MYL-1401O
(Mylan's Proposed Biosimilar to Trastuzumab)

Presentation to the
Oncologic Drugs Advisory Committee

July 13, 2017

Mylan in Collaboration with Biocon

MYL-1401O: A Proposed Biosimilar to Trastuzumab

Introduction

Arnd Annweiler, PhD
Head of Research and Development
Mylan

MYL-1401O
A Proposed Biosimilar to Herceptin®

- Reference Product: US-licensed Herceptin® (trastuzumab)
  - BLA first approved in 1998
  - Humanized Monoclonal Antibody
  - Specific for Human Epidermal Growth Factor Receptor 2 (HER2)
  - Initiation of treatment based on confirmed HER2+ diagnosis

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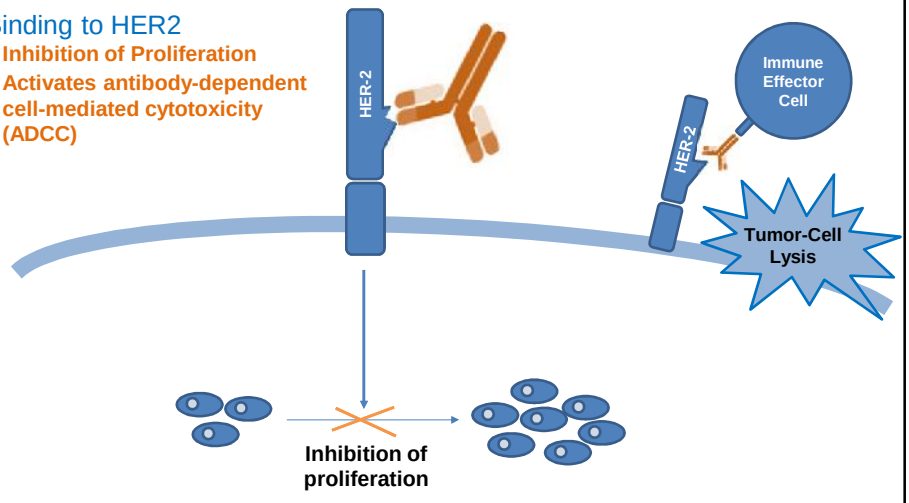
Trastuzumab: MOA as a HER2 Antagonist Conserved Across all Approved Indications

Binding to HER2
- **Inhibition of Proliferation**
- **Activates antibody-dependent cell-mediated cytotoxicity (ADCC)**



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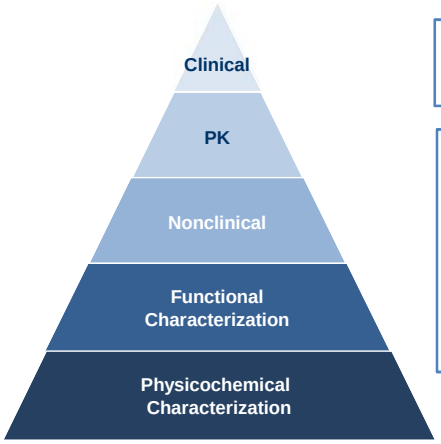
MYL-1401O

Followed the Biosimilar Development Concept and Incorporated FDA Advice



"Totality-of-evidence"

- **Clinical program confirmatory** and not to prove efficacy and safety de novo in all indications

- **Highly similar** to the reference product, notwithstanding minor differences in clinically inactive components
  - Essentially the same molecule
- **No clinically meaningful differences** in terms of **safety, purity and potency**

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Biosimilar Development Concept

Extrapolation to Approved Indications of the Reference Product

Analytical Similarity

Confirmed by Clinical Testing in a Sensitive Population

Mechanism of Action

Considerations on Conditions of Use

Essentially the same molecule will perform in the same way in all indications for which the reference product was tested and approved

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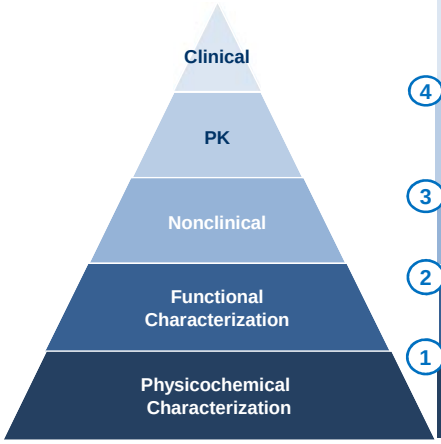
Totality of Data will Demonstrate Biosimilarity of MYL-1401O to Herceptin



5 **HERITAGE**
Confirmatory efficacy and safety study in patients with HER2+ Metastatic Breast Cancer (500 patients)
A sensitive population.
1 supportive MBC study (135 patients)

4 **PK Similarity**
1 PK 3 way bridging study (132 NHV)
1 supportive PK study (22 NHV)

3 **Nonclinical Safety**
2 Cell-based studies, 2 safety pharmacology studies in Cynomolgus Monkey

2 **Function**
Focus on aspects of **molecule and function** relevant to MOA, efficacy, safety, PK, and immunogenicity

1 **Structure**
Extensive characterization of Herceptin and MYL-1401O applying highly sensitive analytics across a wide range of product characteristics

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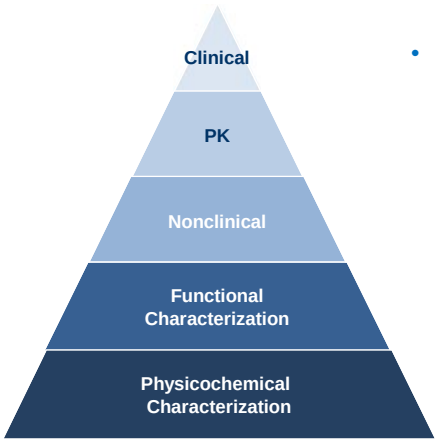
The Totality of Evidence will Support Approval of MYL-1401O as a Biosimilar to Herceptin



- Based on the **totality of evidence,** Mylan proposes approval of MYL-1401O as a **biosimilar to Herceptin** for the **same indications**
  - Treatment of HER2-overexpressing breast cancer
  - Treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma*

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*This indication is protected by orphan drug exclusivity expiring on October 20, 2017."

Agenda

Introduction	**Arnd Annweiler, PhD** *Head of Research and Development* *Mylan*
Analytical and Nonclinical Demonstration of Similarity	**Patrick T. Vallano, PhD** *Head of Global Biologics Scientific Affairs* *Mylan*
Confirmatory Clinical Efficacy and Safety	**Abhijit Barve, MD, PhD** *Head of Global Clinical Research* *Mylan*
Clinical Perspective	**Hope S. Rugo, MD** *Professor of Medicine, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco*
Totality of the Evidence and Concluding Remarks	**Arnd Annweiler, PhD** *Head of Research and Development* *Mylan*

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Additional External Consultants

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David H. Henry, MD

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Vice Chairman, Department of Medicine, Pennsylvania Hospital

Director, AIDS Malignancy Program, University of Pennsylvania Cancer Center, Philadelphia, PA

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Analytical and Nonclinical Demonstration of Similarity

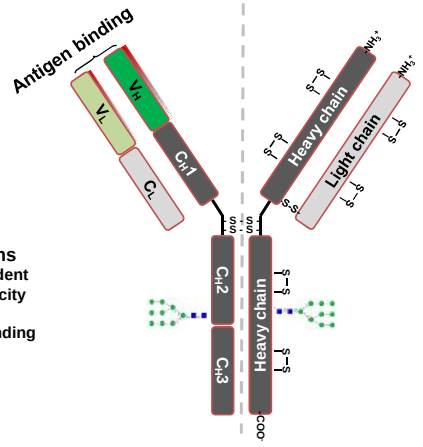
Patrick T. Vallano, PhD
Head of Global Biologics Scientific Affairs
Mylan

Trastuzumab
Humanized IgG1 Monoclonal Antibody

Biological characteristics

Fab
Fab Functions
- HER2 Binding
- Inhibition of Cell Proliferation

Fc
Effector Functions
- Antibody-Dependent Cellular Cytotoxicity (ADCC)
- Fcγ Receptor Binding



Physicochemical characteristics

- Amino Acid Sequence
- Higher Order Structure
- Charge Heterogeneity
- Size Heterogeneity
- Glycan Heterogeneity

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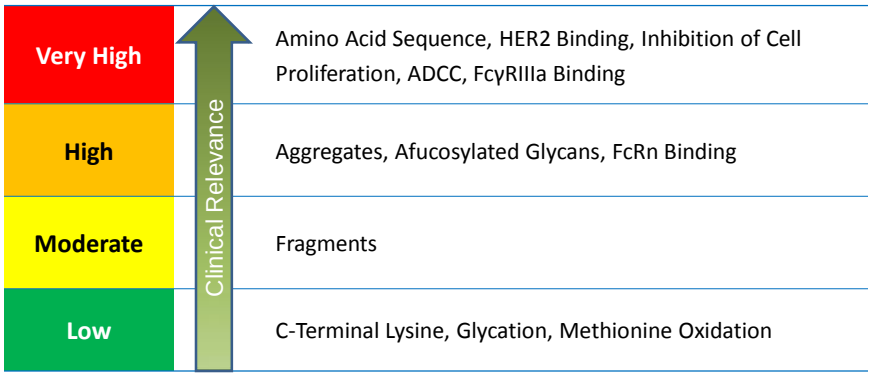
Clinical Relevance of Product Characteristics



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3-Way Analytical Similarity Assessment

- MYL-1401O
- US-Licensed Herceptin
- EU-Approved Herceptin
  - Included to justify the use of EU-Herceptin in the confirmatory clinical study

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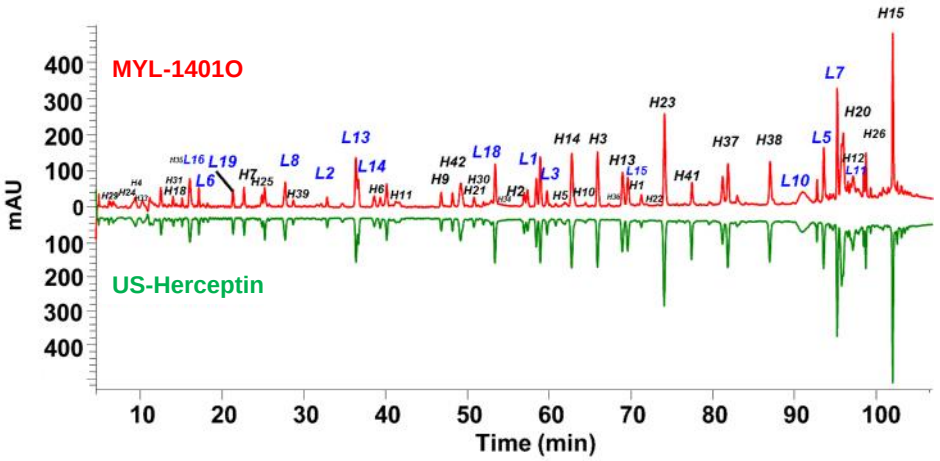
Identical Amino Acid Sequence



100% sequence coverage using multiple proteases and LC-MS/MS analysis

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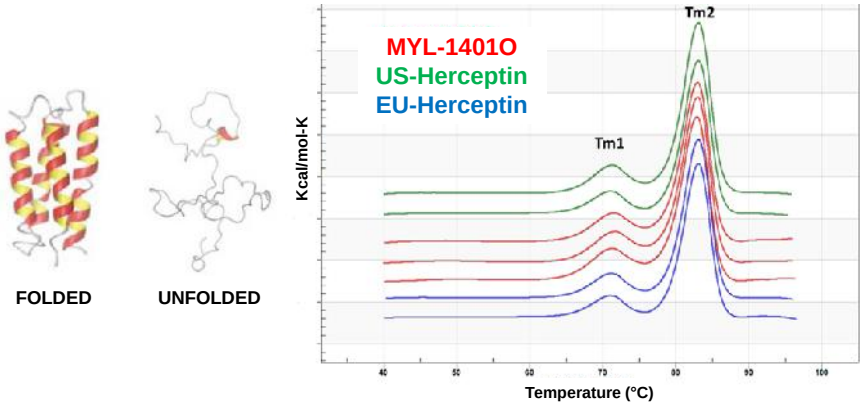
Highly Similar 3-Dimensional Structure

Protein unfolding by Differential Scanning Calorimetry (DSC)



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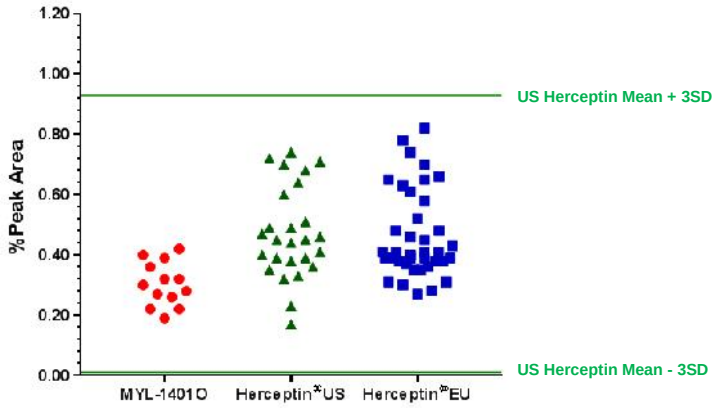
Highly Similar Aggregate Content



Aggregates potentially cause immunogenicity: No differences seen

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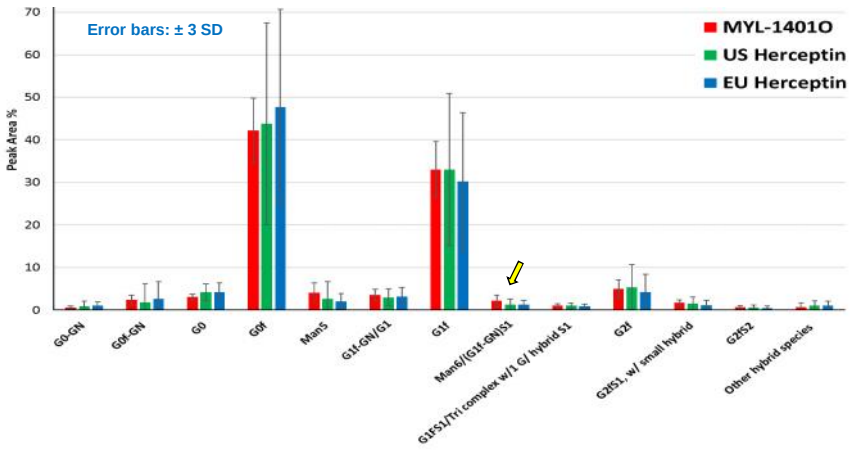
Highly Similar Glycan Variants



High similarity observed for 12 of 13 glycan species

Marginal difference in Man6 content did not impact clinical PK

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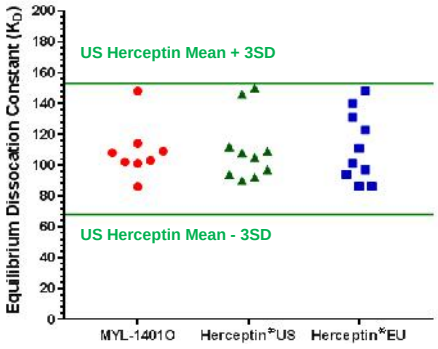
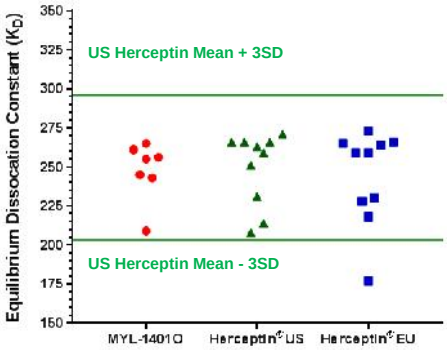
Highly Similar Fc Receptor Binding

FcγRIIIa Receptor



FcRn Receptor



Antibody binding to FcγRIIIa receptors on effector cells mediates ADCC

Binding to FcRn receptors can affect systemic clearance (PK)

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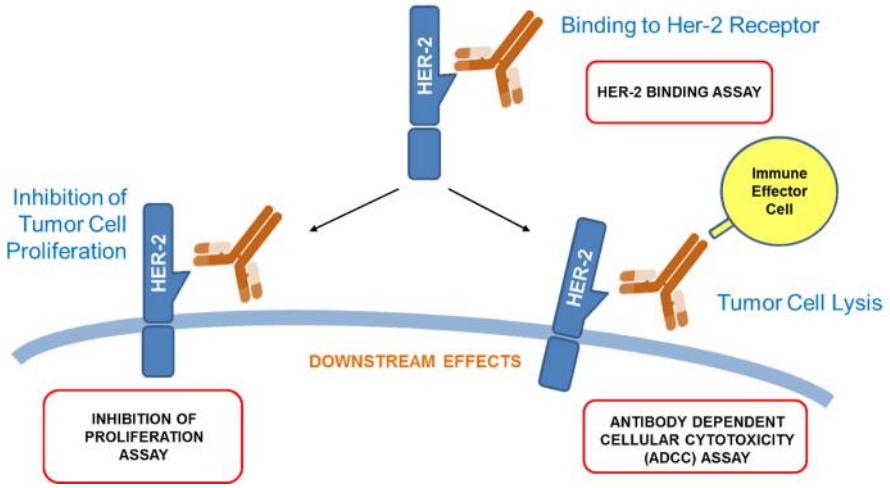
Clinically Relevant Functional Assays



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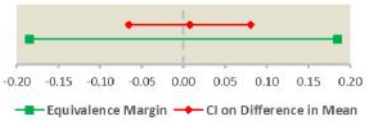
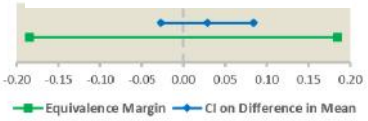
Equivalent Target (HER2) Binding

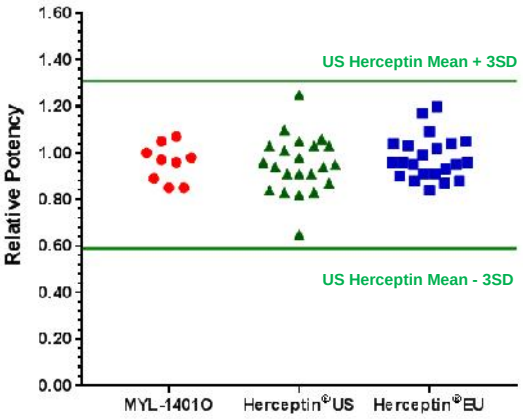
STATISTICAL ANALYSIS RESULTS

MYL-1401O vs. US-Herceptin



EU-Herceptin vs. US-Herceptin





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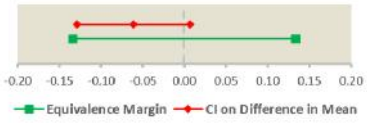
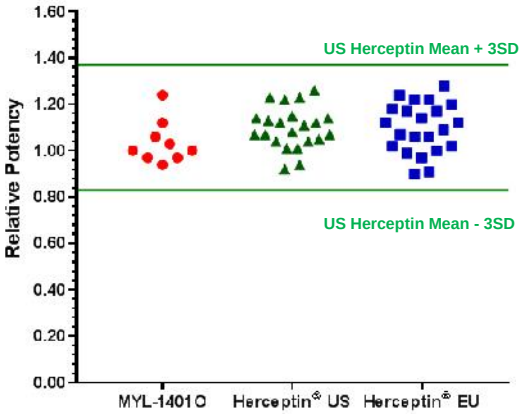
Equivalent Inhibition of Cell Proliferation

STATISTICAL ANALYSIS RESULTS

MYL-1401O vs. US-Herceptin



EU-Herceptin vs. US-Herceptin



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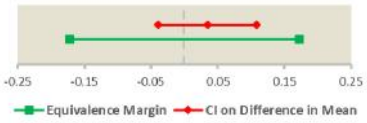
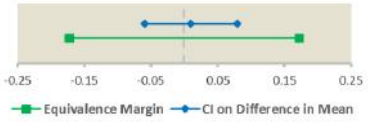
Equivalent ADCC Activity

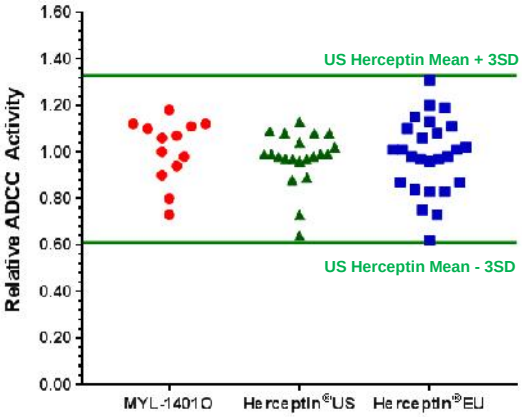
STATISTICAL ANALYSIS RESULTS

MYL-1401O vs. US-Herceptin



EU-Herceptin vs. US-Herceptin





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Analytical Similarity Summary

Over 35 sensitive, state of the art methods were employed to demonstrate the high similarity of MYL-1401O and Herceptin

Product Characteristic	Method
Protein content	Ultra-violet 280 Absorption
Amino acid sequence	Peptide Mapping (Trypsin/Glu-C)
	Intact Mass and LC/HC Mass
Protein Conformation (Secondary and Higher order structure)	Far UV Circular Dichroism
	Fourier transform infrared spectroscopy
	Free Cysteine (Ellman's test)
	Disulfide Bridging (LCMS)
	Near UV Circular Dichroism
	Differential scanning calorimetry
	Intrinsic Fluorescence
	Hydrophobic Interaction Chromatography
Sub-visible Particles	MFI
Aggregates	Size Exclusion Chromatography – UV
	Analytical Ultra Centrifugation (AUC)
	Size Exclusion Chromatography – MALS
Fragments	CE-SDS (Non-Reduced)

Product Characteristic		Method
Glycoform variants	**Non-glycosylated**	CE-SDS (Reduced)
	Afucosylated	HPLC-MS
	Individual Glycan Content	Normal Phase HPLC
	Terminal Sialic acid	Reverse Phase HPLC
Glycation		Boronate Affinity Chromatography
Methionine oxidation		Peptide mapping
Charge variants		IEX-HPLC; CE-IEF
Target binding		HER-2 Binding
Potency		Inhibition of Proliferation
ADCC		ADCC Assay
FcγRIIIa Binding		Surface Plasmon Resonance
FcRn Binding		Surface Plasmon Resonance
Other FcγR Binding (I, IIa, IIb, IIIb)		Surface Plasmon Resonance
C1q Binding/CDC		ELISA/Cell-Based Assay

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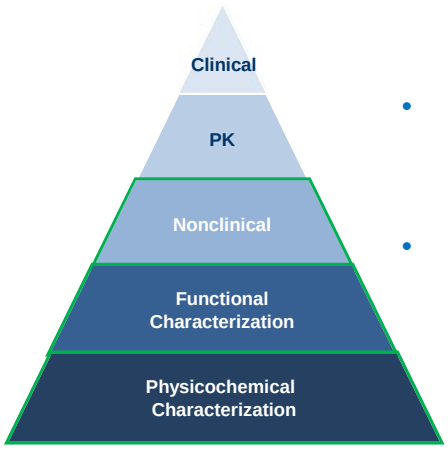
Conclusion



- **MYL-1401O and Herceptin are highly similar in structure and function**
- **No differences in nonclinical toxicity**

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Agenda

Introduction	**Arnd Annweiler, PhD** *Head of Research and Development* *Mylan*
Analytical and Nonclinical Demonstration of Biosimilarity	**Patrick T. Vallano, PhD** *Head of Global Biologics Scientific Affairs* *Mylan*
Confirmatory Clinical Efficacy and Safety	**Abhijit Barve, MD, PhD** *Head of Global Clinical Research* *Mylan*
Clinical Perspective	**Hope S. Rugo, MD** *Professor of Medicine, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco*
Totality of the Evidence and Concluding Remarks	**Arnd Annweiler, PhD** *Head of Research and Development* *Mylan*

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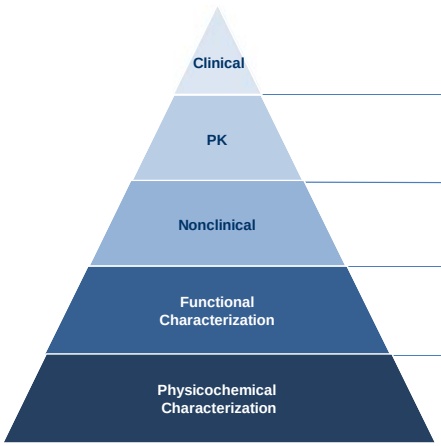
Clinical Demonstration of Biosimilarity

Abhijit Barve, MD, PhD
Head of Global Clinical Research
Mylan

PK and Clinical Program to Support Biosimilarity



Confirmatory Efficacy, and Safety Study in MBC patients (HERITAGE STUDY)
Supportive efficacy assessment in MBC study

PK Bioequivalence Studies in Healthy Volunteers: 1 pivotal and 1 supportive
Supportive PK assessment in 2 MBC studies

Non-clinical Safety: Cell Based Studies
Toxicology Studies in Monkeys

Function: Focus on aspects of **molecule and function** relevant to MOA, efficacy, safety, PK and immunogenicity

Structure: Extensive characterization of Herceptin and MYL-1401O applying highly sensitive analytics

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Overview of PK Evaluation

Study	Design	Population	Dosing Regimen	Sample Size
Pivotal Study				
MYL-Her-1002	3 way PK study Parallel	Healthy Male Volunteers	8 mg/kg i.v. single dose	N=132 (44 per arm)
Supportive Studies				
MYL-Her-1001	2 way PK crossover study	Healthy Male Volunteers	8 mg/kg i.v. single dose	N=22
MYL-Her-3001	Efficacy and safety study	Metastatic Breast Cancer	**Part 1**: 8 cycles with taxanes **Part 2:** Monotherapy until progression	N=500 (250 per arm)
BM200-CT3-001-11	PK, Efficacy and safety study	Metastatic Breast Cancer	8 cycles with taxanes Bmab200 used	N=135 (67-68 per arm)

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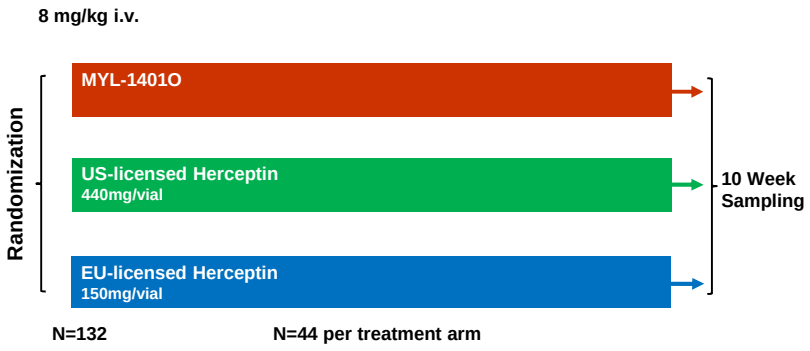
MYL-Her-1002
3-way PK Bridging Study in Healthy Volunteers



- **Primary Objective**: PK equivalence among the 3 products
- **Statistical Evaluation:** 90% CI for the LS Means ratio of C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ to be between 80-125%

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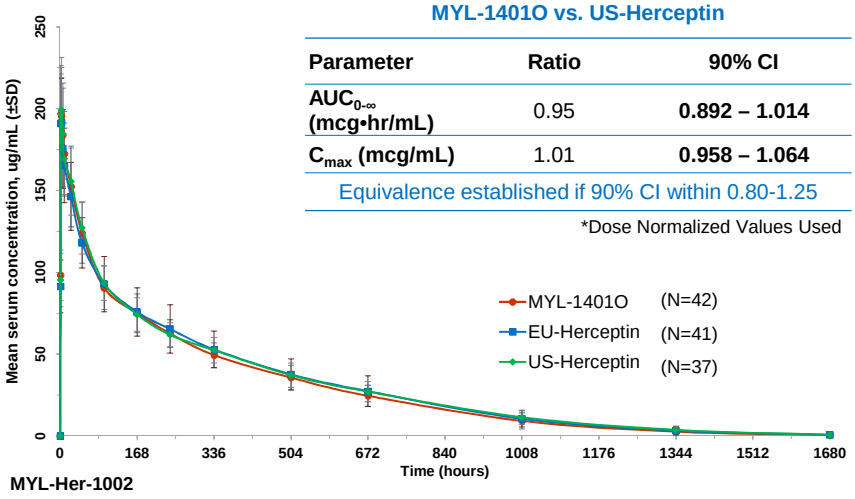
MYL-1401O is Bioequivalent to US-Herceptin



MYL-1401O vs. US-Herceptin

Parameter	Ratio	90% CI
$AUC_{0-\infty}$ (mcg•hr/mL)	0.95	**0.892 – 1.014**
C_{max} (mcg/mL)	1.01	**0.958 – 1.064**

Equivalence established if 90% CI within 0.80-1.25

*Dose Normalized Values Used

MYL-Her-1002

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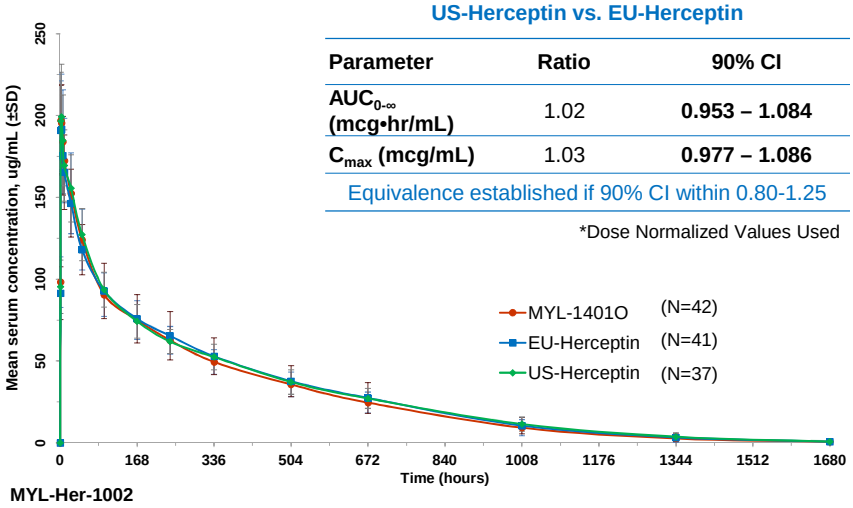
Herceptin US and EU are Bioequivalent

Bridge Between US and EU Herceptin Established



US-Herceptin vs. EU-Herceptin

Parameter	Ratio	90% CI
$AUC_{0-\infty}$ (mcg•hr/mL)	1.02	**0.953 – 1.084**
C_{max} (mcg/mL)	1.03	**0.977 – 1.086**

Equivalence established if 90% CI within 0.80-1.25

*Dose Normalized Values Used

MYL-Her-1002

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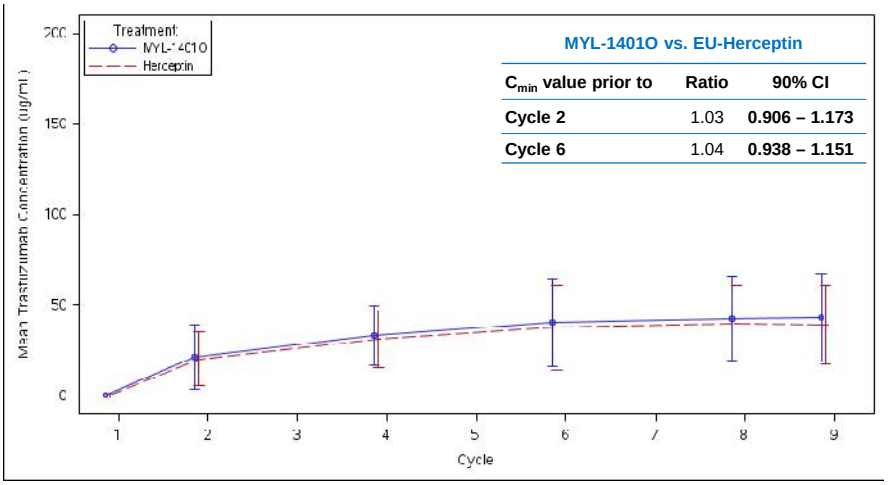
Similar Exposure in MBC Patients

Based on Ratio of Trough Levels Before Cycles 2 & 6



MYL-1401O vs. EU-Herceptin

C_{min} value prior to	Ratio	90% CI
Cycle 2	1.03	**0.906 – 1.173**
Cycle 6	1.04	**0.938 – 1.151**

MYL-Her-3001

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Overview of Clinical Program

Study	Design	Population	Dosing Regimen	Sample Size
Confirmatory Efficacy & Safety Study				
MYL-Her-3001 HERITAGE STUDY	Efficacy and safety study	Metastatic Breast Cancer	**Part 1**: 8 cycles with taxanes **Part 2:** Monotherapy until progression	N=500 (250 per arm)
Supportive Studies				
BM200-CT3-001-11	PK, Efficacy and safety study	Metastatic Breast Cancer	8 cycles with taxanes Bmab200 used	N=135 (67-68 per arm)
MYL-Her-1002	3 way PK study Parallel	Healthy Volunteers	8 mg/kg i.v. single dose	N=132 (44 per arm)
MYL-Her-1001	2 way PK crossover study	Healthy Volunteers	8 mg/kg i.v. single dose	N=22

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Rationale for HERITAGE Study Design

Choice of MBC and ORR for Biosimilar Assessment

- MBC represents a broad and sensitive population for evaluating biosimilar
- Earliest indication approved for Herceptin and demonstrated survival benefits
- Extensive safety and efficacy data available to design a robust study
- Study design allows for assessing safety, immunogenicity, and efficacy with taxanes and as well as monotherapy, and beyond 52 weeks of treatment

- ORR is a sensitive endpoint to detect potential clinically meaningful differences in efficacy
- Good correlation with clinical endpoints like TTP/ PFS in HER2+ MBC

- Choice of ORR and MBC discussed with FDA & EMA as appropriate for biosimilar

MYL-Her-3001

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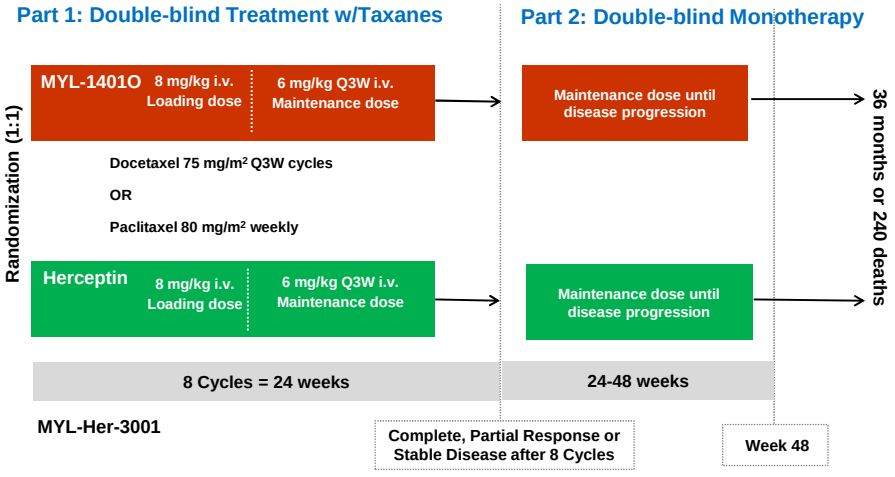
HERITAGE Study*

Confirmatory Safety & Efficacy Study in HER2+ MBC Patients



*Rugo HS et al. on behalf of Heritage Study Investigators, *JAMA*. 2017; 317(1):37-47.

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Standard Selection Criteria for First Line Herceptin Studies in MBC Patients

Inclusion Criteria

- Histologically confirmed diagnosis of breast cancer
- Locally recurrent or MBC not amenable to curative surgery and/or radiation
- HER2 gene amplification by FISH (ratio >2.0) or HER2 overexpression based on IHC3+ or IHC2+ with FISH
- ECOG Performance Status of 0 to 2
- Normal LVEF and adequate liver and bone marrow function
- Patients treated with trastuzumab or taxane in adjuvant setting allowed if metastatic disease diagnosed at least 1 year after last dose

Exclusion Criteria

- Prior systemic therapy in metastatic disease setting
- Prior treatment with neoadjuvant or adjuvant anthracyclines with cumulative dose of doxorubicin of >400 mg/m^2 or epirubicin of >800 mg/m^2
- Surgery or radiotherapy ≤2 weeks preceding Day 1
- Peripheral sensory or motor neuropathy Grade 2 or higher

MYL-Her-3001 37

Study Endpoints for Confirming Efficacy and Safety

Primary Endpoint

- **Ratio** of **best ORR** (defined as a CR or PR per RECIST 1.1) by **Week 24** based on cumulative assessment done by a single central blinded oncologist.

  Equivalence Margin: 0.81-1.24

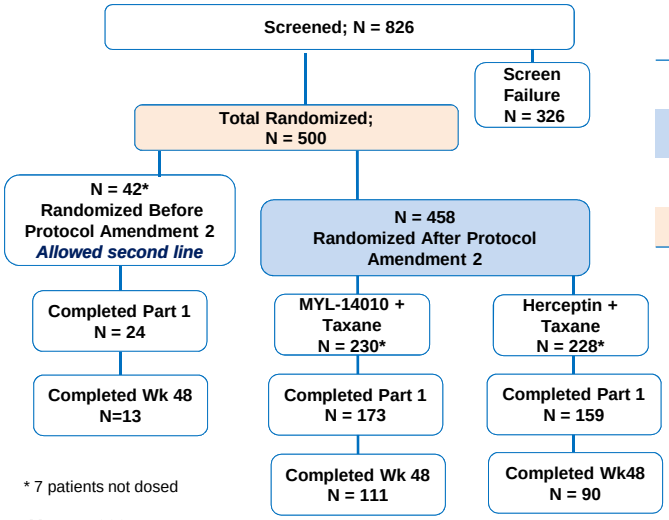
Secondary Endpoints

- TTP, PFS, and OS at Week 48
- OS at 36 months or after 240 deaths
- Comparison of safety and immunogenicity with taxanes
- Comparison of safety and immunogenicity during monotherapy
- Compare the pharmacokinetics in MBC patients

TTP: Time to Progression, PFS: Progression Free Survival, OS: Overall Survival

MYL-Her-3001 38

HERITAGE Study
Disposition and Populations



Populations	
Safety	n=493
ITT1	n=458
PP	N=438
ITT2	N=500

* 7 patients not dosed

MYL-Her-3001

Key Baseline Characteristics and Disease History Comparable (ITT1 Population)

Patient Characteristics	MYL-1401O (N=230)	Herceptin (N=228)
Age Category, n (%)		
<50 years	74 (32.2)	86 (37.7)
ñ50 years	156 (67.8)	142 (62.3)
Race, n (%)		
Asian	70 (30.4)	72 (31.6)
Black	1 (0.4)	2 (0.9)
Caucasian	159 (69.1)	154 (67.5)
Previous Treatment (Adjuvant)		
Trastuzumab	22 (9.6)	16 (7.0)
Taxane	46 (20.0)	42 (18.4)
Assigned Taxane, n (%)		
Docetaxel	193 (83.9)	192 (84.2)
Paclitaxel	35 (15.2)	32 (14.0)
Presence of Visceral Metastases, n (%)		
Yes	172 (74.8)	185 (81.1)
No	58 (25.2)	43 (18.9)

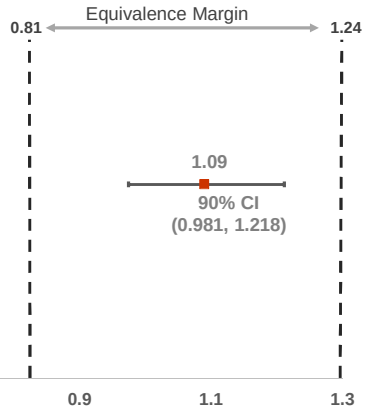
MYL-Her-3001

Primary Endpoint of ORR at Week 24 Met Supporting Similar Efficacy

Best ORR at Week 24 in ITT1 Population

	MYL-1401O N= 230	Herceptin N= 228
ORR n (%)	161 (70.0%)*	146 (64.0%)
Ratio of ORR	**1.09**	
90% CI	(0.981, 1.218)	
Difference in ORR	**6.00%**	
90% CI	(-1.26%,13.11%)	

Ratio of ORR (90% CI)



* 69.6% RR in briefing book. 90%CI (0.974-1.211)

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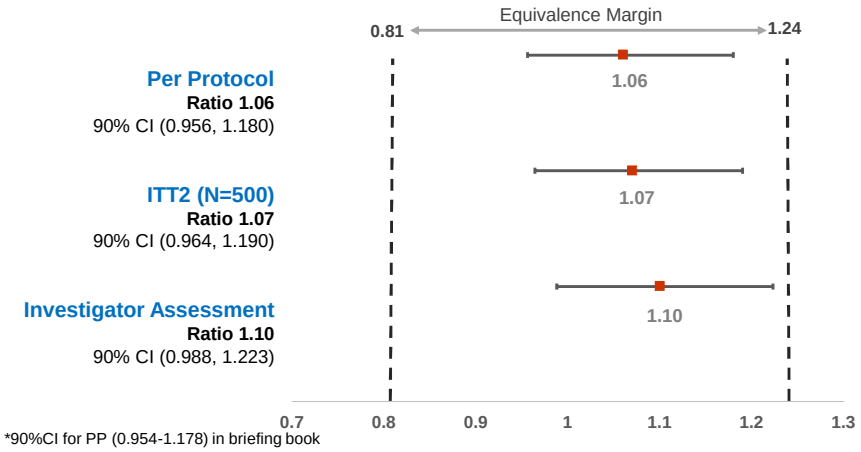
Similar Efficacy Confirmed in Sensitivity Analyses

Sensitivity Analysis for Best ORR at Week 24



*90%CI for PP (0.954-1.178) in briefing book

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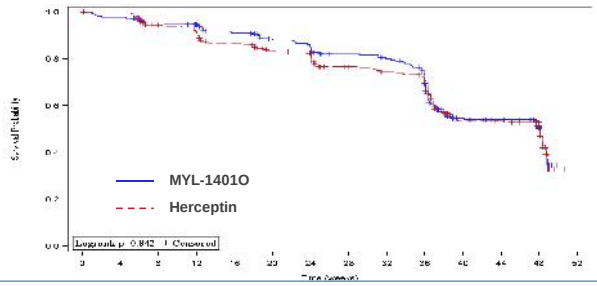
PFS Data at Week 48 Further Supports Similar Efficacy



Subject Status	PFS at Week 48	
	MYL-1401O (N=230)	Herceptin (N=228)
Events, n (%)	102 (44.3)	102 (44.7)
Log-rank test: p-value	0.842	
Unstratified Hazard Ratio (95% CI)	0.97 (0.740, 1.282)	

Median PFS at Week 48 cut-off is estimated to be 11.1 months

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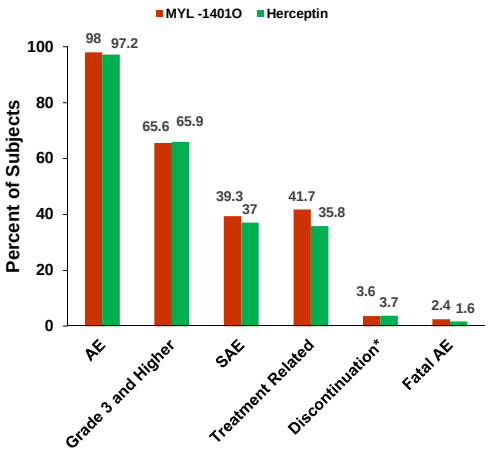
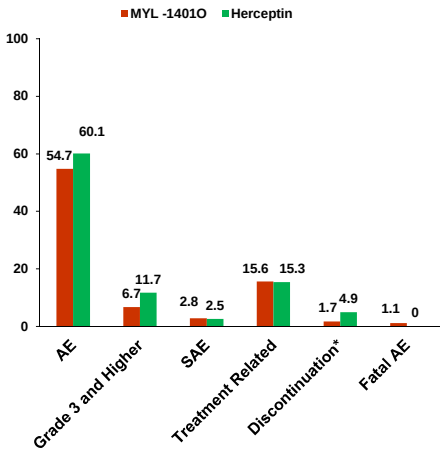
Clinical Safety

Adverse Event Rate Comparable Over 48 Weeks and During Monotherapy

Cumulative AEs Baseline to Week 48



AEs From Weeks 24-48 (Monotherapy)



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* Discontinuation due to AEs

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Rate of SAEs Comparable Between Arms

SAEs Occurring in >2% of Patients at Week 48

Preferred Term	MYL-1401O N = 247 (%)	Herceptin N = 246 (%)
Number of patients with at least 1 SAE	39.3%	37.0%
Neutropenia	27.5%	25.2%
Febrile neutropenia	4.5%	4.1%
Leukopenia	2.0%	4.9%
Pneumonia	2.4%	2.0%
Fatal AEs	**2.4%**	**1.6%**

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Common AEs Occurring in >10% of Patients from Baseline Through Week 48

System Organ Class	Preferred Term	MYL-1401O N=247	Herceptin N=246
Blood and lymphatic system disorders	Neutropenia	57.9%	54.1%
	Leukopenia	17.4%	21.5%
	Anemia	16.6%	17.9%
Gastrointestinal disorders	Diarrhea	21.1%	20.7%
	Nausea	21.1%	15.4%
	Vomiting	10.9%	9.8%
Nervous system disorders	Peripheral sensory neuropathy	13.0%	14.6%
	Neuropathy peripheral	12.6%	12.2%
	Headache	9.7%	11.8%
General disorders	Asthenia	23.1%	16.7%
	Edema peripheral	15.4%	12.6%
	Fatigue	12.1%	15.0%
	Pyrexia	9.7%	13.4%
Musculoskeletal disorders	Arthralgia	13.4%	5.7%
	Myalgia	10.1%	9.3%
Skin and subcutaneous disorders	Alopecia	57.9%	54.9%
	Rash	8.9%	10.2%

MYL-Her-3001 47

Majority of Common AEs Occurred During First 24 Weeks and Possibly Due to Taxanes

	AEs Thru Week 24		AEs From Weeks 24-48	
	MYL-1401O N= 247 (%)	Herceptin N= 246 (%)	MYL-1401O N= 179 (%)	Herceptin N= 163 (%)
Neutropenia	57.5%	53.3%	1.1%	2.5%
Asthenia	**21.9%**	**16.3%**	**2.8%**	**1.8%**
Nausea	**19.8%**	**13.8%**	**2.2%**	**2.5%**
Edema Peripheral	14.2%	11.4%	0.6%	1.8%
Arthralgia	**12.1%**	**4.5%**	**2.8%**	**1.2%**
Vomiting	10.5%	7.7%	1.7%	3.1%
Urinary Tract Inf.	8.5%	6.5%	0.6%	2.5%
Upper Resp. Tract Inf.	6.1%	1.6%	2.2%	1.2%
Infusion Related Reactions	6.9%	4.5%	0	0.6%

MYL-Her-3001 48

Adverse Events of Special Interest in >1% of Patients from Baseline Through Week 48

System Organ Class Preferred Term	MYL-1401O N=247 (%)	Herceptin N=246 (%)
Pulmonary Events	**13.0%**	**12.2%**
Dyspnea	6.9%	7.3%
Pneumonia	2.8%	4.1%
Pneumonitis	1.6%	0.8%
Exertional dyspnea	1.2%	0.8%
Cardiac Disorders	**4.9%**	**4.1%**
Cardiac failure	2.4%	0.4%
Left ventricular dysfunction	0.8%	1.2%
Metabolic cardiomyopathy	0.4%	1.2%
Infusion Related Events	**9.3%**	**8.1%**
Infusion-related reaction	6.9%	4.9%
Hypersensitivity	2.0%	2.8%

MYL-Her-3001

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Objective Evaluation of New Onset Myocardial Dysfunction & LVEF Comparable

New Onset Myocardial Dysfunction Through Week 48

	MYL-1401O (N=247) n (%)	Herceptin (N=246) n (%)
LVEF <50% at least once post-baseline	10 (4.0)	8 (3.3)
LVEF <50% post-baseline & decrease <10% points	1 (0.4)	1 (0.4)
LVEF <50% post-baseline & decrease ≥10% points	**9 (3.6)**	**7 (2.8)**

- LVEF was assessed at BL, Week 12, 24, 38, and 48 and End of Treatment
- Of the 18 patients, 5 patients discontinued treatment due to a cardiac event, 3 in MYL-1401O arm and 2 in the Herceptin arm
- 16 patients had documented LVEF value that showed recovery to above 50%, corroborating the reversibility of cardiac toxicity described for trastuzumab
- 2 patients in Herceptin arm did not have LVEF value to asertain reversibility
- Overall mean and median LVEF over 48 weeks was similar in both arms

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MYL-Her-3001

Immunogenicity Assessment Across Studies Using State-of-the-Art Assay

- Standard 3-step process used: Screening, Confirmatory Assay with titers, and Neutralizing Assay
- Anti-Trastuzumab Antibody (ADA) assay used validated electrochemiluminescence bridging format
- Neutralizing antibody (NAb) used validated cell-based format
- Immunogenicity assessed across all studies
  - Study 1001: NHV No treatment-emergent ADA observed
  - Study 1002: NHV No treatment-emergent ADA observed
  - ADA rate similar in supportive MBC study

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Immunogenicity Similar Between MYL-1401O and Herceptin Over 48 Weeks

Parameters	MYL-1401O (n=247) (%)	HERCEPTIN (n=246) (%)
Baseline ADA Rate (0.1% FPER)	5.9%	9.2%
Positive ADA post-baseline (0.1% FPER)	3.9%	4.4%
Positive ADA post-baseline (1% FPER)	5.9%	6.8%
Overall NAb rate (0.1% FPER)	0.4%	1.3%

- Immunogenicity samples collected at BL and Weeks 6, 12, 18, 24, 36, and 48
- Very low titers; maximum titer was 5.5-11.1 in treatment arms
- Incidence low (1.5-2.1%) at Weeks 36 & 48 (monotherapy) and similar in both arms

MYL-Her-3001

FPER: False positive event rate

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Clinical Data Conclusion

PK Bioequivalence	✓
Demonstrated between MYL-1401O & Herceptin in NHV and patients	
Similar Efficacy	✓
Demonstrated based on ratio of best ORR at Week 24 Supported by PFS at Week 48	
Comparable Safety	✓
Safety comparable in presence of taxanes and monotherapy Adverse events of special interest comparable	
Immunogenicity	✓
Overall ADA rate post-baseline over 48 weeks low in both arms and consistent with literature	

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Agenda

Introduction	**Arnd Annweiler, PhD** *Head of Research and Development* *Mylan*
Analytical and Nonclinical Demonstration of Biosimilarity	**Patrick T. Vallano, PhD** *Head of Global Biologics Scientific Affairs* *Mylan*
Confirmatory Clinical Efficacy and Safety	**Abhijit Barve, MD, PhD** *Head of Global Clinical Research* *Mylan*
Clinical Perspective	**Hope S. Rugo, MD** *Professor of Medicine, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco*
Totality of the Evidence and Concluding Remarks	**Arnd Annweiler, PhD** *Head of Research and Development* *Mylan*

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Clinical Perspective

Hope S. Rugo, MD
Professor of Medicine
UCSF Helen Diller Family Comprehensive Cancer Center

Chair of Steering Committee for HERITAGE Study

Disclosures

- Receives funding through the Regents of the University of California for sponsored and investigator initiated clinical research studies from Genentech/Roche
- Received travel support from Mylan for this meeting

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Patients and Medical Need for Biosimilars

- Over-expression of HER2 implicated in the pathophysiology of approximately 25% of breast[1] and 18% gastric and gastroesophageal tumors[2]

	Breast Cancer	Gastric cancer
Worldwide estimated new cases (2012)	1,676,600[3]	952,000[5]
U.S estimated new cases (2017)	252,710[4]	28,000[4]

- Limited access to treatment is a worldwide issue for patients with breast and gastric cancer
- Significant financial impact due to share of cost for some patients in the US[6]
- Biosimilars have the potential to expand patient access and use

[1] British breast cancer organization (2017); [2] Worl J Gastroenterol 2016 May 21; 22(19):4619–4625; [3] American Cancer Society 2012; [4] American Cancer Society 2017; [5] http://globocan.iarc.fr/old/FactSheets/cancers/stomach-new.asp.

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Trastuzumab In Clinical Practice

Changed Treatment Course of HER2 Overexpressing Tumors

1998: Approved for Metastatic HER-2 Overexpressing Breast Cancer

2006: Approved for Adjuvant Treatment of HER-2 Overexpressing Breast Cancer

2010: Approved for Metastatic HER-2 Overexpressing Gastric Cancer

Also used as neo-adjuvant therapy for HER-2+ early stage breast cancer

- In *metastatic breast cancer*, improves PFS, OS, and ORR[1]
- In *early stage breast cancer*, improves DFS and OS with long-term follow-up[2]
- As *neoadjuvant therapy for breast cancer*, improves pCR and DFS rates[3]
- Improves PFS, OS and ORR in *metastatic gastric cancer*[4]
- Gold standard for the treatment of early- and late-stage HER2+ breast cancer[5]
- Is well tolerated with modest and manageable toxicity

[1]Marty et al, JCO 2005,[2]Cameron et al. Lancet, 2017, [3]Gianni et al. Lancet 2014, [4]Bang et al. Lancet 2010, [5]Denduluri et al., 2016

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HERITAGE Study Data in Clinical Perspective

	HERITAGE STUDY		HISTORICAL DATA
Endpoint	**MYL-1401O**	**Herceptin**	**1st line HER2+ MBC**
ORR 24 Weeks (Primary)	**70%**	**64%**	**55-69%[1-5]**
ORR ratio (90% CI): FDA Requirement	1.09 (0.981, 1.218)		N/A
ORR difference (95% CI): EMA Requirement	6.0% (-2.64%, 14.45%)		N/A
Time to Progression (TTP) 48 Weeks	**11.1 Months**	**11.1 Months**	**11.3 -12.4 Months [1-5]**
Overall Survival 48 Weeks	**89.1%**	**85.1%**	**75%-89% [1-5]**
Safety & Toxicity	Comparable		Consistent
Immunogenicity	**3.9%**	**4.4%**	**3.4%[6]-7.1%[7]**
Exposure	Comparable		Consistent

[1]Slamon et al, NEJM 2001, [2]Mass et al, Clin Breast CA 2005, [3]Marty et al, JCO 2005, [4]Baselga et al, NEJM, 2012, [5]Swain et al, NEJM 2015, [6]Hegg et. al, 2012, [7]Jackisch et al, Ann. Onc 2015

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MYL-1401O in HER2+ Cancers

Efficacy with Trastuzumab Across Indications

- Breast and Gastric Cancer require HER2+ overexpression to qualify for treatment
- Binding of trastuzumab to HER2 receptors is fundamental to activity across all indications
- Mechanism similar across all indications (ADCC & inhibition of proliferation)

Safety with Trastuzumab Across Indications

- Same dose of trastuzumab used across all indications
- ***Recommended Use:***
  - *Adjuvant:* 12-18 weeks with chemo & 24-30 weeks monotherapy (52 weeks maximum)
  - *MBC:* 24 weeks with chemo followed by monotherapy until progression (median use: 12 months); treatment can continue until or after progression (more than 52 weeks)
  - *Gastric:* 24 weeks with chemo followed by monotherapy until progression
- Safety Data from HERITAGE: Median use 12 months
  - Approx. 200 patients continue to receive MYL-1401O or Herceptin beyond 52 weeks
  - Generating additional long-term safety and immunogenicity data

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Potential Use of MYL-1401O in Clinical Practice

- Once approved, any patient receiving Herceptin will be a candidate for MYL-1401O
- Newly diagnosed patients with HER2+ disease will have the option to start with a lower cost biosimilar

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Agenda

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Totality of the Evidence and Concluding Remarks	**Arnd Annweiler, PhD** *Head of Research and Development* *Mylan*

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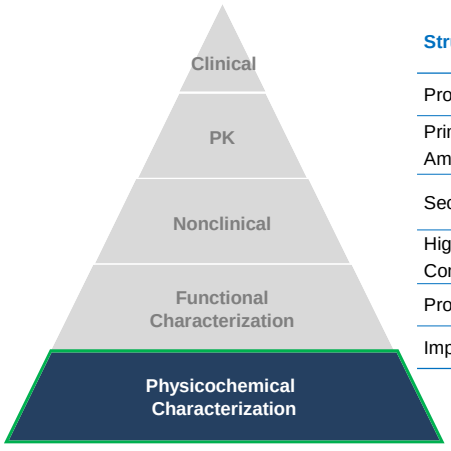
Totality of the Evidence and Concluding Remarks

Arnd Annweiler, PhD
Head of Research and Development
Mylan

Physicochemical Studies Demonstrate MYL-1401O to be Highly Similar to Herceptin



Structure and Impurities	Supports Biosimilarity
Protein Content and Dose	✓
Primary Structure – Identical Amino Acid Sequence	✓
Secondary Structure	✓
Higher Order Structure – 3D Conformation	✓
Protein Variants	✓
Impurities	✓

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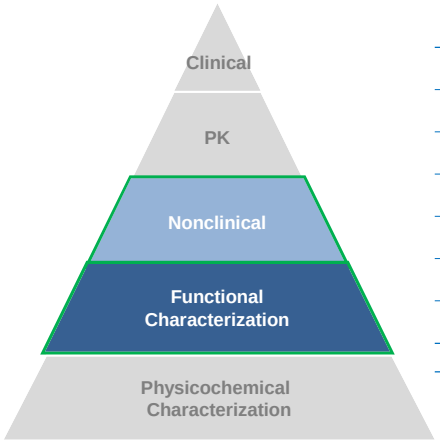
Functional Studies Demonstrate MYL-1401O to be Highly Similar to Herceptin



Molecule Function	Supports Biosimilarity
HER2 Binding	✓
Inhibition of Proliferation	✓
ADCC	✓
FcγRIIIa	✓
FcRn	✓
FcγRIa,RIIa,RIIb,RIIIB	✓
Nonclinical Safety & Toxicity	
Comparable Safety Profile	✓

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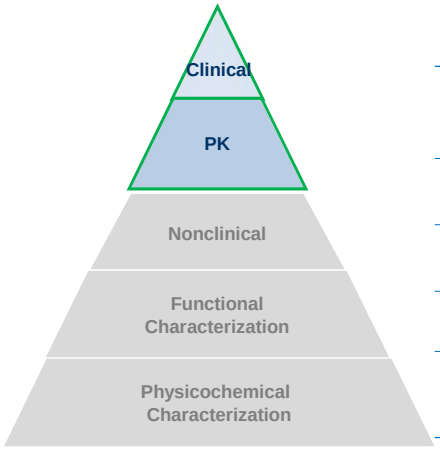
No Clinically Meaningful Differences Confirmed in Clinical Program



Confirmatory Clinical	Supports Biosimilarity
Efficacy in Metastatic Breast Cancer	✓
Comparable Immunogenicity	✓
Comparable Safety	✓
Similar exposure in MBC Patients	✓
PK similarity in Healthy Volunteers	✓

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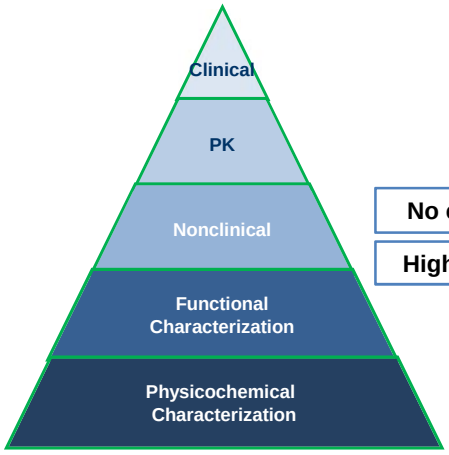
Totality of Evidence Supports Biosimilarity of MYL-1401O to Herceptin



No clinically meaningful differences ✓

Highly similar to the reference product ✓

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Conclusion MYL-1401O: Totality of Evidence Supports Approval as a Biosimilar to Herceptin

- Totality of the evidence supports
  - Biosimilarity
  - Extrapolation from molecule to molecule to all indications for which Herceptin was tested and approved
- MYL-1401O will provide an additional high quality treatment option for patients with HER2+ cancers

*This indication is protected by orphan drug exclusivity expiring on October 20, 2017."

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Back-up Slides

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Evaluation of Cardiac Events
Overall Events Until Week 48 (Investigator Assessed)

	MYL-1401O (N=247)	Herceptin (N=246)	Historical Data
Modified SMQ@ for Cardiac Failure	**12 (4.9%)**	**10 (4.1%)**	**8.3%***
Cardiac failure	6 (2.4%)	1 (0.4%)	
Left ventricular dysfunction	2 (0.8%)	3 (1.2%)	
Metabolic cardiomyopathy	1 (0.4%)	3 (1.2%)	
Cardiotoxicity	2 (0.8%)	0	
Congestive cardiomyopathy	0	1 (0.4%)	
Left ventricular failure	0	1 (0.4%)	
% of patients recovered	8 (66.7%)	5 (50%)	
% with prior anthracycline use	6 (50%)	6 (60%)	
% with chest radiation	1 (8.3%)	1 (10%)	

*CLEOPATRA study S Swain, M Ewer, et al.,The Oncologist 2013 @ Modified SMQ of Cardiac Failure & Cardiomyopathy

MYL-Her-3001

T20-005-70

Consistent Evaluation of LVEF Function

CTCAE Based Events Derived from LVEF Measurement

CTCAE Grade	Definition	MYL-1401O (N=247) n (%)	Herceptin (N=246) n (%)
Grade 4	LVEF <20%	0	0
Grade 3	LVEF 20-39% or > 20% drop from BL	2 (0.8%)	4 (1.6%)
Grade 2	LVEF 40-50% or 10-20% drop from BL	13 (5.3%)	11 (4.5%)
LVEF Changes Grade 2 or Higher		**15 (6.1%)**	**15 (6.1%)**

MYL-Her-3001

T20-005-71

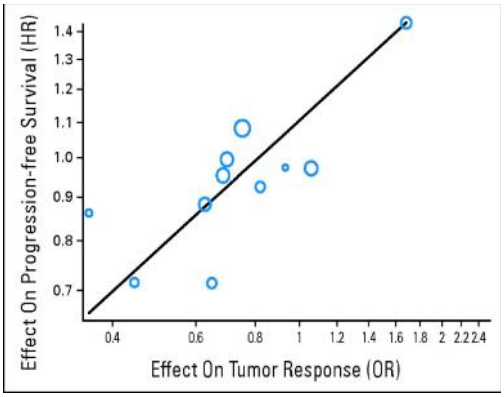
HERITAGE

PK Exposure Summary Estimates Based on Bayesian Model at Cycle 6

		MYL-1401O (N=213)	Herceptin® (N=202)
Dose Given (mg)	Mean (SD)	420 (90.5)	421 (97.8)
Clearance (L/day)	Mean (SD)	0.27 (0.102)	0.28 (0.080)
Volume at Steady State (L)	Mean (SD)	6.4 (1.20)	6.4 (1.14)
Dose-normalized AUC) (ug*day/mL/mg)	Mean (SD)	98 (30.5)	94 (28.9)
Dose-normalized Cmax,ss (ug/mL/mg)	Mean (SD)	0.43 (0.102)	0.42 (0.092)
Half-life (day)	Mean (SD)	25.2 (7.41)	24.5 (6.82)

003-1

HERITAGE
Correlation of ORR and PFS from Literature

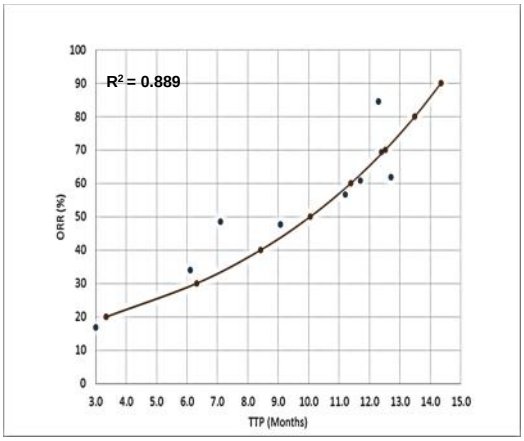


- Graph shows that tumor response is a good predictor for PFS in patients with advanced breast cancer, as the association between these endpoints is quite strong
- Treatment effects on tumor response predict treatment effects on PFS extremely well (ρ=0.96; 95% CI, 0.73 to 1.19)

Evaluation of Tumor Response, Disease Control, Progression-Free Survival, and Time to Progression As Potential Surrogate End Points in Metastatic Breast Cancer
Tomasz Burzykowski, Marc Buyse, Martine J. Piccart-Gebhart, et al.. JCO Volume 26, Number 12, April 20 2008.

T20-011-1

HERITAGE
Correlation of ORR and PFS in HER2+ MBC



- Graph based on data from 5 studies in HER2+ MBC studies with trastuzumab relevant for this program
- Regression model of ORR versus TTP/PFS used
- For ORR versus TTP/PFS, a high correlation observed with R^2 = 0.889
- ORR correlates well and is a good predictor of PFS

*Slamon et al, NEJM 2001, Marty et al, JCO 2005, Gasparini et al, Breast Cancer Res Treat, 2007, Baselga, et.al. 2012; Young-Hyucklm, et al. 2013

T20-011-2