Figure 1. Mean serum trastuzumab concentration vs. time profile (Study MYL-HER-1002)

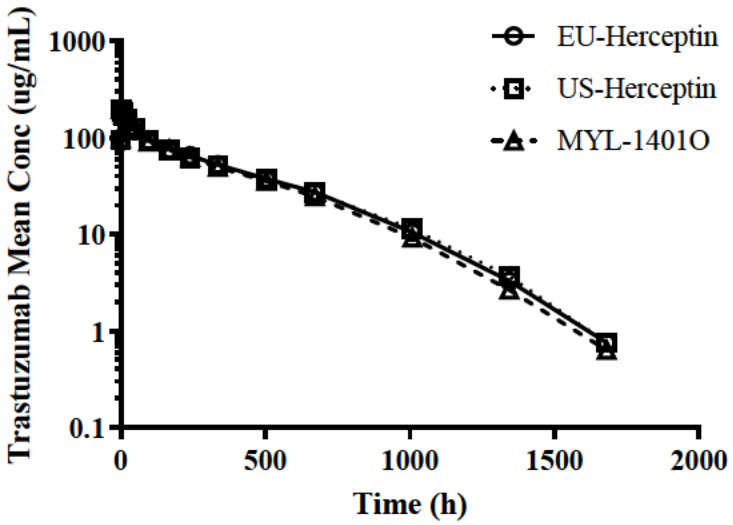

Table 4. Summary of PK parameters (Study MYL-HER-1002)

PK parameters	Geometric Mean (% CV)		
	MYL-1401O (n=42)	US-licensed Herceptin (n=37)	EU-approved Herceptin (n=41)
C_{Max} (µg/mL)	205 (13%)	204 (15%)	198 (14%)
$AUC_{0\text{-}t}$ (µg /mL*hr)	48,949 (17%)	51,244 (14%)	50,621(20%)
$AUC_{0\text{-}inf}$ (µg/mL*hr)	49,140 (17%)	51,643 (14%)	50,876 (20%)
V_c (L)	3.09 (26%)	3.28 (23%)	3.23 (28%)
CL (L/day)	0.313 (17%)	0.298 (14%)	0.301 (20%)

% CV: coefficient of variation, V_c: central volume, CL: clearance

Immunogenicity

3.2.6 Is the immunogenicity assay capable of detecting the antidrug antibodies (ADA) in the presence of concentration of product in the study samples?

Detection, confirmation, and titration of ADAs were determined utilizing a Meso Scale Discovery assay. The drug tolerance of the ADA assay was 175 µg/mL with a positive control reference concentration of 31.25 ng/mL. The sensitivity, low positive control, and high positive control of the ADA assay were 2.46, 20, and 1000 ng/mL, respectively.

Refer to the immunogenicity assay review by the Office of Biological Products review for details regarding the assays.

3.2.7 Is the sampling plan adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of anti-drug antibodies (ADA) formation?

The sampling schedules in the studies were appropriate to minimize interference from the presence of the product in the samples, if the ADA assay is not drug-tolerant. The sampling schedules for the studies were as follows:

- Study MYL-HER-1002: Predose on Day 1 and post-dose on Day 71 or at early termination.
- Study MYL-HER-3001: Pre-dose weeks 0 (baseline), 6, 12, 18, 24, 36, and 48

1.2.8 What is the incidence of anti-drug antibodies (ADA)? (Provide the incidence of pre-existing antibodies at baseline and the incidence of ADA throughout the study.)

In Study MYL-HER-1002, no positive binding ADA were observed in subjects at pre- and pose-dose of MYL-1401O, US-licensed Herceptin and EU-approved Herceptin.

In Study MYL-HER-3001, similar incidences of ADAs through week 48 were observed for MYL-1401O and EU-approved Herceptin (**Table 5**) when utilizing a confirmatory cut-point with a 1.0% false-positive error rate.

Table 5. Immunogenicity results for binding ADA in Study MYL-HER-3001

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

The data indicate that there is no increase in immunogenicity risk for MYL-1401O as compared to EU-approved Herceptin, and supports the demonstration that there are no clinically meaningful differences between MYL-1401O and US-licensed Herceptin. Of note, a scientific bridge was established between MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin, supporting the relevance of comparative data, including immunogenicity data, generated using EU-approved Herceptin to support a demonstration of no clinically meaningful differences between MYL-1401O and US-licensed Herceptin.

3.2.9 Do the anti-drug antibodies (ADA) have neutralizing activity?

FDA determined that based on the applicant's ADA assessment, which included the specific assay capabilities for detection of ADA, the results observed from Study MYL-HER-3001, and what is publicly known about the incidence and nature of both ADA and neutralizing ADA to US- licensed Herceptin, that an evaluation of neutralizing ADA was not necessary to further inform on the immunogenicity assessment of MYL-1401O. Thus, neutralizing ADA results from Study MYL-HER-3001 was not reviewed.

3.2.10 What is the impact of anti-drug antibodies (ADA) on the PK, activity, and safety of the therapeutic protein?

No apparent impact of ADA on PK, activity, or safety endpoints was observed from Study MYL-HER-3001 (data not shown).

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 Pharmacokinetics

4.1.1.1 How are the concentrations of the pharmacologically active moieties (parent and/or any relevant catabolites) measured in the plasma and other matrices in the clinical pharmacology studies?

Total serum trastuzumab samples were determined using a validated Enzyme-Linked Immunosorbent Assay (ELISA). The method for the quantification of MYL-1401O, US-licensed Herceptin and EU-approved Herceptin in human serum was validated at (b) (4) (Report #'s 8246068, 8246062, and 8264133). The partial validation report (8294527) was reviewed and deemed sufficient to support the quantitation of US-licensed Herceptin in Study MYL-HER-1002. A summary of the ELISA assay validation for MYL-1401O and EU-approved Herceptin is show in Table 6.

Briefly, monoclonal Anti-idiotype antibody to trastuzumab is coated on a 96-well microtiter plate and then blocked using a non-specific protein (SuperBlock). MYL-1401O or EU-approved Herceptin is used to prepare calibration standards in neat human serum. QCs are made by spiking MYL-1401O or EU-approved Herceptin in neat human serum. Following the minimum required dilution, calibration standards and QCs are added to designated sample wells. The bound antibody is detected by the subsequent additions of HRP-conjugated anti-idiotype antibody to trastuzumab and the chromogenic substrate TMB. Color development is stopped using sulfuric acid and the product of this reaction is detected with a spectrophotometer at wavelength of 450 nm, with a background subtraction at 630 nm. The concentration of MYL-1401O or EU-approved Herceptin in samples is then back-calculated from the calibration curve. Data was collected using a VersaMax Plate Reader and processed using Softmax Pro GxP version 5.0.1.

Table 6. Summary of MYL-1041O and EU-approved Herceptin Assay Validation Reports

Analyte	EU-approved Herceptin	MYL-1041O
Matrix	Human Serum	
Reference or analytical standard	Lot H4078B02, 150.0 mg/Vial, 20.70 mg/mL H0702B01, 150.0 mg/Vial, 21.55 mg/mL	Lot DBBMPTV12-0003, 150.0 mg/Vial, 20.80 mg/mL DEVB-V10-0001, 150.0 mg/Vial, 21.5 mg/mL & 22.9 mg/mL
Minimum dilution	1:10	
Standard curve concentrations (ng/mL)	20 (anchor), 75 (LLOQ), 200, 320, 450, 600, 800, 1100, 1500 (ULOQ) and 2000 (anchor) ng/mL	
Limit of detection	20 ng/mL	
LLOQ	75 ng/mL	
ULOQ	1500 ng/mL	
Standard curve accuracy (%Bias) from 75-1500 ng/ml	-4.1% and 2.3%	-1.2% and 3.8%
Inter-assay Precision (%CV)	LLOQ (75 ng/ml): 7.6% Low (250 ng/ml): 4.5%% Mid (750 ng/ml): 5.7%% High (1150 ng/ml): 12.2 % ULOQ (1500 ng/ml): 12.0%	LLOQ (75 ng/ml): 4.4% Low (250 ng/ml): 9.9% Mid (750 ng/ml): 6.2% High (1150 ng/ml): 8.9% ULOQ (1500 ng/ml): 12.2%
Inter-assay Accuracy	LLOQ (75 ng/ml): -5.6% Low (250 ng/ml): -10.3% Mid (750 ng/ml): -8.8% High (1150 ng/ml): -10.6% ULOQ (1500 ng/ml): -12.2%	LLOQ (75 ng/ml): 2.6% Low (250 ng/ml): -6.6% Mid (750 ng/ml): -8.6% High (1150 ng/ml): -8.0% ULOQ (1500 ng/ml): - 1.9 %
Intra-assay Precision (%CV)	LLOQ (75 ng/ml): 3.9% Low (250 ng/ml): 2.2% Mid (750 ng/ml): 5.7% High (1150 ng/ml): 7.5% ULOQ (1500 ng/ml): 18.6%	LLOQ (75 ng/ml): 11.2% Low (250 ng/ml): 2.8% Mid (750 ng/ml): 3.3% High (1150 ng/ml): 3.1% ULOQ (1500 ng/ml): 8.2%
Intra-assay Accuracy	LLOQ (75 ng/ml): -2.6% Low (250 ng/ml): -10.8% Mid (750 ng/ml): -11.7% High (1150 ng/ml): -10.9% ULOQ (1500 ng/ml): -4.7%	LLOQ (75 ng/ml): 11.1% Low (250 ng/ml): - 4.1% Mid (750 ng/ml): -13.4% High (1150 ng/ml): -14.5% ULOQ (1500 ng/ml): -10.7%
Hook effect	No hook effect was observed at the ULOQ	
Linearity in normal human serum sample (% difference from preceding dilution)	Dilutional linearity from 1:100 through 1:2000 with mean accuracy ranging between 102.9% and 119.2	Dilutional linearity from 1:100 through 1:2000 with mean accuracy ranging between 98.1% and 111.3

Interference	No matrix effect	
Analyte Room Temperature:	Mean accuracy ranging between 81.8% - 87.5% for 8 hours and 84.3%- 86.0% and 24 hours	Mean accuracy ranging between 79.9% - 83.9% for 8 hours and 81.6%- 82.2% and 24 hours
Analyte Freeze/Thaw Stability:	Mean accuracy ranging from 91.7% and 101.7% over 6 cycles	Mean accuracy ranging from 79.8% and 82.8% over 6 cycles
Long-term Stability	-20ºC and -80º: 181 and 729 days, respectively	

In Study MYL-HER1002, total serum trastuzumab levels were determined though the same ELISA assay as described above and analyzed by (b) (4). A total of 84 sample analysis batches were performed. Of the 84 analysis batches 4 runs failed due to the QC not meeting the pre-specified analysis criteria and 2 runs failed due to labelling errors. Incurred sample reproducibility was performed on 152 samples and 99.3% of samples met the pre-specified criteria. One sample exhibited poor precision and was therefore classed as a failure. Samples were stored at -80°C until time of analysis. The maximum sample storage duration between collection and analysis for MYL-1041O samples was 213 days, which was within the established stability interval of 729 days. The maximum sample storage duration between collection and analysis for EU-approved Herceptin and US-licensed Herceptin samples was 174 days, which was within the established stability interval of 729 days for EU-approved Herceptin and 182 days for US-licensed Herceptin. A summary of the ELISA assay results are show in **Table 7**.

Table 7. Summary of ELISA assay parameters from Study MYL-HER-1002

Analyte	EU-approved Herceptin	MYL-1041O
Matrix	Human Serum	
Reference or analytical standard	Lot H4078B02, 150.0 mg/Vial, 20.70 mg/mL	Lot DBBMPTV12-0003, 150.0 mg/Vial, 20.80 mg/mL
Minimum dilution	1:10	
Standard curve concentrations (ng/mL)	20 (anchor), 75 (LLOQ), 200, 320, 450, 600, 800, 1100, 1500 (ULOQ) and 2000 (anchor) ng/mL	
Limit of detection	20 ng/mL	
LLOQ	75 ng/mL	
ULOQ	1500 ng/mL	
Standard curve accuracy (%Bias) from 75-1500 ng/ml	-1.7% and 3.1%	-1.3% and 3.7%
Inter-assay Precision (%CV)	LLOQ (75 ng/ml): 3.5% Low (250 ng/ml): 4.1%% Mid (750 ng/ml): 5.7%% High (1150 ng/ml): 10.6 % ULOQ (1500 ng/ml): 4.6%	LLOQ (75 ng/ml): 4.7% Low (250 ng/ml): 4.3% Mid (750 ng/ml): 6.1% High (1150 ng/ml): 8.0% ULOQ (1500 ng/ml): 3.8%

Inter-assay Accuracy	LLOQ (75 ng/ml): 3.1% Low (250 ng/ml): -6.6% Mid (750 ng/ml): -7.8% High (1150 ng/ml): -4.8% ULOQ (1500 ng/ml): -1.7%	LLOQ (75 ng/ml): 3.7% Low (250 ng/ml): 2.7% Mid (750 ng/ml): -4.6% High (1150 ng/ml): -4.4% ULOQ (1500 ng/ml): - 0.4%

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BRIAN D FURMANSKI
07/19/2017

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NAM ATIQUR RAHMAN
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I concur.