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

Arthritis Advisory Committee
February 9, 2016

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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.

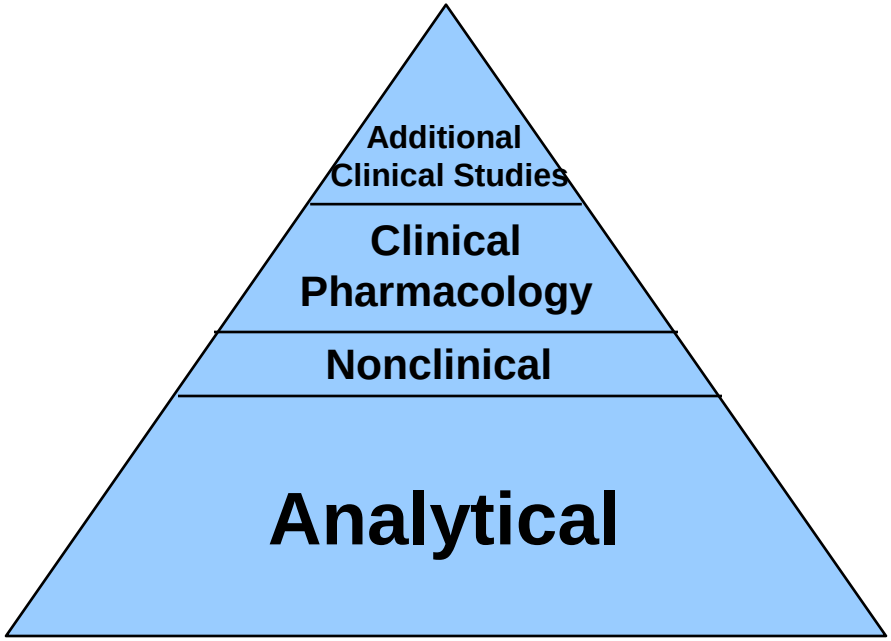
Overview of FDA's Approach to the Development of Biosimilars

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)



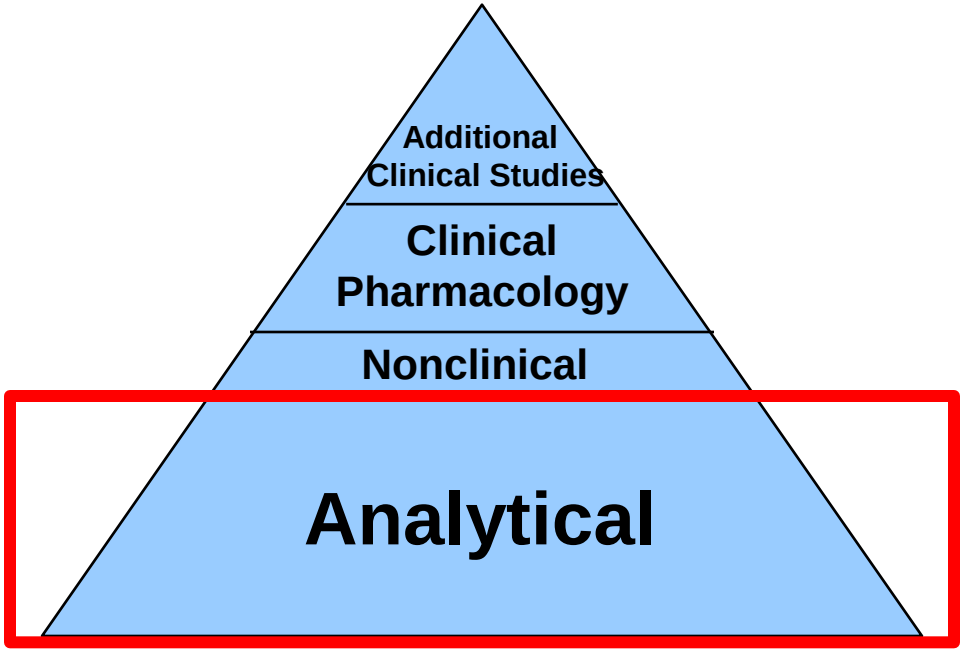
Key Concept #2:
Stepwise Evidence Development

- 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

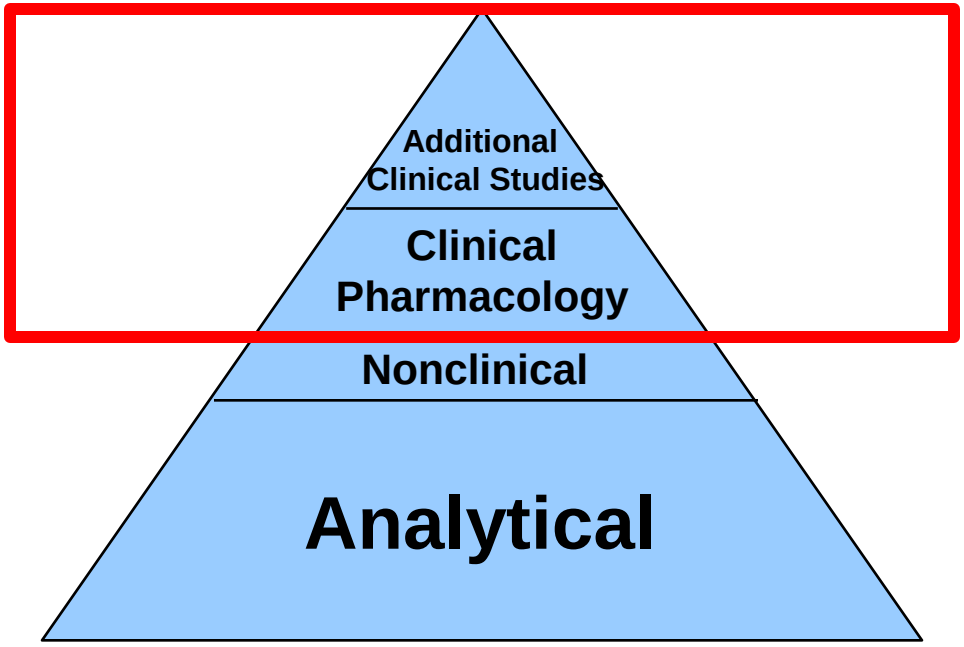
- Animal toxicity data are useful when uncertainties remain about the safety of the proposed product prior to initiating clinical studies

- 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 clinical data intended to demonstrate biosimilarity in one condition 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 CT-P13, a Proposed Biosimilar to US-licensed Remicade

Arthritis Advisory Committee
February 9, 2016

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

Overview of the BLA

- Applicant: Celltrion, Inc.
- Product: CT-P13, proposed biosimilar to US-licensed Remicade, the reference product (RP)
- Dosing and route of administration: Same as the RP
- Indications for which CT-P13 is developed: Same as the RP
  - Rheumatoid arthritis (RA)
  - Ankylosing spondylitis (AS)
  - Psoriatic arthritis (PsA)
  - Plaque psoriasis (PsO)
  - Adult and pediatric Crohn's disease (CD)
  - Adult and pediatric Ulcerative colitis (UC)

US: United States

Overview of CT-P13 Development Program

- To support a demonstration that CT-P13 is **highly similar** to US-licensed Remicade, Celltrion 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
  - Potency, including TNF-α binding and neutralization

TNF-α: Tumor necrosis factor alpha

Overview of CT-P13 Development Program

- To support a demonstration of **no clinically meaningful differences** between CT-P13 and US-licensed Remicade, Celltrion provided:
  - Studies to demonstrate similarity in exposure (i.e. PK) in healthy subjects and in patients with AS
  - Comparative clinical efficacy and safety study in RA
  - Supportive clinical efficacy and safety study in AS
  - Immunogenicity data in:
    - Patients with RA, AS, IBD, and healthy subjects, and
    - Patients who were transitioned from Remicade to CT-P13

PK: Pharmacokinetics; IBD: Inflammatory bowel disease

Clinical Development – Controlled Studies

Protocol	Patient Population	Design/Objectives	Duration	Sample size/ Randomization	Treatment arms
Study 1.4	Healthy subjects	R, DB, PG, SD 3-way PK bridging, Safety & IG	Single dose	N=250 1:1:1	• CT-P13 • EU-Remicade • US-Remicade
Study 1.1	AS	R, DB, PG PK, Efficacy, Safety & IG	54 weeks	N=250 1:1	• CT-P13 • EU-Remicade
Study 3.1	RA, MTX-IR	R, DB, PG Comparative Clinical Study	54 weeks	N=606 1:1	• CT-P13 + MTX • EU-Remicade + MTX
B1P13101 Japan	RA, MTX-IR	R, DB, PG PK and Efficacy	54 weeks	N=108 1:1	• CT-P13 + MTX • EU-Remicade + MTX
Study 1.2 Philippines	RA, MTX-IR	R, DB, PG Pilot Study	54 weeks	N=19 1:1	• CT-P13 + MTX • EU-Remicade + MTX
Study 3.3 Russia	RA, MTX-IR	R, DB, PG Pilot Study	54 weeks	N=15 1:1	• CT-P13 + MTX • EU-Remicade + MTX

R: Randomized, DB: Double-blind, PG: Parallel group, SD: Single dose, MTX: Methotrexate, IR: Incomplete responder, IG: Immunogenicity

Clinical Development – Extension Studies

Protocol	Patient Population	Design/ Objectives	Duration	Sample size	Treatment (CT-P13)
Study 1.3	AS, Enrolled from controlled study 1.1	OLE, Safety & Immunogenicity	Wks 62-102 (~1year)	N=174	• CT-P13 → CT-P13 (n=88) • EU-Remicade → CT-P13 (n=86)
Study 3.2	RA, Enrolled from controlled study 3.1	OLE, Safety & Immunogenicity	Wks 62-102 (~1year)	N=302	• CT-P13 → CT-P13 (n=158) • EU-Remicade→ CT-P13 (n=144)

Clinical Development – Inflammatory Bowel Disease

Protocol	Patient Population	Design/ Objectives	Duration	Sample size	Treatment (CT-P13)
Study 4.1	IBD	Open-label Safety & Efficacy	Ongoing	N=10	• CT-P13
PMS study Korea	IBD	PMS, Safety & Efficacy	Ongoing	N=173	• CT-P13
Study 3.4	IBD	R, DB, PG Efficacy, Safety, Immunogenicity	Ongoing	N=99	• CT-P13 • EU-Remicade • US-Remicade

OLE: Open-label extension, PMS: Post-marketing surveillance; EU-European Union; IBD: Inflammatory bowel disease

Overview of CT-P13 Development Program

- To justify the relevance of the data generated using a non-US-licensed comparator, i.e. EU-approved Remicade, Celltrion provided:
  - Extensive analytical 3-way bridging data
  - Clinical study to demonstrate 3-way similarity in exposure (PK) between CT-P13, US-licensed Remicade, and EU-approved Remicade in healthy subjects

The BPCI Act defines the “reference product” as the single biological product licensed under section 351(a) of the PHS Act against which a proposed biosimilar product is evaluated in a 351(k) application (see section 351(i)(4) of the PHS Act)

Overview of CT-P13 Development Program

- To support an extrapolation of data on safety and efficacy across indications, Celltrion provided:
  - An extensive data package to address the scientific considerations* for extrapolation of data to support biosimilarity for the indications eligible for licensure:
    - The mechanism(s) of action (MOA) 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

*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:

- Does the Committee agree that CT-P13 is highly similar to the reference product, US-licensed Remicade, notwithstanding minor differences in clinically inactive components?

Discussion Question 2:

- Does the Committee agree that there are no clinically meaningful differences between CT-P13 and US-licensed Remicade in the studied conditions of use (RA and AS)?

Discussion Questions

Discussion Question 3:

- Does the Committee agree that there is sufficient scientific justification to extrapolate data from the comparative clinical studies of CT-P13 in RA and AS to support a determination of biosimilarity of CT-P13 for the following additional indications for which US-licensed Remicade is licensed (PsA, PsO, adult and pediatric CD, and adult and pediatric* UC)?
- If not, please state the specific concerns and what additional information would be needed to support extrapolation. Please discuss by indication if relevant.

*Remicade's indication for pediatric UC is protected by orphan drug exclusivity expiring on September 23, 2018. FDA is interested in the Committee's views regarding the scientific justification for extrapolation for this indication, but FDA is not asking the Committee to vote on licensure of CT-P13 for pediatric UC because FDA will not be able to license a proposed biosimilar product for this indication until the orphan exclusivity expires.

Voting Question

- Does the Committee agree that based on the totality of the evidence, CT-P13 should receive licensure as a biosimilar product to US-licensed Remicade for each of the indications for which US-licensed Remicade is currently licensed and CT-P13 is eligible for licensure (RA, AS, PsA, PsO, adult CD, pediatric CD, adult UC)?

  a. Please explain the reason for your vote. If you voted no, explain whether this was applicable to all or some of the indications and why.

CT-P13
Product Quality Review

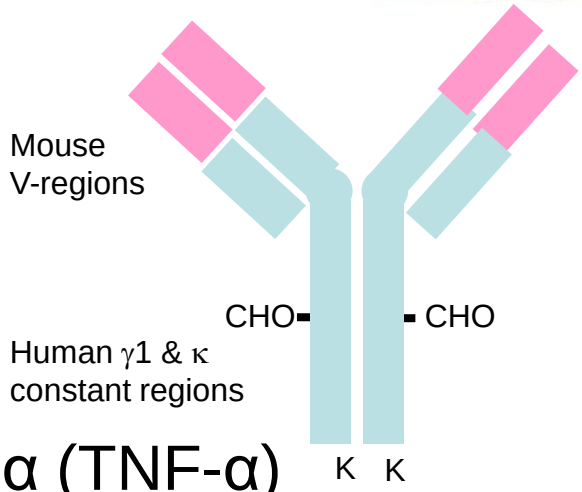
Arthritis Advisory Committee
February 9, 2016

Kurt Brorson, Ph.D., Product Quality Team Leader
Office of Biotechnology Products
CDER, FDA

Outline

- Infliximab Structure and Mechanism of Action
- CT-P13 Manufacturing
- Studies to Support High Similarity
- Analytical Similarity Assessment

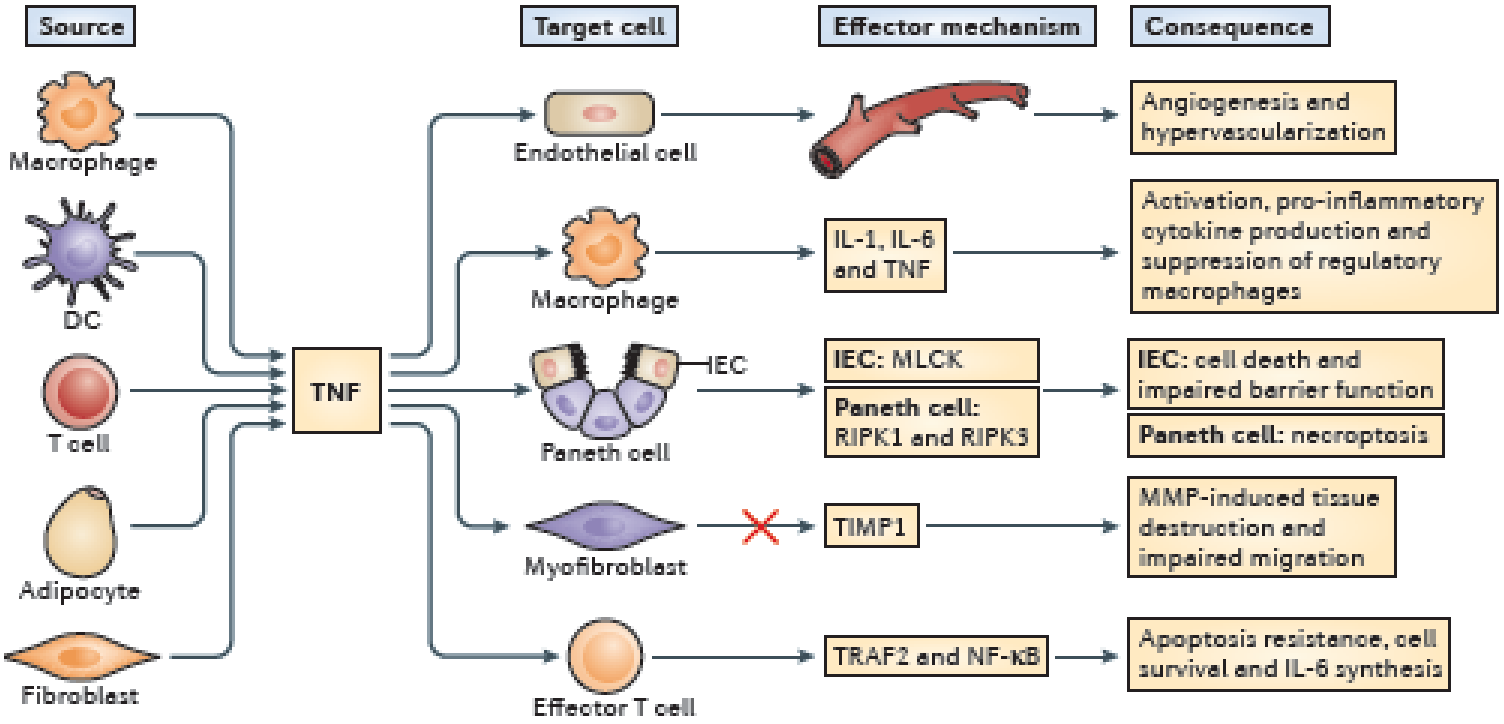
Infliximab Structure



- Remicade: Janssen
- Chimeric IgG1κ monoclonal antibody
- Neutralizes human tumor necrosis factor-α (TNF-α)
- Molecular weight: ~149.1 kilodaltons
- Produced by a recombinant cell line cultured in bioreactors
- Possesses heterogeneity typical of mammalian cell culture-derived mAbs

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 Remicade

MOA of Remicade	RA	AS	PsA	PsO	CD/ Pediatric CD	UC/ Pediatric 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:						
Apoptosis of lamina propria activated T cells	-	-	-	-	Likely	Likely
Suppression of cytokine secretion	-	-	-	-	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

*MOA= Mechanism of Action

CT-P13 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 all scales
  - Minor process changes: comparable product
- Critical Quality Attributes (CQA's) include potency, binding, aggregates, glycosylation, charge variants, host cell protein and viral safety
- Drug substance facility was inspected in Feb 2015

CT-P13 Drug Product

- Lyophilized powder for reconstitution and i.v. infusion
- Produced by aseptic processing and tested for sterility
- Container closure: 20mL Type I borosilicate glass vial
- Same strength and formulation as US-licensed Remicade
- Expiry supported by stability studies
- The drug product facility was inspected in Feb 2015

Ingredient	Quantity/Vial
Sucrose	500 mg
Sodium dihydrogen phosphate monohydrate	2.2 mg
di-Sodium hydrogen phosphate dihydrate	6.1 mg
Polysorbate 80	0.5 mg

Analytical Similarity Evaluations

- Analytical comparison of CT-P13 and US-licensed Remicade is used to support a demonstration that CT-P13 is “highly similar” to US-licensed Remicade
- Pairwise comparisons of CT-P13, US-licensed Remicade and EU-approved Remicade are used to support the analytical bridge between the three products
- Bridge is needed:
  - to justify the relevance of data generated using EU-approved Remicade as the comparator in some clinical and non-clinical studies intended to support a demonstration of biosimilarity to US-licensed Remicade

Methods Used to Evaluate Analytical Similarity

Quality Attribute	Methods
Primary Structure	• A.A. analysis • Peptide mapping (LC-MS; HPLC) • N-term and C-term sequencing • Reduced mass by MS
Bioactivity	• In vitro TNFα neutralization • TNFα binding (ELISA) • Cytokine release inhibition, PBMCs • Cell based binding affinity
Purity	• Reduced/non-reduced CE-SDS • CT-13 specific ELISA
Fc Receptor Binding	• Surface Plasma Resonance
Protein Content	• Concentration (UV_{280})
Sub-visible Particles	• Micro Fluid 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 PBMCs, NK cells • C1q binding (ELISA) • Apoptosis (FACS) • Wound healing • Reverse signaling
High molecular weight variants/aggregates	• Size exclusion chromatography (SEC) • SEC-Multi Angle Laser Light Scatter
Physicochemical Analysis	• N-linked glycan analysis • N-linked Oligosaccharide profiling • Glycation (LC-ES-MS) • Thermal stability (DSC) • pI (IEF) • Charge variant dist. (IEC-HPLC) • Oxidized species (LC-MS) • Disulfide bonds • Free SH • Monosaccharide analysis • Sialic acid analysis

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

Analytical Methods: Studies to Support CT-P13 High Similarity

Highly Critical Quality Attributes (QA) include:

- Amino acid identity:
  - Expression construct encodes the same primary amino acid sequence as the reference product
  - Tryptic peptide mapping
  - Orthogonal tests including mass spectroscopy and amino acid sequencing
- *In vitro* TNF-α neutralization
  - Cell culture-based assay
- TNF-α binding
  - ELISA

Additional Analytical Methods: Studies to Support CT-P13 High Similarity

Analyzed Using Quality Ranges

- CDC
- ADCC of PBMCs, NK cells
- Protein concentration (UV_{280})
- FcγRI, -IIa,-IIb, -IIIb
- FcγRn binding (SPR)
- C1q binding (ELISA)

Additional Assessment

- Subvisible particulates (USP)
- 1°, 2°, 3° structure (FTIR,CD, DSC)
- Monomer, Aggregates (SEC-HPLC)
- Charge variant distribution (IEC-HPLC)
- N-linked glycan analysis
- N-Linked oligosaccharide profiling
- FcγRIIIa- Multiple Variants
- Some *in vitro* tests used to evaluate mechanism of action

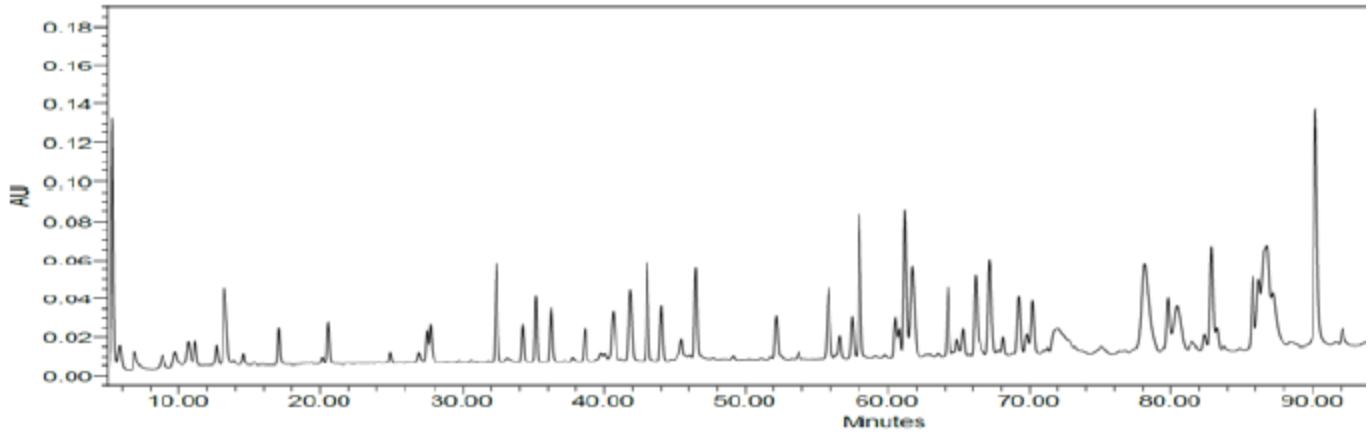
Number of Lots Tested

Assay	CT-P13	US Remicade	EU Remicade
TNF-α Neutralization (Highly Critical QA)	13	16	13
TNF-α Binding (Highly Critical QA)	16	27	23
Total Lots Tested for Similarity Exercise	26	45	41

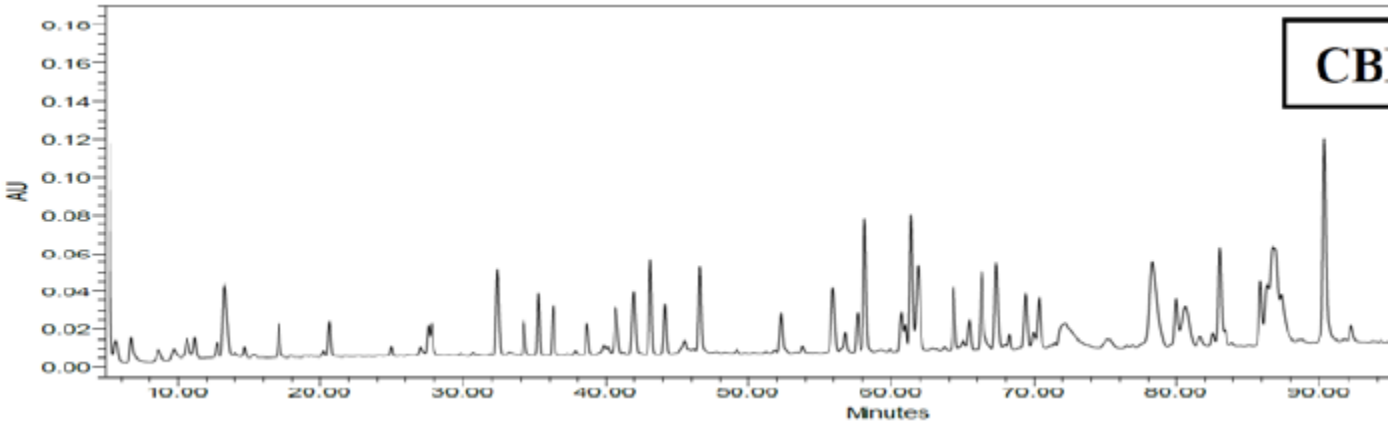
*Every lot not assessed for all attributes

Primary Structure

CT-P13



US-licensed Remicade



Tryptic digest followed by Reverse Phase (RP) chromatography

RP-HPLC peaks analyzed by mass spectroscopy

Other methods used to confirm: N- and C-terminal sequencing, MS/MS, amino acid analysis

CT-P13 Statistical Equivalence Testing for Bioactivity

Arthritis Advisory Committee
February 9, 2016

Office of Biostatistics

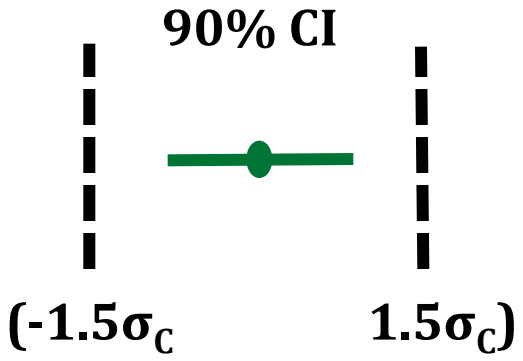
Meiyu Shen, Ph.D., CMC Statistical Reviewer
Office of Biostatistics, CDER, FDA

Highly Critical Quality Attributes for Statistical Equivalence Analysis

- Assays that assessed the primary Remicade mechanism of action that were tested using equivalence testing:
  - TNF-α Binding Affinity (ELISA)
  - *In vitro* TNF-α Neutralization

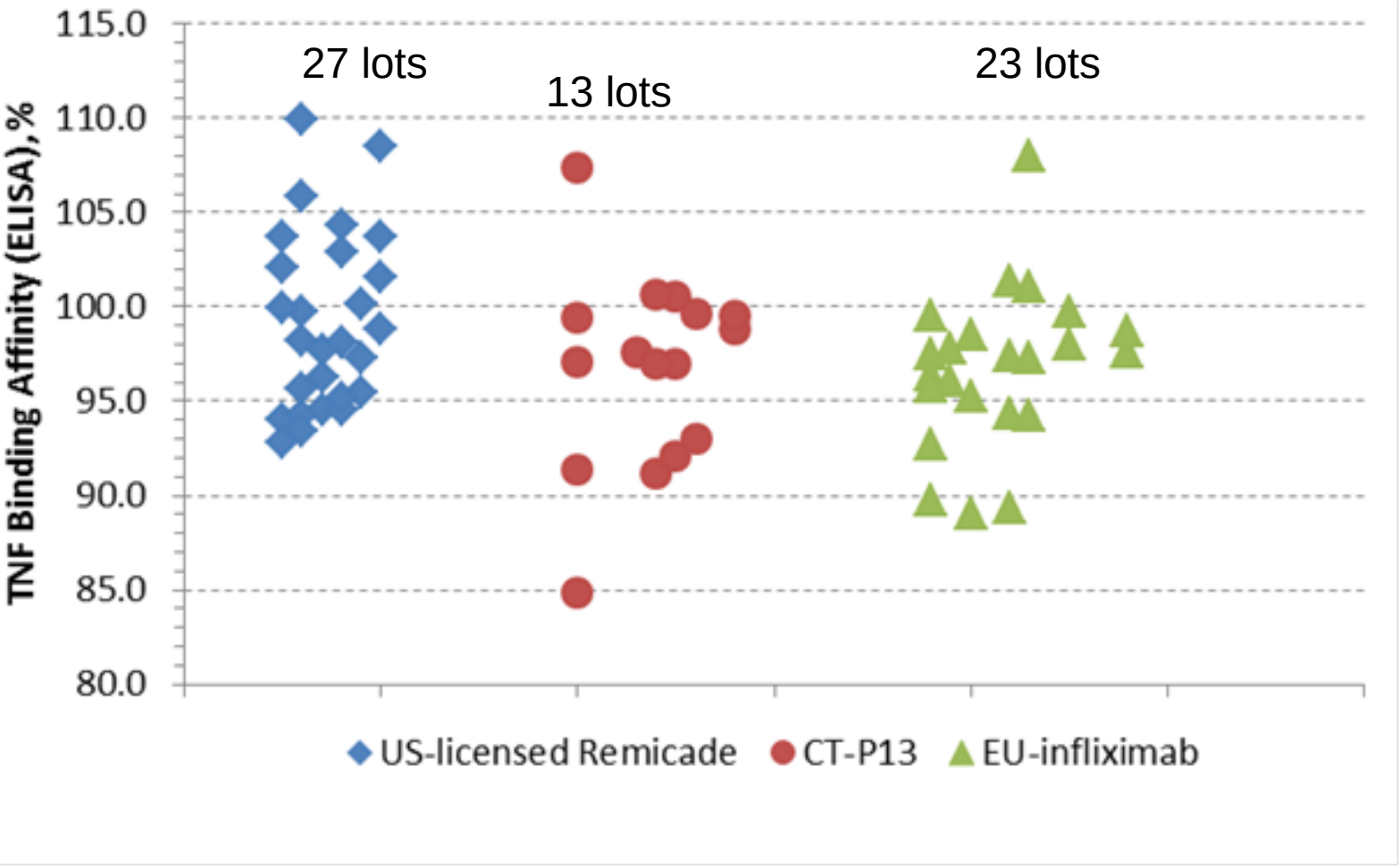
Statistical Equivalence Test

- 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



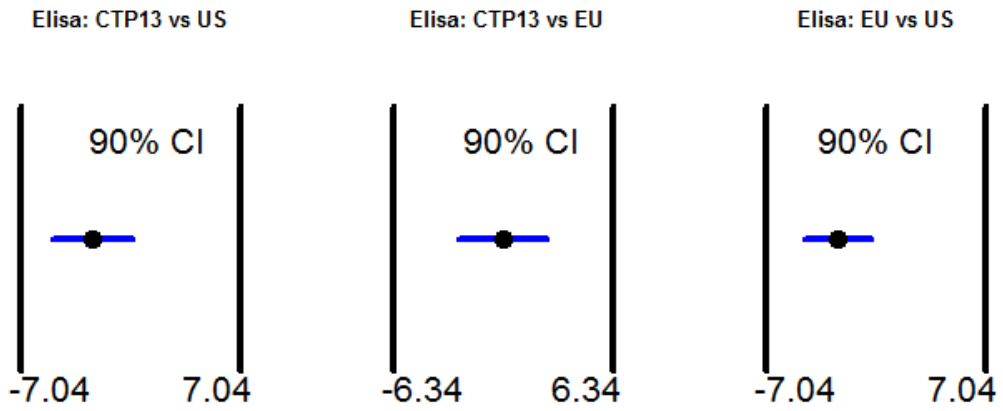
- Equivalence margin=$1.5\sigma_C$:
  - σ_C is estimated from comparator data measured by applicant.

TNF-α Binding Affinity (ELISA)

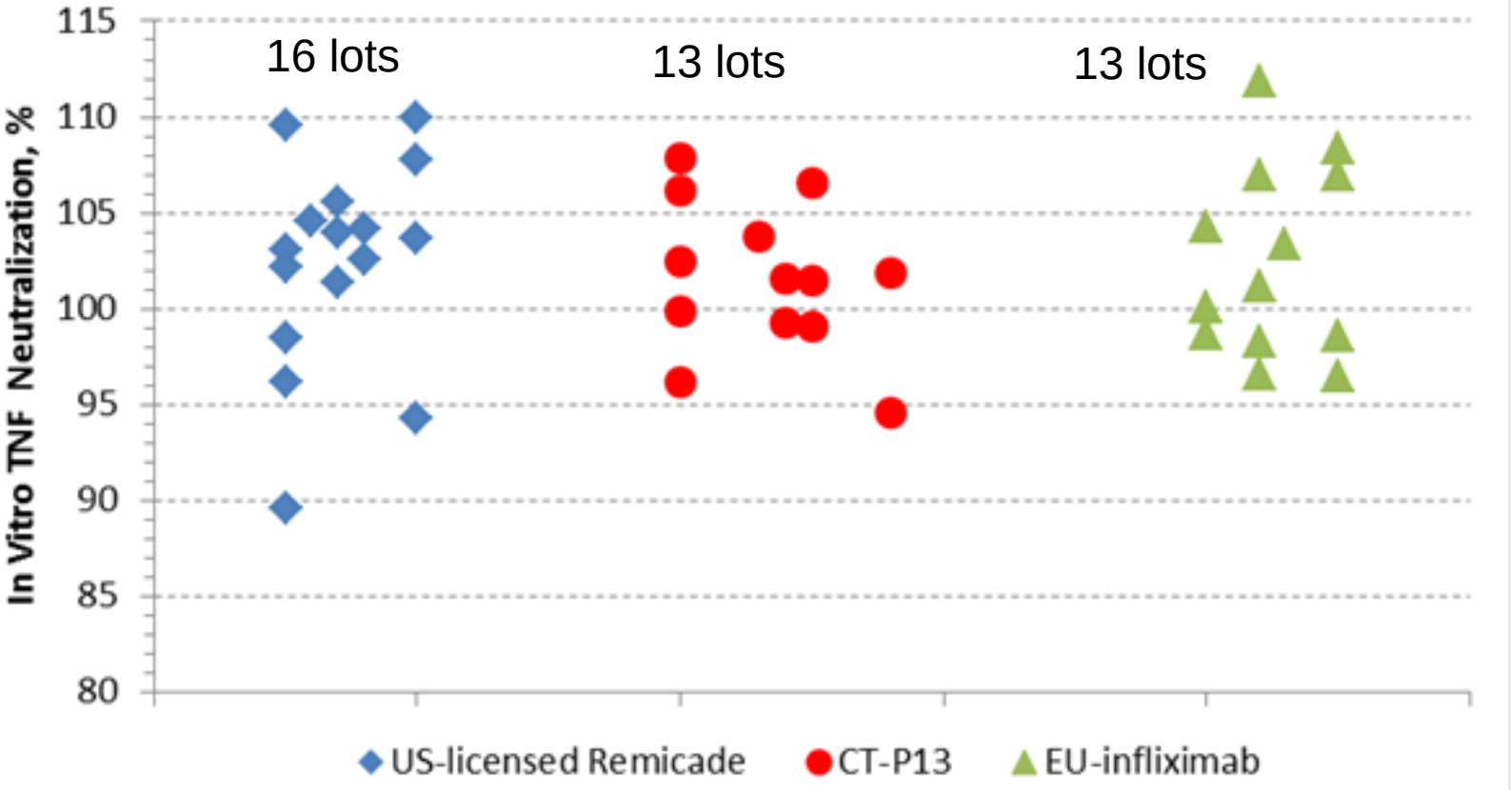


Equivalence Test: TNF-α Binding Affinity (ELISA)

Comparison	Mean difference	90% confidence interval for mean difference		Equivalence margin	Equivalent
		Lower limit	Upper limit		
CT-P13 vs. US	-2.50	-5.09	0.09	(-7.04, 7.04)	Yes
CT-P13 vs. EU	-0.05	-2.60	2.50	(-6.34, 6.34)	Yes
EU vs. US	-2.45	-4.58	-0.31	(-7.04, 7.04)	Yes

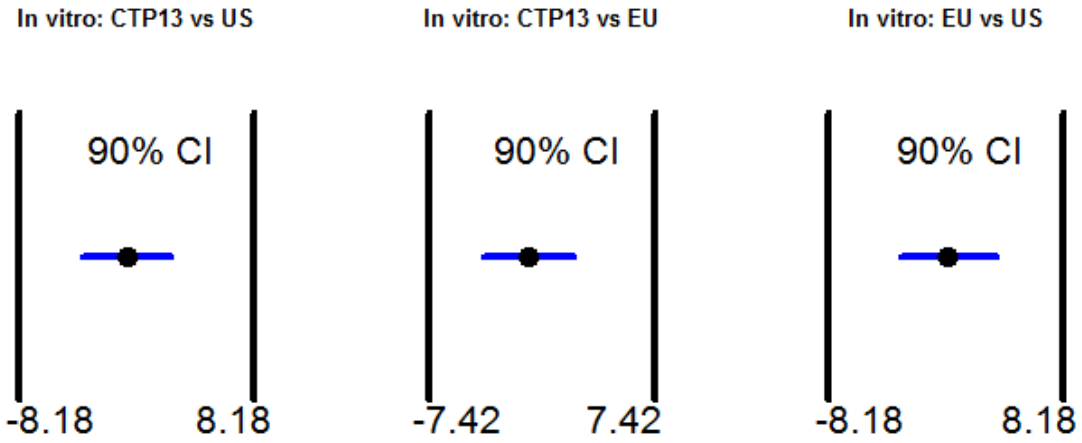


In Vitro TNF-α Neutralization



Equivalence Test: *In Vitro* TNF-α Neutralization

Comparison	Mean difference	90% confidence interval for mean difference		Equivalence margin	Equivalent
		Lower limit	Upper limit		
CT-P13 vs. US	-0.71	-3.79	2.36	(-8.18, 8.18)	Yes
CT-P13 vs. EU	-0.84	-3.83	2.15	(-7.42, 7.42)	Yes
EU vs. US	0.12	-3.20	3.45	(-8.18, 8.18)	Yes

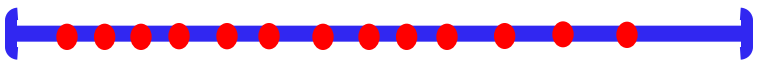


Conclusion of Statistical Analyses for Highly Critical QAs

- TNF-α binding affinity (ELISA)
  - CT-P13 vs US passes equivalence
  - CT-P13 vs EU passes equivalence
  - EU vs US passes equivalence
- *In vitro* TNF-α neutralization
  - CT-P13 vs US passes equivalence
  - CT-P13 vs EU passes equivalence
  - EU vs US passes equivalence
- Statistical equivalence testing results of TNF-α binding affinity (ELISA) and in vitro TNF-α neutralization support the conclusion that CT-P13 is highly similar to US-licensed Remicade
  - and support the analytical bridge between 3 products.

Quality Range Analysis

- Quality Range = Mean ± X SD
  - Mean and SD of quality attribute data 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



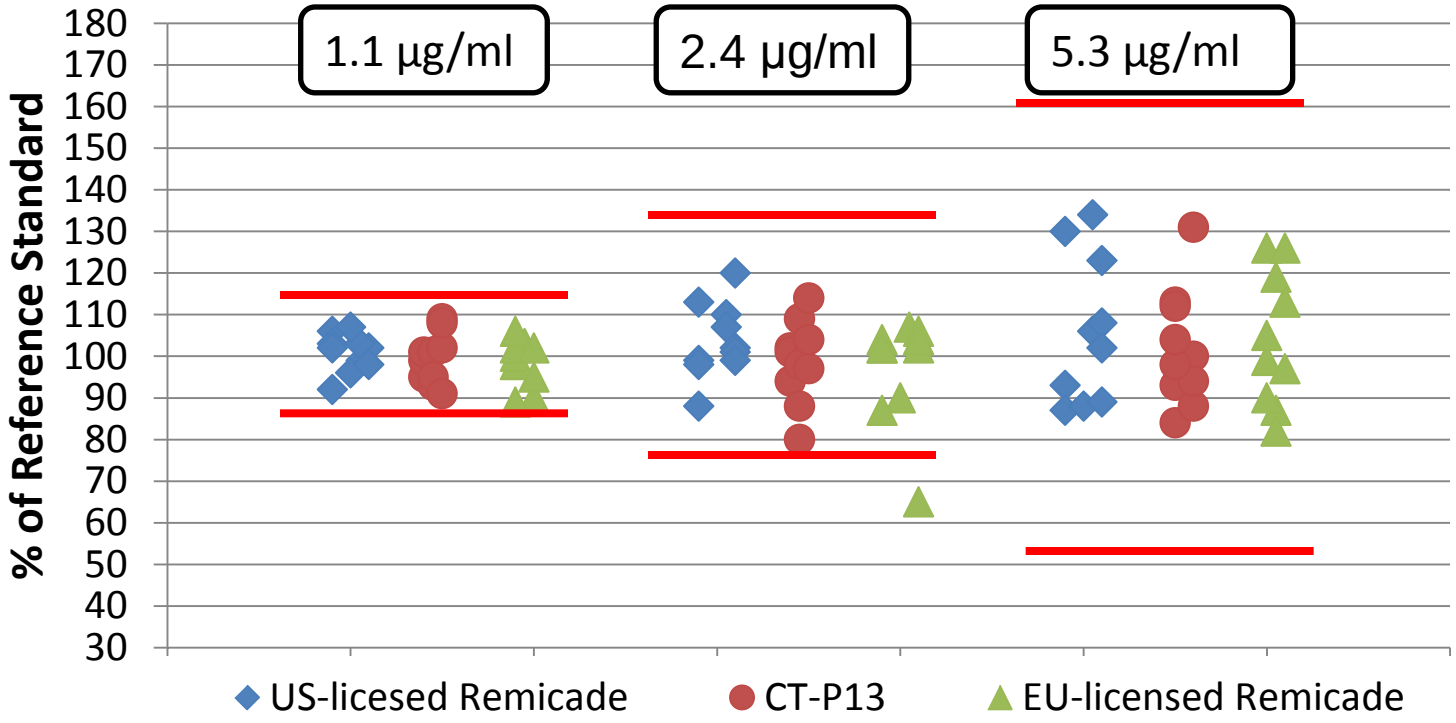
- **Quality range of comparator**
- **Batch values of test**

CT-P13 Product Quality Review (cont'd)

Arthritis Advisory Committee
February 9, 2016

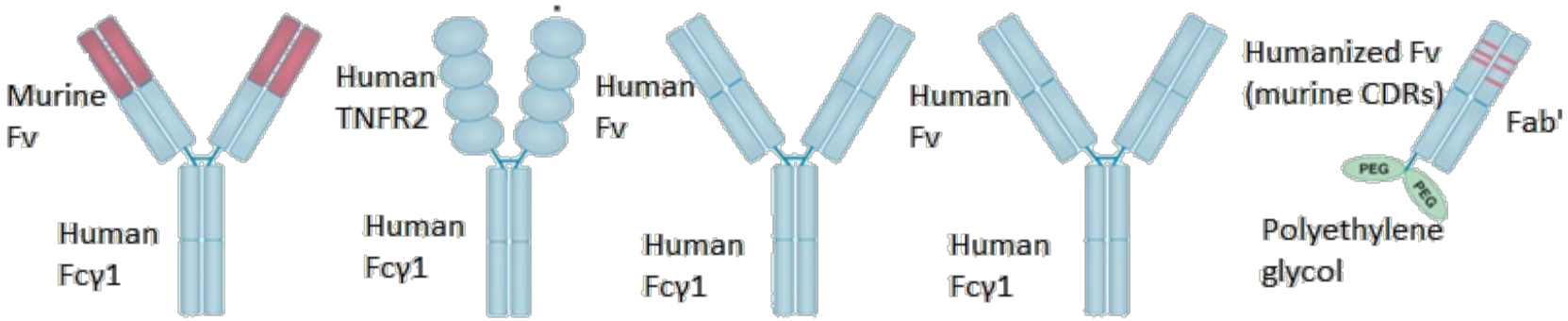
Kurt Brorson, Ph.D., Product Quality Team Leader
Office of Biotechnology Products
CDER, FDA

Quality Range (QR) Analysis: Reverse Signaling in mTNF+ PBMCs



- 100% of CT-P13 lots within the QR

Fc in TNF Blocker MOA



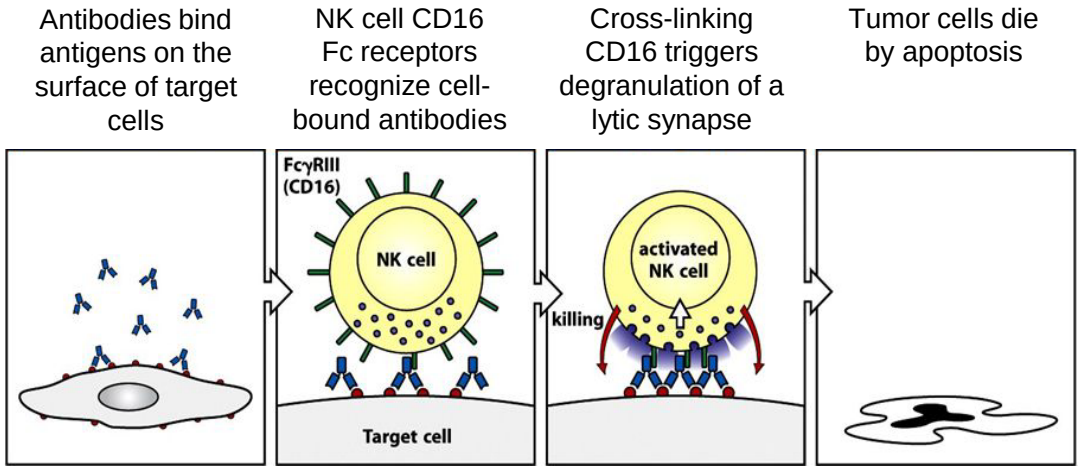
	Infliximab	Etanercept	Adalimumab	Golimumab	Certolizumab (pegol)
ADCC	High	Low	High	High	None
CDC	High	Low	High	High	None
RA	Yes	Yes	Yes	Yes	Yes
CD/UC	Yes/Yes	No/NS	Yes/Yes	NS/Yes	Yes[#]/NS

NS=Not Studied

[#] approved indication in CD is based on reducing signs and symptoms and maintaining clinical response rather than achieving and maintaining /sustaining remission

Arora T, *et al* Cytokine 42, 124-31 (2009); Kaymakcalan Z, *et al* Clinical Immunology 131, 308-16 (2009); Mitoma H, *et al* Arthritis & Rheumatism 58, 1248-1257 (2008)

ADCC: Proposed Role in Anti-TNF MoA



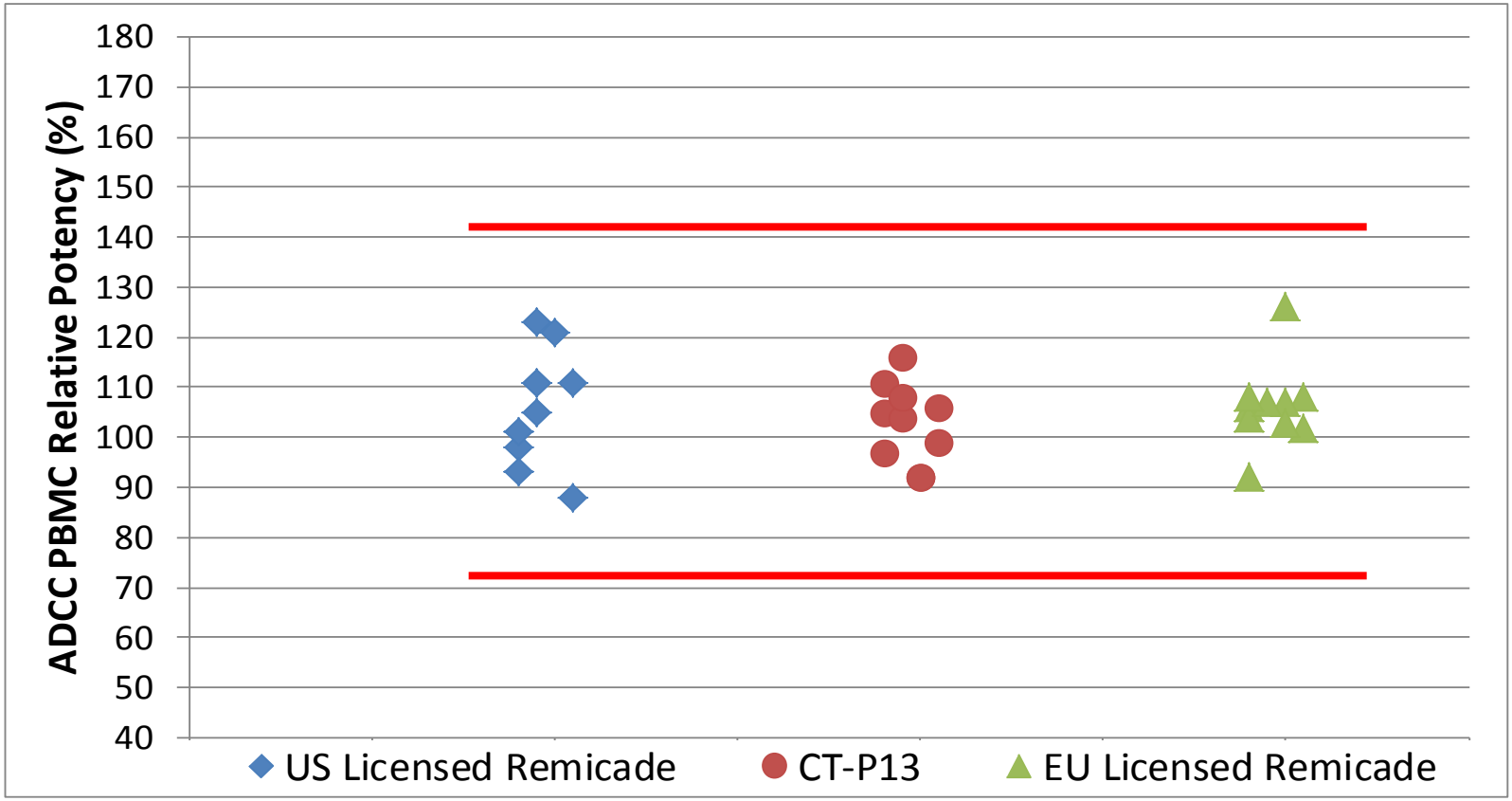
Janeway's Immunobiology, 2011

- Role in host defense against pathogens and tumors
- Lysis of mTNF-a $^{+}$ T cells at sites of inflammation

- Product comparison with different effector:target cell combinations assessed

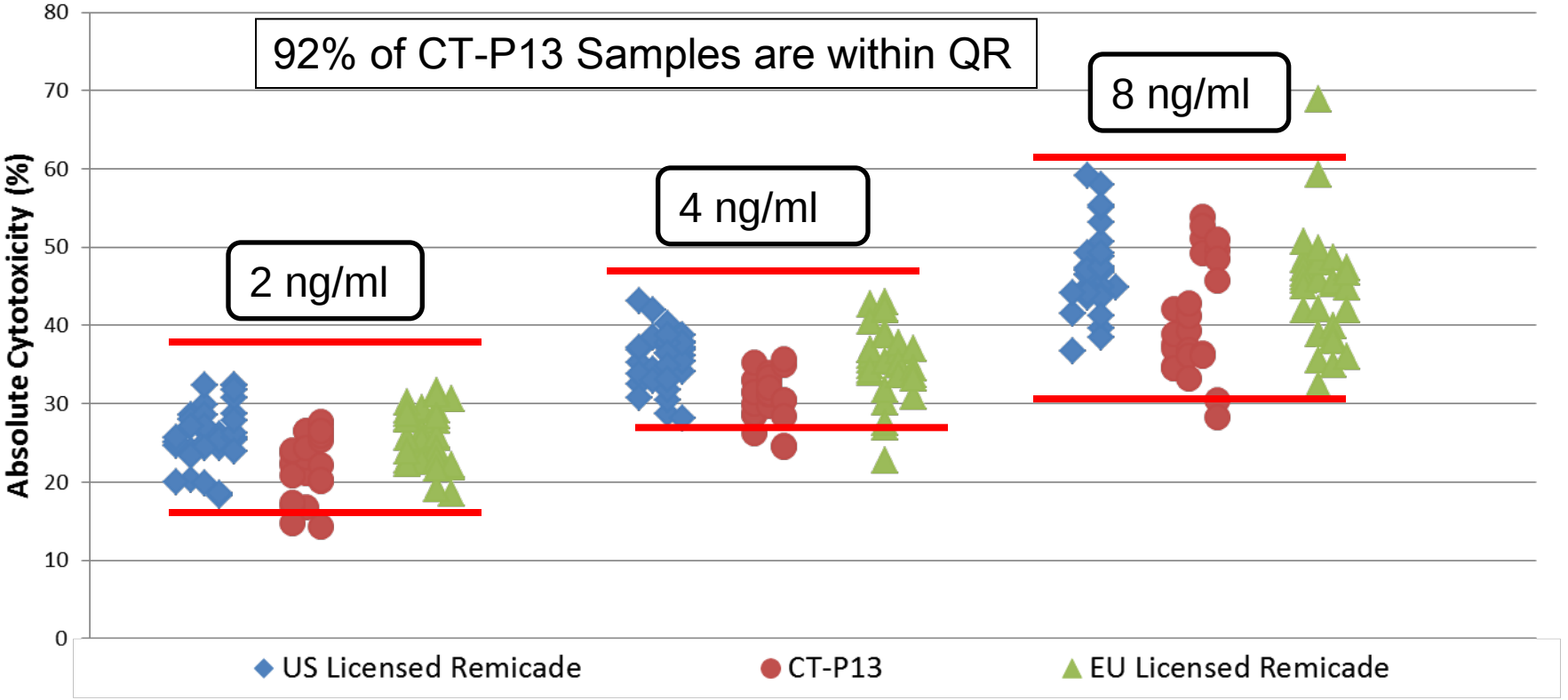
- PBMC: Jurkat mTNF-a tranfectoma target
- NK cells: Jurkat mTNF-a transfectoma target
- PBMC: LPS-activated macrophage target

QR Analysis: PBMC ADCC



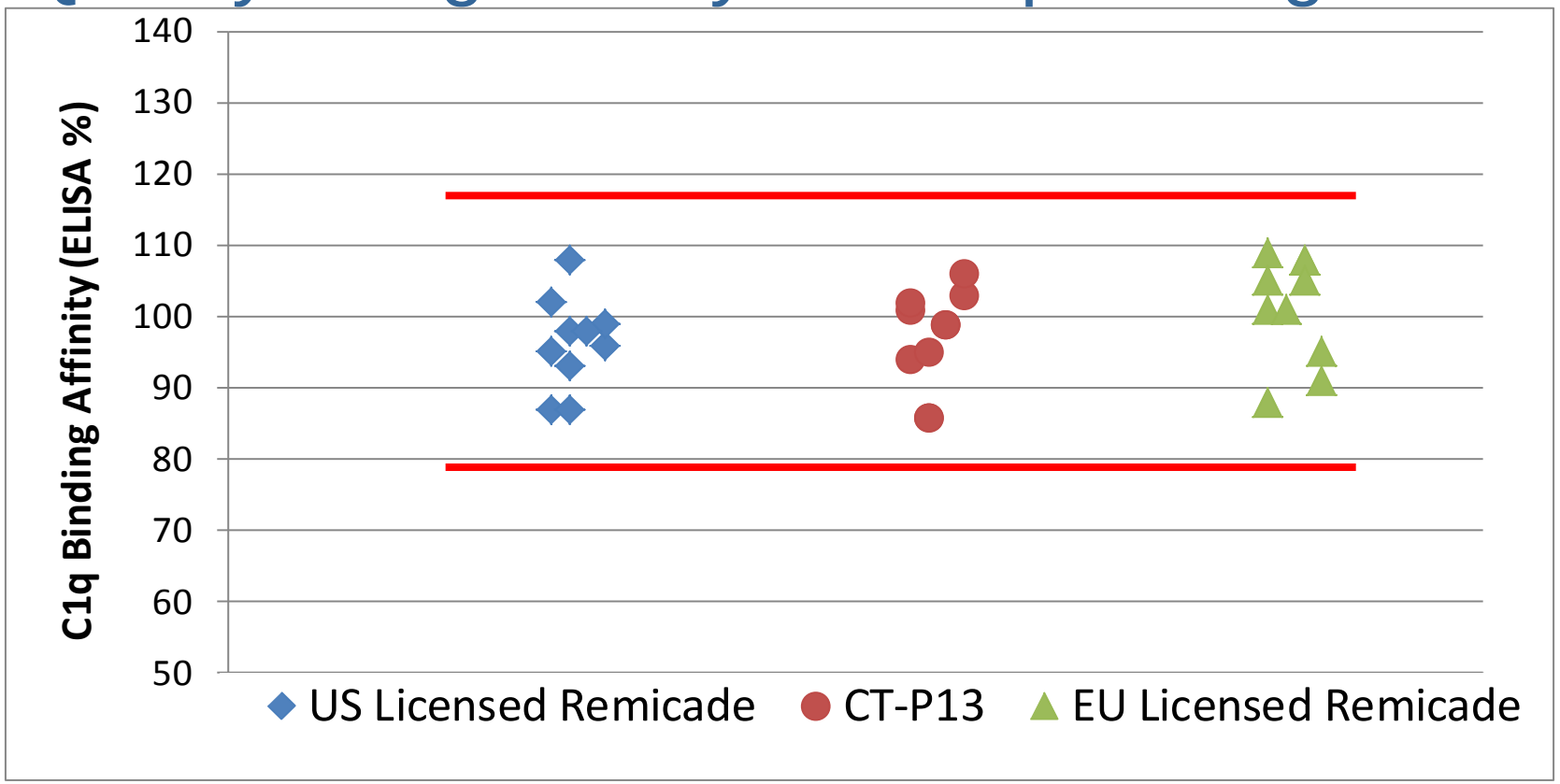
- ADCC assay uses
  - Transfected transmembrane TNF-α Jurkat cells as target cells
  - PBMC from healthy donor as effector cells

QR Analysis: NK-ADCC Cytotoxicity



- NK-ADCC assay:
  - Transfected transmembrane TNF-α Jurkat cells used as target cells
  - NK cells purified from peripheral blood used as effector cells

Quality Range Analysis: C1q Binding



- C1q binding is required to initiate CDC and offers a low variability assay of an Fc function
- 100% of CT-P13 lots within the QR

Each Potential MOAs of Remicade Addressed by a Biological Assay

MOA of Remicade	RA	AS	PsA	PsO	CD Pediatric CD	UC Pediatric UC	Similarity Criteria Met
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:							
Apoptosis of lamina propria activated T cells	-	-	-	-	Likely	Likely	✓
Suppression of cytokine secretion	-	-	-	-	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	✓

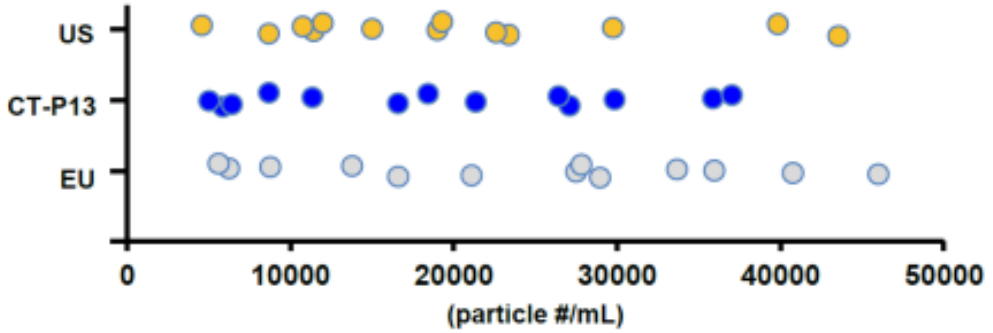
* Modest shift in mean activity of CT-P13 vs. reference product, within the established quality range

Sub-Visible Particle Analysis

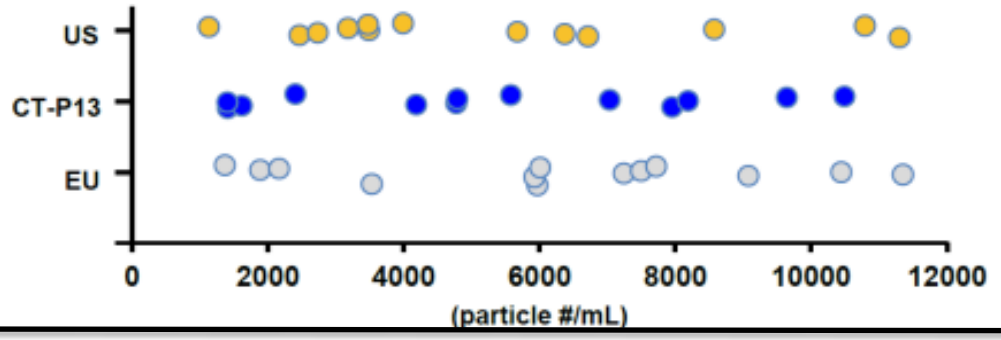
- Immune system potentially sensitive to proteinaceous sub-visible particles
- Evaluation of sub-visible particles beyond typical product analysis bolsters confidence in application of EU product immunogenicity data for US decision making.
- Potential assays for sub-visible particles
  - Micro flow imaging (MFI)
  - Light obscuration

Sub-Visible Particles by MFI

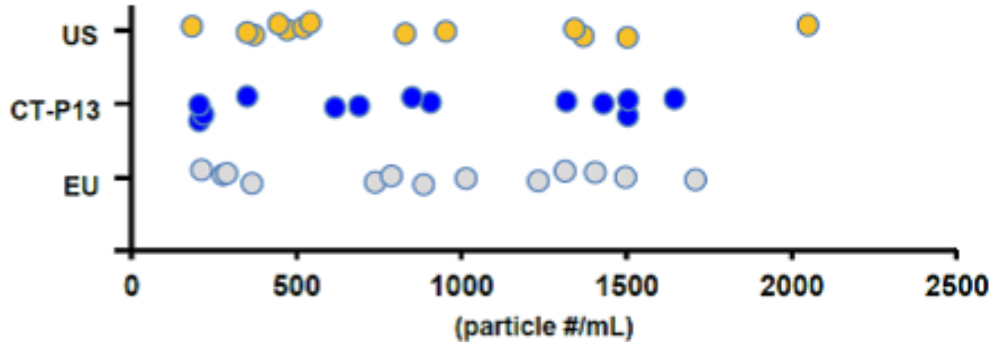
1.00 ≤, < 100.00 (µm)



2.00 ≤, < 100.00 (µm)



5.00 ≤, < 100.00 (µm)



Overall Analytical Conclusion

- Extensive analytical study to determine similarity:
  - Functional and Bioactivity Assays
  - Protein Analytical Assays
  - Physicochemical Assays
  - Higher Order Structural Assays
- An analytical bridge was established between the EU-approved Remicade, US-licensed Remicade and CT-P13
- The totality of the evidence provided by the above analytical evaluation supports the conclusion that CT-P13 is highly similar to US-Licensed Remicade

CT-P13
Clinical Pharmacology Review

Arthritis Advisory Committee
February 9, 2016

Lei He, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology II
Office of Clinical Pharmacology

Overview of Clinical Pharmacology

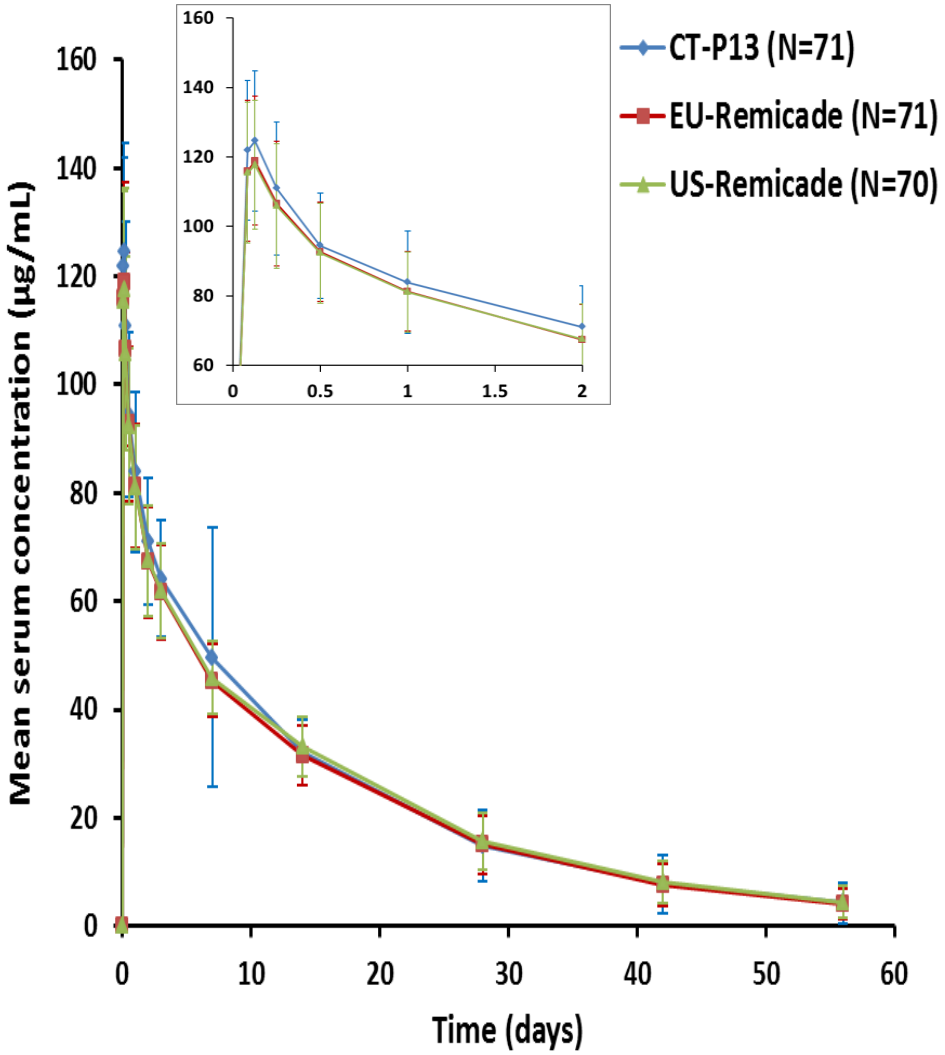
- The objectives of the clinical pharmacology program are:
  - To evaluate the pharmacokinetic (PK) similarity between CT-P13 and US-licensed Remicade
  - To assess the PK element of the scientific bridge between CT-P13, US-licensed Remicade and EU-approved Remicade
- PK was assessed in:
  - **Study 1.4 (Pivotal)**
    - 3-way PK bridging/similarity study in healthy subjects
  - Study 1.1 (Supportive)
    - PK study in Ankylosing Spondylitis (AS) patients
  - Study 3.1(Supportive)
    - Comparative clinical study in Rheumatoid Arthritis (RA) patients
- PK similarity was demonstrated between CT-P13, EU-approved Remicade and US-licensed Remicade

Study 1.4: Study Design

- **Study Design:** Randomized, double-blind, three-arm, parallel group, single dose in healthy subjects
- **Objectives:**
  - Primary: PK
  - Secondary: safety, tolerability and immunogenicity
- **Treatments:**
  - CT-P13: 5 mg/kg, 2-h IV infusion
  - US-licensed Remicade: 5 mg/kg, 2-h IV infusion
  - EU-approved Remicade: 5 mg/kg, 2-h IV infusion
- **Subjects:** healthy subjects, N=71/arm
- **Endpoints:**
  - Primary: Cmax, AUC0-t, AUC0-∞

Study 1.4: PK Results

PK similarity demonstrated between CT-P13, EU-approved Remicade and US-licensed Remicade



PK Similarity Analysis

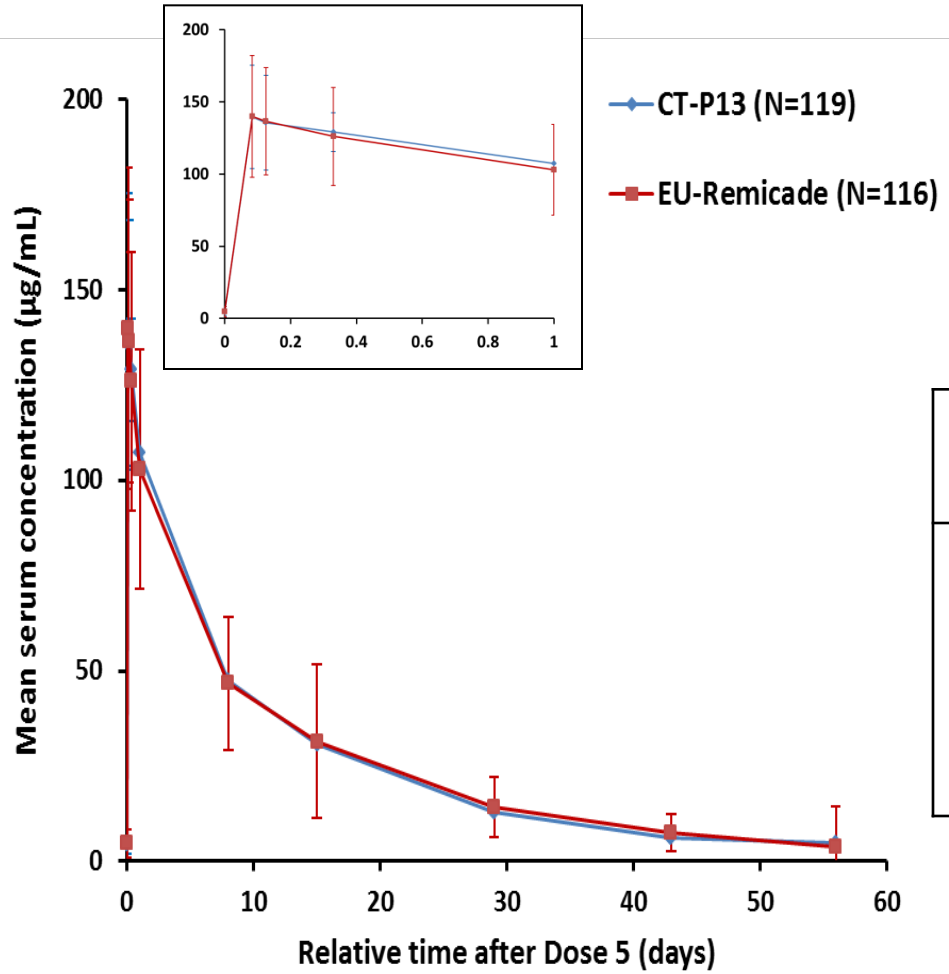
Comparison	PK Variables	GMR (90%CI) (%)
CT-P13 vs. US-Remicade	Cmax	106.97 (102.03, 112.15)
	AUC0-t	98.23 (92.32, 104.51)
	AUC0-∞	98.82 (92.10, 106.02)
CT-P13 vs. EU-Remicade	Cmax	105.70 (100.84, 110.81)
	AUC0-t	101.37 (95.07, 108.08)
	AUC0-∞	102.30 (95.12, 110.01)
EU-Remicade vs. US-Remicade	Cmax	100.91 (96.81, 105.79)
	AUC0-t	96.90 (91.66, 102.44)
	AUC0-∞	96.60 (90.37, 103.25)

Study 1.1: Study Design

- **Study Design:** Randomized, double-blind, two-arm, parallel group, multiple-dose in AS patients
- **Objectives:**
  - Primary: PK
  - Secondary: efficacy, safety and immunogenicity
- **Treatments:**
  - CT-P13: 5 mg/kg on weeks 0, 2, 6, and every 8 weeks
  - EU-approved Remicade: 5 mg/kg on weeks 0, 2, 6, and every 8 weeks
- **Subjects:** AS subjects, N=125/arm
- **Endpoints:**
  - Primary: Cmax,ss, AUCtau,ss

Study 1.1: PK Results

- PK is similar between CT-P13 and EU-Remicade in AS patients



- 5 mg/kg IV at weeks 0, 2, 6, and every 8 weeks

K Similarity Analysis

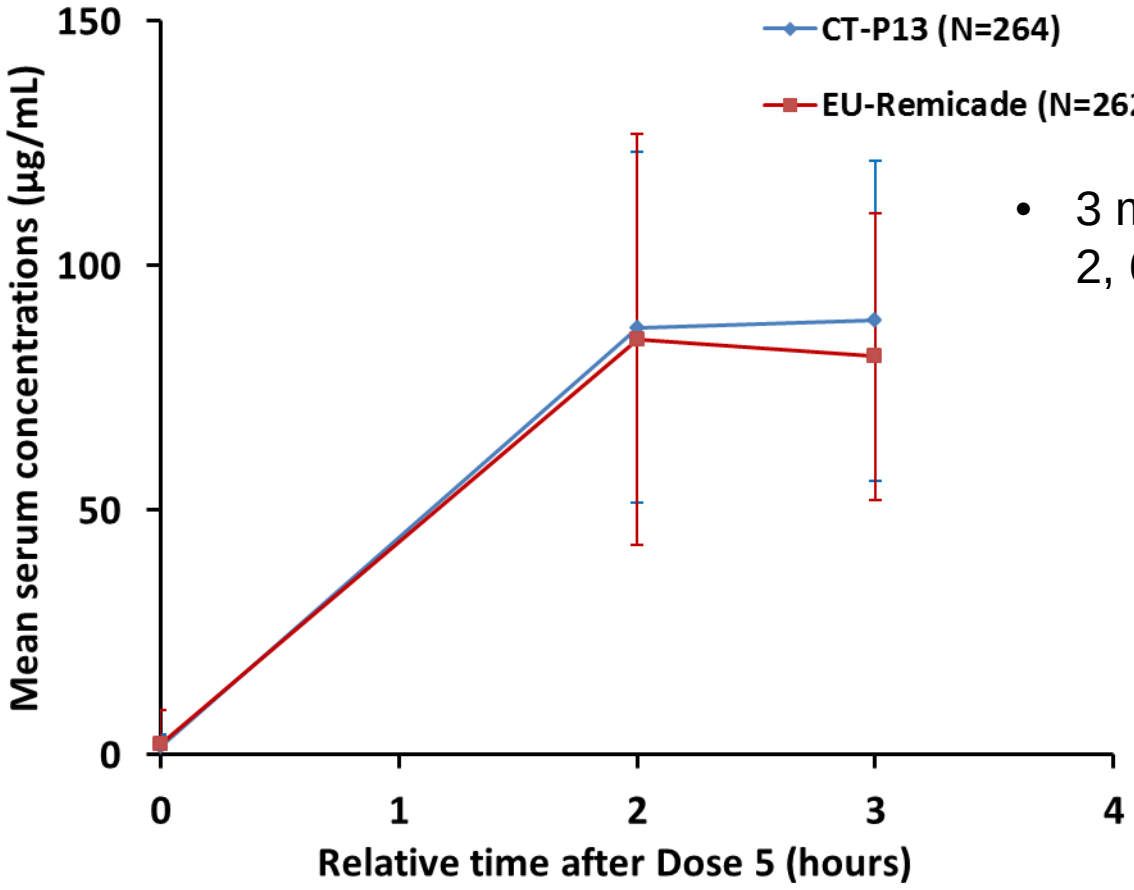
Comparison	PK Variables	GMR 90% CI (%)
CT-P13 vs. EU-Remicade	Cmax,ss	103.53 (97.47, 109.96)
	AUCtau,ss	104.61 (94.80, 115.43)

Study 3.1: Study Design

- **Study Design:** Randomized, double-blind, parallel-group, comparative clinical study in patients with RA
- **Objectives:**
  - Primary: Efficacy
  - Secondary: safety, PK, and immunogenicity
- **Treatments:**
  - CT-P13: 3 mg/kg on Weeks 0, 2, 6, and then every 8 weeks
  - EU-approved Remicade: 3 mg/kg on Weeks 0, 2, 6, and then every 8 weeks
- **Subjects:** RA patients, N=606 (302 on CT-P13, 304 on EU-Remicade)
- **Endpoints:**
  - Primary: ACR20 response at Week 30
- **PK Assessment**: sparse sampling

Study 3.1: PK Results

- Similar PK between CT-P13 and EU-Remicade in RA patients



- 3 mg/kg IV at weeks 0, 2, 6, and every 8 weeks

Clinical Pharmacology Conclusions

- PK similarity was demonstrated between CT-P13 and the US-licensed Remicade
- PK data support the scientific bridge between CT-P13, US-licensed Remicade and EU-approved Remicade to justify the relevance of comparative data generated using EU-approved Remicade
- The overall PK results support the demonstration of no clinically meaningful differences between CT-P13 and US-licensed Remicade

Analytical and PK Bridge Established Between CT-P13, US-licensed Remicade, and EU-approved Remicade

- Applicant has provided the analytical and PK data to establish the scientific bridge between CT-P13, US-licensed Remicade, and EU-approved Remicade to justify the relevance of comparative data generated with EU-approved Remicade

351 (k) BLA 125544
CT-P13, Proposed Biosimilar to US-Licensed Remicade

Clinical Efficacy Review

Arthritis Advisory Committee Meeting
February 9, 2016

Gregory Levin, PhD, Mathematical Statistician
Division of Biometrics II, Office of Biostatistics
Food and Drug Administration

Outline

- Study 3.1 summary
  - Design and analysis plan
  - Results
- Study 1.1 summary
  - Design and analysis plan
  - Results
- Potential statistical issues
- Conclusions

Study 3.1 Design

- 54-week, randomized, double-blind, parallel-group, comparative clinical study in 606 patients with active rheumatoid arthritis (RA) despite methotrexate (MTX) use
  - 1:1 randomization to CT-P13: EU-Remicade
  - Sites in Europe, Asia, Latin America (no U.S. sites)
- Primary endpoint: ACR20 response at Week 30
  - And ability to remain on treatment
- Secondary endpoints included ACR50/70, DAS28, ACR components, radiographic score

Study 3.1 Statistical Analyses

- No correspondence with applicant before data unblinding
- Applicant's planned primary analysis: compare 95% CI for difference in ACR20 response to ±15% margin
  - Margin revised to ±13% based on FDA feedback
- FDA analyses
  - Primary: compare 90% CI to ±12% margin
  - Secondary: 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 weighing clinical importance of different losses in effect against feasibility of different study sizes
  - Lower bound corresponds to retention of ~50% of conservative historical estimates of effect of Remicade
    - FDA meta-analysis: estimated effect of 28% (95% CI: 24%, 33%)
- Lack of agreed-upon margin not problematic because primary analysis rules out ±12% margin

Primary Efficacy Results

ACR20 Response at Week 30

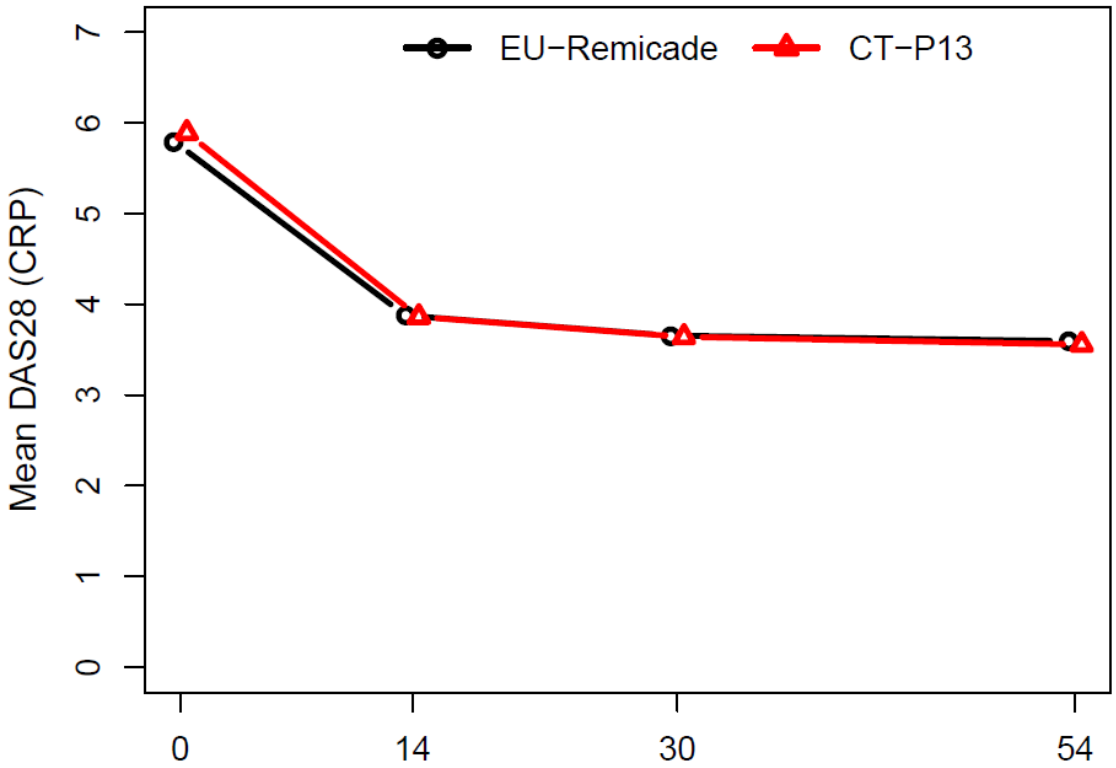
	All Randomized Patients (N=606)	Per-Protocol Population (N=496)
CT-P13	184/302 (61%)	180/246 (73%)
EU-Remicade	178/304 (59%)	174/250 (70%)
Estimated Difference (95% CI)	2% (-6%, +10%)	3% (-5%, +11%)
Estimated Difference (90% CI)	2% (-5%, +9%)	3% (-3%, +10%)

Secondary Efficacy Results

Endpoint (Week 30)	Mean Difference[1] (95% CI)
Swollen joint count (scale: 0–66)	-0.1 (-1.0, 0.7)
Tender joint count (scale: 0–68)	0.2 (-1.2, 1.7)
HAQ physical ability (scale: 0–3)	-0.06 (-0.15, 0.04)
Patient pain (scale: 0–100)	-1.5 (-5.4, 2.4)
Patient global (scale: 0–100)	-1.1 (-5.0, 2.8)
Physician global (scale: 0–100)	-0.6 (-3.9, 2.6)
DAS28 (CRP)	-0.06 (-0.28, 0.16)
Radiographic score (Week 54)	0.7 (-0.4, 1.9)

[1] CT-P13 minus EU-Remicade mean difference, analyses in completers

Mean DAS28 over Time



Number of Patients with Data

EU−Remicade	302	280	259	223
CT−P13	299	276	254	231

Study 1.1 Design and Results

- 54-week, randomized, double-blind, parallel-group study in 250 patients with ankylosing spondylitis (AS)
- Primary objective: PK comparisons
- Secondary objective: efficacy comparison

ASAS20 Response at Week 30

CT-P13 (N=112)	EU-Remicade (N=116)	Odds Ratio (95% CI)	Difference[1] (95% CI)
79 (71%)	84 (72%)	0.91 (0.51, 1.62)	-4% (-16%, +8%)

[1] Supportive FDA analysis in all randomized patients

Study 1.1 Additional Results

Endpoint (Week 30)	Mean Difference[1] (95% CI)
BASDAI score (0–10)	-0.3 (-0.8, 0.3)
BASFI score (0–10)	-0.0 (-0.6, 0.5)
BASMI score (0–10)	-0.1 (-0.4, 0.3)
Spinal pain score (0–100)	1.6 (-4.5, 7.7)
Disease status score (0–100)	-2.5 (-8.4, 3.3)

[1] CT-P13 minus EU-Remicade mean difference, analyses in completers

Disposition and Missing Data

- 23%/27% dropout on CT-P13/EU-Remicade in Study 3.1
  - ~15% withdrawal before Week 30 evaluations
  - Due to design: treatment discontinuation = study withdrawal
- No noticeable difference between arms in dropout patterns
- Missing data potentially problematic for evaluation of ACR20 and other key endpoints (e.g., DAS28) at Week 30 *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

Study 3.1:
ACR20 Tipping Point Results

Shift for CT-P13[1]	Shift for EU-Remicade[1]				
	-0.700	**-0.525**	**-0.350**	**-0.175**	**0.000**
-0.700	0.03 (-0.04, 0.10)	0.00 (-0.07, 0.07)	-0.02 (-0.09, 0.05)	-0.05 (-0.12, 0.02)	-0.07 (-0.14, -0.01)
-0.525	0.06 (-0.01, 0.13)	0.03 (-0.04, 0.10)	0.00 (-0.06, 0.07)	-0.02 (-0.09, 0.05)	-0.05 (-0.11, 0.02)
-0.350	0.08 (0.01, 0.15)	0.06 (-0.01, 0.13)	0.03 (-0.03, 0.10)	0.01 (-0.06, 0.07)	-0.02 (-0.08, 0.05)
-0.175	0.11 (0.04, 0.18)	0.09 (0.02, 0.15)	0.06 (-0.01, 0.12)	0.03 (-0.03, 0.10)	0.01 (-0.06, 0.07)
0.000	0.14 (0.07, 0.21)	0.11 (0.05, 0.18)	0.09 (0.02, 0.15)	0.06 (0.00, 0.13)	0.03 (-0.03, 0.10)

[1] Assumed difference in Week 30 ACR20 response between completers and dropouts. Responses in CT-P13/EU-Remicade completers were 0.72/0.75.

Assay Sensitivity and Constancy

- Assay sensitivity: ability to detect meaningful differences between products (in studied indication) if they exist
- Constancy assumption: historical estimates of effect of Remicade unbiased for setting of comparative study
- Support for assay sensitivity and constancy (ICH E9)
  - Historical sensitivity to drug effects
  - Similar design/conduct between historical and current trials
  - Appropriate trial conduct

Historical Effect of Remicade

Study	Week	N	ACR20 % Response		Absolute Difference in % Response
			MTX + Placebo	MTX + Remicade	
1	30	174	20%	50%	30%
2	22	721	24%	55%	31%
3	28	275	42%	59%	18%
4	18	173	49%	76%	27%
5	14	96	23%	61%	38%
Meta-analysis (95% CI)					28% (24%, 33%)

Appropriate Design and Conduct

- Key characteristics of Study 3.1 largely similar to historical studies showing large, consistent effects of Remicade
  - Inclusion criteria, concomitant meds, baseline characteristics, within-group responses
- Appropriate trial conduct
  - No issues identified except high withdrawal rate
- Totality of information generally supportive of assay sensitivity and constancy

Conclusions

- Large comparative clinical study in RA demonstrated similar efficacy of CT-P13 and EU-Remicade
  - Supported by findings from smaller study in AS
- Potential statistical issues explored
  - Similarity margin selection
  - Impact of missing data
  - Assay sensitivity and constancy assumption
- Collective evidence supports conclusion of no clinically meaningful differences between CT-P13 and US-Remicade with respect to efficacy in studied indications

CT-P13
Clinical Safety and Immunogenicity

Arthritis Advisory Committee
February 9, 2016

Juwaria Waheed, M.D.
Medical Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Food and Drug Administration

Overview of Safety

- Safety population
  - 803 subjects (patients and healthy subjects) exposed to at least one dose of CT-P13
- No new safety signals
  - Types and incidence of TEAEs, SAEs, AE leading to discontinuation were similar
  - Most common TEAEs were infections
  - Most frequent AEs leading to discontinuation: hypersensitivity reactions, infusion-related reactions and infections
- Four deaths occurred across the CT-P13 development program:
  - Two on CT-P13 and two on EU-Remicade
- Anaphylaxis by Sampson criteria*
  - Similar between CT-P13 and EU-Remicade (7 vs. 7 across controlled studies)
  - Did not increase following transition from EU-Remicade to CT-P13
- Immunogenicity
  - Incidence of ADA similar between CT-P13 and EU-Remicade
  - ADA incidence remained unchanged following transitioning from EU-Remicade to CT-P13

*Sampson et.al. J Allergy Clin Immunol 2006; 117:391-7

Overview of Safety: Controlled Studies

	Rheumatoid Arthritis Study 3.1		Ankylosing Spondylitis Study 1.1		Healthy Volunteers Study 1.4		
	CT-P13 3mg/kg (n=302)	EU-Remi 3mg/kg (n=300)	CT-P13 5mg/kg (n=128)	EU-Remi 5mg/kg (n=122)	CT-P13 5mg/kg (n=71)	EU-Remi 5mg/kg (n=71)	US-Remi 5mg/kg (n=71)
Total # of TEAEs	732	738	362	375	67	28	54
# of pts with ≥1 TEAE, n (%)	213 (71)	211 (70)	95 (74)	82 (67)	37 (42)	21 (30)	33 (46)
Total # of SAEs	49	39	12	11	1	1	0
# of pts with ≥1 SAE, n (%)	42 (14)	31 (10)	10 (8)	8 (7)	1 (1)	1 (1)	0
TEAEs leading to discontinuation	40	52	12	9	0	0	0
# of pts (%)	33 (11)	47 (16)	11 (9)	9 (7)			
Infections, n	237	231	91	107	18	12	26
# of pts with ≥1 infection, n (%)	127 (42)	137 (46)	55 (43)	49 (40)	18 (25)	12 (17)	24 (34)
Serious Infections (SIE), n	13	8	2	4	0	0	0
# of pts with ≥1 SIE, n (%)	13 (4)	7 (2)	2 (2)	3 (3)			
Infusion-related reactions (IRR)	12	11	0	4	0	0	0
# of pts with IRR, n (%)	10 (3)	11 (4)	0	4 (3)	0	0	0
Anaphylaxis, n (%)	6 (2)	4 (1)	1 (<1)	3 (2)	0	0	0
Death, n	0	1	1	1	0	0	0

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

Adverse Events of Special Interest: Controlled Studies

	Ankylosing Spondylitis Study 1.1				Rheumatoid Arthritis Study 3.1				Integrated RR (95% CI)
	EU-Remicade (N=122)		CT-P13 (N=128)		EU-Remicade (N=300)		CT-P13 (N=302)		
	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	
Latent TB	6 (5%)	4.6	10 (8%)	7.3	26 (9%)	8.6	28 (9%)	9.3	1.2 (0.7, 1.8)
Active TB	1 (1%)	0.7	2 (2%)	1.4	0	0.0	3 (1%)	0.9	3.2 (0.5, 20.4)
Infection	49 (40%)	48.4	55 (43%)	52.5	137 (46%)	60.4	127 (42%)	53.8	1.0 (0.8, 1.1)
Serious Infection	3 (3%)	2.2	2 (2%)	1.4	7 (2%)	2.2	13 (4%)	4.2	1.4 (0.6, 3.5)
Pneumonia	0	0.0	2 (2%)	1.4	5 (2%)	1.6	8 (3%)	2.5	1.8 (0.6, 5.1)
Malignancy and Lymphoma	0	0.0	2 (2%)	1.4	4 (1%)	1.3	3 (1%)	0.9	1.2 (0.2, 5.7)
Infusion-related Reaction	15 (12%)	11.8	11 (9%)	8.2	43 (14%)	14.8	30 (10%)	9.8	0.7 (0.5, 1.0)
Vascular disorder	1 (1%)	0.7	4 (3%)	2.9	16 (5%)	5.3	25 (8)	8.3	1.7 (0.9, 3.0)
Cardiac disorder	6 (5%)	4.6	5 (4%)	3.6	12 (4%)	3.9	5 (2%)	1.6	0.6 (0.3, 1.2)
Opportunistic Infection	2 (2%)	1.5	0	0.0	6 (2%)	1.9	4 (1%)	1.3	0.6 (0.2, 1.8)

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

[1]Incidence rate of first event per 100 person-years

Adverse Events of Special Interest: Extension Studies

	Ankylosing Spondylitis Study 1.3				Rheumatoid Arthritis Study 3.2				Integrated RR (95% CI)
	CT-P13 → CT-P13 (N=90)		EU-Remi → CT-P13 (N=84)		CT-P13 → CT-P13 (N=159)		EU-Remi →CT-P13 (N=143)		
	n (%)	Rate[1]	n (%)[1]	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	
Latent TB	5 (6%)	4.1	7 (8%)	5.3	11 (7%)	5.0	7 (5%)	3.4	1.0 (0.3, 3.2)
Active TB	1 (1%)	0.8	1 (1%)	0.7	0	0.0	0 (0.0%)	0.0	1.1 (0.1, 16.9)
Infection	23 (26%)	25.4	29 (35%)	30.5	50 (31%)	32.3	47 (33%)	34.9	1.1 (0.9, 1.5)
Serious Infection	2 (2%)	1.5	1 (1%)	0.7	4 (3%)	1.7	3 (2%)	1.4	0.7 (0.2, 2.6)
Pneumonia	0	0.0	0	0.0	1 (1%)	0.4	0	0.0	NA
Malignancy and Lymphoma	1 (1%)	0.8	0	0.0	1 (1%)	0.4	4 (3%)	1.9	1.7 (0.1, 18.6)
Infusion-related Reaction	7 (8%)	5.7	6 (7%)	4.5	11 (7%)	5.0	4 (3%)	1.9	0.6 (0.3, 1.4)
Vascular disorder	3 (3%)	2.3	2 (2%)	1.4	4 (3%)	1.7	3 (2%)	1.4	0.8 (0.3, 2.4)
Cardiac disorder	4 (4%)	3.2	3 (4%)	2.1	1 (1%)	0.4	1 (1%)	0.5	0.9 (0.2, 3.2)
Opportunistic Infection	1 (1%)	0.8	1 (1%)	0.7	1 (1%)	0.4	1 (1%)	0.5	1.1 (0.2, 7.7)

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

[1]Incidence rate of first event per 100 person-years

Immunogenicity Assessment

- Generally, 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
- ADA against infliximab have been implicated in reduced clinical efficacy, hypersensitivity, and infusion reactions*

*Remicade FDA-approved labeling

Incidence of ADA: CT-P13 Controlled and Extension Studies

Proportion of ADA positive subjects	Rheumatoid Arthritis				Ankylosing Spondylitis			
	Study 3.1		OLE Study 3.2		Study 1.1		OLE Study 1.3	
	CT-P13 3mg/kg (N=302) n (%)	EU-Remi 3mg/kg (N=300) n (%)	CT-P13 → CT-P13 3mg/kg (N=159) n (%)	EU-Remi → CT-P13 3mg/kg (N=143) n (%)	CT-P13 5mg/kg (N=128) n (%)	Remicade 5mg/kg (N=122) n (%)	CT-P13 → CT-P13 5mg/kg (N=90) n (%)	EU-Remi → CT-P13 5mg/kg (N=84) n (%)
Screening	9 (3%)	6 (2%)	7 (4%)	4 (3%)	2 (2%)	1 (<1%)	2 (2%)	1 (1%)
Week 14	69 (23%)	70 (23%)	-	-	11 (9%)	13 (11%)	-	-
Week 30	122 (40%)	122 (40%)	-	-	32 (25%)	25 (20%)	-	-
Week 54	124 (41%)	108 (36%)	-	-	25 (20%)	28 (23%)	-	-
Week 78	-	-	71 (44%)	66 (46%)	-	-	21 (23%)	25 (30%)
Week 102	-	-	64 (40%)	64 (45%)	-	-	21 (23%)	23 (27%)

Impact of ADA: CT-P13 Controlled and Extension Studies

- Similar rates of ADA formation between CT-P13 and EU-approved Remicade at multiple timepoints in both RA and AS
- ADA formation had similar impact in both CT-P13 and EU-approved Remicade-treated patients:
  - Similar decreases in PK parameters
  - Similar decreases in ACR responses
  - Similar rates of infusion reactions and anaphylaxis

Immunogenicity in Study 1.4

Assay	The number (%) of ADA positive subjects at different visit	**Study 1.4 Healthy Subjects** (5 mg/kg single dose)		
		CT-P13 (N=71)	EU-Remi (N=71)	US-Remi (N=70)
ECLA	Screening	2 (3%)	1 (1%)	1 (1%)
	Week 8	10 (14%)	5 (7%)	2 (3%)
ELISA	Screening	4 (6%)	0	1 (1%)
	Week 8	19 (27%)	18 (25%)	8 (11%)

The observed ADA difference:

- Lower than expected incidence rate with US-licensed Remicade in this small study:
  - Unexpected, given analytical bridge between all 3 products
  - Published data: US- and EU-Remicade ADA were similar and >25% after single i.v. dose in healthy subjects*
- Did not impact PK differentially
- Did not correlate with infusion reactions or hypersensitivity

*Udata 2014

Immunogenicity in Study 3.4

- Similar ADA incidence between CT-P13 and US-licensed Remicade with repeat standard doses in CD patients

Proportion of ADA positive subjects n (%)	**Study 3.4 Crohn's Disease** (5 mg/kg at week 0, 2, 6, and 14)			
	CT-P13 (N=54)	US-Remicade (N=43)	EU-Remicade (N=12)	Total US + EU Remicade (N=55)
Baseline (Week 0)	1 (2%)	0	0	0
Week 14	8 (14.8%)	5 (12%)	2 (33%)	7 (16%)

Immunogenicity: Conclusions

- Similar immunogenicity was observed:
  - Between CT-P13 and EU-approved Remicade in two different settings, RA and AS, using two approved dosing regimens, 3 and 5 mg/kg, either with or without concomitant immunosuppression
  - Between CT-P13 and US-licensed Remicade in patients with CD (interim analysis results)
- An analytical bridge was established between CT-P13, EU-approved Remicade, and US-licensed Remicade
- The totality of evidence from immunogenicity studies support a demonstration of no clinically meaningful differences between CT-P13 and US-licensed Remicade

Summary of Safety and Immunogenicity

- Safety outcomes, including immunogenicity, were similar between patients treated with CT-P13 or comparator products

- No new safety signals were identified in the CT-P13 clinical program

- The safety and immunogenicity results support the conclusion that there are no clinically meaningful differences between CT-P13 and the US-licensed Remicade

Considerations for Extrapolation of Biosimilarity

Arthritis Advisory Committee
February 9, 2016

Nikolay P. Nikolov, M.D.
Clinical Team Leader
Collaborative Review by DPARP, DDDP, and DGIEP
OND, CDER, FDA

Extrapolation Considerations: Indications for Which CT-P13 is Being Developed

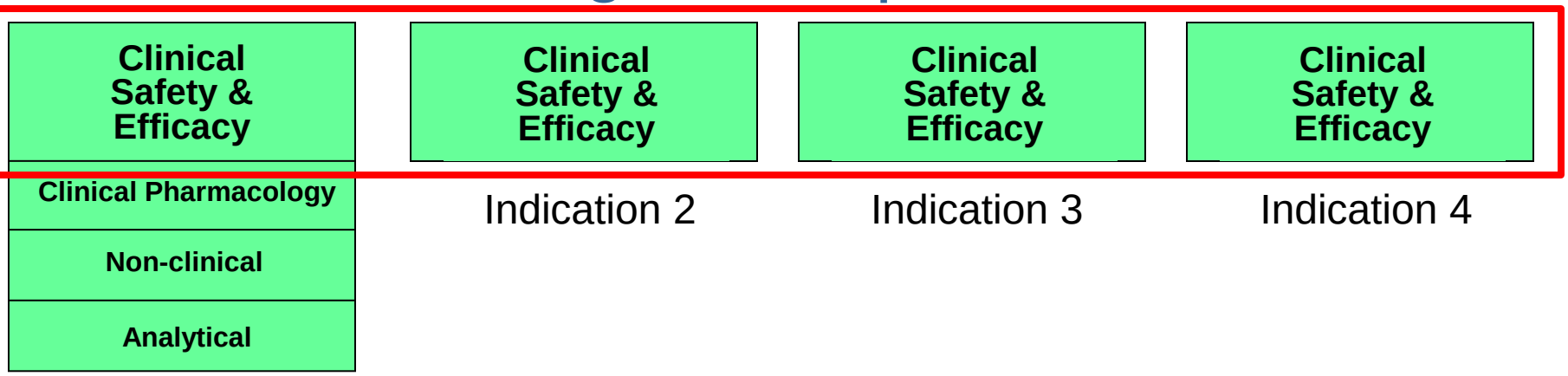
Indications studied in CT-P13 clinical program:

- Rheumatoid Arthritis (RA)
- Ankylosing Spondylitis (AS)

Limited or no clinical data on the use of CT-P13 in:

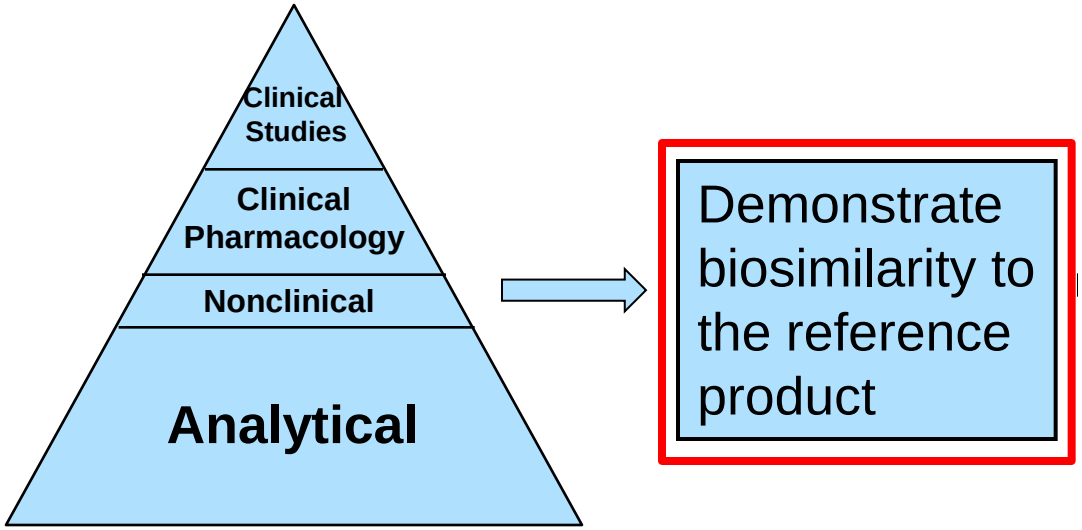
- Psoriatic Arthritis (PsA)
- Plaque Psoriasis (PsO)
- Adults and pediatric Crohn‘s Disease (CD)
- Adults and pediatric Ulcerative Colitis (UC)

Extrapolation Considerations: "Stand-alone" Drug Development



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

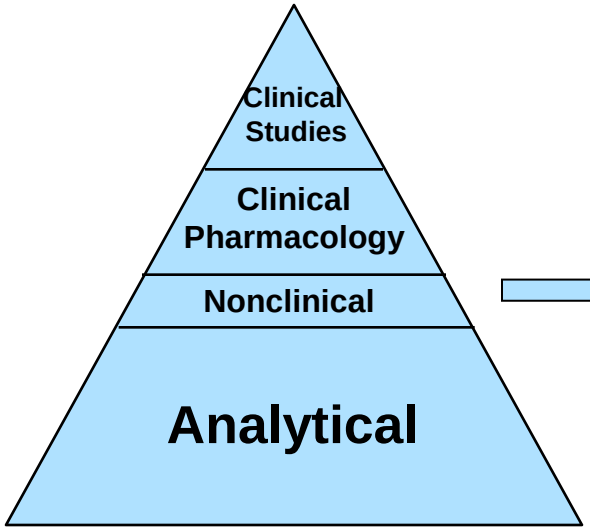
Clinical Safety & Efficacy	Clinical Safety & Efficacy	Clinical Safety & Efficacy	Clinical Safety & Efficacy
Clinical Pharmacology	Indication 2	Indication 3	Indication 4
Non-clinical			
Analytical			



Demonstrate biosimilarity to the reference product

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

Clinical Safety & Efficacy	Clinical Safety & Efficacy	Clinical Safety & Efficacy	Clinical Safety & Efficacy
Clinical Pharmacology	Indication 2	Indication 3	Indication 4
Non-clinical			
Analytical			



Demonstrate biosimilarity to the reference product

Extrapolate, considering for each indication:

- MOA(s)
- PK
- Immunogenicity
- Toxicities

MOA: mechanism of action

Extrapolation Considerations: Totality of the Evidence

- CT-P13 is highly similar to US-licensed Remicade:
  - Primary-, secondary-, and tertiary structure
  - Post-translational profile and *in vitro* functional characteristics
  - Purity and stability
  - Potency, including TNFα binding and neutralization
- No clinically meaningful differences between CT-P13 and US-licensed Remicade based on:
  - Similar clinical pharmacokinetics
  - Similar efficacy, safety, and immunogenicity in RA and AS, using the two approved dosing regimens
- Scientific justification for extrapolation of clinical data to include addressing each known MOAs of Remicade

Extrapolation Considerations: PK in Different Patient Populations

- No notable differences were observed in PK parameters for US-licensed Remicade in CD patients, as compared to patients with other conditions of use, including RA and PsO*
- PK characteristics were similar between pediatric and adult patients with CD or UC following the administration of 5 mg/kg US-licensed Remicade*
- Similar PK profile would be expected for CT-P13 in patients with PsA, PsO, adult and pediatric CD, and adult and pediatric UC

*Remicade FDA-approved labeling

Extrapolation Considerations: Safety and Immunogenicity

- Similar immunogenicity rates were observed:
  - Between CT-P13 and EU-approved Remicade in two different settings, RA and AS, using two approved dosing regimens, 3 and 5 mg/kg, either with or without concomitant immunosuppression
  - Between CT-P13 and US-licensed Remicade in patients with CD
- Similar immunogenicity would be expected for patients with PsA, PsO, adult and pediatric CD, and adult and pediatric UC, receiving CT-P13
- Across different doses and patient populations, the treatment-related toxicities are expected to be similar

Extrapolation Considerations: Known and Potential MOA of Remicade

MOA of Remicade	RA	AS	PsA	PsO	CD Pediatric CD	UC Pediatric UC	Similarity Criteria Met
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:							
Apoptosis of lamina propria activated T cells	-	-	-	-	Likely	Likely	✓
Suppression of cytokine secretion	-	-	-	-	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	✓

* Modest shift in mean activity of CT-P13 vs. reference product, within the established quality range

Extrapolation Considerations: Psoriatic Arthritis and Plaque Psoriasis

- The primary MOA of infliximab in RA, AS, PsA, PsO is TNF-α binding and neutralization
- The potential MOAs for CT-P13 and US-licensed Remicade are the same based on Celltrion's data
- Similar PK, safety, and immunogenicity profiles are expected for CT-P13 in patients with PsA, PsO as seen in RA and AS
- It is reasonable to extrapolate clinical data of CT-P13 from RA and AS to support a determination of biosimilarity of CT-P13 in the PsA and PsO

Extrapolation Considerations: Inflammatory Bowel Disease

- ADCC is within the quality range of the reference product
- The MOA of TNF inhibitors in treating IBD is complex and ADCC is only one of several plausible mechanisms of action
- Clinical trials supporting the original approvals in IBD used doses that were in the therapeutic plateau and no exposure-response relationship was observed during efficacy assessments; thus, clinical outcome measures (e.g., clinical response, clinical remission) lack discriminative capacity to assess the effect of small differences in NK-based ADCC and FcγRIII binding

Extrapolation Considerations: Inflammatory Bowel Disease

- TNF-α binding and potency to neutralize TNF-α, reverse signaling, and Fc region-mediated potential mechanisms of action are highly similar between CT-P13 and US-licensed Remicade, supporting the demonstration of same potential mechanisms of actions for IBD
- Similar PK, safety, and immunogenicity profiles are expected for CT-P13 in patients with IBD as seen in RA and AS
- It is reasonable to extrapolate clinical data of CT-P13 from RA and AS to support a determination of biosimilarity of CT-P13 in the IBD indications

Summary of FDA Findings

- The totality of the evidence, provided by Applicant, supports a conclusion that:
  - CT-P13 is biosimilar to US-licensed Remicade based on data to demonstrate:
    - CT-P13 is highly similar to US-licensed Remicade
    - No clinically meaningful differences exist between CT-P13 and US-licensed Remicade
  - Scientific justification for extrapolating the clinical data supports a finding of biosimilarity for all indications for which US-licensed Remicade is licensed

Thank you!

FDA Arthritis Advisory Committee Meeting
Charge to the Committee

351(k) BLA for CT-P13, a Proposed Biosimilar to US-licensed Remicade

February 9, 2016

Nikolay P. Nikolov, M.D.
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

- CT-P13 is highly similar to US-licensed Remicade:
  - Primary-, secondary-, and tertiary structure
  - Post-translational profile and *in vitro* functional characteristics
  - Purity and stability
  - Potency, including TNF-α binding and neutralization
- No clinically meaningful differences between CT-P13 and US-licensed Remicade based on:
  - Similar clinical pharmacokinetics
  - Similar efficacy, safety, and immunogenicity in RA and AS, using two approved dosing regimens
- Scientific justification for extrapolation of clinical data to the indications sought for licensure

Question 1 (Discussion)

- Does the Committee agree that CT-P13 is highly similar to the reference product, US-licensed Remicade, notwithstanding minor differences in clinically inactive components?

Question 2 (Discussion)

- Does the Committee agree that there are no clinically meaningful differences between CT-P13 and US-licensed Remicade in the studied conditions of use (RA and AS)?

Question 3 (Discussion)

- Does the Committee agree that there is sufficient scientific justification to extrapolate data from the comparative clinical studies of CT-P13 in RA and AS to support a determination of biosimilarity of CT-P13 for the following additional indications for which US-licensed Remicade is licensed (PsA, PsO, adult and pediatric CD, and adult and pediatric* UC)?
- If not, please state the specific concerns and what additional information would be needed to support extrapolation. Please discuss by indication if relevant.

*Remicade's indication for pediatric UC is protected by orphan drug exclusivity expiring on September 23, 2018. FDA is interested in the Committee's views regarding the scientific justification for extrapolation for this indication, but FDA is not asking the Committee to vote on licensure of CT-P13 for pediatric UC because FDA will not be able to license a proposed biosimilar product for this indication until the orphan exclusivity expires.

Question 4 (Voting)

- Does the Committee agree that based on the totality of the evidence, CT-P13 should receive licensure as a biosimilar product to US-licensed Remicade for each of the indications for which US-licensed Remicade is currently licensed and CT-P13 is eligible for licensure (RA, AS, PsA, PsO, adult CD, pediatric CD, adult UC)?

  a. Please explain the reason for your vote. If you voted no, explain whether this was applicable to all or some of the indications and why.

Considerations for Extrapolation of Biosimilarity

BACKUP Slides Shown

Arthritis Advisory Committee
February 9, 2016

Nikolay P. Nikolov, M.D.
Clinical Team Leader
Collaborative Review by DPARP, DDDP, and DGIEP
OND, CDER, FDA

Extrapolation Considerations: FcγRIIIA-V158F Polymorphism

- Louis et al (2004) proposed FcγRIIIA-V158F polymorphism to be associated with differential responses to infliximab in 200 consecutive CD patients

- Louis et al (2006), in a subanalysis of 344 CD patients from ACCENT I study, found:
  - No association between FcγRIIIA-V158F polymorphism and clinical response to infliximab
  - A trend towards a greater decrease in CRP after infliximab in V/V homozygotes

CRP: C-reactive Protein

Extrapolation Considerations: FcγRIIIA-V158F Polymorphism

		FCGR3A genotype				
		Total (n=102)	VV (n=12, 11.7 %)	VF (n=38, 37.3 %)	FF (n=52, 51 %)	p Value
0 week	CDAI	239.2	236.8	250.9	231.5	n.s.
	CRP	3	4.84	2.68	2.79	n.s.[a]
8 weeks	CDAI	88.9	81.6	86.1	92.7	n.s.
	ΔCDAI	150	155.2	162.4	132.8	n.s.
	ΔCDAI%	62.6	66.2	65.7	59.5	n.s.
	CRP	0.44	0.49	0.41	0.46	n.s.[a]
	ΔCRP	2.58	4.35	2.34	2.33	<0.001
	ΔCRP%	67.7	83.8	65.8	65.1	0.044
30 weeks	CDAI	126.5	110.7	147.4	118	n.s.
	ΔCDAI	118	135	108.7	119.2	n.s.
	ΔCDAI%	36.9	33.9	34.2	39.5	n.s.
	CRP	1.06	1.25	1.24	0.89	n.s.
	ΔCRP	1.95	3.59	1.53	1.83	n.s.
	ΔCRP%	16.1	39.1	−37.2	47.4	n.s.

Moroi R et al, Immunogenetics 2013

Extrapolation Considerations: FcγRIIIA-V158F Polymorphism

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Moroi R et al, Immunogenetics 2013

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	ΔCDAI%	62.6	66.2	65.7	59.5	n.s.
	CRP	0.44	0.49	0.41	0.46	n.s.[a]
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30 weeks	CDAI	126.5	110.7	147.4	118	n.s.
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	ΔCDAI%	36.9	33.9	34.2	39.5	n.s.
	CRP	1.06	1.25	1.24	0.89	n.s.
	ΔCRP	1.95	3.59	1.53	1.83	n.s.
	ΔCRP%	16.1	39.1	−37.2	47.4	n.s.

Moroi R et al, Immunogenetics 2013