Landscape Assessment of Biosimilar Submissions

BsUFA III Regulatory Science Pilot Program:
Progress Update

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Disclaimer

- **This presentation reflects the views of the presenter and should not be construed to represent those of the FDA.**

Agenda

- **Background & Methods**
- **Adalimumab Biosimilar Results**
  - **Comparative Analytical Data**
  - **Comparative Pharmacokinetic Studies + Comparative Clinical Studies**
- **Conclusions**

Aim: Better understand the quality attributes used to compare adalimumab and trastuzumab biosimilars to their reference products

BsUFA III Research Pilot ***Priority A****: Characterize relationships between product quality attributes with clinical performance*

Background & Research Questions

Comparative analytical assessments are foundational in biosimilar development to detect potential differences between products. When differences are present, it is critical to understand:

1. If quality data, combined with clinical PK data, are sufficient to establish biosimilarity between candidates and their reference products (RPs)
2. In cases where differences are present, the steps taken to determine that they do not preclude a determination of highly similar

Methodology*

Comparative Analytical Assessments

- **Collect** structural and functional quality attribute data
- **Evaluate** analytical biosimilarity results
- **Document** resolutions for observed analytical differences

Clinical Pharmacology Studies

- **Collect** clinical pharmacology and immunogenicity data
- **Evaluate** AUC, C_{max}, ADAs and nAbs, and other endpoints
- **Document** instances where endpoints fell outside of acceptance margins

Comparative Clinical Studies

- **Collect** clinical efficacy and safety data
- **Evaluate** treatment differences, response rates, C_{trough}, adverse events, and other endpoints
- **Document** new issues that arose and resolution of residual uncertainty

Analysis Plan

Harmonize attributes and clinical study endpoints → **Visualize similarities & differences** → **Identify patterns in difference resolution** → **Synthesize findings for manuscript**

*Adapted methodology from Guillen et al. (2022)

ADA: Anti-Drug Antibody; AUC: Area Under the Curve; C_{max}: Maximum Concentration; C_{trough}: Trough Concentration; nAb: Neutralizing Antibody; PK: Pharmacokinetic; RP: Reference Product

Documented how differences between biosimilar and the US-RP were resolved

Quality Data

In some cases, results from a particular assay did not meet pre-specified acceptability criteria; however, this alone did not preclude a demonstration of high similarity

- In cases where data for an individual quality attribute exhibited differences, the project extracted **quantitative** and **qualitative** information **explaining how the difference was resolved**
- These explanations include results from other assays in the comparative analytical assessment, as well as references to clinical pharmacology study results (when applicable)

Clinical Data

In a few studies, certain comparative PK endpoints were outside pre-specified margins, or issues involving safety or immunogenicity arose

- In such cases, a description of the issue, comparison to the US- and/or EU-RP, and accompanying explanation of the resolution was provided
- For example, the sponsor conducting another PK similarity study or explaining how immunogenicity concerns (e.g., ADA incidence) were minor and clinical studies did not show significant difference in efficacy or safety

Note: Only results from adalimumab biosimilars are presented today, but results were similar from trastuzumab biosimilar submissions

Adalimumab Biosimilar Results

Comparative Analytical Assessment

Analytical similarity assessments covered a wide range of quality attributes to evaluate physicochemical and functional aspects of each biosimilar product compared to its US-RP

Each sponsor conducts a risk assessment, ranking the quality attributes by their potential impact on four factors: potency, immunogenicity, PK, and safety. This assessment informs which of the following approaches is used to evaluate the results of the analytical similarity assessment.

Quantitative comparison approaches:

- **Quality Range (QR):** based on the mean ± XSD of US-RP lots, using a pre-specified multiplier (X usually varies between 2-3); in general, ≥90% biosimilar product lot values should fall within the QR
- **Equivalence Testing*:** statistical equivalence testing based on standard deviation and confidence intervals derived from an independent set of US-RP lots

Qualitative comparison approach: comparison of images or graphical representation of analyzed data, or comparison with expected values

Examples of Quality Attributes Assessed			
Physicochemical Attributes		**Functional/Potency Attributes**	
Quantitative QAs	**Qualitative QAs**	**Quantitative QAs**	**Qualitative QAs**
• Size variants • **Charge variants** • Fc-mediated binding • **Glycan structures (e.g., high mannose, galactose)** • Protein concentration • Post-translational modifications	• Primary structure • Higher order structures • Thermal stability • N-linked oligosaccharide profile • Other impurities (e.g., host cell protein)	• Soluble TNFα binding • Inhibition of TNFα-induced apoptosis • Reverse signaling • Inhibition of cell proliferation • ADCC and CDC • HER2 binding • Fc-mediated binding	• Induction of regulatory macrophages • tmTNFα binding • Other HER2 signaling assays • Inhibition of cytokine production/release • Inhibition of AKT phosphorylation

*FDA does not mandate statistical equivalence testing even for highest risk QAs; some sponsors elect to use the QR (X=2 or 2.58) approach instead

Source: FDA Guidance Document

Differences observed across Physico-Chemical/Functional Categories did not preclude a determination of high similarity

Highlighted differences across the Charge Variants Physico-Chemical/Functional Category		
Quality Attribute	**No. Biosimilars Evaluated per QA & No. with Differences**	**Resolution Description**
Charge heterogeneity (acidic)	• 8/9 evaluated • 6/8 showed differences (all trended higher)	• Binding, potency, and functional assay results of each fraction tested and shown to be similar • Reduced biological activity observed for one acidic fraction (abundance <3% of total peak area in all lots tested); difference due to source which can be measured and controlled • Due to deamidation in a region not expected to influence PK or potency • Comparable PK profile and FcRn binding
Charge heterogeneity (basic)	• 7/9 evaluated • 6/7 showed differences (all trended higher)	• Attributed to cause which is not expected to impact biological activity • Potency of each fraction tested but no change in potency observed
Charge heterogeneity (main)	• 7/9 evaluated • 5/7 showed differences (all trended lower)	• Attributed to cause which is not expected to impact biological activity

Differences observed across Physico-Chemical/Functional Categories did not preclude a determination of high similarity

Highlighted differences across the Glycosylation Physico-Chemical/Functional Category		
Quality Attribute	**No. Biosimilars Evaluated per QA & No. with Differences**	**Resolution Description**
Afucosylation	• 7/9 evaluated • 6/7 showed differences (all trended higher)	• Minor (i.e., <~2.3%) and had no impact on FcγRIIIa binding and ADCC biological activity assays • Limited to early manufacturing process batches • Real time release testing established
Galactosylation	• 9/9 evaluated • 8/9 showed differences (7 higher, 1 lower)	• No impact on biological activities (e.g., CDC activity) • Often limited to early manufacturing process batches • Release testing using an assay (e.g., HPLC) established
High Mannose	• 9/9 evaluated • 7/9 showed differences (all trended lower)	• Potential effect on ADCC activity as well as PK (e.g., clearance) • No significant differences in ADCC activity and clinical pharmacology study results also demonstrated similarity • Often limited to early manufacturing process batches • As per literature, up to 5% difference in high mannose not expected to impact clearance • Release testing using an assay (e.g., HPLC) established
Sialylation	• 8/9 evaluated • 6 showed differences (5 higher, 1 lower)	• No impact on ADCC function nor comparative PK study results • Sialic acid levels <1%, differences minor • Limited to early manufacturing process batches and not in commercial process lots • Release testing using an assay established

Adalimumab Biosimilar Results

Pharmacology and Comparative Clinical Studies

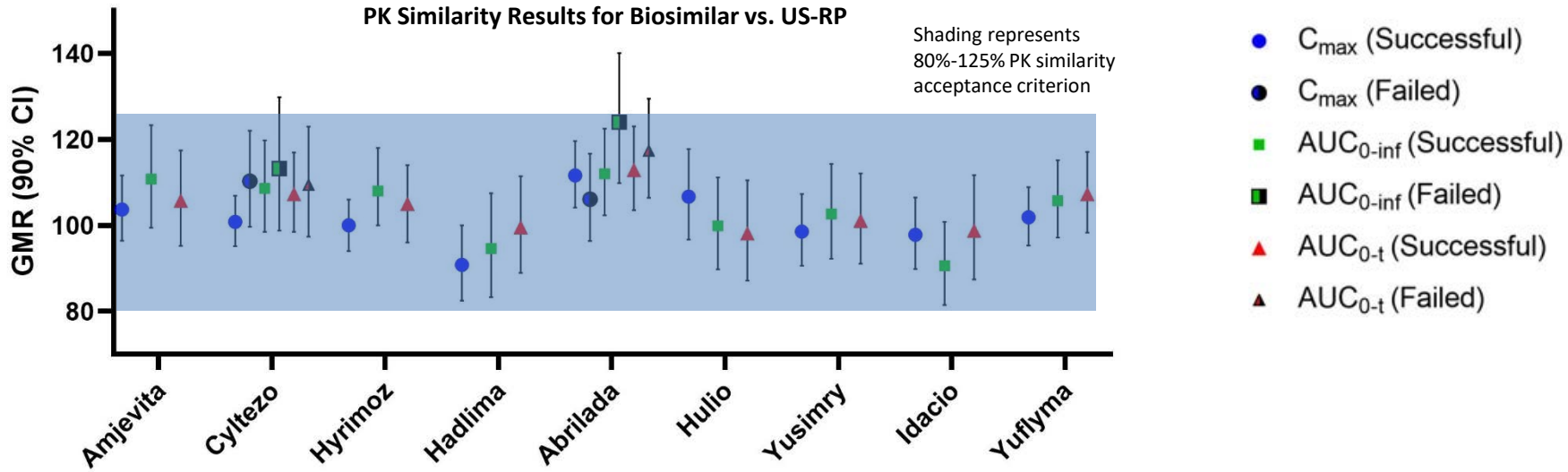
Sponsors conducted studies comparing the clinical pharmacology, safety, and immunogenicity of their adalimumab biosimilars to US-RP

- Sponsors conducted between 1-3 studies each investigating the comparative PK, safety, and immunogenicity of their products
  - In 3 cases, sponsors conducted an additional primary PK study to demonstrate no clinically meaningful differences
- In addition, several sponsors also conducted various supportive PK studies
  - 6 sponsors investigated different presentations (e.g., pre-filled syringe vs. autoinjector)
  - 3 sponsors investigated different formulations (e.g., trial vs. commercial)

	Amjevita	Cyltezo	Hyrimoz	Hadlima	Abrilada	Hulio	Yusimry	Idacio	Yuflyma
Sample Size	203	Study #1: 193 Study #2: 324	Study #1: 219 Study #2: 318	189	Study #1: 210 Study #2: 359	180	210	237	312
Observation Period	Day 63	#1: Day 79 #2: Day 71	#1: Day 72 #2: Day 72	Day 71	#1: Day 42 #2: Day 49	Day 65	Day 65	Day 71	Day 71
1° Endpoints Assessed	Maximum concentration (C_{max}), Area Under the Curve (AUC) to last time point (AUC_t), AUC extrapolated to infinity (AUC_{inf})								
2° Endpoints Assessed	Incidence of binding anti-drug antibodies (ADAs), incidence of neutralizing antibodies (nAbs)								
Acceptance Margin	90% confidence intervals for the ratios of geometric means within the interval of 80% to 125%								
Incidence of Binding ADAs	43% vs. 50%	#1: 96% vs. 93% #2: 93% vs. 88%	#1: 67% vs. 68% #2: 58% vs. 69%	100% (both)	#1: 86% vs. 94% #2: 77% vs. 80%	70% (both)	82% vs. 83%	80% vs. 75%	70% (both)
Incidence of nAbs	18% vs. 22%	#1: 53% vs. 35% #2: 60% vs. 64%	#1: 60% vs. 51% #2: 54% vs. 63%	84% (both)	#1: 54% vs. 66% #2: 65% vs. 63%	59% vs. 57%	60% vs. 65%	72% vs. 71%	59% vs. 57%

First number mentioned is always biosimilar, vs. RP

All adalimumab biosimilars demonstrated PK similarity, although in three cases sponsors conducted a second clinical pharmacology study



Highlighted Differences across Clinical Pharmacology Studies and their Resolution

Product	Observation	Resolution Description
Cyltezo	In initial PK study, upper 90% CI for GMR of **AUC_{inf}** (biosimilar vs. US- and EU-RP) exceeded acceptance margin	• Possible causative factors include **high overall variability** and influence of body weight on exposure • Review noted initial PK study used trial formulation while second PK study used the commercial formulation • In second PK study, sample size increased, injection site restricted to lower abdomen, and body weight included as a covariate in the ANCOVA analysis and predefined in protocol
Hyrimoz	In initial PK study, upper 90% CIs for GMRs of **AUC_t** and **AUC_{inf}** (biosimilar vs. EU-RP) exceeded acceptance margin	• PK similarity between biosimilar and US-RP established; however, results demonstrated lower exposure from EU-RP • **Observed variability** for AUC_t (>40%) **was higher** than anticipated variability (31%); therefore, study may not have been **adequately powered** for PK similarity • Consequently, the applicant conducted another PK similarity study with an increased sample size
Abrilada	In initial PK study, upper 90% CIs for GMRs of **AUC_t** (biosimilar vs. US-RP) and **AUC_{inf}** (biosimilar vs. US- & EU-RP) exceeded acceptance margin	• Based on **higher-than-expected inter-subject variability**, initial study considered **inadequately powered** for PK similarity • Information from first study subsequently supported design and sample size calculation in second PK similarity study, for which all endpoints demonstrated PK similarity

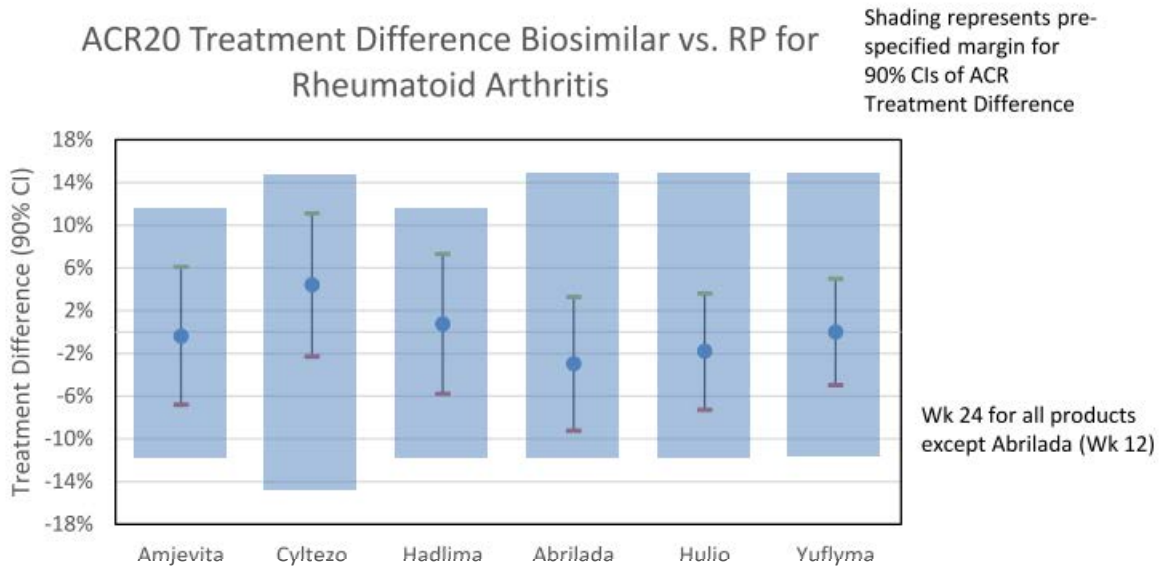
Sponsors also conducted comparative clinical studies (CCS) investigating clinical efficacy and safety of their products versus the US-RP

- Sponsors conducted between one and two CCS each
  - Six conducted studies in patients with rheumatoid arthritis (RA) on methotrexate (MTX)
  - Four conducted studies in patients with chronic plaque psoriasis (PsO)
- Primary endpoints were either ACR20 Response (RA) or % Change in PASI (PsO)
- Pre-specified margins for treatment difference CIs between the biosimilar and US-RP ranged from -15% to +15% (RA) and -18 to +18% (PsO)

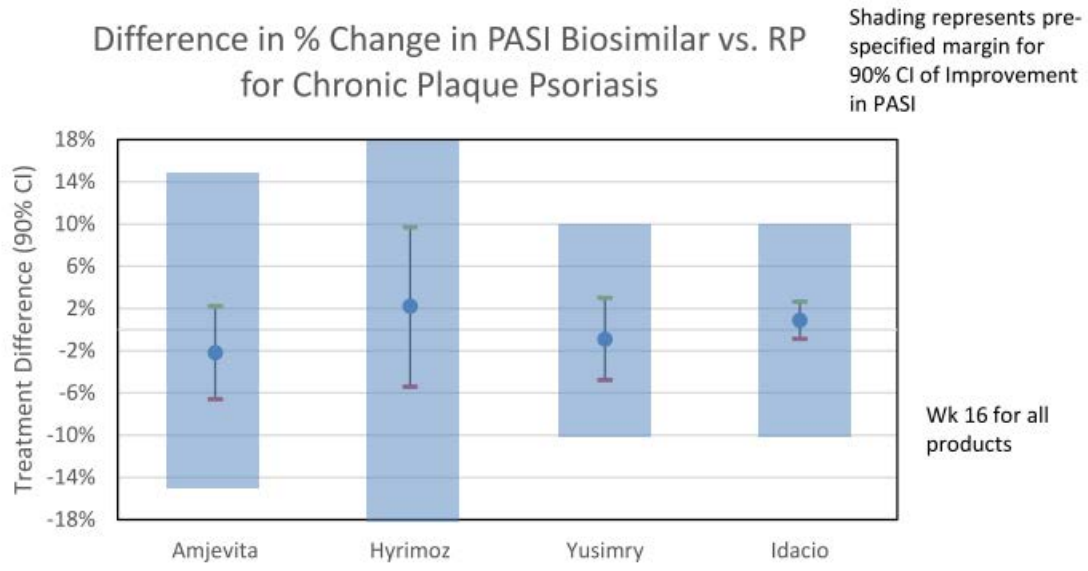
	Amjevita	Cyltezo	Hyrimoz	Hadlima	Abrilada	Hulio	Yusimry	Idacio	Yuflyma
Study Population	#1: Moderate to severe **RA** on MTX #2: Moderate to severe **PsO**	Moderate to severe **RA** on MTX	Chronic **PsO**	Moderate to severe **RA** on MTX	Moderate to severe **RA**	Moderate to severe **RA** on MTX	Moderate to severe chronic **PsO**	Moderate to severe chronic **PsO**	Moderate to severe **RA** on MTX
Sample Size	#1: 526 #2: 347	645	465	544	597	728	545	443	648
1° Efficacy Endpoint(s) Assessed	#1: ACR20 at Wk 24 #2: % change in PASI at Wk 16	ACR20 at Wks 12 & 24	% Change in PASI75 at Wk 16	ACR20 at Wk 24	ACR20 at Wk 12	ACR20 at Wk 24	% Change in PASI75 at Wk 16	% Change in PASI75 at Wk 16	ACR20 at Wk 24
Pre-specified Acceptance Margin	#1: -12% to +12% #2: -15% to +15%	Wk 12: -12% to +15% Wk 24: -15% to 15%	-18% to +18%	-12% to +12%	-12% to +15%	-12% to +15%	-10% to +10%	-10% to +10%	-12% to +15%

First number mentioned is always biosimilar, vs. RP

All adalimumab biosimilars met primary efficacy endpoints compared to RP



	Amjevita	Cyltezo	Hadlima	Abrilada	Hulio	Yuflyma
ACR20 Response	71.2% vs. 72.1%	68.4% vs. 64.0%	68.0% vs. 67.4%	68.4% vs. 71.3%	72.5% vs. 74.3%	82.7% vs. 82.7%



	Amjevita	Hyrimoz	Yusimry	Idacio
% Change in PASI	71.2% vs. 72.1%	58.1% vs. 55.9%	83.1% vs. 82.3%	92.14% vs. 93.02%

- All studies met primary endpoint, with the point estimates and 90% CIs within pre-specified margins
- Trough drug concentrations were also assessed, allowing for evaluation of the impact of immunogenicity on PK and efficacy
  - C_{trough} were comparable between the biosimilar and RP at each time point
  - Presence of ADAs was associated with decreased C_{trough} and increased clearance in all treatment groups
  - Response rates were similar between biosimilar and RP in ADA+ and ADA- patients, respectively

First number mentioned is always biosimilar, vs. RP

Conclusions

Conclusions: Landscape Assessment of Biosimilar Submissions

Quality Data

Comparative analytical assessments demonstrated **high structural and functional similarity** between the biosimilar and US-RP for all adalimumab biosimilars

Analytical differences were observed among QAs in the Charge Variants, Glycosylation, and Purity/Impurity categories, **none of which precluded a determination of high similarity**

- For 90% (27/30) of QAs with at least one difference, analytical data alone were sufficient to address residual uncertainty
- PK study results were also referenced as supplementary evidence for 10% (3/30) of QAs

Clinical Data

In 3 cases, initial PK study results showed differences in AUC, which were attributed to greater than expected inter-subject variability

- All follow-up studies with increased sample size **demonstrated no clinically meaningful differences**
- No additional safety or efficacy issues were raised

Clinical results demonstrated comparable efficacy and safety, although they did not appear to play a role in resolving residual uncertainty from analytical similarity assessments or PK studies

- Efficacy: all primary endpoints were within equivalence margins
- Safety and Immunogenicity: similar incidence of ADAs/nAbs; rates of AEs considered balanced between treatment groups
- No references in review documentation describing residual uncertainties that comparative clinical efficacy studies resolved

Conclusion: Results from comparative analytical and clinical PK studies typically sufficient to demonstrate that these adalimumab biosimilars were highly similar to the US-RP except for minor differences that were not clinically meaningful.

Similar conclusions were observed during review of trastuzumab analytical and clinical data.

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