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Overview of the Regulatory Pathway and FDA's Guidance for the Development and Approval of Biosimilar Products in the US

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Overview of Presentation

- Overview
  - Background
  - Definitions
  - Approval Pathway for Biosimilars – General Requirements

- Development of Biosimilars
  - Approach to Development
  - Specific Development Concepts

Overview

Background

- The **Biologics Price Competition and Innovation Act of 2009 (BPCI Act)** was passed as part of health reform (Affordable Care Act) that President Obama signed into law on March 23, 2010.

- BPCI Act creates an ***abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with*** an FDA-licensed reference product.

What is an Abbreviated Licensure Pathway for Biological Products?

- A biological product that is demonstrated to be "***highly similar***" to an FDA-licensed biological product (the reference product) may rely for licensure on, among other things, publicly-available information regarding FDA's previous determination that the reference product is safe, pure and potent.
- This licensure pathway permits a biosimilar biological product to be licensed under 351(k) of the Public Health Service Act (PHS Act) based on **less than a full complement of product-specific preclinical and clinical data** → **abbreviated** licensure pathway**.**

Definition: Biosimilarity

Biosimilar or **Biosimilarity** means:

- that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; and

- there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product.

Definition: Reference Product

Reference Product means**:**

- the **single biological product, licensed under section 351(a) of the PHS Act,** against which a biological product is evaluated in an application submitted under section 351(k) of the PHS Act.

– An application submitted under section 351(a) of the PHS Act is a "stand-alone" application that contains all information and data necessary to demonstrate that the proposed product is safe, pure and potent.

– In contrast, an application submitted under section 351(k) needs to demonstrate that the proposed product is biosimilar to the reference product. For licensure, a proposed biosimilar relies on (among other things) comparative data with the reference product, as well as publicly-available information regarding FDA's previous determination that the reference product is safe, pure and potent.

Definition: Interchangeability

Interchangeable or **Interchangeability** means**:**

- the biological product is **biosimilar** to the reference product;
- it can be expected to produce the **same clinical result** as the reference product **in any given patient**; and
- for a product that is administered more than once to an individual, the risk in terms of **safety or diminished efficacy of alternating or switching** between use of the product and its reference product is not greater than the risk of using the reference product without such alternation or switch.

Note: The interchangeable product **may be substituted** for the reference product without the intervention of the health care provider who prescribed the reference product.

General Requirements

A 351(k) application must include information demonstrating that the biological product:

- Is **biosimilar** to a reference product;
- Utilizes the **same mechanism(s) of action** for the proposed condition(s) of use -- but only to the extent the mechanism(s) are known for the reference product;
- **Condition(s) of use** proposed in labeling **have been previously approved** for the reference product;
- Has the **same route of administration**, **dosage form**, and **strength** as the reference product; and
- Is manufactured, processed, packed, or held in a facility that **meets standards** designed to assure that the biological product continues to be safe, pure, and potent.

General Requirements: 351(k) Application

The PHS Act requires that a 351(k) application include, among other things, **information demonstrating biosimilarity based upon data derived from**:

- **Analytical studies** demonstrating that the biological product is "highly similar" to the reference product notwithstanding minor differences in clinically inactive components;
- **Animal studies** (including the assessment of toxicity); and
- A **clinical study or studies** (including the assessment of immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD)) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and for which licensure is sought for the biosimilar product.

FDA may determine, in its discretion, that an element described above is unnecessary in a 351(k) application.

Use of Non-US-Licensed Comparator Products

- The PHS Act defines the "reference product" for a 351(k) application as the "single biological product licensed under section 351(a) against which a biological product is evaluated."
- Data from animal studies and certain clinical studies comparing a proposed biosimilar product with a non-US-licensed product may be used to support a demonstration of biosimilarity to a US-licensed reference product.
- Sponsor should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product.

Support for Use of Non-US-Licensed Comparator

- Type of bridging data needed would include:
  - Direct physicochemical comparison of all 3 products (proposed biosimilar to US-licensed reference product; proposed biosimilar to non-US-licensed comparator product; US-licensed reference product to non-US-licensed comparator product)
  - Likely 3-way bridging clinical PK and/or PD study
  - All three pair-wise comparisons should meet the pre-specified acceptance criteria for analytical and PK and/or PD similarity.

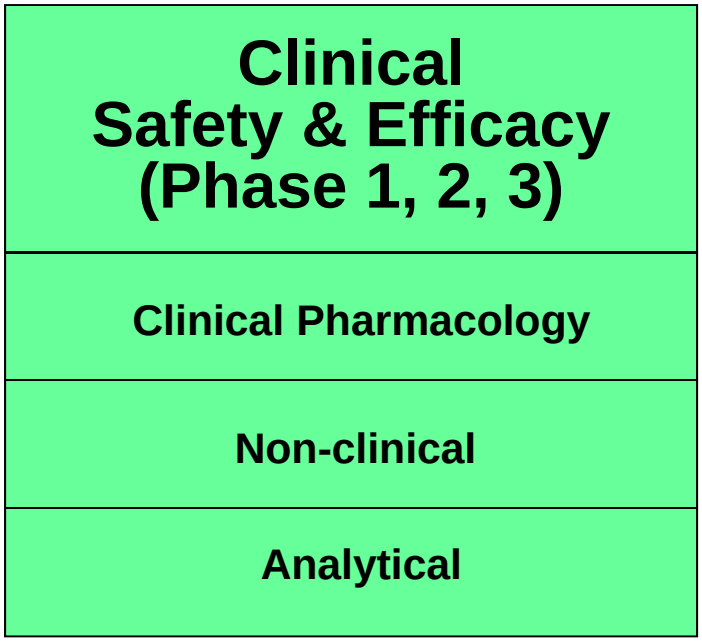
- A sponsor should justify the extent of comparative data needed to establish a bridge to the U.S.-licensed reference product.

Overview of FDA's Approach to the Development of Biosimilars

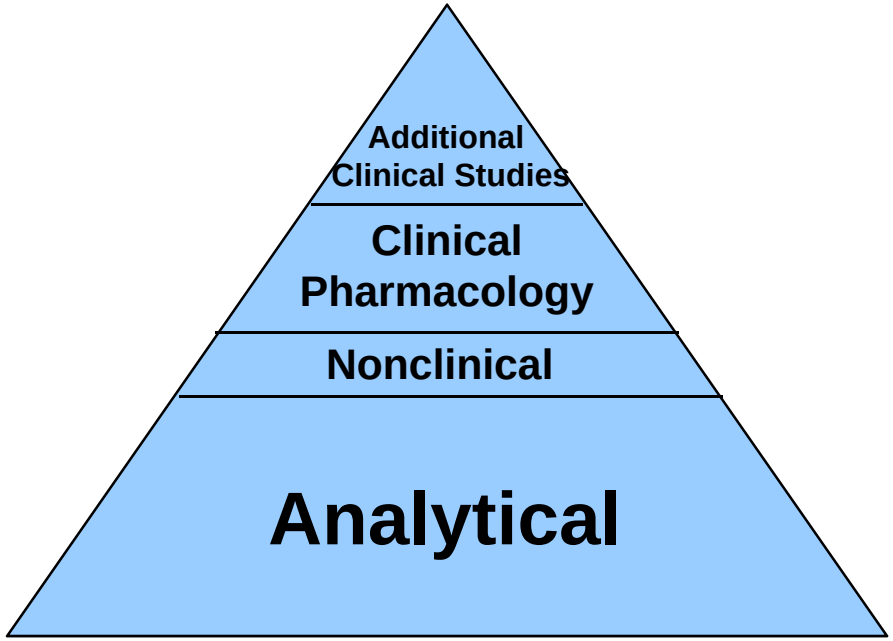
Key Development Concepts

Key Concept #1: Goals of "Stand-alone" and Biosimilar Development are Different

"Stand-alone" Development Program, 351(a)
Goal: To establish safety and efficacy of a new product



"Abbreviated" Development Program, 351(k)
Goal: To demonstrate biosimilarity (or interchangeability)

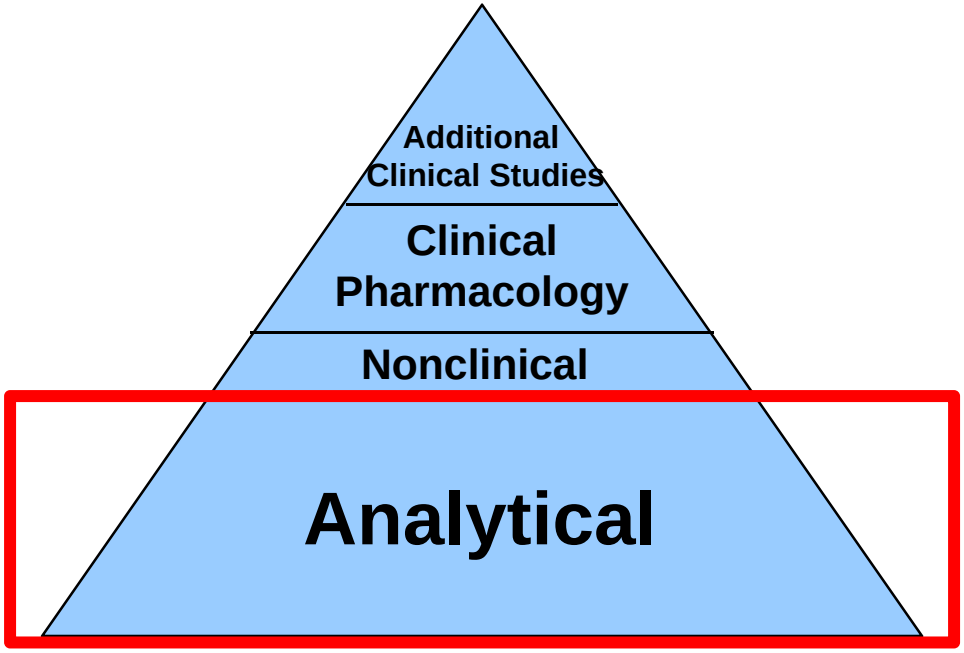


Key Concept #2:
Stepwise Evidence Development

- FDA has outlined a **stepwise approach** to generate data in support of a demonstration of biosimilarity
- Evaluation of residual uncertainty at each step
- *Totality-of-the-evidence* approach in evaluating biosimilarity
- Apply a step-wise approach to data generation and the evaluation of residual uncertainty about biosimilarity
  - What differences have been observed and what is the potential impact?
  - What is the residual uncertainty and what study(ies) will address the residual uncertainty?
- There is no one "pivotal" study that demonstrates biosimilarity
- No "one size fits all" assessment

Key Concept #3:
Analytical Similarity Data -
The Foundation of a Biosimilar Development Program

- Extensive **structural and functional characterization**



"Abbreviated" Development Program, 351(k) BLA

Assessing Analytical Similarity

- Comparative assessment of attributes including:
  - Amino acid sequence and modifications
  - Folding
  - Subunit interactions
  - Heterogeneity (size, aggregates, charge, hydrophobicity)
  - Glycosylation
  - Bioactivity
  - Impurities
- If a molecule is known to have multiple biological activities, where feasible, each should be demonstrated to be highly similar between the proposed biosimilar product and the reference product
- **Understand** the molecule and function and identify **critical quality attributes**

Generating Analytical Similarity Data

- Characterize reference product quality characteristics and product variability
- Manufacturing process for the proposed biosimilar product should be designed to produce a product with minimal or no difference in product quality characteristics compared to the reference product
- Identify and evaluate the potential impact of differences observed and what study(ies) will address the residual uncertainty
- **Understanding the relationship** between quality attributes and the clinical safety & efficacy profile aids ability to determine **residual uncertainty** about biosimilarity and to predict expected “clinical similarity” from the quality data.

Statistical Analysis of Analytical Similarity Data

- Statistical analyses of the analytical similarity data are conducted to support a demonstration that the proposed biosimilar product is highly similar to the reference product
- Quality attributes are ranking based on criticality with regard to their potential impact on activity, PK/PD, safety, immunogenicity, and other factors
- Data are then analyzed by various testing methodologies
  - Equivalence testing for certain highly critical attributes
  - Quality range (mean ± X SD) for other highly critical to low criticality attributes
  - Raw/graphical comparisons for other attributes with very low criticality or not amenable to other testing methodologies

Animal Data

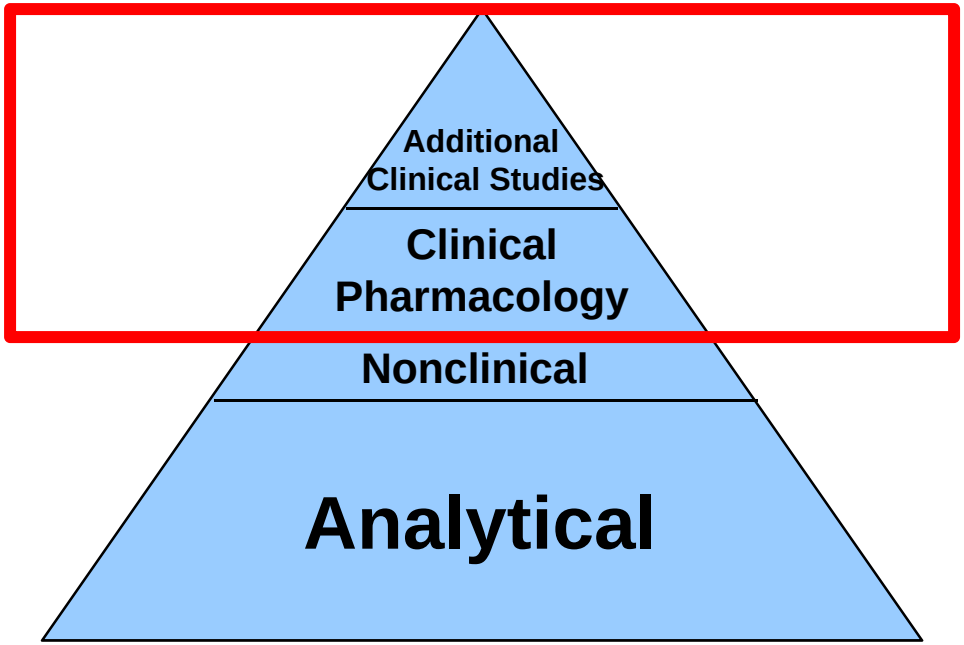
- Animal toxicity data are useful when uncertainties remain about the safety of the proposed product prior to initiating clinical studies

- The scope and extent of animal studies, including toxicity studies, will depend on publicly available information and/or data submitted in the biosimilar application regarding the reference product and the proposed biosimilar product, and the extent of known similarities or differences between the two

- A comparison of PK/PD in an animal model may be useful

Key Concept # 4: Role of Clinical Studies

- The nature and scope of clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the two products **after** conducting structural and functional characterization and, where relevant, animal studies.



"Abbreviated" Development Program, 351(k) BLA

Type of Clinical Data

- As a scientific matter, FDA expects an adequate clinical PK, and PD if relevant, comparison between the proposed biosimilar product and the reference product.

- As a scientific matter, at least 1 clinical study that includes a comparison of the immunogenicity of the proposed and reference product generally will be expected.

- As a scientific matter, a comparative clinical study will be necessary to support a demonstration of biosimilarity if there are **residual uncertainties** about whether there are clinically meaningful differences between the proposed and reference products based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment.

Comparative Human PK and PD Data

- PK and/or PD is generally considered the most sensitive clinical study/assay in which to assess for differences between products, should they exist
- PK
  - Demonstrate PK similarity in an adequately sensitive population to detect any differences, should they exist
- PD
  - Similar PD using PD measure(s) that reflects the mechanism of action (MOA) or reflects the biological effect(s) of the drug
- PK and PD similarity data supports a demonstration of biosimilarity with the assumption that similar exposure (and pharmacodynamic response, if applicable) will provide similar efficacy and safety (i.e., an exposure-response relationship exists)

Comparative Clinical Study

- A comparative clinical study for a biosimilar development program should be designed to investigate whether there are clinically meaningful differences in safety and efficacy between the proposed product and the reference product.
- Population, endpoint, sample size and study duration should be adequately sensitive to detect differences, should they exist.
- Typically, an equivalence design would be used, but other designs may be justified depending on product-specific and program-specific considerations.
- Assessment of safety and immunogenicity

Extrapolation

- The potential exists for a biosimilar product to be approved for one or more conditions of use for which the US-licensed reference product is licensed based on extrapolation of data intended to support a demonstration of biosimilarity in one condition of use (e.g., indication) to other conditions of use.

- Sufficient scientific justification for extrapolating data is necessary.

Extrapolation Considerations

- FDA guidance outlines factors/issues that should be considered when providing scientific justification for extrapolation including, for example*,
  - The MOA(s) in each condition of use for which licensure is sought
  - The PK and bio-distribution of the product in different patient populations
  - The immunogenicity of the product in different patient populations
  - Differences in expected toxicities in each condition of use and patient population
- Differences between conditions of use do not necessarily preclude extrapolation
- Ensure totality of the evidence, including scientific justification for extrapolation, supports approach

*This list is a subset of the issues outlined in the FDA guidance document

Summary

- The content of a biosimilar development program is based on stepwise evidence development and the evaluation of residual uncertainty about biosimilarity between the proposed biosimilar product and the reference product.

- Approval of a proposed biosimilar product is based on the integration of various information and the totality of the evidence submitted by the biosimilar sponsor to provide an overall assessment that the proposed product is biosimilar to the reference product.

Thank you for your attention.

Introductory Remarks

351(k) BLA for ABP 501, a Proposed Biosimilar to US-licensed Humira

Arthritis Advisory Committee

July 12, 2016

Nikolay P. Nikolov, MD
Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Food and Drug Administration

Overview of the BLA

- Applicant: Amgen
- Product: ABP 501, proposed biosimilar to US-licensed Humira (US-Humira)
- Dosing and route of administration: Same as US-Humira
- Indications sought for licensure of ABP 501:
  - Rheumatoid arthritis (RA)
  - Polyarticular Juvenile Idiopathic Arthritis (JIA), 4 years of age or older
  - Psoriatic arthritis (PsA)
  - Ankylosing spondylitis (AS)
  - Adult Crohn's disease (CD)
  - Adult Ulcerative colitis (UC)
  - Plaque psoriasis (PsO)

US: United States

Overview of ABP 501 Development Program

- To support a demonstration that ABP 501 is **highly similar** to US-licensed Humira, Amgen provided extensive data package that included analytical similarity assessment of:
  - Primary-, secondary-, and tertiary structure
  - Post-translational profile and *in vitro* functional characteristics
  - Purity and stability
  - TNF-α binding and potency

TNF-α: Tumor necrosis factor alpha

Overview of ABP 501 Development Program

- To support a demonstration of **no clinically meaningful differences** between ABP 501 and US-licensed Humira, Amgen provided:
  - Studies to demonstrate similarity in exposure (i.e. PK) in healthy subjects
  - Comparative clinical efficacy and safety study in patients with RA
  - Comparative clinical efficacy and safety study in patients with PsO
  - Immunogenicity data in:
    - Patients with RA, PsO, and healthy subjects, and
    - Patients with PsO who were transitioned from EU-Humira to ABP 501

PK: Pharmacokinetics

Overview of ABP 501 Clinical Program

Study	Design	Objectives	Subjects	Treatments	Endpoints
PK Similarity Study					
20110**217**	R, PG, SD, 3-way PK bridging	PK, safety, and immunogenicity	203 Healthy Subjects	40 mg SC: • ABP 501 • US-Humira • EU-Humira	Cmax, AUCt and AUCinf
Comparative Clinical Studies					
20120**262**	26 Weeks, R, DB, PG	Efficacy, safety, immunogenicity, PK	526 RA Patients	40 mg SC Q2W+MTX: • ABP 501 • US-Humira	ACR20
20120**263**	R, DB, PG (Week 1-16)	Efficacy, safety, immunogenicity, PK	350 PsO Patients	80 mg SC Day 1, then 40 mg SC Q2W from Wk2: • ABP 501 • EU-Humira	% PASI
	Single transition from EU-Humira to ABP 501 (Week 16 to 48)	Safety, immunogenicity, PK	Patients on EU-Humira arm re-randomized to transition to ABP 501	40 mg SC Q2W: • ABP→ABP • EU-Humira→ABP • EU-Humira→EU Humira	Safety, Immunogenicity

Overview of ABP 501 Development Program

- To justify the relevance of the data generated using a non-US-licensed comparator, i.e. EU-approved Humira, Amgen provided:
  - Extensive analytical 3-way bridging data between ABP 501, US-licensed Humira, and EU-approved Humira
  - Clinical exposure (PK) bridging data between ABP 501, US-licensed Humira, and EU-approved Humira in healthy subjects

Overview of ABP 501 Development Program

- Amgen also provided an extensive data package to address the scientific considerations* for extrapolation of data to support that there are no clinically meaningful differences for the additional indications sought for licensure:
  - The mechanism(s) of action (MOA) in each condition of use
  - The PK and bio-distribution of the product in different patient populations
  - The immunogenicity of the product in different patient populations
  - Differences in expected toxicities in each condition of use and patient population

*Guidance for Industry "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", April 2015

Discussion Questions

Discussion Question 1:

- Please discuss whether the evidence from analytical studies supports a demonstration that ABP 501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components.

Discussion Question 2:

- Please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between ABP 501 and US-licensed Humira in the studied conditions of use (RA and PsO).

Discussion Questions

Discussion Question 3:

- Please discuss whether the data provides adequate scientific justification to support a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira for the following additional indications for which US-licensed Humira is licensed:
  - JIA in patients 4 years of age and older
  - PsA
  - AS
  - Adult CD
  - Adult UC
- If not, please state the specific concerns and what additional information would be needed to support extrapolation. Please discuss by indication if relevant.

Voting Question

- Does the totality of the evidence support licensure of ABP 501 as a biosimilar product to US-licensed Humira for the following indications for which US-licensed Humira is currently licensed and for which Amgen is seeking licensure (RA, JIA in patients 4 years of age and older, PsA, AS, adult CD, adult UC, and PsO)?

- Please explain the reason for your vote.

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Product Quality Review

351(k) BLA for ABP 501, a Proposed Biosimilar to US-licensed Humira

Arthritis Advisory Committee

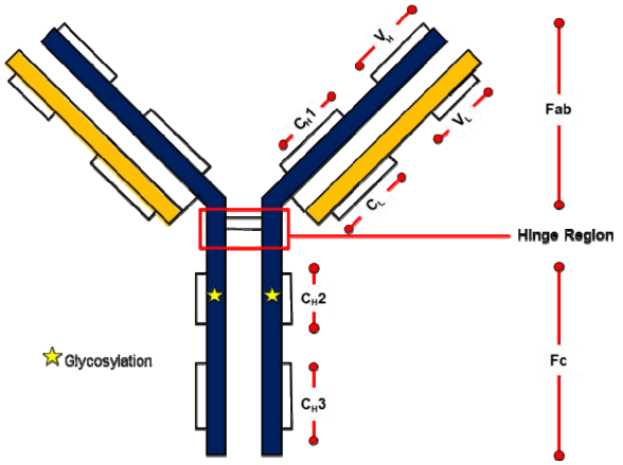
July 12, 2016

Joel Welch, PhD
Product Quality Team Leader
Office of Biotechnology Products
CDER, FDA

Outline

- Adalimumab Structure and Mechanism of Action
- ABP 501 Manufacturing
- Studies to Support High Similarity
- Analytical Similarity Assessment

Adalimumab Structure

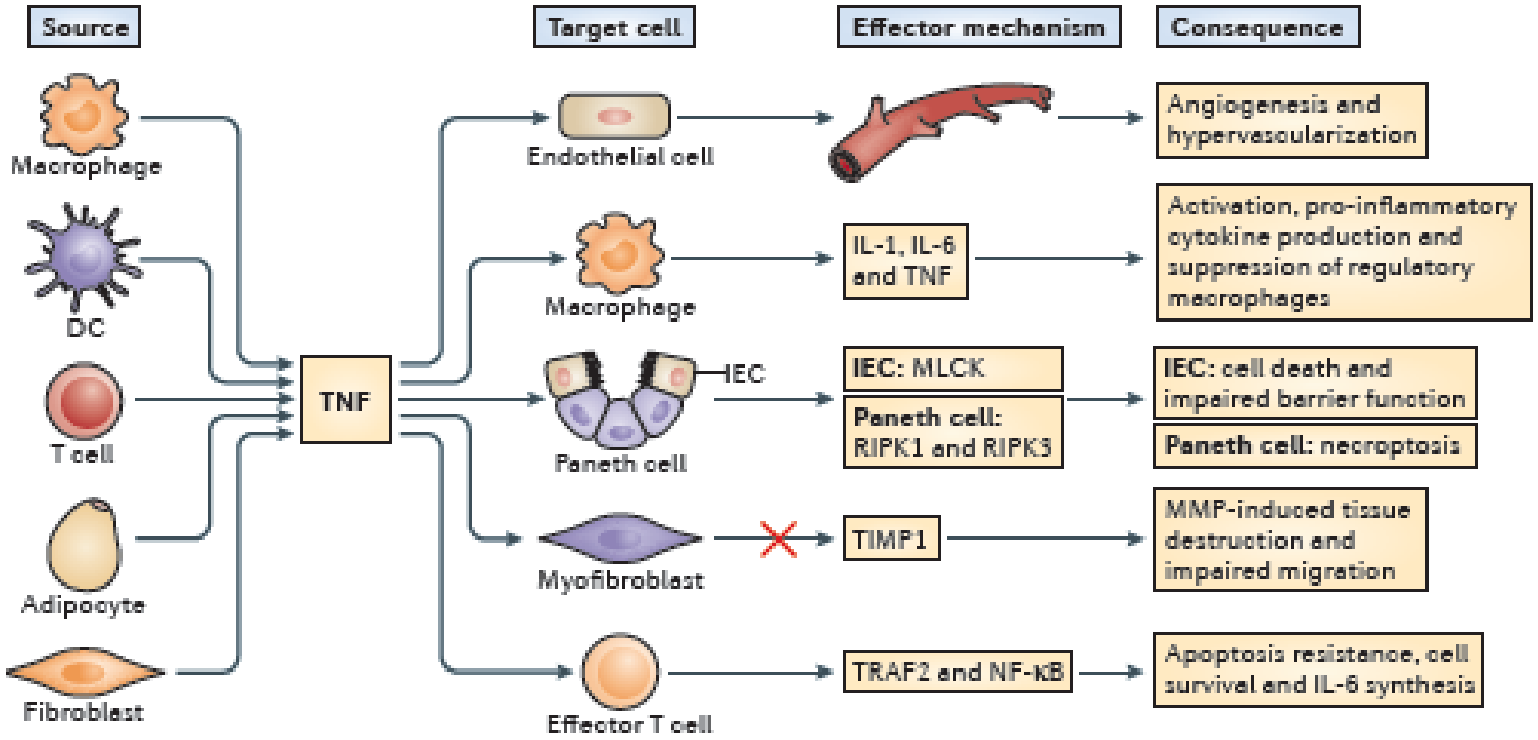


- Humira: AbbVie
- Human IgG1κ monoclonal antibody
- Neutralizes human tumor necrosis factor-α (TNF-α)
- Molecular weight: ~148 kilodaltons
- Produced by a recombinant cell line cultured in bioreactors
- Possesses heterogeneity typical of mammalian cell culture-derived mAbs

Source: Figure excerpted from the Amgen 351(k) BLA submission

TNF-α: A "Master" Cytokine

Soluble (17kDa) and membrane-bound (26kDa) forms



Neurath MF Nature Reviews *Immunology* 14,329–342(2014)

Known and Potential MOAs of Humira

MOA of Humira*	RA, JIA	AS	PsA	PsO	CD	UC
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF						
	Yes	Yes	Yes	Yes	Likely	Likely
Reverse (outside-to-inside) signaling via tmTNF						
					Likely	Likely
Mechanisms involving the Fc region of the antibody:						
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible
Induction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible
Induction of regulatory MΦ in mucosal healing	-	-	-	-	Plausible	Plausible

*Based on FDA summary of existing literature

CDC = Complement Dependent Cytotoxicity ADCC = Antibody Dependent Cell-mediated Cytotoxicity

ABP 501 Drug Substance

- Bioreactor production culture (mammalian cells)
- Standard biotechnology purification scheme
  - Viral safety procedures in place (testing and clearance)
- Drug substance lot history
  - 5 years of lots at 2000 L scale
  - Minor process changes: comparable product
- Critical Quality Attributes (CQAs) include potency, binding, ADCC, aggregates, glycosylation, charge variants, host cell protein and viral safety
- Drug substance facility was inspected in May-June 2016

ABP 501 Drug Product

- A sterile, single-use solution for subcutaneous injection
- Produced by aseptic processing and tested for sterility
- Container closure system: 1 mL prefilled syringe (PFS)
- Different formulation than US-licensed Humira
- Expiry supported by stability studies

Analytical Similarity Evaluations

- Analytical comparison of ABP 501 and US-licensed Humira is used to support a demonstration that ABP 501 is “highly similar” to US-licensed Humira
- Pairwise comparisons of ABP 501, US-licensed Humira and EU-approved Humira are used to support the analytical bridge between the three products
- Bridge is needed to justify the relevance of data generated using EU-approved Humira as the comparator in some clinical studies intended to support a demonstration of biosimilarity to US-licensed Humira

Lots Tested in the Analytical Similarity Assessment

- **10 ABP 501 lots –** Including all lots used in the clinical trials
- A total of **24 US-licensed Humira and 18 EU-Approved Humira** lots. This includes 5 lots each of US-licensed Humira and EU-Approved Humira used in the clinical trials

Methods Used to Evaluate Analytical Similarity

Quality Attribute	Methods
Primary Structure	• Peptide mapping with ultraviolet (UV) and mass spectrometry (MS) detection • Intact Molecular Mass (LC-MS) • Reduced and Deglycosylated Molecular Mass (LC-MS)
Bioactivity	• Apoptosis Inhibition (Bioassay) • sTNFα binding (ELISA)
Purity	• Reduced/non-reduced CE-SDS
Fc Receptor Binding	• FcγRIIIa V type binding affinity (AlphaLISA) • FcγRIIIa F type binding affinity (AlphaLISA) • FcγR Ia, IIa binding affinity (AlphaLISA) • FcRn binding affinity (cell-based)
Protein Content	• Concentration (UV_{280})
Sub-visible Particles	• MicroFlow Imaging • Light Obscuration
Higher Order Structure	• 2^{O} Structure (Fourier Transform-IR; Circular Dichroism)

Quality Attribute	Methods
Biologic Analysis and mechanism of action exploration	• CDC • ADCC of NK cells • C1q binding (ELISA) • Specificity against Ltα • Inhibition of sTNFα-induced IL-8 in HUVEC • Binding to tmTNFα • Inhibition of T-Cell proliferation (MLR)
High molecular weight variants/aggregates	• Size exclusion chromatography (SEC) • SEC-Multi Angle Laser Light Scatter • SEC- Analytical Ultracentrifugation • Field Flow Fractionation
Physicochemical Analysis	• Glycan Profiling • Thermal stability (DSC) • pI (cIEF) • Charge variant Dist.(ciEF and CEX-HPLC) • Disulfide Bond Structure
General Properties	• Deliverable Volume • Osmolality • Polysorbate • pH • Appearance

Methods were validated or qualified at time of testing and demonstrated to be fit for intended use

Analytical Methods: Studies to Support ABP 501 High Similarity

High Criticality Quality Attributes

- Primary Sequence
  - Expression construction encodes the same primary amino acid sequence
  - Tryptic Peptide Mapping
  - Measurements of Molecular Mass (LC-MS)
- Apoptosis inhibition (Cell based assay)
- TNF-α binding (ELISA)

Additional Analytical Studies to Support ABP 501 High Similarity

Analyzed Using a Quality Range

- ADCC
- CDC
- FcγRIIIa binding
- FcRn binding
- Protein concentration
- Aggregates
- Charge Variants
- Purity (Fragments)
- N-linked glycan analysis
- ≥ 5 μm non-spherical subvisible particles (MFI)
- Deliverable Volume

Additional Assessment

- 2°, 3° structure (CD, FT-IR, DSC)
- Isoelectric Point
- Additional FcγR binding
- Aggregates (Alternate detectors)
- Subvisible particulates (Alternate detectors)
- Appearance
- Polysorbate
- HCP
- DNA
- Osmolality
- pH
- Binding to tmTNF-α
- C1q Binding
- Some *in vitro* tests used to evaluate mechanism of action

ABP 501 Statistical Equivalence Testing for Bioactivity

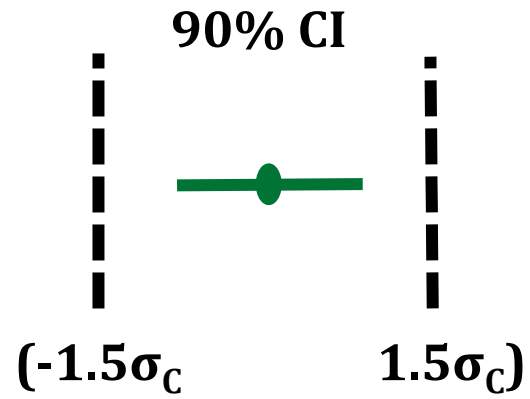
Meiyu Shen, PhD
CMC Statistical Reviewer
Office of Biostatistics
CDER, FDA

Highly Critical Quality Attributes for Statistical Equivalence Analyses

- Assays that assessed the primary mechanism of action that were tested using equivalence testing:
  - Apoptosis inhibition bioassay
    - potency
  - sTNF-α binding

Statistical Equivalence Test

- The null hypothesis H0:
  - Mean(Test) – Mean (Comparator) $\geq 1.5\sigma_C$ or Mean(Test) – Mean (Comparator) $\leq -1.5\sigma_C$;
- Test and comparator are equivalent if

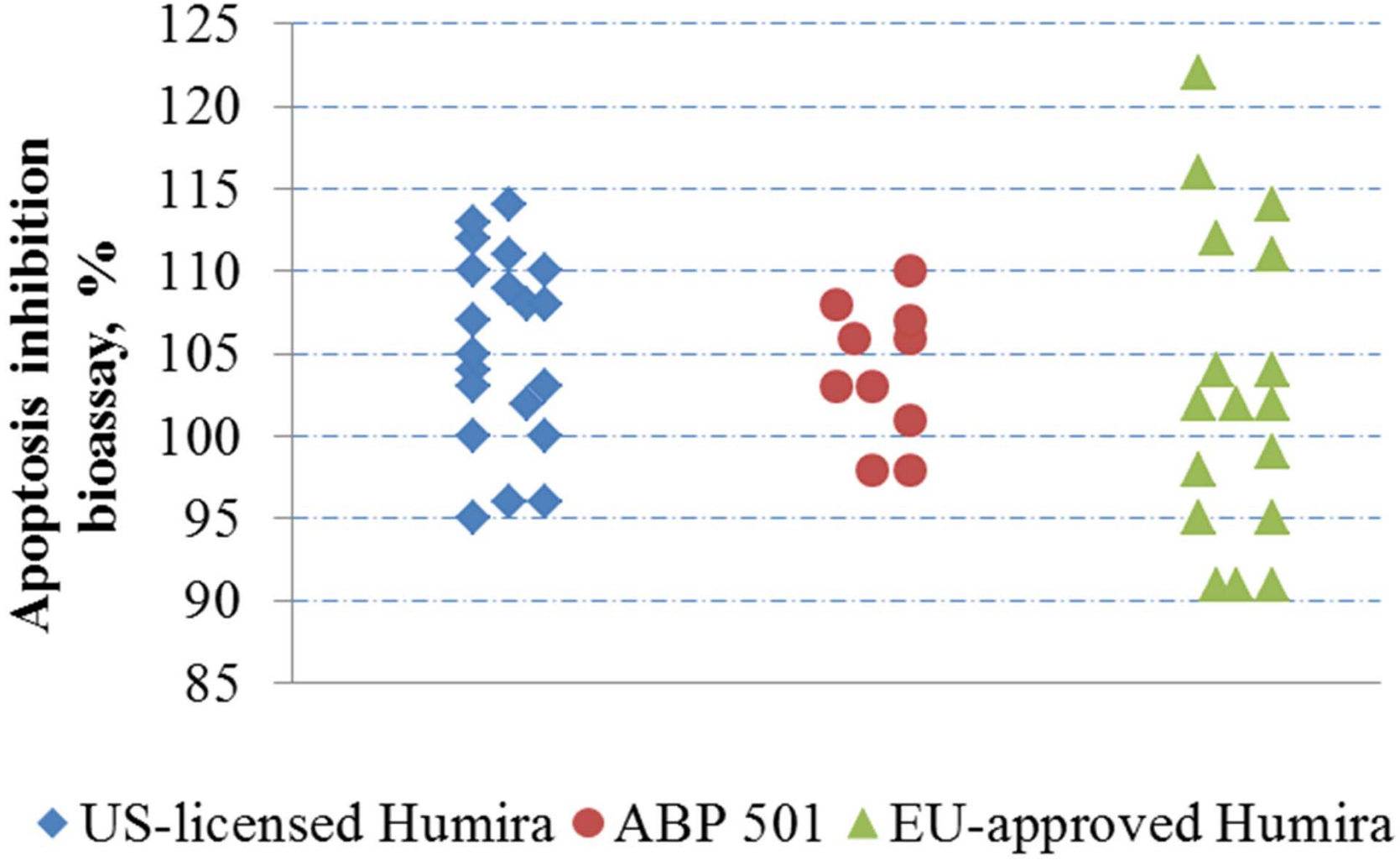


- Equivalence margin=$1.5\sigma_C$:
  - σ_C is estimated from comparator data measured by the applicant.

Unequal Sample Size

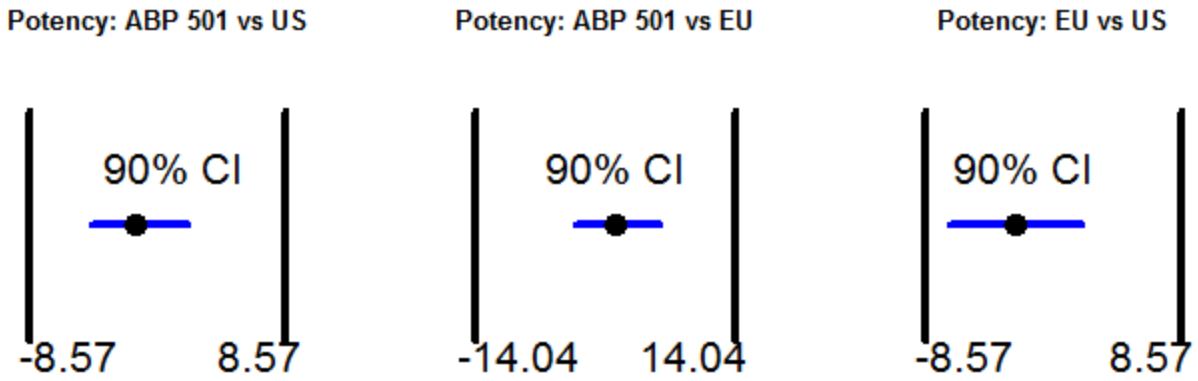
- The confidence interval for the mean difference is calculated using Satterthwaitte approximation method

Apoptosis Inhibition Bioassay (Potency)



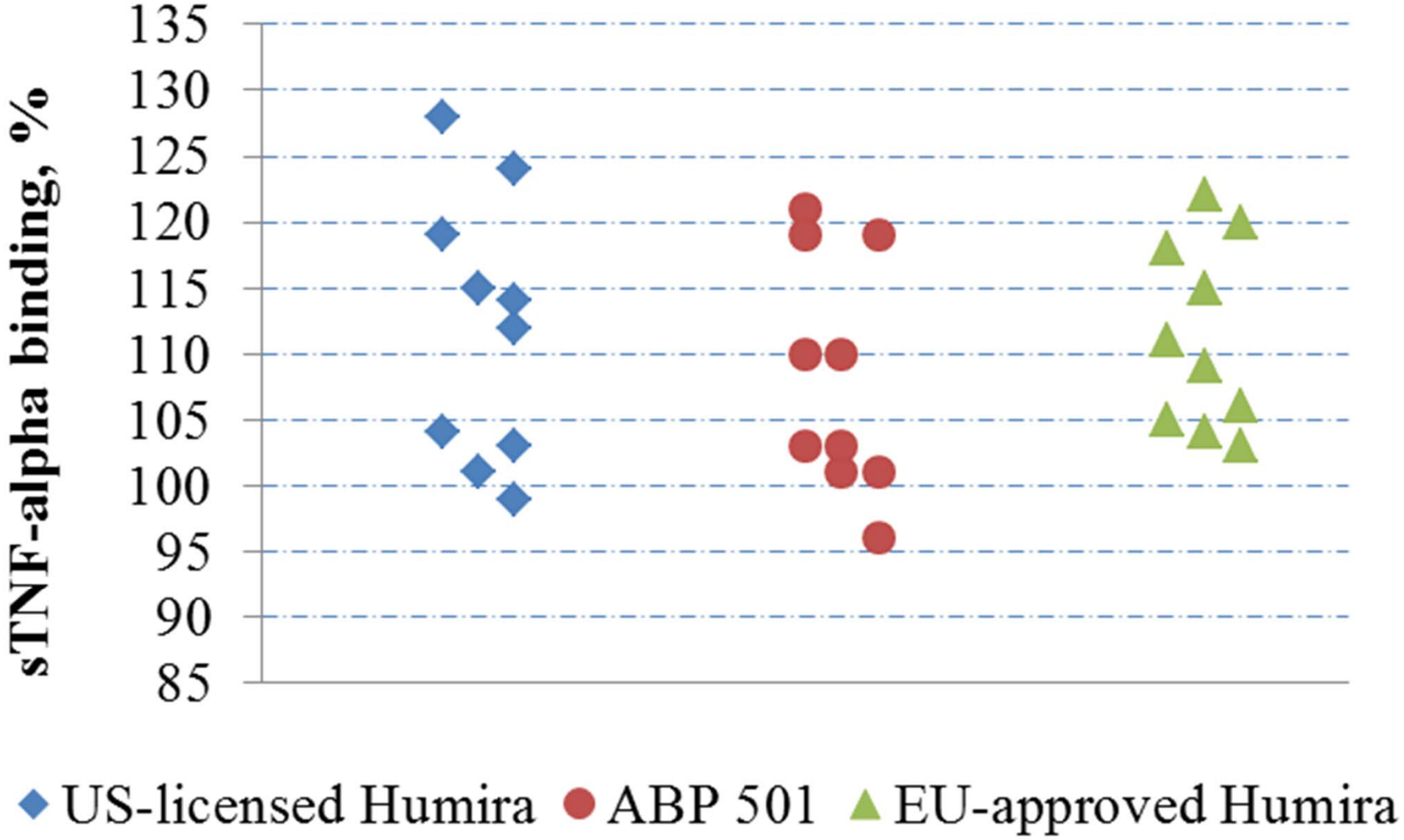
Apoptosis Inhibition Bioassay (Potency)

Comparison	# of lots	Mean difference	90% CI for mean difference	Equivalence margin	Pass equivalence test?
ABP vs. US	(10, 21)	-1.43	(-4.50, 1.93)	(-8.57, 8.57)	Yes
ABP vs. EU	(10, 17)	1.12	(-3.37, 5.82)	(-14.04, 14.04)	Yes
EU vs. US	(17, 21)	-2.55	(-6.97,1.88)	(-8.57, 8.57)	Yes



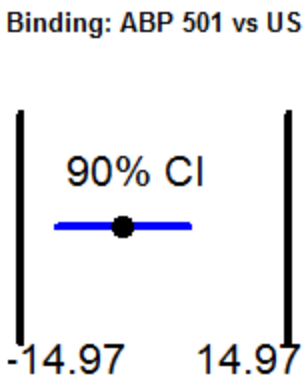
* If $n_b < 1.5n_C$, 90% CI is adjusted by the imbalance of two groups' sample size

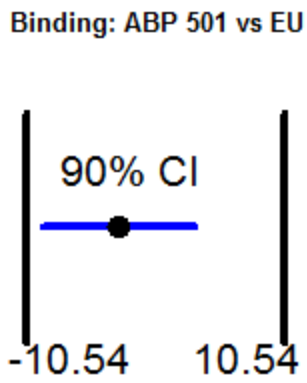
sTNF-alpha Binding

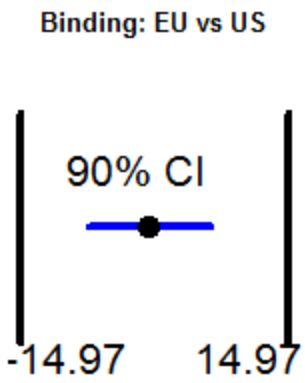


sTNF-alpha Binding

Comparison	# of lots	Mean difference	90% CI for mean difference	Equivalence margin	Pass equivalence test?
ABP vs. US	(10, 10)	-3.60	(-10,93, 3.73)	(-14.97, 14.97)	Yes
ABP vs. EU	(10, 10)	-3.00	(-9.23, 3.23)	(-10.54, 10.54)	Yes
EU vs. US	(10, 10)	-0.60	(-7.34,6.14)	(-14.97, 14.97)	Yes







Equivalence Testing Summary

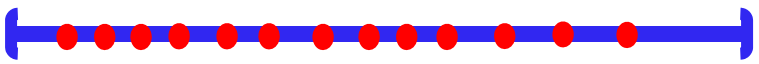
- Apoptosis Inhibition Bioassay (Potency)
  - All 3-way comparisons passed equivalence testing
- sTNF-alpha binding
  - All 3-way comparisons passed equivalence testing

ABP 501
Product Quality Review
Continued

Joel Welch, PhD
Product Quality Team Leader
Office of Biotechnology Products,
CDER, FDA

Quality Range Analysis

- Quality Range = Mean ± X SD
  - Mean and SD of quality attribute range from the comparator measured by applicant
  - Multiplier (X) should be scientifically justified
- Comparison of test and reference support a finding of high similarity if High proportion (e.g., 90%) of observed batch values of the test fall within the quality range derived from the comparator



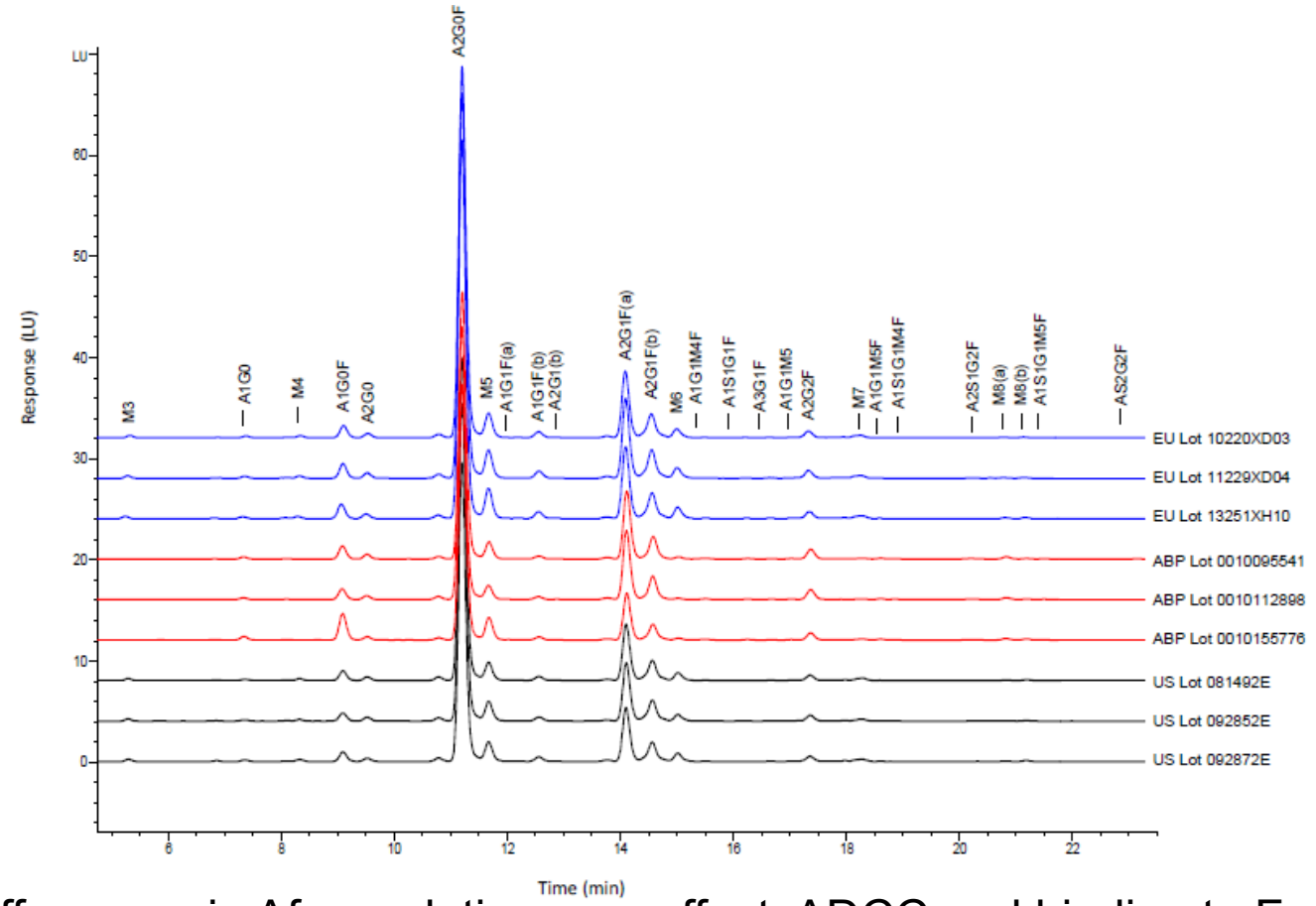
- **Quality range of comparator**
- **Batch values of test**

Additional Analytical Methods to Support ABP 501 High Similarity

Analyzed Using a Quality Range

- ADCC
- CDC
- FcγRIIIa binding
- FcRn binding
- Protein concentration
- Aggregates
- Charge Variants
- Purity (CE-SDS)
- Glycan Mapping
- ≥ 5 μm non-spherical subvisible particles (MFI)
- Deliverable Volume

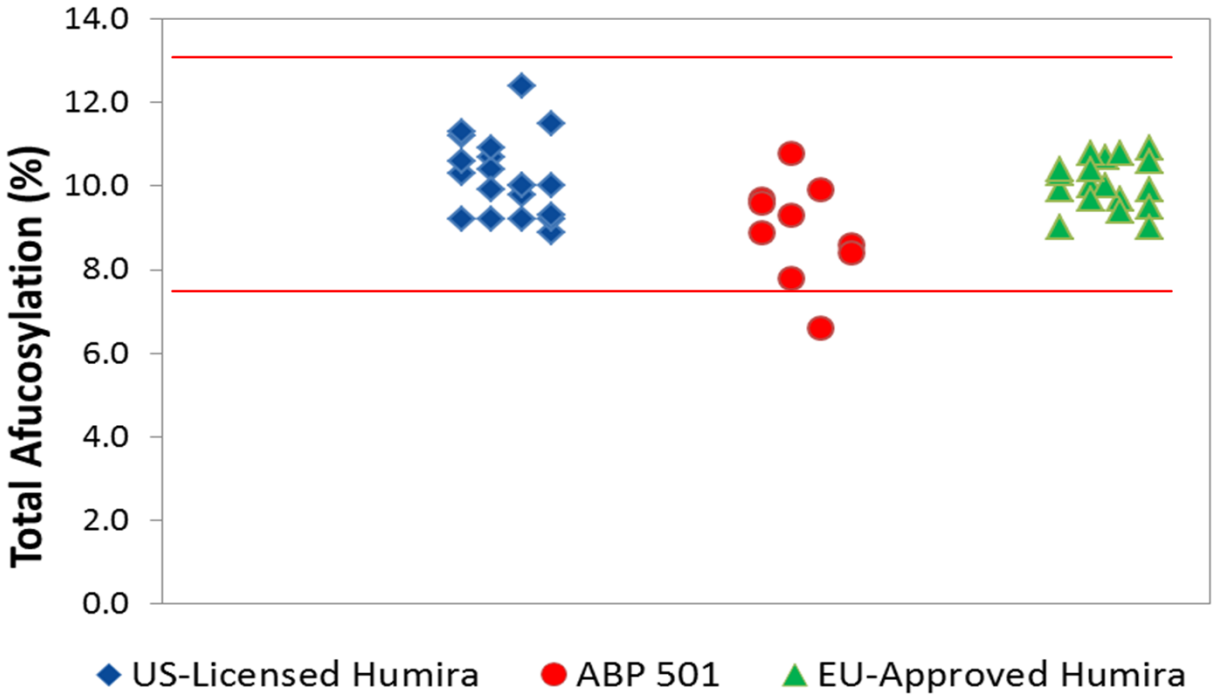
Glycan Mapping



- Large Differences in Afucosylation may affect ADCC and binding to FcγRIIIa
- Large Differences in high mannose may affect PK and ADCC
- Large Differences in galactosylation may affect CDC
- Large Differences in sialyation may affect PK

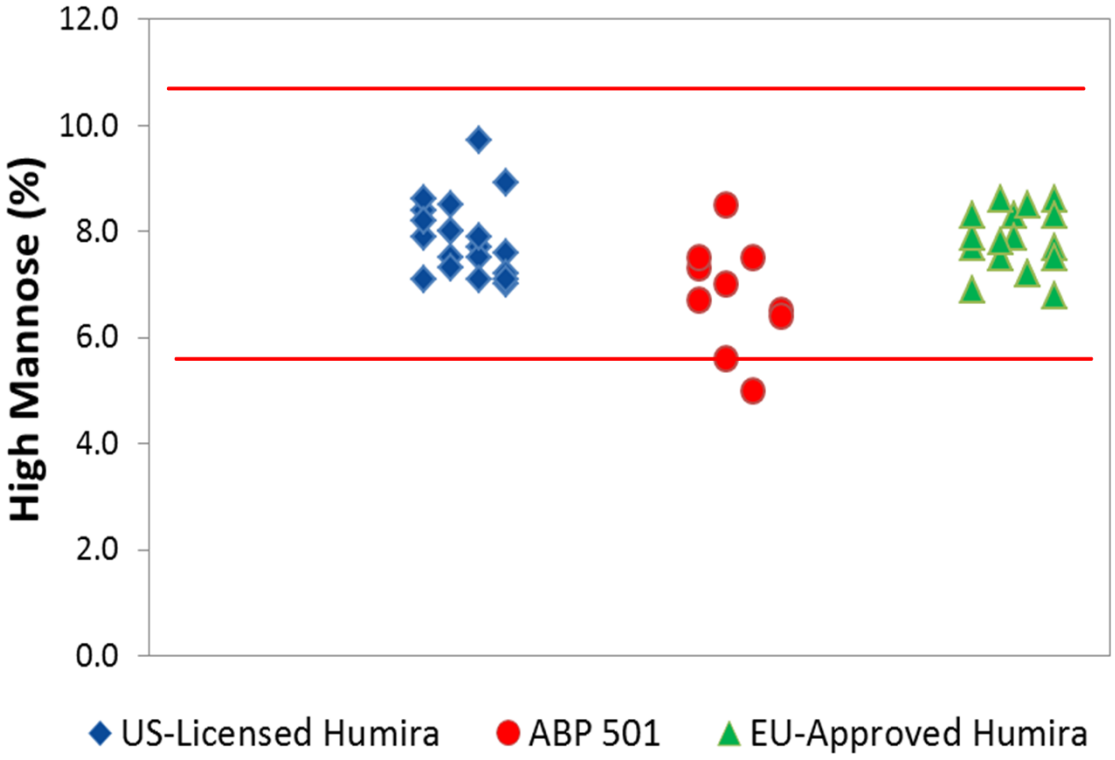
Differences described based on literature review

Total Afucosylation Levels



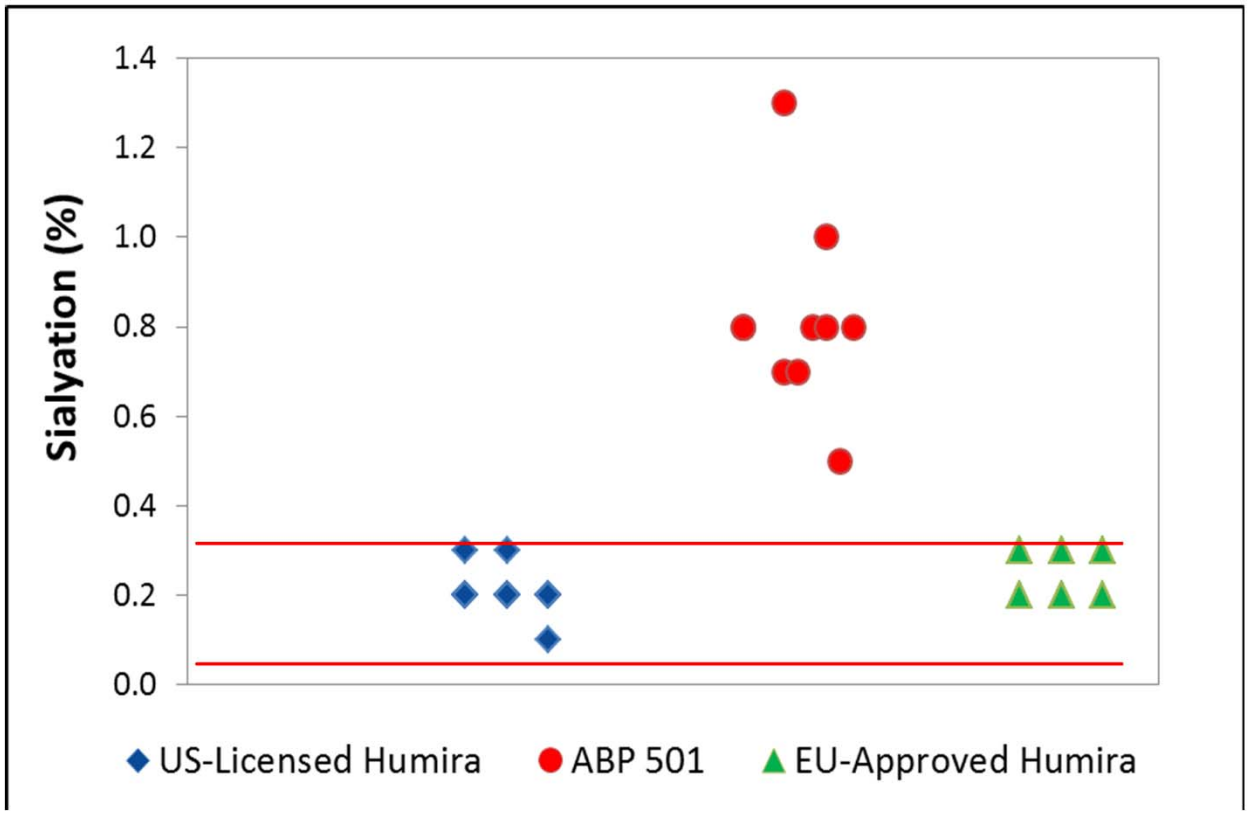
Source: FDA analysis of the Amgen 351(k) BLA submission

High Mannose Levels



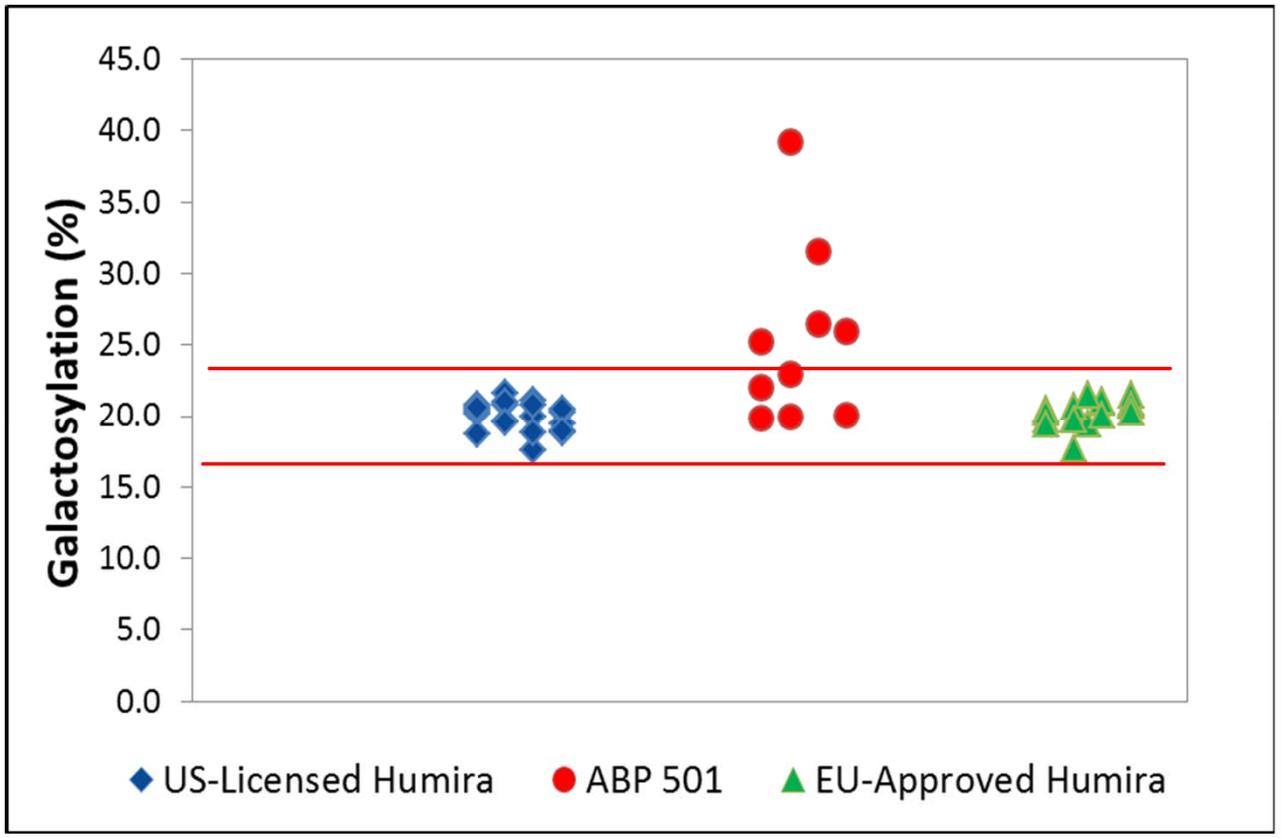
Source: FDA analysis of the Amgen 351(k) BLA submission

Sialylation Levels



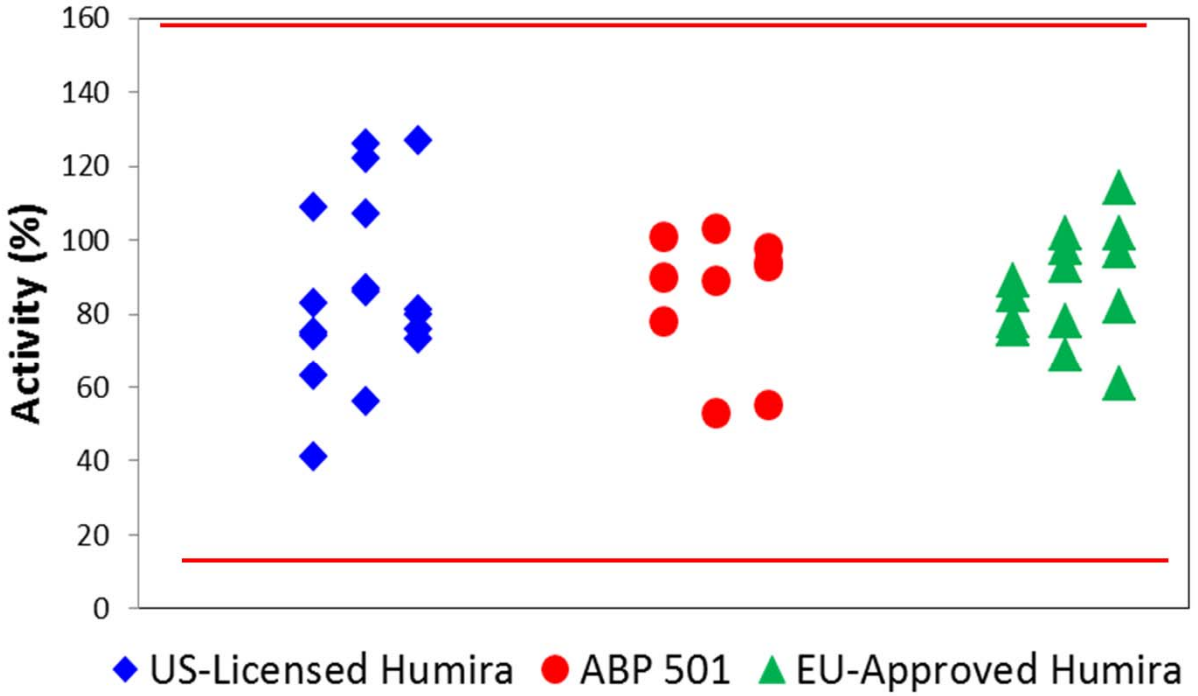
Source: FDA analysis of the Amgen 351(k) BLA submission

Galactosylation Levels



Source: FDA analysis of the Amgen 351(k) BLA submission

ADCC Activity

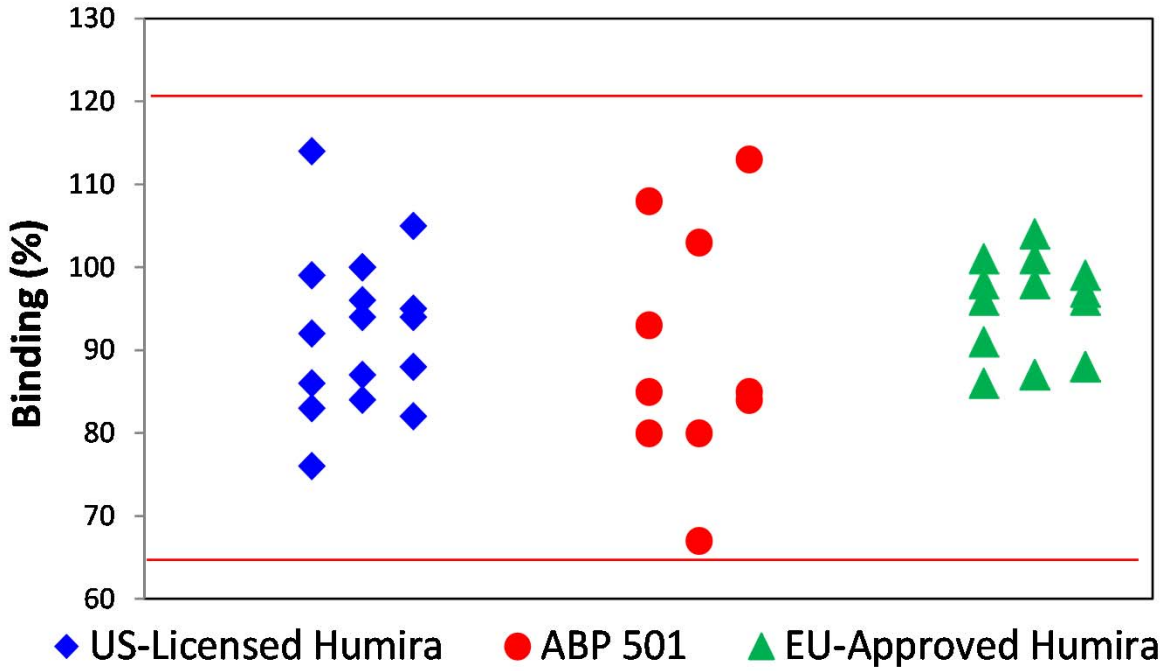


ADCC assay uses:

- CHO M7 cells that express tmTNF-α on cell surface as target
- NK92-M1 transfected with human FcγRIIIa as effector cells

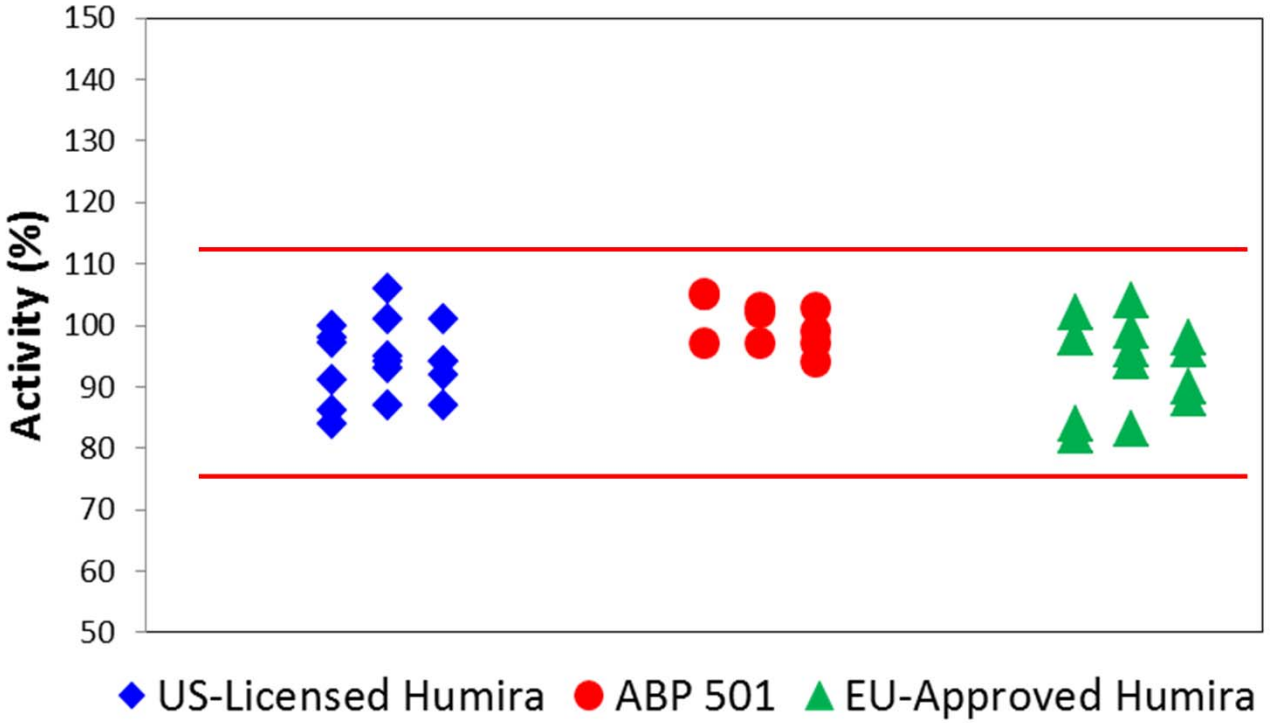
Source: FDA analysis of data from Amgen 351(k) BLA submission

FcγIIIa Binding



Source: FDA analysis of the Amgen 351(k) BLA submission

CDC Activity

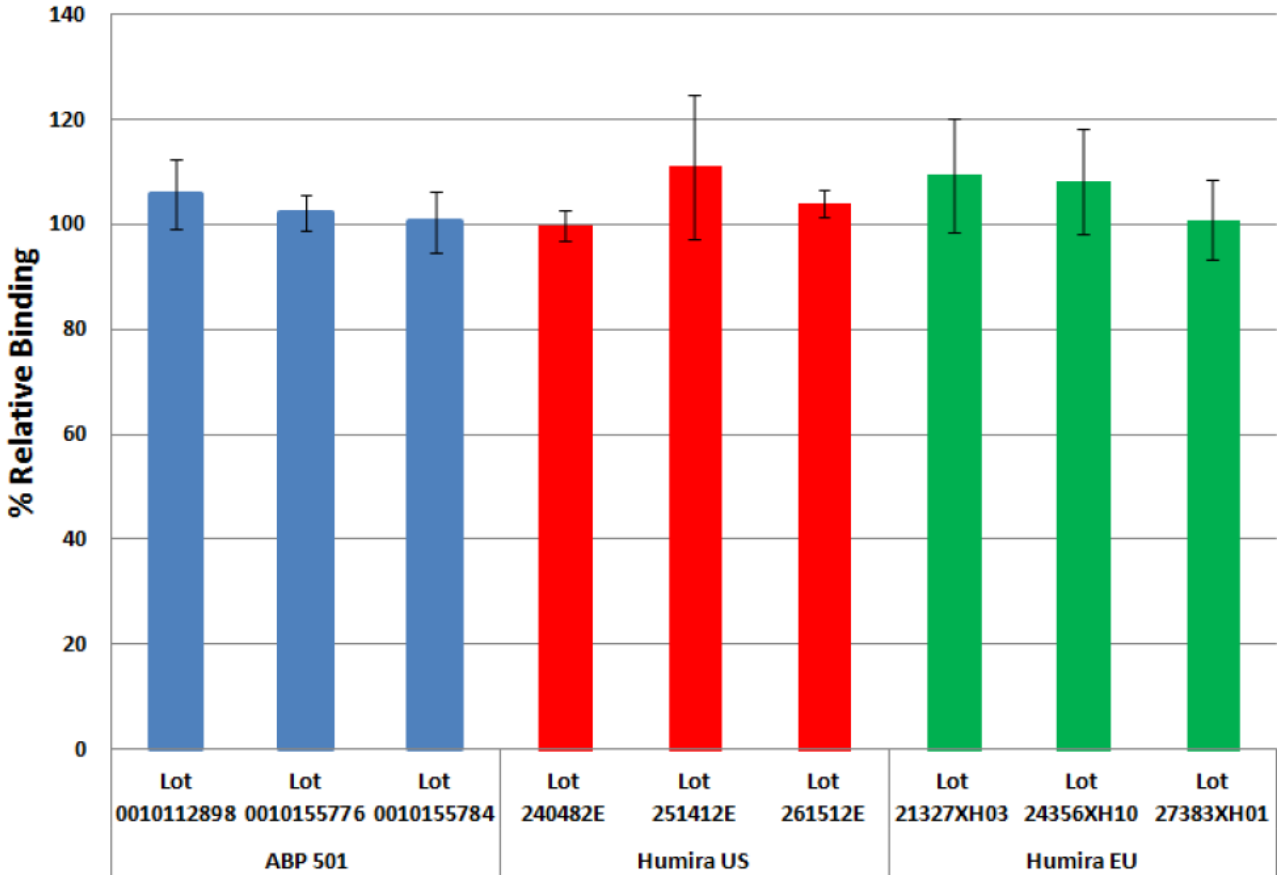


Source: FDA analysis of data from Amgen 351(k) BLA submission

Summary: Glycan Profile

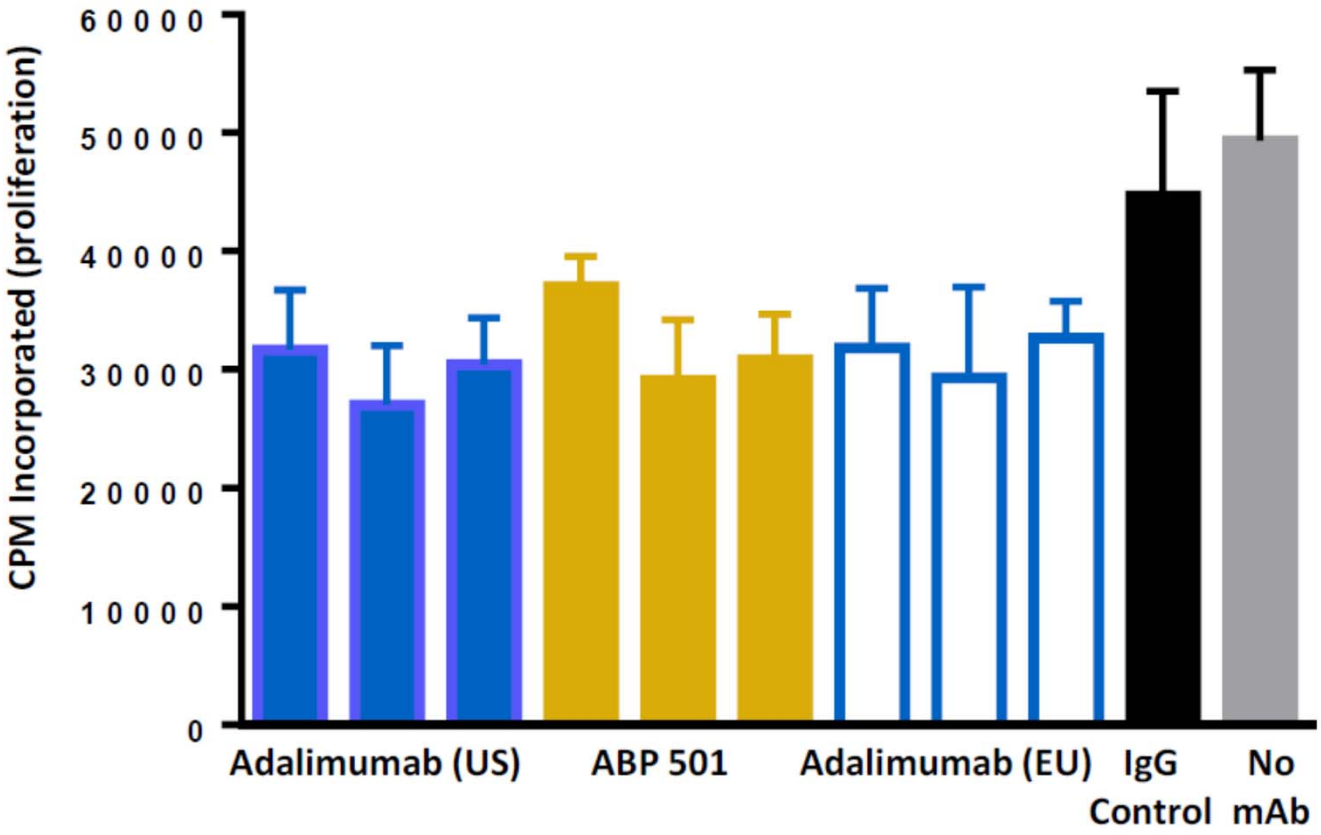
- Chromatographic profile is visually similar with no new peaks observed
- ABP 501 has a slightly different glycosylation pattern
  - Lower levels of high mannose
  - Lower levels of afucosylation
  - Higher levels of galactosylation
  - Higher levels of sialyation
- Slight differences are mitigated by:
  - Similar FcγRIIIa binding
  - Similar PK profiles
  - Similar ADCC activity
  - Similar CDC activity
- Slight change in levels of glycans do not preclude a determination of high similarity

tmTNFα Binding Affinity



Source: Figure excerpted from the Amgen 351(k) BLA submission

MLR: Inhibition of Proliferation



Source: Figure excerpted from the Amgen 351(k) BLA submission

Extrapolation Considerations: Known and Potential MOA of Humira

MOA of Humira	RA, JIA	AS	PsA	PsO	CD	UC	Similarity Criteria Met
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF							
	Yes	Yes	Yes	Yes	Likely	Likely	✓
Binding to tmTNF (Reverse /outside-to-inside signaling)							
	-	-	-	-	Likely	Likely	✓*
Mechanisms involving the Fc region of the antibody:							
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible	✓
Induction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible	✓
Induction of regulatory MΦ in mucosal healing	-	-	-	-	Plausible	Plausible	✓

*Pending additional functional data for reverse signaling assay

Overall Conclusion for Analytical Similarity

- Extensive analytical studies to support a demonstration of high similarity included:
  - Functional and Bioactivity Assays
  - Protein Analytical Assays
  - Physicochemical Assays
  - Higher Order Structural Assays
- Adequate scientific bridge established between US-licensed Humira and EU-approved Humira
- Additional data in support of reverse signaling is pending. Data will be evaluated during 351(k) BLA review and if supportive, would further support a demonstration that ABP 501 is highly similar to US-licensed Humira.

Clinical Pharmacology Review

351(k) BLA for ABP 501, a Proposed Biosimilar to US-licensed Humira

Arthritis Advisory Committee

July 12, 2016

Jianmeng Chen, MD, PhD
Division of Clinical Pharmacology II
Office of Clinical Pharmacology
Food and Drug Administration

Overview of Clinical Pharmacology

- The goal of the clinical pharmacology program is:
  - To evaluate the pharmacokinetic (PK) similarity between ABP 501 and US-licensed Humira
  - To assess the PK element of the scientific bridge between ABP 501, US-licensed Humira, and EU-approved Humira

Studies with PK Information

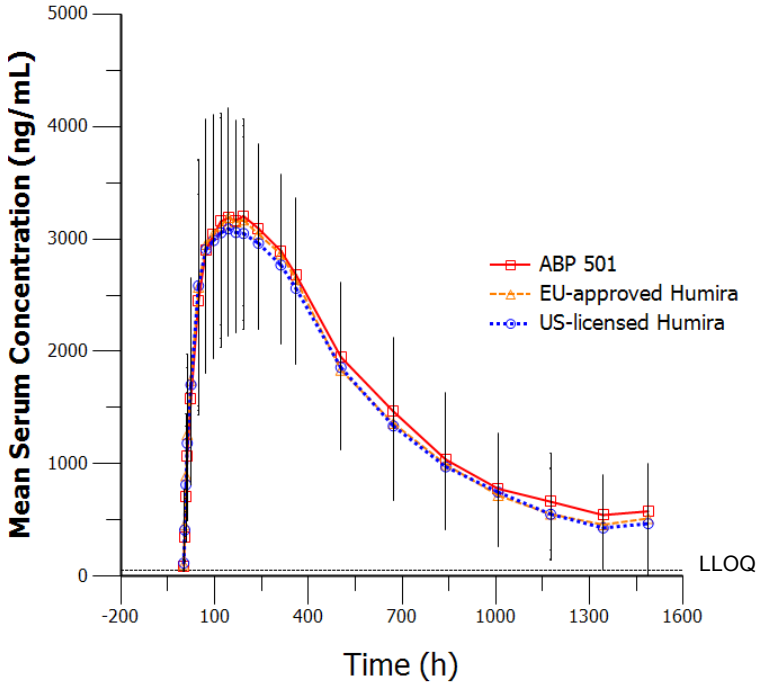
Study	Objectives	Design	Subjects (Planned)	Treatments
Key PK Study				
20110**217**	PK similarity, ABP 501, US-Humira, EU-Humira	SC, R, SD, SB, 3-arm parallel	203 healthy subjects	40 mg (PFS) SC
Supportive PK Studies				
20120**262**	Clinical comparability in RA, ABP 501 vs. US-Humira	SC, R, MD, DB	526 Patients with RA	40 mg SC Q2W+MTX, 26W
20120**263**	Clinical comparability in PsO, ABP 501 vs. EU-Humira	SC, R, MD, DB, re-randomization at W16	350 Patients with PsO	80 mg SC d1, 40 mg SC Q2W beginning at W2, 52 W

Study 217: Design

- **Study Design:** Randomized, single-blind, three-arm, parallel group, single dose in healthy subjects
- **Objectives:**
  - Primary: PK
  - Secondary: safety, tolerability and immunogenicity
- **Treatments: single dose 40mg SC, with PFS**
  - ABP501
  - US-licensed Humira
  - EU-approved Humira
- **Subjects:** healthy subjects, N=67-69/arm
- **Endpoints:**
  - Primary: Cmax, AUC0-t, AUC0-∞

Study 217: PK Results

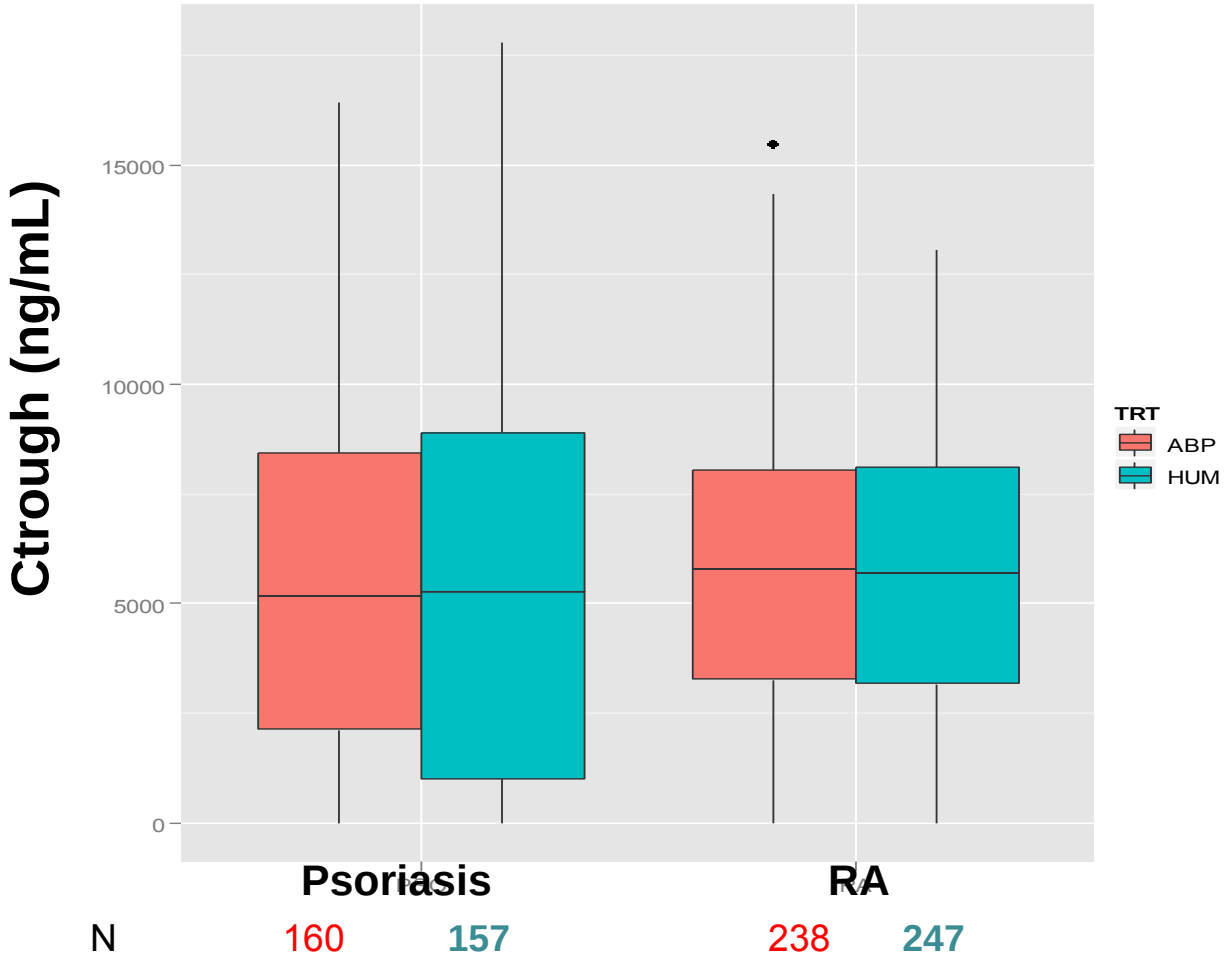
- PK similarity is demonstrated between ABP 501, US-licensed Humira, and EU-approved Humira



PK Similarity Analysis

Comparison	PK Variables	GMR (90%CI) (%)
ABP 501 vs. US-Humira	Cmax	103.23 (94.37, 112.93)
	AUC0-t	102.83 (90.48, 116.87)
	AUC0-∞	107.52 (94.19, 122.74)
ABP 501 vs. EU-Humira	Cmax	96.22 (87.80, 105.45)
	AUC0-t	101.60 (89.14, 115.80)
	AUC0-∞	104.95 (91.82, 119.95)
EU-Humira vs. US-Humira	Cmax	107.29 (94.36,121.98)
	AUC0-t	101.21 (84.28, 121.55)
	AUC0-∞	102.45 (84.89, 123.64)

Supportive Studies 262 and 263: Similar Ctrough



Clinical Pharmacology Conclusions

- PK similarity was demonstrated between ABP 501 and the US-licensed Humira

- PK data support the scientific bridge between ABP 501, US-licensed Humira and EU-approved Humira to justify the relevance of comparative data generated using EU-approved Humira

- The overall PK results support a demonstration of biosimilarity between ABP 501 and US-licensed Humira

Clinical Efficacy: Study 262

351(k) BLA for ABP 501, a Proposed Biosimilar to US-licensed Humira

Arthritis Advisory Committee

July 12, 2016

Yongman Kim, PhD
Mathematical Statistician
Division of Biometrics II, Office of Biostatistics
Food and Drug Administration

Outline

- Study 262 summary
  - Design and analysis plan
  - Results
- Potential statistical issues
- Conclusions

Study 262 Design

- 24-week, randomized, double-blind, parallel-group, comparative clinical study in 526 patients with active rheumatoid arthritis (RA) despite methotrexate (MTX) use
  - 1:1 randomization to ABP 501: US-licensed Humira
  - Sites in Europe, Latin & North America (including U.S. sites)
- Primary endpoint: ACR20 response at Week 24
  - And ability to remain on treatment
- Secondary endpoints included ACR50/70, DAS28-CRP, ACR components

Study 262 Statistical Analyses

- Primary analysis of Week 24 ACR20 response
  - Applicant: compare 90% CI for ratio in ACR20 response to (0.738, 1/0.738) margin
  - FDA: compare 90% CI for difference in ACR20 response to ±12% margin
- Secondary analyses: confidence intervals for mean differences in key endpoints
- Sensitivity: tipping point analyses to address missing data

Margin Selection

- Similarity margin is critical aspect of design
- Justification of ±12% margin on absolute difference scale
  - 12% based on balancing clinical importance of different losses in effect against feasibility of different study sizes
  - Lower bound corresponds to retention of roughly 50% of conservative estimates of effect of Humira from the published literature
    - FDA meta-analysis: estimated effect of 35% (95% CI: 28%, 42%)
- Lack of agreed-upon metric and margin not problematic because FDA-suggested analysis rules out ±12% margin

Primary Efficacy Results

ACR20 Response at Week 24

	All Randomized Patients (N=526)		Per-Protocol Population (N=463)
	Applicant	FDA	
ABP 501	194/260 (74.6%)	188/264 (71.2%)	176/230 (76.5%)
US-Humira	189/261 (72.4%)	189/262 (72.1%)	178/233 (76.4%)
Estimated Ratio[1] (90% CI)	1.039 (0.954, 1.133)		1.01 (0.927, 1.098)
Estimated Difference[2] (90% CI)		-0.4% (-6.8%, +6.1%)	0.4% (-6.0%, +6.9%)

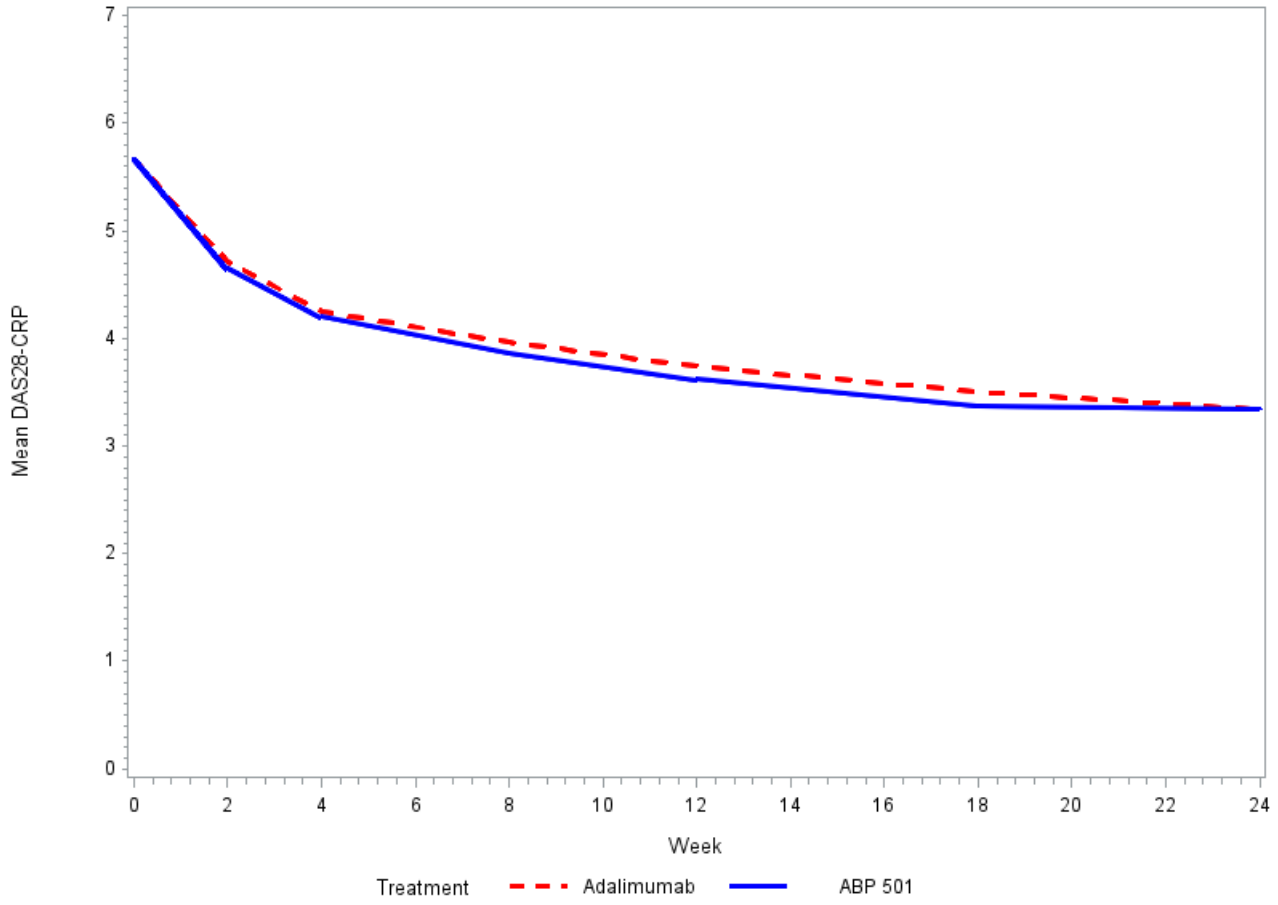
[1] Applicant's analysis for ratio with margin of (0.738, 1/0.738), using last observation carried forward (LOCF)
[2] FDA's suggested analysis for difference with ±12% margin, considering dropouts as non-responders

Secondary Efficacy Results

Endpoint (Week 24)	Mean Difference[1] (95% CI)
Swollen joint count (scale: 0–66)	-0.2 (-1.1, 0.7)
Tender joint count (scale: 0–68)	-0.7 (-2.2, 0.9)
HAQ physical ability (scale: 0–3)	0.03 (-0.06, 0.12)
Patient pain (scale: 0–100)	-0.8 (-4.6, 3.1)
Patient global (scale: 0–10)	-0.04 (-0.41, 0.33)
Physician global (scale: 0–10)	-0.10 (-0.40, 0.21)
C-reactive Protein (scale: ≥0)	0.05 (-1.67, 1.78)
DAS28-CRP	0.01 (-0.20, 0.21)

[1] ABP 501 minus US-Humira mean difference, analyses in completers

Mean DAS28-CRP over Time



Disposition and Missing Data

- 8%/4% dropout on ABP 501/US-Humira in Study 262
  - Due to design: treatment discontinuation = study withdrawal
- No noticeable difference between arms in dropout patterns
- Missing data impact should be explored for evaluation of ACR20 and other key endpoints (e.g., DAS28-CRP) at Week 24 *regardless of adherence*

Tipping Point Sensitivity Analyses

- Consider varying (missing-not-at-random) assumptions about average unobserved outcomes among dropouts on two arms
- Identify assumptions (tipping point) under which confidence interval no longer rules out unacceptable differences in efficacy
- Discuss plausibility of tipping point

ACR20 Tipping Point Results

Shift for ABP 501[1]	Shift for US-Humira[1]				
	-0.700	**-0.525**	**-0.350**	**-0.175**	**0.000**
-0.700	0.002 (-0.063, 0.067)	-0.005 (-0.072, 0.061)	-0.014 (-0.080, 0.052)	-0.019 (-0.085, 0.047)	-0.023 (-0.088, 0.042)
-0.525	0.013 (-0.052, 0.078)	0.005 (-0.060, 0.071)	-0.003 (-0.068, 0.063)	-0.008 (-0.073, 0.057)	-0.012 (-0.077, 0.053)
-0.350	0.024 (-0.041, 0.088)	0.016 (-0.049, 0.081)	0.008 (-0.057, 0.072)	0.003 (-0.062, 0.067)	-0.001 (-0.066, 0.063)
-0.175	0.035 (-0.030, 0.100)	0.027 (-0.038, 0.093)	0.019 (-0.046, 0.084)	0.014 (-0.051, 0.079)	0.010 (-0.055, 0.075)
0.000	0.048 (-0.016, 0.111)	0.040 (-0.025, 0.105)	0.032 (-0.033, 0.096)	0.026 (-0.038, 0.090)	0.023 (-0.041, 0.086)

[1] Assumed difference in Week 24 ACR20 response between completers and dropouts. Responses in ABP 501/US-Humira completers were 0.77/0.75.

Assay Sensitivity and Constancy

- Assay sensitivity: ability to detect meaningful differences between products (in studied indication) if they exist
- Constancy assumption: estimates of effect of Humira unbiased for setting of comparative study
- Support for assay sensitivity and constancy (ICH E10)
  - Historical sensitivity to drug effects
  - Similar design/conduct between historical and current trials
  - Appropriate trial conduct

Assay Sensitivity and Constancy

	Study 1	Study 2	Study 3	Study 4	Study 262
Selected inc/exc criteria	≥9 TJC; ≥6 SJC; CRP >1 mg/dL; RF+ or ≥1 join erosion	≥9 TJC; ≥6 SJC	≥9 TJC; ≥6 SJC	≥9 TJC; ≥6 SJC	≥6 TJC; ≥6 SJC; ESR >28 mm/hr or CRP >1 mg/dL; RF+ or ACCP+
Anti-TNF experience allowed?	No	No	No	No	Yes (28%)
Concomitant DMARDS	Stable MTX, corticosteroids, NSAIDS	Stable MTX, corticosteroids, NSAIDS	Stable MTX	Stable MTX	Stable MTX
Region/Country	US & Canada	US & Canada	Korea	Taiwan	EU, WU, NA, & LA
Baseline Characteristics	TJC: 27; SJC: 19; Disease Duration: 11 yrs; HAQ-DI: 1.5	TJC: 28; SJC: 17; Disease Duration: 12 yrs; HAQ-DI: 1.6	TJC: 19; SJC: 12; Disease Duration: 6 yrs; KHAQ-DI: 1.4	TJC: 33; SJC: 22; Disease Duration: 6 yrs; HAQ-DI: 1.7	TJC: 24; SJC: 14; Disease Duration: 9 yrs; HAQ-DI: 1.5
Time of ACR20 Evaluation	Week 24	Week 24	Week 24	Week 12	Week 24
ACR20 Response on Humira	63%	67%	62%	54%	72%
Withdrawal on Humira	22% by Week 52	7% by Week 16 (34% escaped to ADA)	9%	N.A.	6%

1 Keystone EC et al, Arthritis & Rheumatism. 2004; 50: 1400-1411
2 Weinblatt ME et al, Arthritis & Rheumatism. 2003; 48: 35-45
3 Kim HY et al, J Rheumatology 2007; 10: 9-16
4 Chen DY et al, J Formosan Medical Association. 2009; 108: 310-319

Conclusions

- Large comparative clinical study in RA demonstrated similar efficacy of ABP 501 and US-licensed Humira
- Potential statistical issues explored
  - Similarity margin selection
  - Impact of missing data
  - Assay sensitivity and constancy assumption
- Collective evidence supports a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira

Clinical Efficacy: Study 263

351(k) BLA for ABP 501, a Proposed Biosimilar to US-licensed Humira

Arthritis Advisory Committee

July 12, 2016

Kathleen Fritsch, PhD
Mathematical Statistician
CDER/OTS/OB
Food and Drug Administration

Study 263
Comparative Clinical Study in Plaque Psoriasis
ABP 501 vs. EU-approved Humira

Part 1: Similarity (Week 1 to 16)

- 350 subjects with moderate to severe psoriasis
- ABP 501 vs. EU-approved Humira
- Primary endpoint: Percent change in PASI at Week 16
- Secondary endpoints: PASI 75, sPGA response, BSA

Part 2: Transition (Week 16 to 52)

- Subjects with PASI >50 at Week 16 continue study
- ABP 501subjects continue ABP 501
- EU-approved Humira randomized 1:1 to ABP 501 or EU-approved Humira
- Assessments at Weeks 32 and 50

PASI = Psoriasis Area Severity Index, sPGA = static Physician's Global Assessment, BSA = Body Surface Area

Statistical Analysis Plan

- Primary Endpoint – Percent Improvement in PASI at Week 16
  - Statistical model: ANCOVA model adjusted for baseline PASI, geographic region, and prior biologic use for psoriasis
  - 95% confidence interval
  - Similarity margin: ± 15%.
  - Analysis Population: Full analysis set (FAS) – subjects randomized and dispensed medication with at least one post-baseline visit
  - Missing Data: last observation carried forward (LOCF)

Subject Disposition (Treatment)

	ABP 501 N=175	EU-approved Humira N=175
Treated	174 (99%)	173 (99%)
Completed treatment through Week 16	167 (95%)	165 (94%)
Discontinued treatment by Week 16	8 (5%)	10 (6%)
Adverse event	4 (2%)	5 (3%)
Consent withdrawn	3 (2%)	2 (1%)
Lost to follow-up	--	1 (<1%)
Protocol violation	1 (<1%)	2 (1%)

Primary Endpoint: Percent Improvement in PASI at Week 16

Mean (SD)	ABP 501 N=172	EU-approved Humira N=173
Baseline PASI	19.7 (8.1)	20.5 (7.9)
Week 16 PASI	3.7 (5.1)	3.3 (5.8)
Percent Improvement	80.9 (24.2)	83.1 (25.2)
Difference[a]	-2.2	
95% CI[b]	(-7.4, 3.0)	
90% CI	(-6.6, 2.2)	
Margin	±15	

[a] Model Estimate adjusted for prior biologic use, region, and baseline PASI
[b] Applicant's primary analysis
Full Analysis Set (FAS) using LOCF

Results were comparable in Per Protocol Set and under alternate handling of missing data

Secondary Endpoints (Week 16)

	ABP 501 N=172	EU-approved Humira N=173	Difference[a]	90% Conf. Int.
PASI 75	74.4%	82.7%	-7.7%	(-15.2, -0.3)
sPGA (clear/ almost clear)	58.7%	65.3%	-7.4%	(-15.6, 0.9)
Change in BSA	18.0	22.1	-1.9	(-3.8, -0.1)

[a] Model Estimate adjusted for prior biologic use, region, and baseline
Full Analysis Set (FAS) using LOCF

PASI 75 = ≥ 75% Reduction in PASI, sPGA = static Physician's Global Assessment, BSA = Body Surface Area

Supportive Endpoints (Week 16)

	ABP 501 N=172	EU-appr. Humira N=173	Difference [a]	90% Conf. Int.
PASI 75	74.4%	82.7%	-7.7%	(-15.2, -0.3)
PASI 50	92.4%	94.2%	-2.7%	(-7.0, 1.6)
PASI 90	47.1%	47.4%	+0.3%	(-8.4, 9.0)

[a] Model Estimate adjusted for prior biologic use, region, and baseline
Full Analysis Set (FAS) using LOCF

Interpretation of Study 263

- Key assumptions
  - Assay sensitivity (ability to detect meaningful differences if they exist)
  - Appropriate quality of study conduct
  - Appropriateness of margin

Published Humira Studies in Psoriasis

	Gordon (2006)	Saurat (2008)	Menter (2008)	Study 263
Selected inclusion criteria	BSA ≥ 5	BSA ≥ 10 PASI ≥ 10 PGA ≥ Mod	BSA ≥ 10 PASI ≥ 12 PGA ≥ Mod	BSA ≥ 10 PASI ≥ 12 PGA ≥ Mod
Location	US, Canada	Europe, Canada	US, Canada	Europe, Canada
Baseline PASI	16.7	20.2	19.0	20.5
Total Sample size	102	161	1212	347
% Imp. in PASI *Humira* *Placebo*	(Week 12) 70% 14%	(Week 16) 81% 22%	(Week 12) 76% 15%	(Week 16) 83% --
Difference	56%	59%	61%	

- Assay sensitivity assumption appears reasonable
- No issues identified with study conduct

Gordon KB et al, J Am Acad Dermatol. 2006 Oct; 55(4): 598-606; Saurat JH et al, Br J Dermatol. 2008; 158: 558-66; Menter A et al, J Am Acad Dermatol. 2008; 58(1): 106-15

Margin Selection

- Applicant did not provide justification for the ±15% margin in the protocol
- Margin was not discussed with FDA prior to the study
- Question: Can we use data from the published literature to assess the reasonableness of the proposed margin?
  - Percent preservation of treatment effect
  - Study power

Margin Selection (Percent Preservation)

- Limited data in published literature on Percent Improvement in PASI for Humira

	Gordon (2006)	Saurat (2008)	Menter (2008)
Total Sample size	102	161	1212
Treatment Difference	56%	59%	61%

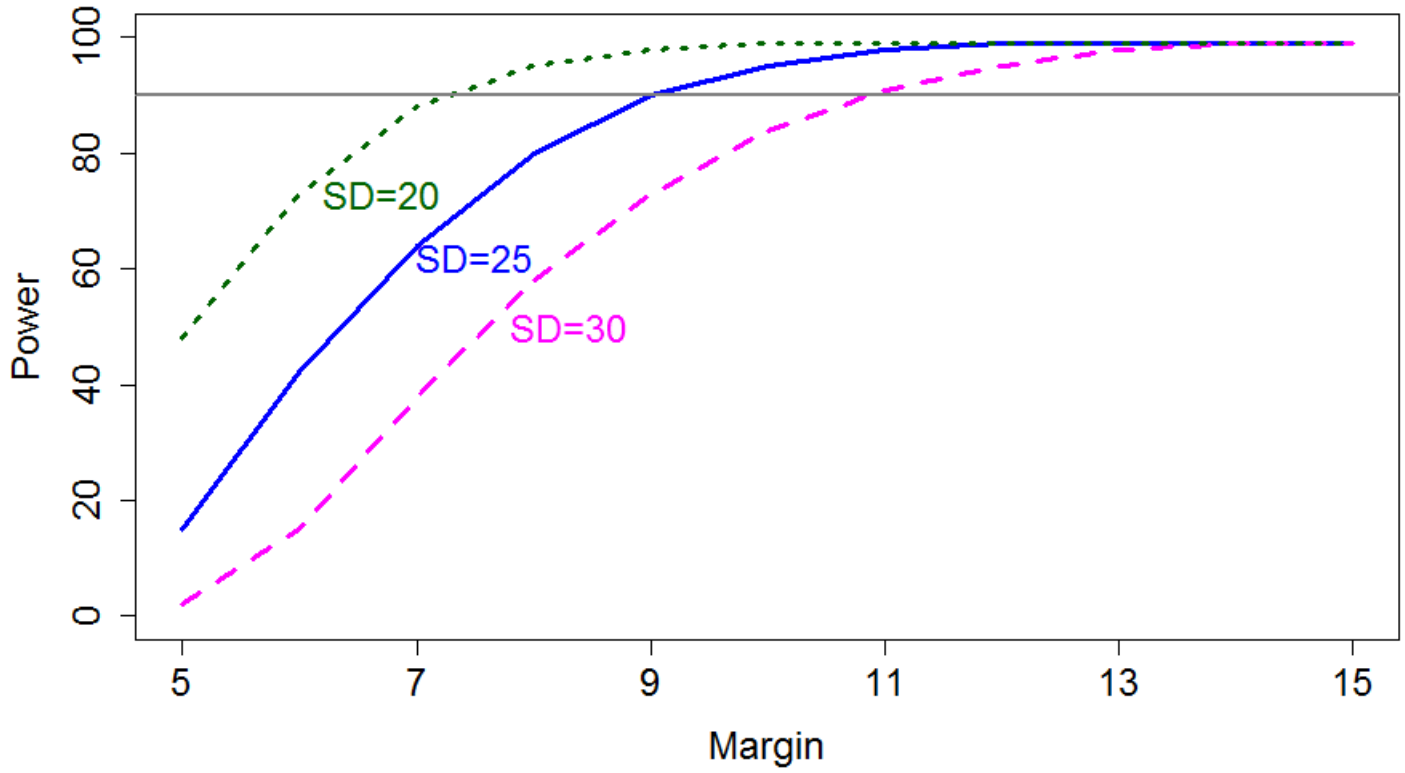
  - No published standard deviations or confidence intervals
  - 15% corresponds to retention of ~75% of historical treatment effect of Humira relative to placebo (using point estimate of 60%)

Margin Selection (Power)

- Use data from the published literature to estimate power for the proposed study design
- Need a reasonable estimate of variability for the percent improvement endpoint
  - No standard deviations in published Humira studies
  - Published studies for Remicade and Enbrel included standard deviation (SD) estimates
    - Remicade: SD=21 [Reich (2005)]
    - Enbrel: SD=31 [Leonardi (2003)]
  - Using SD estimates within this range may be reasonable

Leonardi CL et al, N Engl J of Med. 2003; 349:2014-22 Reich K et al, Lancet. 2005; 366:1367-74

Power under Various Margins (assuming true treatment difference is 0) N=340



Summary of Efficacy Results in Study 263

- Primary Endpoint: Percent improvement in PASI
  - Treatment difference: -2.2
  - 90% Confidence Interval: (-6.6, 2.2)
  - Study would meet criteria for margins of ± 7% or larger (± 15% pre-specified)
  - Consistent results under sensitivity analyses for missing data
- Secondary endpoints are consistent with the primary endpoint
  - increased variability expected for dichotomized endpoints
  - magnitude of difference depends on cut-point
- Study 263 supports a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira

References

- Gordon KB et al, J Am Acad Dermatol. 2006 Oct; 55(4): 598-606
- Saurat JH et al, Br J Dermatol. 2008; 158: 558-66
- Menter A et al, J Am Acad Dermatol. 2008; 58(1): 106-15
- Leonardi CL et al, N Engl J of Med. 2003; 349:2014-22
- Reich K et al, Lancet. 2005; 366:1367-74

Safety and Immunogenicity

351(k) BLA for ABP 501, a Proposed Biosimilar to US-licensed Humira

Arthritis Advisory Committee

July 12, 2016

Keith M Hull, MD, PhD
Medical Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Food and Drug Administration

Overview of Safety

- Safety population
  - 1076 subjects (patients and healthy subjects) exposed to at least one dose of ABP 501
- No unexpected safety signals were reported
  - Types and incidence of Adverse Events (AE), Serious Adverse Events (SAEs), AEs of Special Interest, and AEs leading to discontinuation were similar between ABP 501, US-licensed Humira, and EU-approved Humira
  - Most commonly reported AEs were infections
- No deaths occurred during the ABP 501 development program
- Hypersensitivity and Injection site reactions
  - No clinically meaningful differences of hypersensitivity reactions or injection site reactions were observed between treatment arms
  - One case of anaphylaxis was reported
  - No increase in AEs following transition from EU-approved Humira to ABP 501
- Immunogenicity
  - Incidence of ADA/NAb similar between ABP 510, US-licensed Humira, and EU-approved Humira
  - ADA incidence remained unchanged following transitioning from EU-Humira to ABP 501

Overview of Safety: Controlled Studies

	Rheumatoid Arthritis Study 262		Plaque Psoriasis Study 263		Healthy Subjects Study 217		
	ABP 501 40 mg (n=264)	US-Humira 40 mg (n=262)	ABP 501 40 mg (n=174)	EU-Humira 40 mg (n=173)	ABP 501 40 mg (n=67)	US-Humira 40 mg (n=69)	EU-Humira 40 mg (n=67)
AEs, n (%)	132 (50)	143 (55)	117 (67)	110 (64)	39 (58)	33 (48)	46 (69)
SAEs, n (%)	10 (4)	13 (5)	6 (3)	5 (3)	0	0	1 (2)
Withdrawal due to AEs, n (%)	5 (2)	2 (1)	7 (4)	5 (3)	0	0	1 (2)
Infections, n (%)	61 (23)	68 (26)	59 (34)	58 (34)	9 (13)	4 (6)	9 (13)
Malignancies, n (%)	1 (<1)	1 (<1)	1 (1)	1 (1)	0	0	0
Liver Enzyme Elevations, n (%)	13 (5)	10 (4)	4 (2)	2 (1)	0	0	4 (6)
Injection site reactions, n (%)	6 (2)	13 (5)	3 (2)	26 (5)	1 (1)	0	1 (1)
Anaphylaxis, n	0	0	1 (1)	0	0	0	0
Death, n	0	0	0	0	0	0	0

Source: FDA safety analysis of data from Amgen 351(k) BLA submission
SAE: serious adverse event, TEAE: treatment-emergent adverse event

Immunogenicity Assessment

- Immunogenicity assessment of a proposed biosimilar product is a component of 351(k) applications
- Anti-drug antibodies (ADA) mediate immune reactions that are frequently observed with biologics and can impact:
  - PK
  - Efficacy
  - Safety (e.g. hypersensitivity reactions, anaphylaxis)

Incidence of ADA: ABP 501 Controlled and Extension Studies

	Rheumatoid Arthritis Study 262		Plaque Psoriasis Study 263 Week 16		Plaque Psoriasis Study 263 Post-Week 16			Healthy Subjects Study 217		
	ABP 501 (n=264)	US-Humira (n=262)	ABP 501 (n=174)	EU-Humira (n=173)	Cont'd ABP 501 (n=152)	Cont'd EU-Humira (n=79)	EU-Humira → ABP501 (n=77)	ABP 501 (N=67)	US-Humira (N=69)	EU-Humira (N=67)
ADA (+), n (%)	101 (38)	100 (38)	96 (55)	110 (64)	104 (68)	59 (75)	56 (73)	29 (43)	34 (50)	34 (51)
NAb +, n (%)	24 (9)	29 (11)	17 (10)	24 (14)	21 (14)	16 (20)	19 (25)	12 (18)	15 (22)	14 (21)

Source: FDA safety analysis of data from Amgen 351(k) BLA submission
ADA: Anti-drug antibodies (binding); NAb: Neutralizing anti-drug antibodies

Impact of ADA

- Similar rates of ADA and NAb formation between ABP 501, US-licensed Humira, and EU-approved Humira at multiple timepoints, in both RA and PsO
- Similar ADA and NAb incidence following transitioning from EU-approved Humira to ABP 501
- ADA and NAb formation had similar impact in both ABP 501 and US- and EU-Humira-treated patients:
  - Similar decreases in systemic exposure
  - Similar rates of injection site reactions and hypersensitivity irrespective of ADA status
  - No clear differential impact on clinical efficacy outcomes:
    - Small differences in outcomes between ABP 501 and Humira were observed in the limited number of NAb positive patients

Impact of Neutralizing ADA

Numerical differences were seen in subgroup analyses of NAb positive patients:

Study 263 , PsO	Baseline PASI Score	Week 4	Week 16
ABP 501, % PASI Δ *NAb positive*	**19.62** *n=0*	**40.76** *n=0*	**48.46** *n=17*
EU-Humira, % PASI Δ *NAb positive*	**19.96** *n=0*	**52.02** *n=1*	**61.91** *n=24*

Study 262, RA	Week 4	Week 26
ABP 501, ACR20 *NAb positive*	**41.7** *n=5*	**66.7** *n=24*
US-Humira, ACR20 *NAb positive*	**51.7** *n=4*	**72.4** *n=29*

- Present when majority of subjects were NAb negative, i.e. at Week 4
- No differences between NAb titers
- NAb did not impact PK differentially
- NAb did not correlate with injection site reactions, hypersensitivity reactions, including anaphylaxis

Immunogenicity: Conclusions

- Small differences in efficacy between the NAb positive patients of the ABP 501 and Humira groups, but conclusions are limited due to small numbers of patients and are not corroborated by differences in PK or safety outcomes
- Immunogenicity was otherwise similar between ABP 501, US-licensed Humira, and EU-approved Humira in RA and PsO, using two approved dosing regimens with and without concomitant immunosuppression
- These results support a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira

Overall Summary of Safety

- Safety outcomes, including immunogenicity, were similar between patients treated with ABP 501 or comparator products

- No new safety signals were identified in the ABP 501 clinical program

- The safety and immunogenicity results support a demonstration that there are no clinically meaningful differences between ABP 501 and the US-licensed Humira

Considerations for Extrapolation

351(k) BLA for ABP 501, a Proposed Biosimilar to US-licensed Humira

Arthritis Advisory Committee

July 12, 2016

Nikolay P. Nikolov, MD
Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products
Food and Drug Administration

Extrapolation Considerations: Indications Being Sought for Licensure of ABP 501

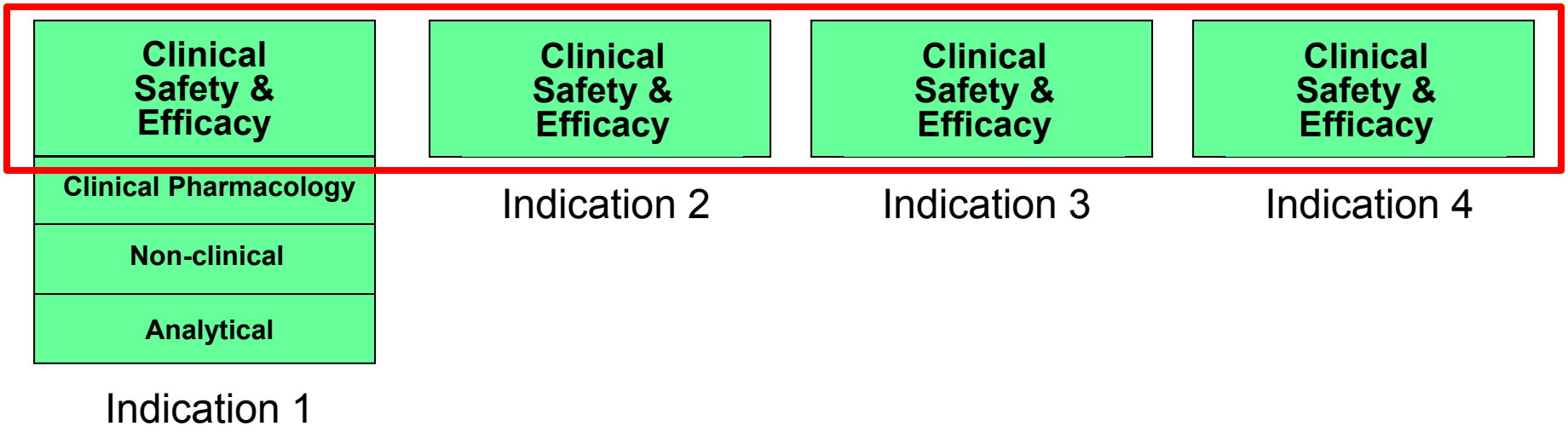
Indications studied in ABP 501 clinical program:

- Rheumatoid Arthritis (RA)
- Plaque Psoriasis (PsO)

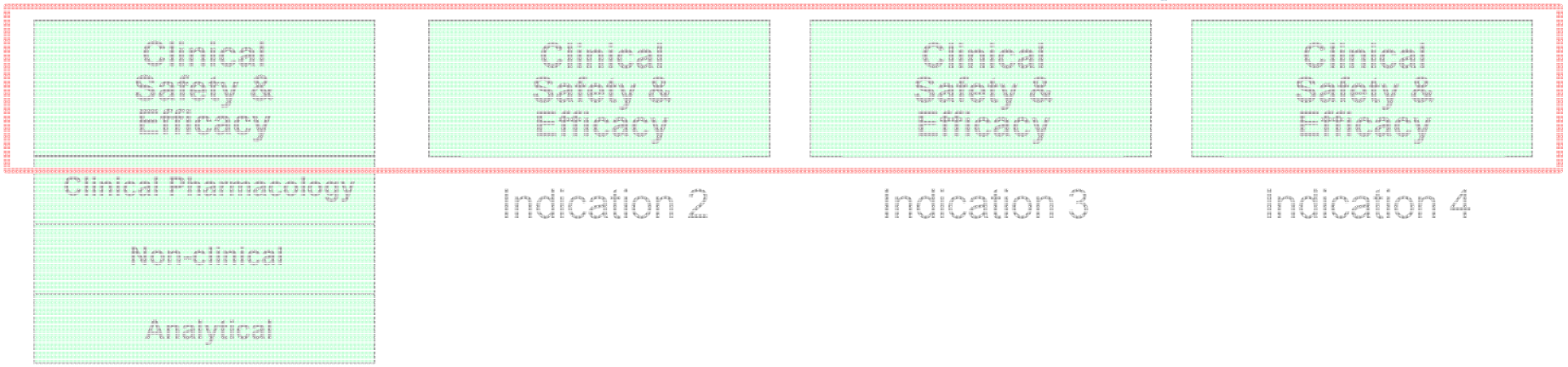
No clinical data on the use of ABP 501 in:

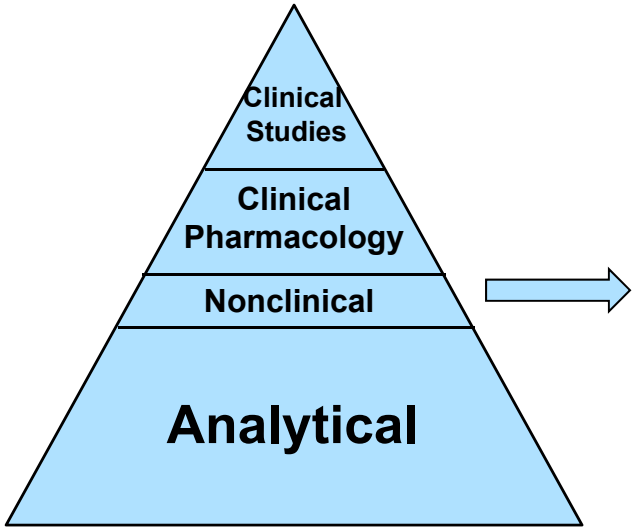
- Psoriatic Arthritis (PsA)
- Juvenile Idiopathic Arthritis (JIA) in patients 4 years of age or older
- Ankylosing Spondylitis (AS)
- Adult Crohn‘s Disease (CD)
- Adult Ulcerative Colitis (UC)

"Stand-alone" Drug Development



Extrapolation Considerations: "Stand-alone" vs. Biosimilar Development



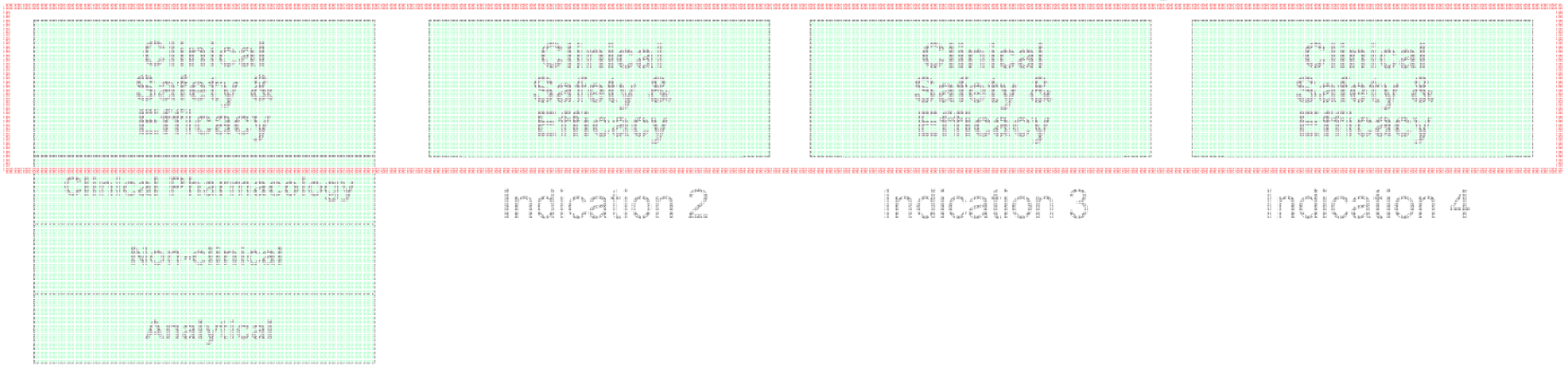


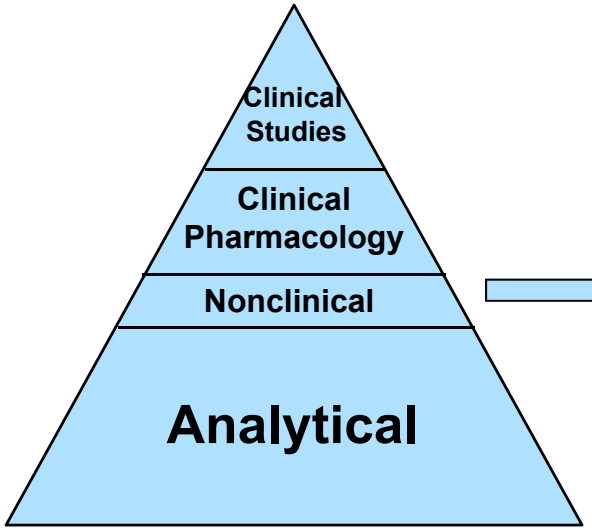
Demonstrate:

- High similarity
- NCMD to the reference product in one or more indications

NCMD: no clinically meaningful differences

Extrapolation Considerations: "Stand-alone" vs. Biosimilar Development





Demonstrate:
- High similarity
- NCMD to the reference product in one or more indications

Demonstration may include extrapolation of data, considering for each indication:
- MOA(s)
- PK
- Immunogenicity
- Toxicities

MOA: mechanism of action

Extrapolation Considerations: Totality of the Evidence

Amgen provided evidence to support a demonstration that:

- ABP 501 is highly similar to US-licensed Humira:
  - Primary-, secondary-, and tertiary structure
  - Post-translational profile and *in vitro* functional characteristics
  - Purity and stability
  - Potency, including TNF-α binding and neutralization
- There are no clinically meaningful differences between ABP 501 and US-licensed Humira based on:
  - Similar clinical pharmacokinetics
  - Similar efficacy, safety, and immunogenicity in RA and PsO, using two approved dosing regimens

Amgen also provided scientific justification to support that there are no clinically meaningful differences for the additional indications sought for licensure

Extrapolation Considerations: PK, Safety, and Immunogenicity

- Similar PK, safety, and immunogenicity rates were observed:
  - Between ABP 501 and Humira in:
    - Two different settings, RA and PsO, using
    - Two approved dosing regimens, either with or without concomitant immunosuppression
  - Between ABP 501 and Humira in healthy subjects
- Given the degree of analytical similarity, the PK profile, treatment-related toxicities, and immunogenicity would be expected to be similar between ABP 501 and US-licensed Humira across different doses and patient populations

Extrapolation Considerations: Known and Potential MOA of Humira

MOA of Humira	RA, JIA	AS	PsA	PsO	CD	UC	Similarity Criteria Met
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF							
	Yes	Yes	Yes	Yes	Likely	Likely	✓
Binding to tmTNF (Reverse /outside-to-inside signaling):							
	-	-	-	-	Likely	Likely	✓*
Mechanisms involving the Fc region of the antibody:							
Induction of CDC on tmTNF-expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible	✓
Induction of ADCC on tmTNF-expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible	✓
Induction of regulatory MΦ in mucosal healing	-	-	-	-	Plausible	Plausible	✓

*Pending additional functional data for reverse signaling assay

Extrapolation Considerations: JIA, PsA, AS, Adult CD, UC

- High analytical similarity between ABP 501 and US-licensed Humira
- TNF-α binding and potency, tmTNF binding, and Fc region-mediated potential MOA are similar between ABP 501 and US-licensed Humira, supporting the demonstration of same MOA for the indications being sought for licensure
- Clinical data support the demonstration of no clinically meaningful differences in patients with RA and PsO
- It is reasonable to extrapolate data to support that there are no clinically meaningful differences between ABP 501 and US-licensed Humira in JIA, PsA, AS, adult CD, and adult UC

Summary

- The totality of the evidence, provided by Applicant, supports:
  - A demonstration that ABP 501 is biosimilar to US-licensed Humira based on data demonstrating:
    - ABP 501 is highly similar to US-licensed Humira
    - No clinically meaningful differences exist between ABP 501 and US-licensed Humira
  - Licensure of ABP 501 for the indications for which US-licensed Humira is licensed and for which Amgen is seeking licensure.*

***Based on the premise that the additional data provided by the sponsor would not preclude a demonstration that ABP 501 is biosimilar to US-licensed Humira**

Thank you!

Charge to the Committee

351(k) BLA for ABP 501, a Proposed Biosimilar to US-licensed Humira

Arthritis Advisory Committee

July 12, 2016

Nikolay P. Nikolov, MD
Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products
Food and Drug Administration

Biosimilarity Definition: Section 351(k) of the PHS Act

- "the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components"

  and

- "there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product."

Issues for Consideration

Amgen provided evidence to support a demonstration that:

- ABP 501 is highly similar to US-licensed Humira:
  - Primary-, secondary-, and tertiary structure
  - Post-translational profile and *in vitro* functional characteristics
  - Purity and stability
  - Potency, including TNF-α binding and neutralization
- There are no clinically meaningful differences between ABP 501 and US-licensed Humira based on:
  - Similar clinical pharmacokinetics
  - Similar efficacy, safety, and immunogenicity in RA and PsO, using two approved dosing regimens

Amgen also provided scientific justification to support that there are no clinically meaningful differences for the additional indications sought for licensure

Discussion Question 1

- Please discuss whether the evidence from analytical studies supports a demonstration that ABP 501 is highly similar to US-licensed Humira, notwithstanding minor differences in clinically inactive components.

Discussion Question 2

- Please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between ABP 501 and US-licensed Humira in the studied conditions of use (RA and PsO).

Discussion Question 3

- Please discuss whether the data provides adequate scientific justification to support a demonstration of no clinically meaningful differences between ABP 501 and US-licensed Humira for the following additional indications for which US-licensed Humira is licensed:
  - JIA in patients 4 years of age and older
  - PsA
  - AS
  - Adult CD
  - Adult UC
- If not, please state the specific concerns and what additional information would be needed to support extrapolation. Please discuss by indication, if relevant.

Voting Question

- Does the totality of the evidence support licensure of ABP 501 as a biosimilar product to US-licensed Humira for the following indications for which US-licensed Humira is currently licensed and for which Amgen is seeking licensure (RA, JIA in patients 4 years of age and older, PsA, AS, adult CD, adult UC, and PsO)?

- Please explain the reason for your vote.