CT-P13 (Infliximab Biosimilar)

Arthritis Advisory Committee

February 9, 2016

CELLTRION, Inc.

Introduction

Elizabeth Pollitt, PhD

Vice President

Head of CMC for Regulatory Affairs

CELLTRION, Inc.

Agenda

Introduction **Structural and Functional Studies** **Non-Clinical Studies**	**Elizabeth Pollitt, PhD** Vice President Head of CMC for Regulatory Affairs **CELLTRION, Inc.**
Clinical Review **Pharmacology, Immunology, Efficacy and Safety** **Totality of Evidence**	**Alex Kudrin, MD, PhD, MBA** Vice President Head of Clinical Development **CELLTRION, Inc.**
Use of CT-P13 in IBD	**Peter Lakatos, MD** Associate Professor Head of Gastroenterology/Hepatology **Semmelweis University**
Clinical Perspective	**Vibeke Strand, MD, MACR, FACP** Adjunct Clinical Professor Division of Immunology/Rheumatology **Stanford University**

External Responders

- **Shomron Ben-Horin, MD**
  Associate Professor of Medicine
  Director of IBD Service, Gastroenterology
  Sheba Medical Center & Tel-Aviv
  University Tel-Aviv, Israel

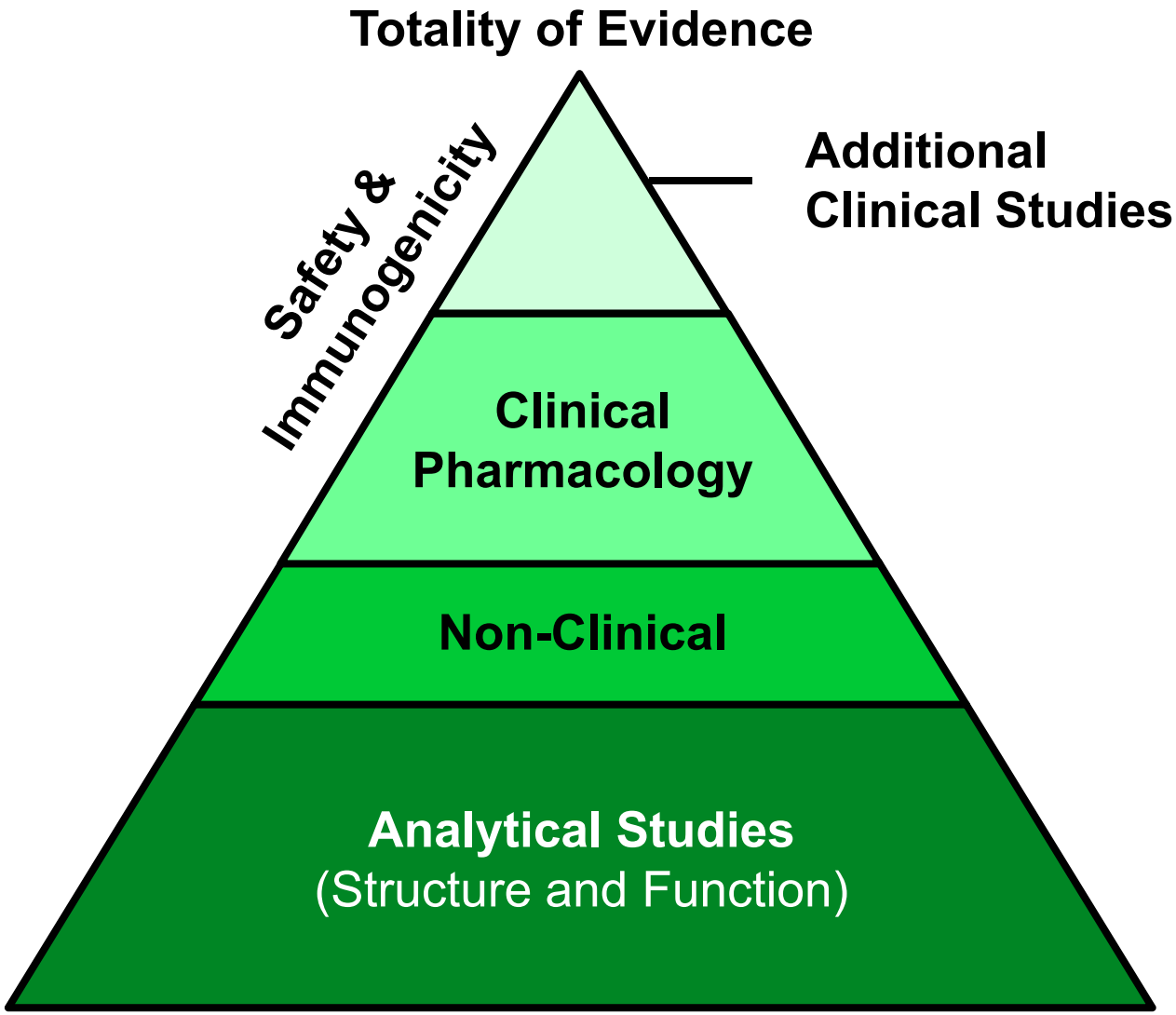
- **Stephen B. Hanauer, MD, FACG**
  Professor of Medicine
  Gastroenterology and Hepatology
  Northwestern Feinberg School of Medicine
  Medical Director, Digestive Health Center
  Chicago, IL, USA

- **Michael McGuckin, PhD**
  Professor & Deputy Director
  Mater Research Institute
  University of Queensland, Australia

- **Falk Nimmerjahn, PhD**
  Professor of Genetics & Immunology
  University of Erlangen-Nuremberg
  Erlangen, Germany

- **Kevin Winthrop, MD, MPH**
  Associate Professor
  Divisions of Infectious Diseases
  Public Health and Preventive Medicine
  Oregon Health and Science University
  Portland, OR, USA

Stepwise Path to Demonstrate Biosimilarity and Address Residual Uncertainty



CT-P13 Development Program Fulfills Regulatory Requirements

Requirement	CT-P13 BLA Fulfillment of Requirement
Reference Product	US Remicade® (infliximab)
Analytical Data	Demonstrated highly similar structure and function
Non-Clinical Studies	Confirmed similar pharmacology and toxicology
Clinical Studies	Compared PK/PD, immunogenicity, efficacy, safety
Mechanism of Action	Principally mediated by binding and neutralization of soluble and transmembrane TNFα
Conditions of Use	Same as reference product[1]
Route of Administration, Dosage Form & Strength	Same as reference product
Fulfillment of "Biosimilar" Definition	High structural and functional similarity with no clinically meaningful differences
Fulfillment of Bridging Criteria	3-way analytical data 3-way PK similarity data

[1] Not seeking interchangeability

Totality of Data Support Extrapolation Across All Indications

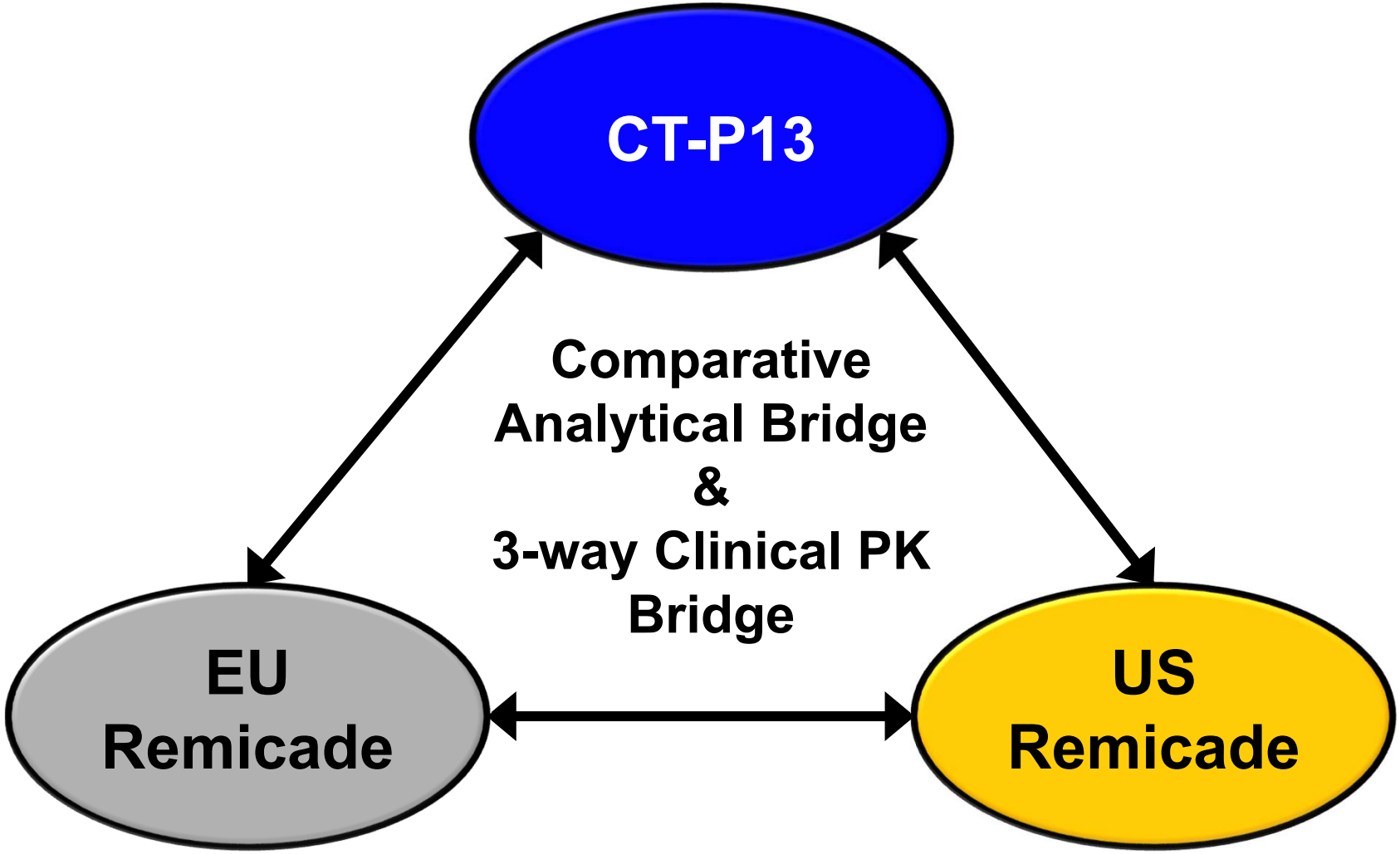
Biosimilar Guidance[1]	Scientific Justification
MoA for Each Indication	▪ Consistent pathogenesis across indications ▪ Common MoA across indications ▪ Comparative structural and functional assays support biosimilarity and comparable MoA
PK and Bio-distribution Across Indications	▪ Well-characterized linear PK across clinical indications as studied in 3 distinct populations
Immunogenicity in Different Populations	▪ Similar immunogenicity and immunogenicity-related safety in studied populations
Expected Toxicities in Indicated Population	▪ Well-characterized Remicade®[2] safety profile across indications ▪ Similar safety in sensitive populations
Other Factors that May Affect Safety or Efficacy	(none determined)

[1] Adapted from FDA Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (2015)
[2] Throughout the remainder of this presentation, symbols indicating proprietary names (®, TM) are not displayed. The appearance of product names without these symbols does not imply that these names are not protected.

CT-P13 Global Data Package Supportive of Biosimilarity

Requirement	Relevant CT-P13 Studies	Remicade Source	Indication
Analytical Data	▪ Structural and physicochemical tests ▪ Functional and biological assays	EU	All
MoA	▪ Extensive analysis of MoA	EU	All
Non-Clinical	▪ Cross-reactivity, PK and toxicology studies	EU	n/a
PK/PD	▪ Repeat dose PK/PD assessments	EU	AS, RA
Immunogenicity	▪ Cross-immune reactivity ▪ ADA data in CD patients ▪ Repeat dose PK assessment	US/EU US/EU EU	IBD IBD AS, RA
Clinical Safety and Efficacy	▪ Repeat dose efficacy and safety studies	EU	RA

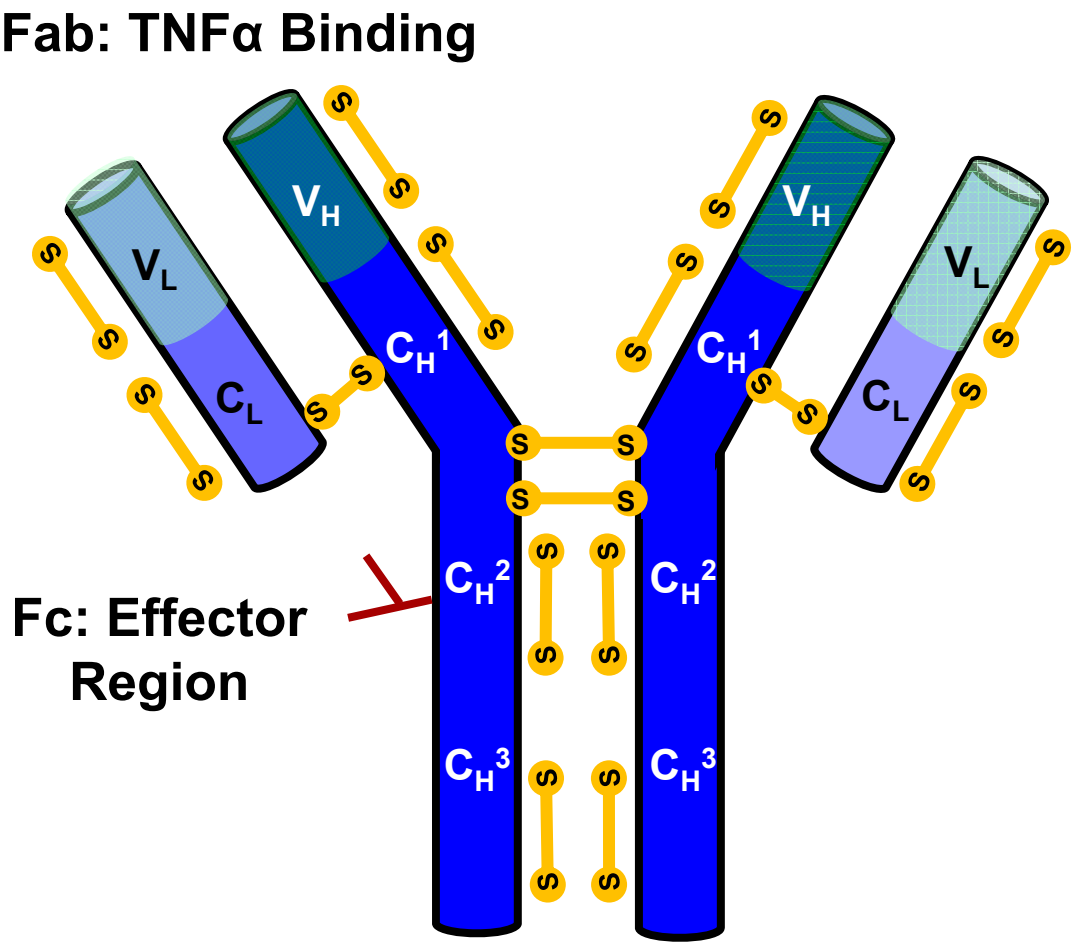
Scientific Bridge to US Remicade



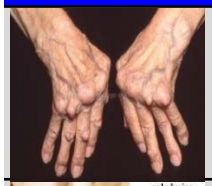
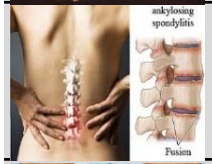
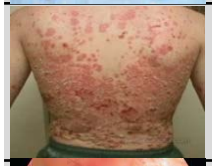
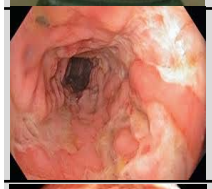
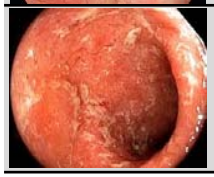
Remicade is a TNFα Inhibitor Used in US for 18 Years

- Therapeutic effect mediated by TNFα blockade
- Structure and function well-understood
- Well-characterized, linear PK
- Established efficacy and safety profile
- Experience in > 4.2 million patients
- Clinical guidelines support use in all indications

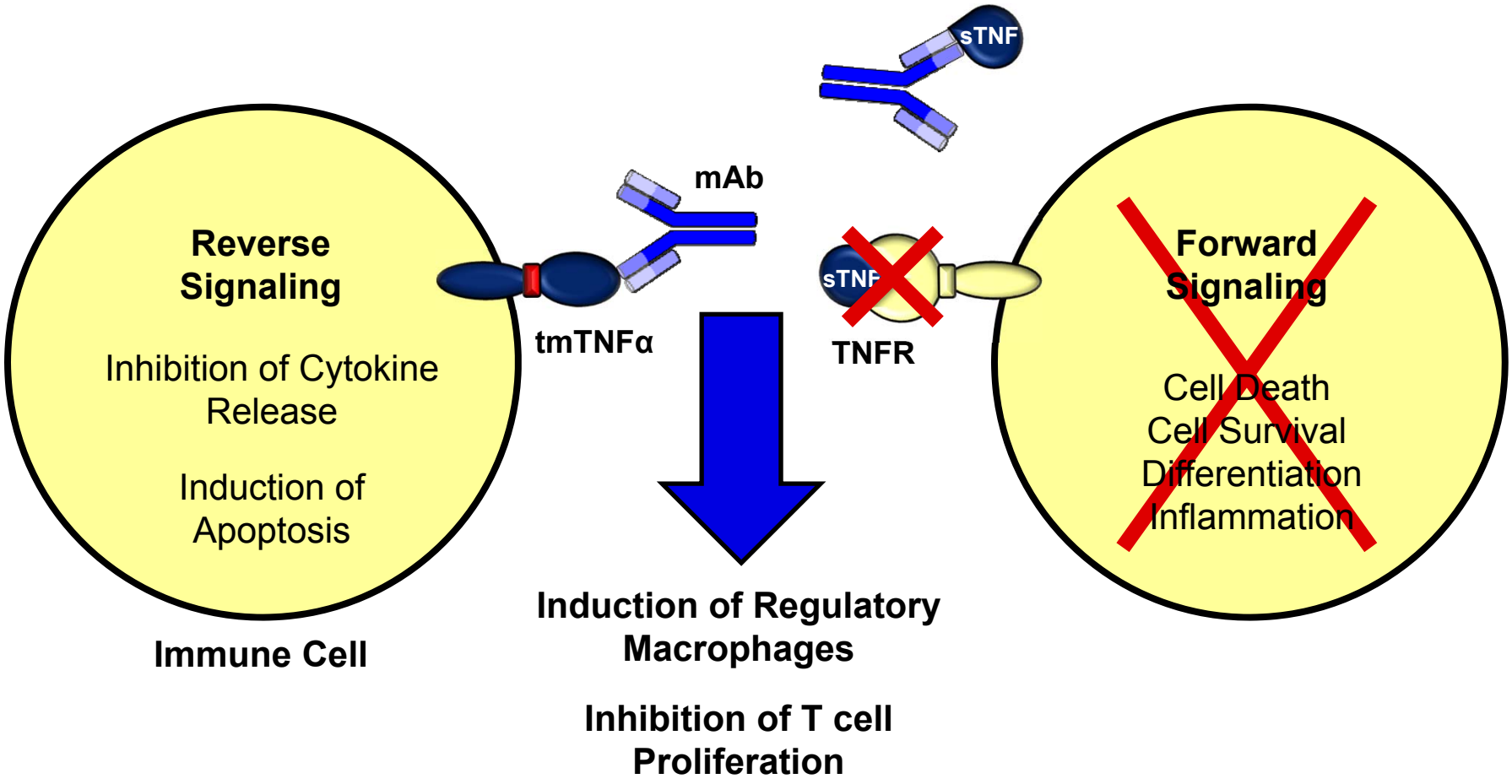
Structure of Remicade (Infliximab) is Well-Characterized



CT-P13 Proposed Indications, Dosing & Administration Identical to Remicade

	Indication	Regimen	Dosage & Administration
	**Rheumatoid Arthritis (RA)**	In combination with methotrexate (moderately to severely active disease)	3 mg/kg at Week 0, 2, 6 → q8wk (up to 10 mg/kg or q4wk)
	**Ankylosing Spondylitis (AS)**	Active disease	5 mg/kg at Week 0, 2, 6 → q6wk
	**Psoriatic Arthritis (PsA)**	Option for combination with methotrexate	5 mg/kg at Week 0, 2, 6 → q8wk
	**Plaque Psoriasis (Ps)**	Chronic severe	
	**Crohn's Disease (CD)**	Adult and pediatric patients (moderately to severely active disease and inadequate response to conventional therapy)	5 mg/kg at Week 0, 2, 6 → q8wk (up to 10 mg/kg q8wk)
	**Ulcerative Colitis (UC)**		5 mg/kg at Week 0, 2, 6 → q8wk

Infliximab Binding and Neutralization of sTNFα and tmTNFα



CT-P13 Analytical Studies

Structural and Physicochemical

Functional and Biological

Biosimilarity Studies Conducted Comparing CT-P13, EU, US Remicade

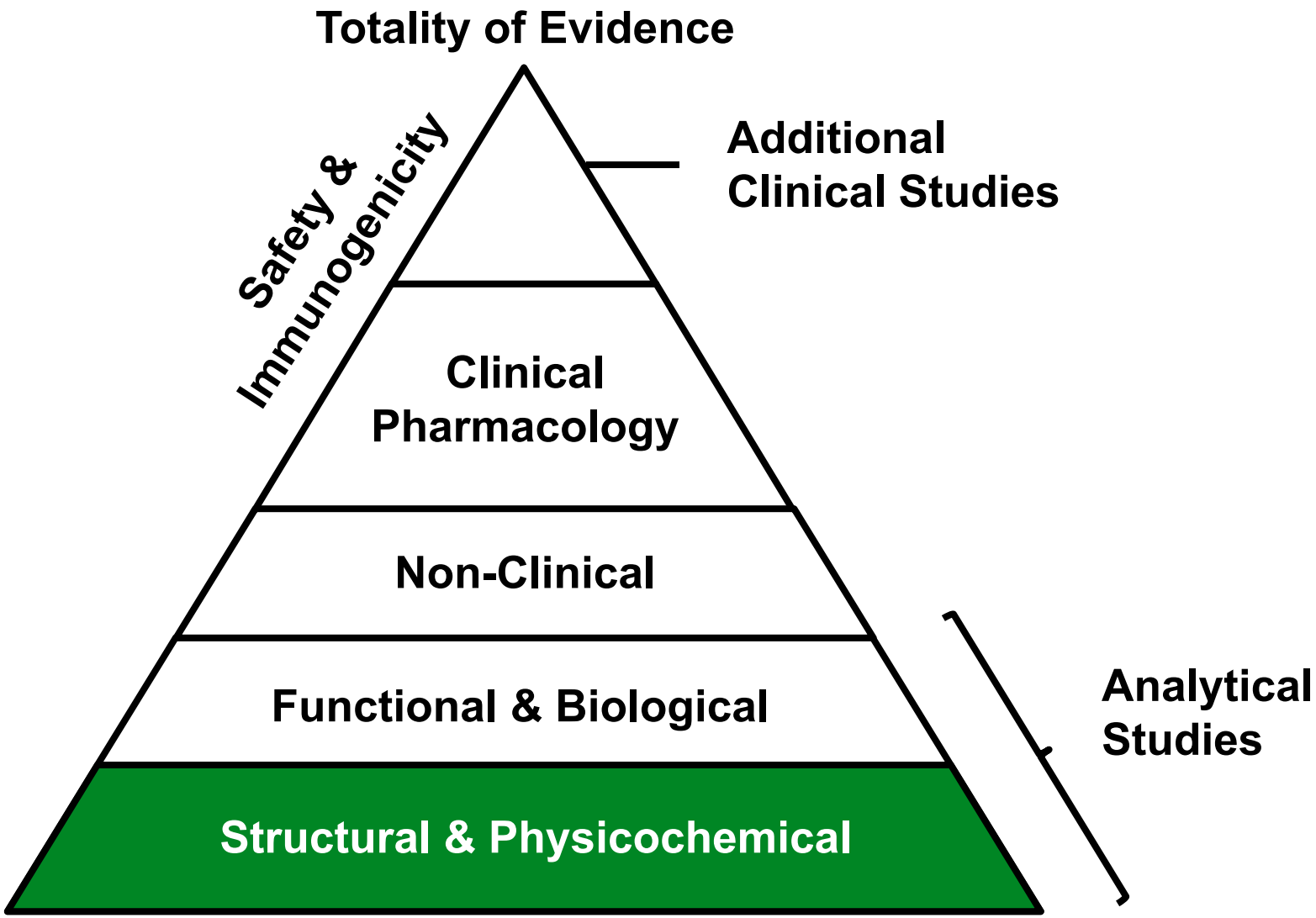
- Analytic biosimilarity studies (3-way)
  - CT-P13 vs. US Remicade
  - EU Remicade vs. US Remicade

Statistical Analysis Recommended by FDA for Analytical Similarity

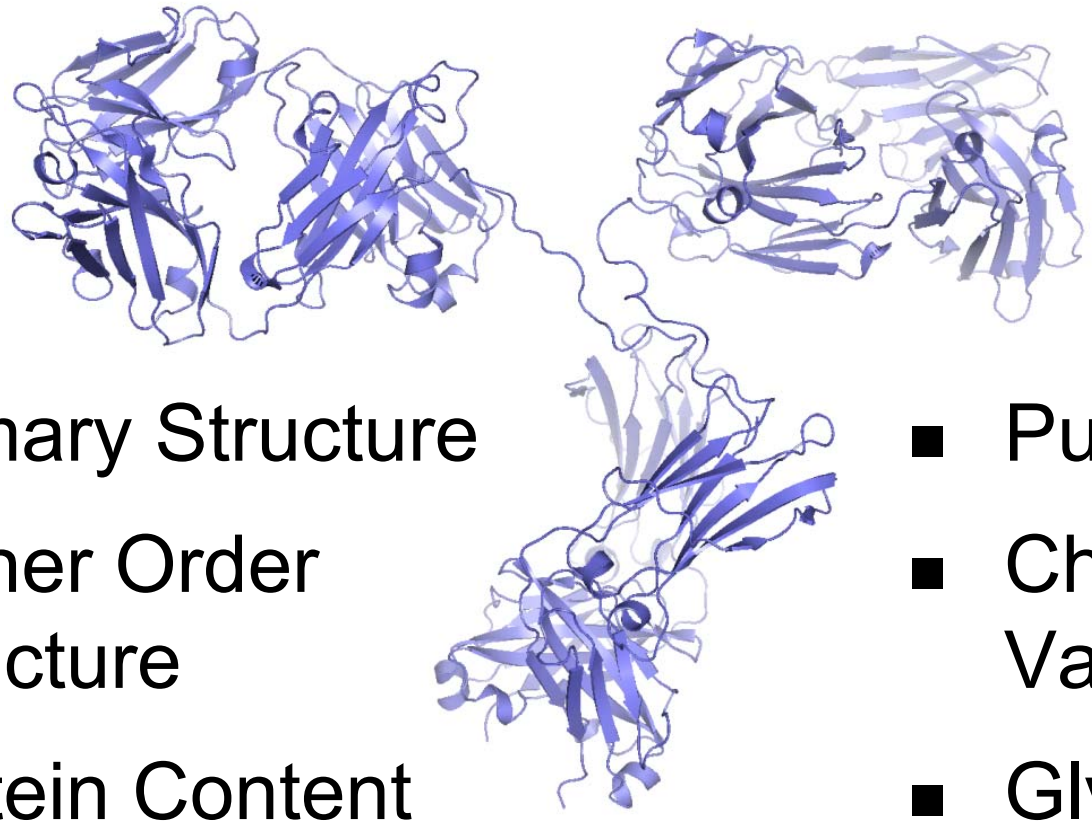
Quality Attribute	Test[1]	Limits
Most Relevant to Primary MoA or PK	Equivalence test: 90% CI of mean difference	$\pm 1.5\sigma_R$
Less Relevant to Primary MoA or PK	≥ 90% lots within quality range	± 3SD
Qualitative Test	Presentation of raw/ graphical data	Visual

[1] Tsong *et al*., 2015.

Structural & Physicochemical Biosimilarity Studies



Analysis of Quality Attributes Using Orthogonal Analytical Methods



- Primary Structure
- Higher Order Structure
- Protein Content
- Purity/Impurity
- Charge Variants
- Glycosylation

Analytical Methods in Structural and Physicochemical Biosimilarity Studies

Primary Structure

- Peptide Mapping (HPLC)
- Peptide Mapping (LC-MS)
  - Deamidation – HC Asn57, HC Asn318, HC Asn364, HC Asn387, LC Asn41
  - Oxidation – HC Met255
  - C-terminal variant – HC Lys450
- Intact Mass (LC-MS)
  - Light chain
  - Heavy chain K0 – G0, G0F, G1F, G2F
  - Heavy chain K1 – G0F, G1F, G2F
- Amino Acid Analysis/Molar Absorptivity
  - Aspartic acid, Glutamic acid, Serine, Histidine, Glycine, Threonine, Arginine, Alanine, Tyrosine, Valine, Methionine, Phenylalanine, Isoleucine, Leucine, Lysine, Proline, Molar Absorptivity, Extinction Coefficient
- N-terminal Sequencing
  - Heavy chain
  - Light chain
- C-terminal Sequencing
  - Heavy chain
  - Light chain

Higher Order Structure

- FTIR
  - Amide I
  - Amide II
  - A
  - B
  - C
- DSC
  - Transition 1
  - Transition 2
  - Transition 3
- CD
- Free Thiol Analysis
- Disulfide Bond
  - H3-H12: 22-98
  - H15-H16: 147-203
  - H20-L19: 223-214
  - H21-H21: 229-229/232-232
  - H23-H29: 264-324
  - H37-H42: 370-428
  - L2-L7: 23-88
  - L10-L17: 134-194
- Antibody Array

Content

- Protein Concentration (UV_{280})

Glycosylation

- HPAEC-PAD
  - G0F, Man5, G0, G1F, G2F, SA1, SA2
- NP-UPLC
  - G0F-GN, G0, G0F, MAN5, G1F-GN, G1, G1F, G1F', G2, G2F, G1-GN+NGNA, G1F-GN+NGNA, G1F+NGNA, G1F'+NGNA, G2+NGNA, G2F+NGNA, G2F+2NGNA, Unknown species
- N-linked Glycan Analysis
  - Man5, G0F-GlcNAc. G0, G0F, G1F, G2F, G1F1NeuGc, G2F1NeuGc
- Sialic Acid Analysis
- Monosaccharide Analysis
  - Fuc, GlcNAc, Gal, Man
- Glycation (LC-ES-MS)
  - Light chain
  - Heavy chain

Purity/Impurity

- SEC-HPLC
  - Monomer
  - Dimer
- SEC-MALS
  - Monomer
  - Dimer
  - Monomer (MW)
  - Dimer (MW)
- AUC
  - Monomer
  - Higher species
- Non-reduced/Reduced CE-SDS
  - Intact IgG (NR)
  - H+L (R)
  - Non-glycosylated HC (R)
- Sub-visible particles (MFI & HIAC)

Charge Variants

- IEF
- IEC-HPLC
  - Peak 1, Peak 2, Peak 3, Peak 4, Peak 5, Peak 6

Excipients

- pH
- Polysorbate 80
- Sucrose

Conclusion of Statistical Analysis of Structure: EU vs. US Remicade

Attribute	Clinical Relevance	Test	EU vs. US Bridge (High Similarity)
Primary Structure	Efficacy, Safety, Immunogenicity	Peptide Mapping (HPLC)	Yes
		Peptide Mapping with LC-MS	No[1]
		Intact Mass (Reduced) (LC-MS)	Yes
		Amino Acid Analysis	Yes
		Extinction Coefficient	Yes
		N-terminal Sequencing	Yes
		C-terminal Sequencing	Yes
Higher Order Structure	Efficacy & Immunogenicity	Fourier Transform Infrared Spectroscopy (FTIR)	Yes
		Differential Scanning Calorimetry (DSC)	Yes
		Circular Dichroism (CD)	Yes
		Free Thiol Analysis	Yes
		Disulfide Bond	Yes
		Antibody Array	Yes
Content	Efficacy (PK)	Protein Concentration (UV_{280})	Yes
Purity/ Impurity	Efficacy & Immunogenicity	Size-exclusion Chromatography (SEC)-HPLC	Yes
		Size-exclusion Chromatography (SEC)-MALS	Yes
		Analytical Ultracentrifugation (AUC)	Yes
		Sub-visible Particles (MFI & HIAC)	Yes
	Efficacy	Non-reduced Capillary Electrophoresis (CE)-SDS	Yes
		Reduced Capillary Electrophoresis (CE)-SDS	Yes
Charge Variants	Efficacy	Isoelectric Focusing (IEF)	Yes
		Ion Exchange Chromatography (IEC)-HPLC	No[2]
Glyco-sylation	Immunogenicity	High Performance Anion Exchange Chromatography (HPAEC-PAD)	Yes
		Normal Phase-Ultra Performance Liquid Chromatography (NP-UPLC)	Yes
		N-linked Glycan Analysis	No[3]
		Sialic Acid Analysis	Yes
		Monosaccharide Analysis	Yes
		Glycation	Yes
Excipients	Efficacy, Safety, Immunogenicity	pH, Polysorbate 80, Sucrose	Yes

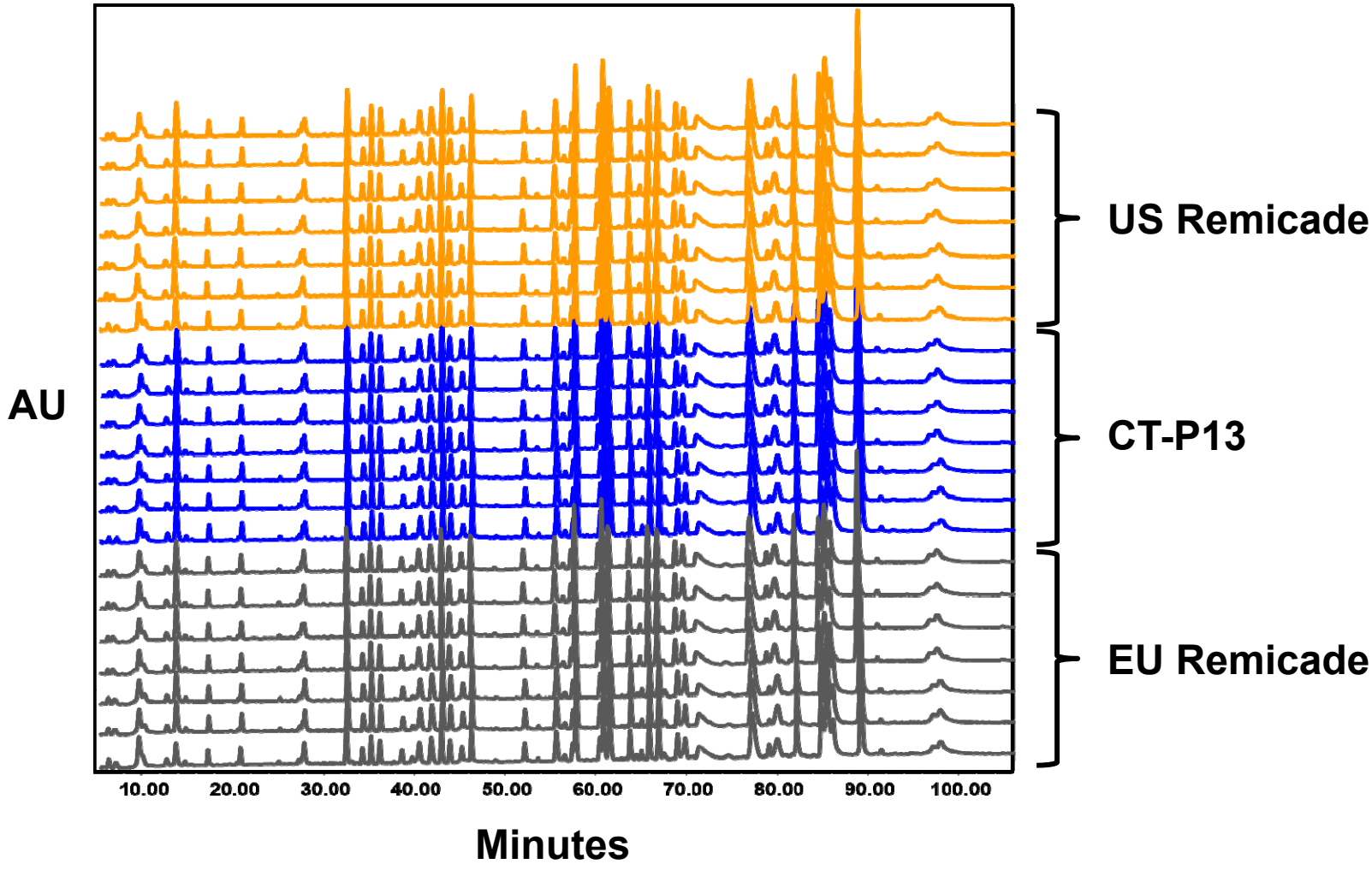
Yes: within quality range; [1] 88% - C-terminal lysine; [2] 70% - Peak 3 & 6, 80% - Peak 5; [3] 88% - G0 & G1F1NeuGc

Conclusion of Statistical Analysis of Structure: CT-P13 vs. US Remicade

Attribute	Clinical Relevance	Test	CT-P13 vs. US (High Similarity)
Primary Structure	Efficacy, Safety, Immunogenicity	Peptide Mapping (HPLC)	Yes
		Peptide Mapping with LC-MS	Yes
		Intact Mass (Reduced) (LC-MS)	Yes
		Amino Acid Analysis	Yes
		Extinction Coefficient	Yes
		N-terminal Sequencing	Yes
		C-terminal Sequencing	Yes
Higher Order Structure	Efficacy & Immunogenicity	Fourier Transform Infrared Spectroscopy (FTIR)	Yes
		Differential Scanning Calorimetry (DSC)	Yes
		Circular Dichroism (CD)	Yes
		Free Thiol Analysis	Yes
		Disulfide Bond	Yes
		Antibody Array	Yes
Content	Efficacy (PK)	Protein Concentration (UV_{280})	Yes
Purity/ Impurity	Efficacy & Immunogenicity	Size-exclusion Chromatography (SEC)-HPLC	No[1]
		Size-exclusion Chromatography (SEC)-MALS	No[1]
		Analytical Ultracentrifugation (AUC)	Yes
		Sub-visible Particles (MFI & HIAC)	Yes
	Efficacy	Non-reduced Capillary Electrophoresis (CE)-SDS	No[1]
		Reduced Capillary Electrophoresis (CE)-SDS	Yes
Charge Variants	Efficacy	Isoelectric Focusing (IEF)	Yes
		Ion Exchange Chromatography (IEC)-HPLC	No[2]
Glyco-sylation	Immunogenicity	High Performance Anion Exchange Chromatography (HPAEC-PAD)	No[3]
		Normal Phase-Ultra Performance Liquid Chromatography (NP-UPLC)	No[4]
		N-linked Glycan Analysis	No[5]
		Sialic Acid Analysis	Yes
		Monosaccharide Analysis	Yes
		Glycation	No[6]
Excipients	Efficacy, Safety, Immunogenicity	pH, Polysorbate 80, Sucrose	Yes

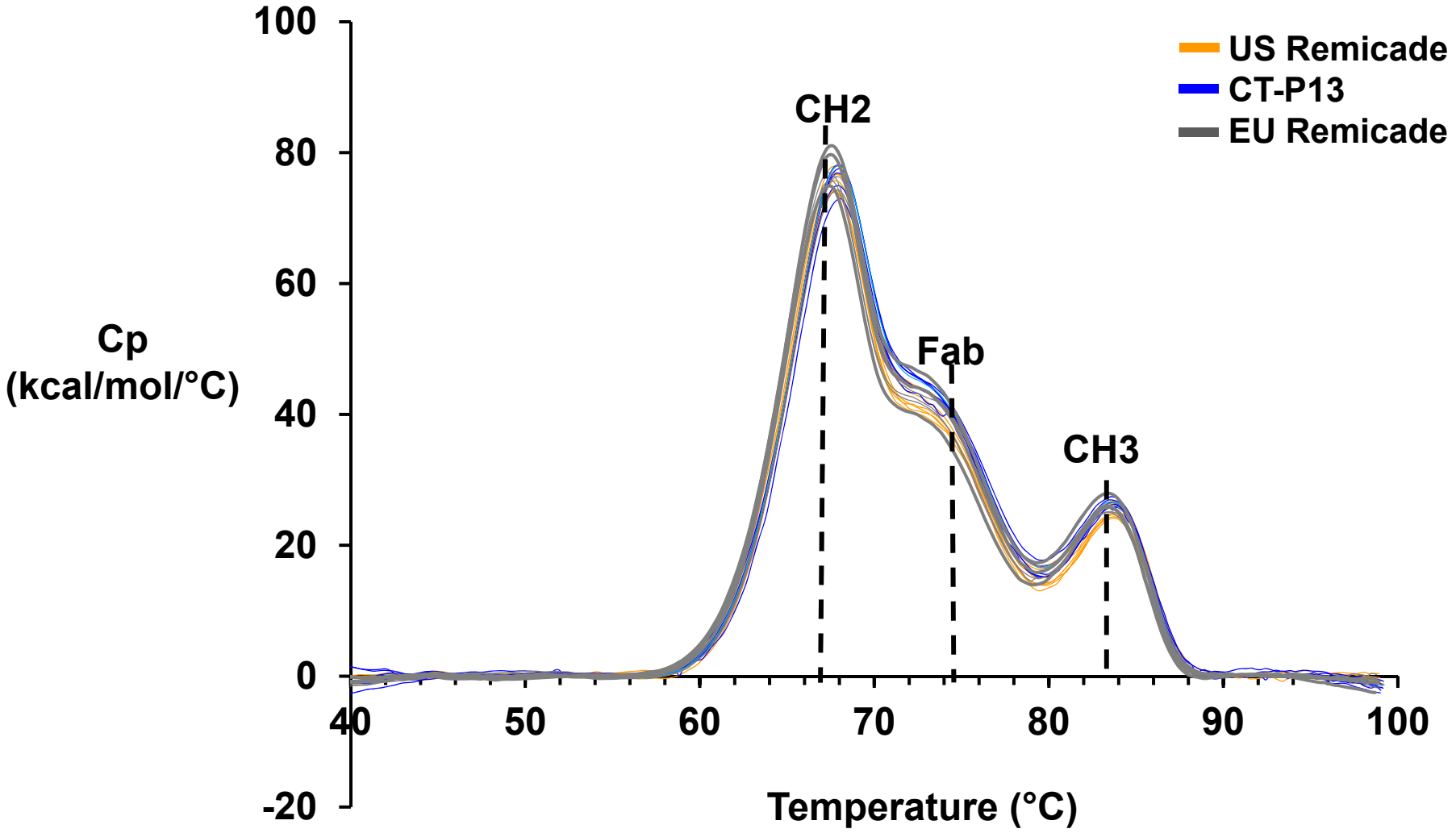
Yes: within quality range; [1] 0%; [2] 40% - Peak 1, 0% - Peak 4; [3] 9% - G0; [4] 0% - G0, G1F&G1FGN, 4% - G1F'+NGNA, 87% - G1&G2F+NGNA, 39% - G2F+2NGNA; [5] 0% - G0, G1F1NGNA & G2F1NGNA; [6] 0% LC, 0% HC

Primary Structure: Peptide Mapping by HPLC[1]

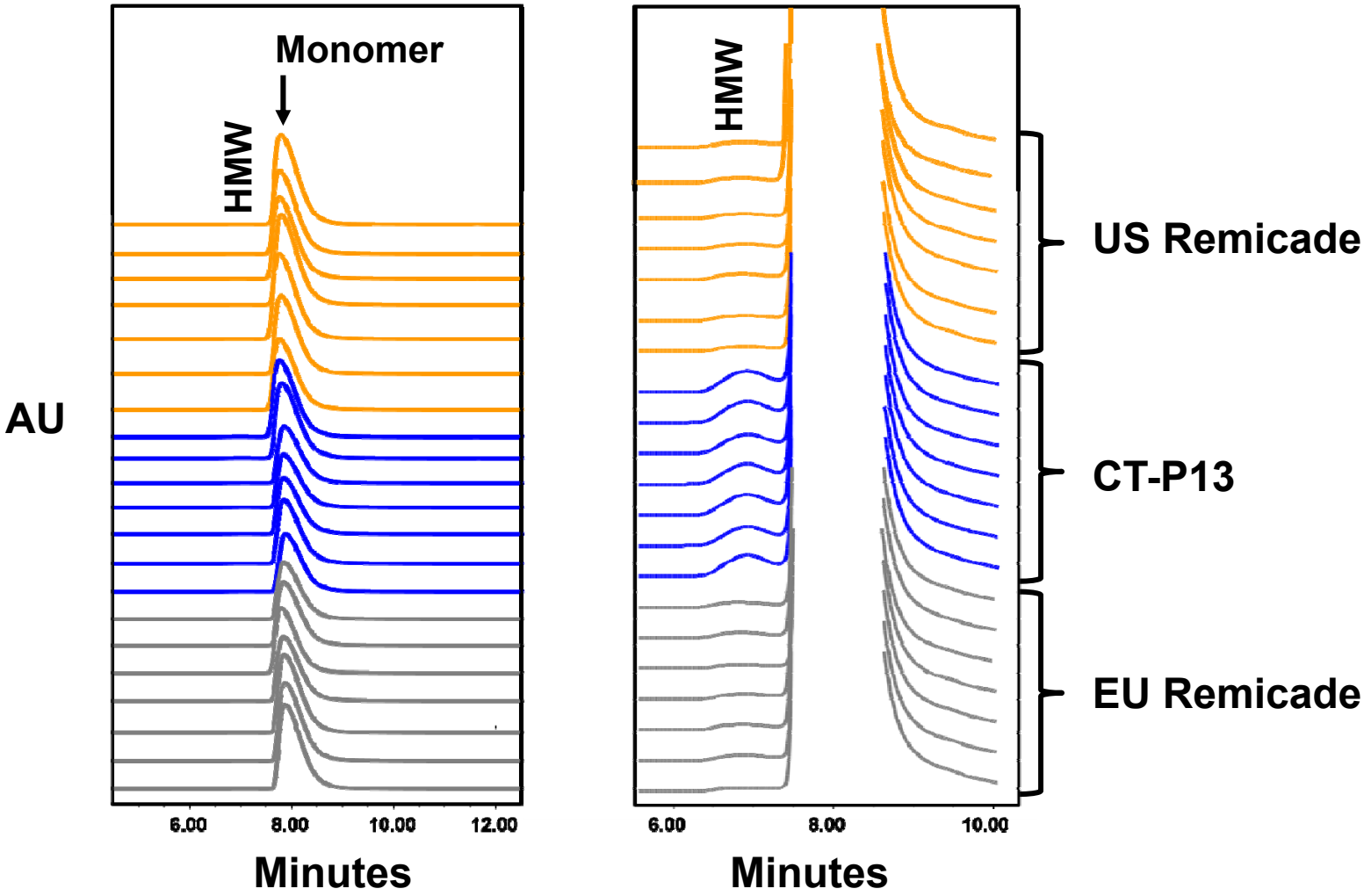


[1] High-Performance Liquid Chromatography

Higher Order Structure: Differential Scanning Calorimetry (DSC)

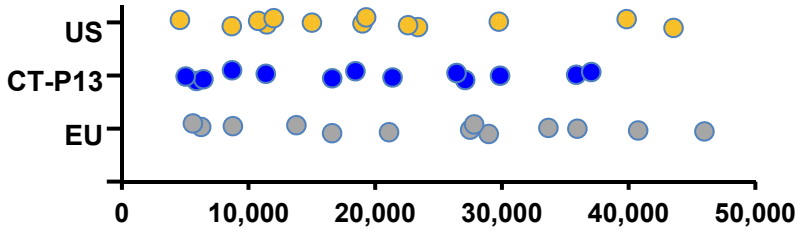
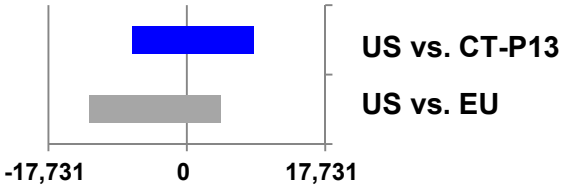
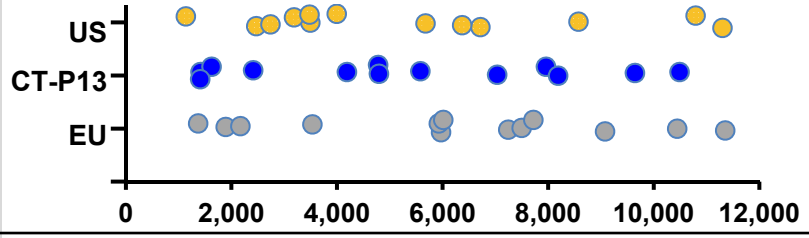
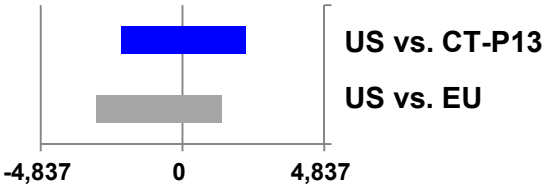
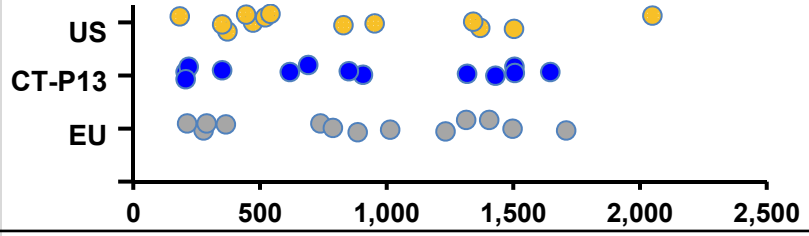
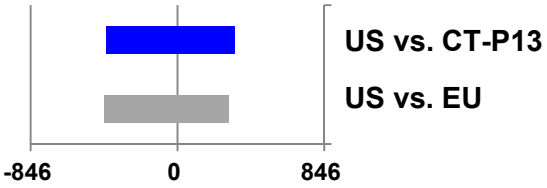
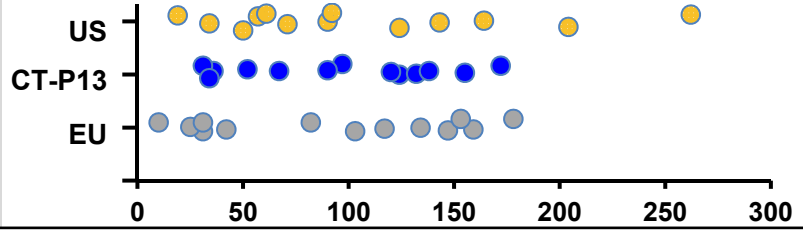
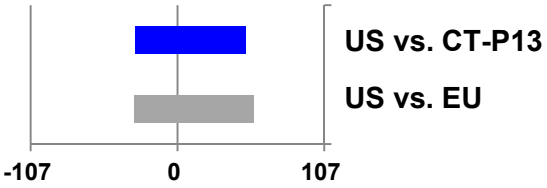


Purity/Impurity: SEC-HPLC[1]

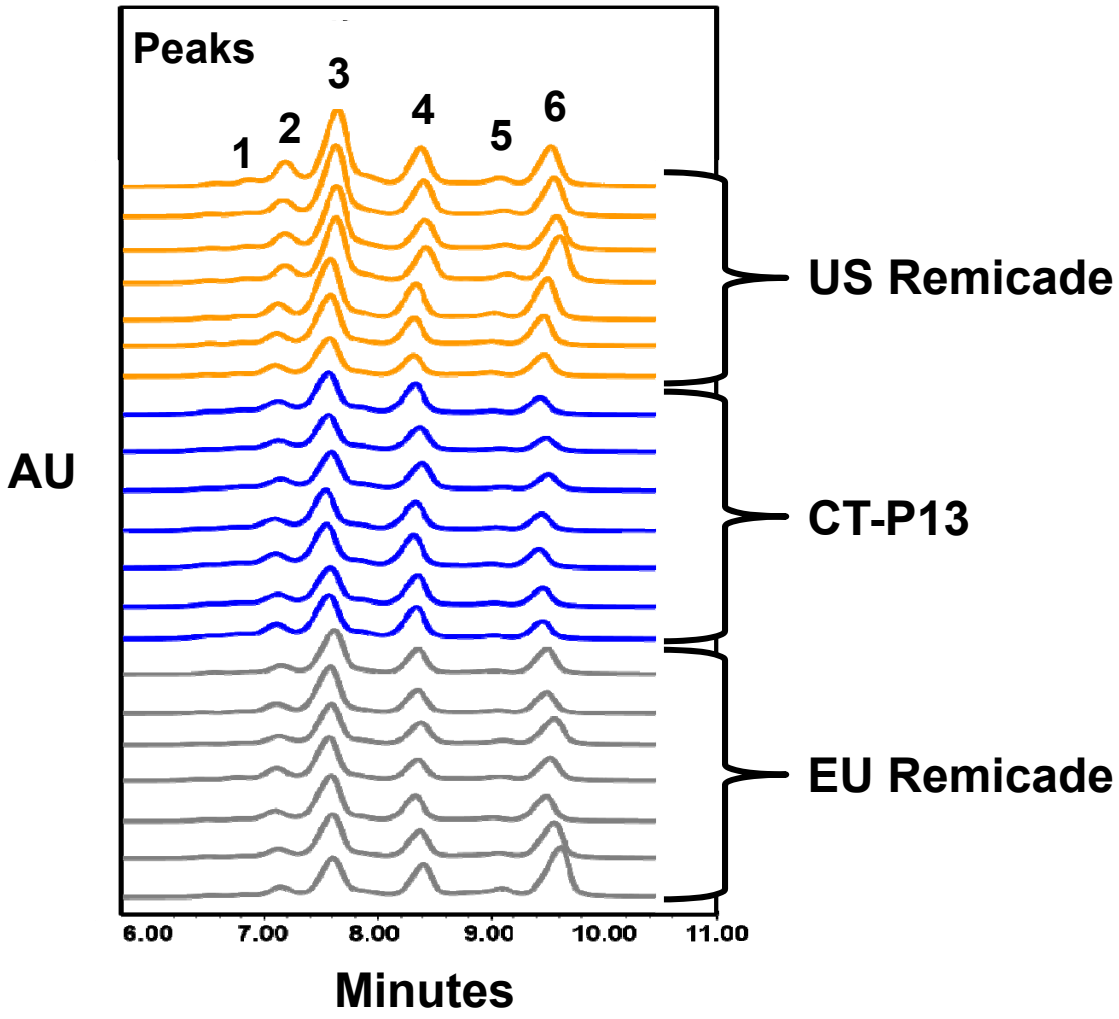


[1] Size Exclusion Chromatography with High Performance Liquid Chromatography

Sub-Visible Particles in Small Size Ranges by MFI

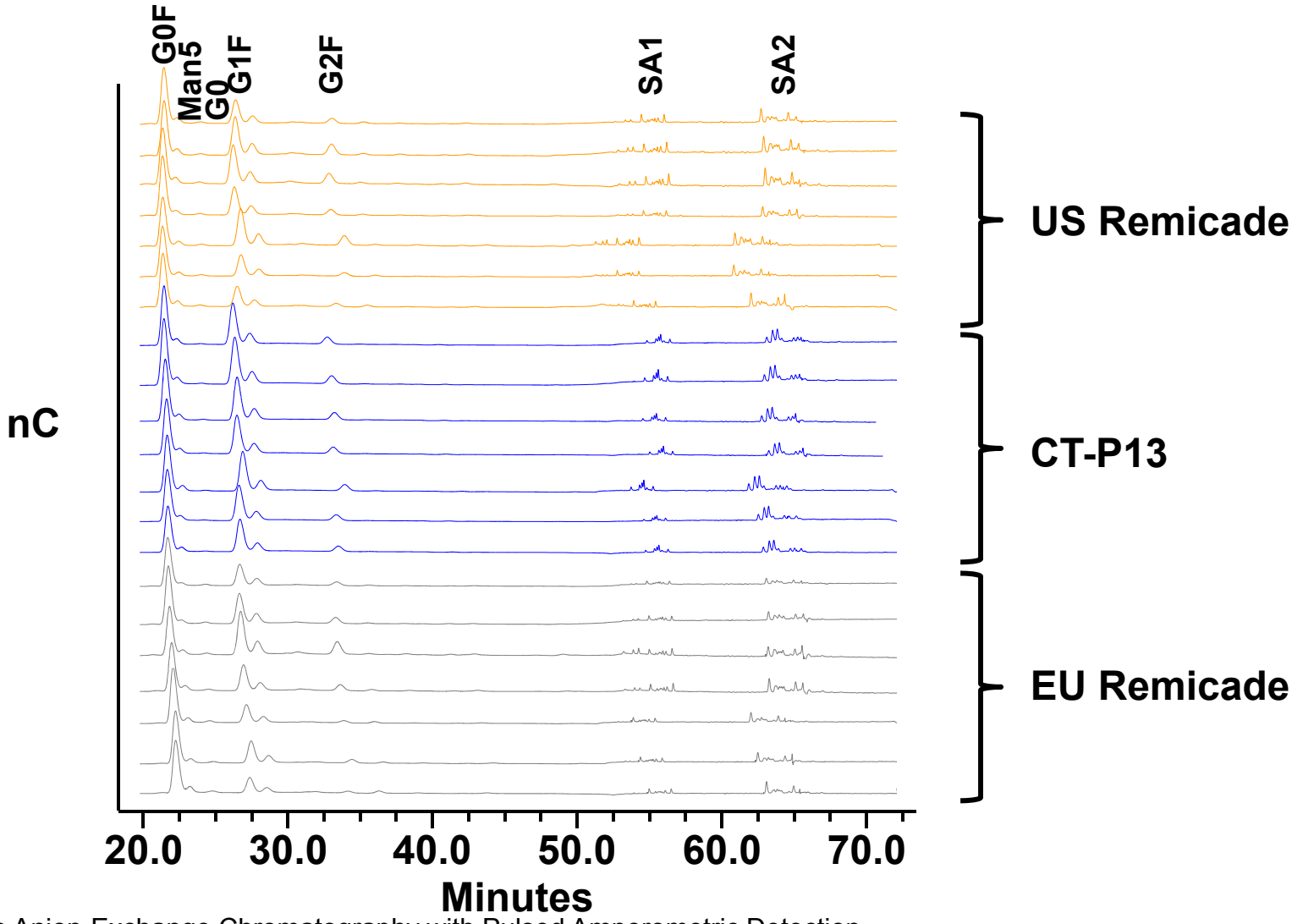
Size Range	Cumulative Counts/mL	Equivalence Test Result
1 ≤, < 100 µm		
2 ≤, < 100 µm		
5 ≤, < 100 µm		
10 ≤, < 100 µm		

6 Charge Variant Peaks: IEC-HPLC[1]



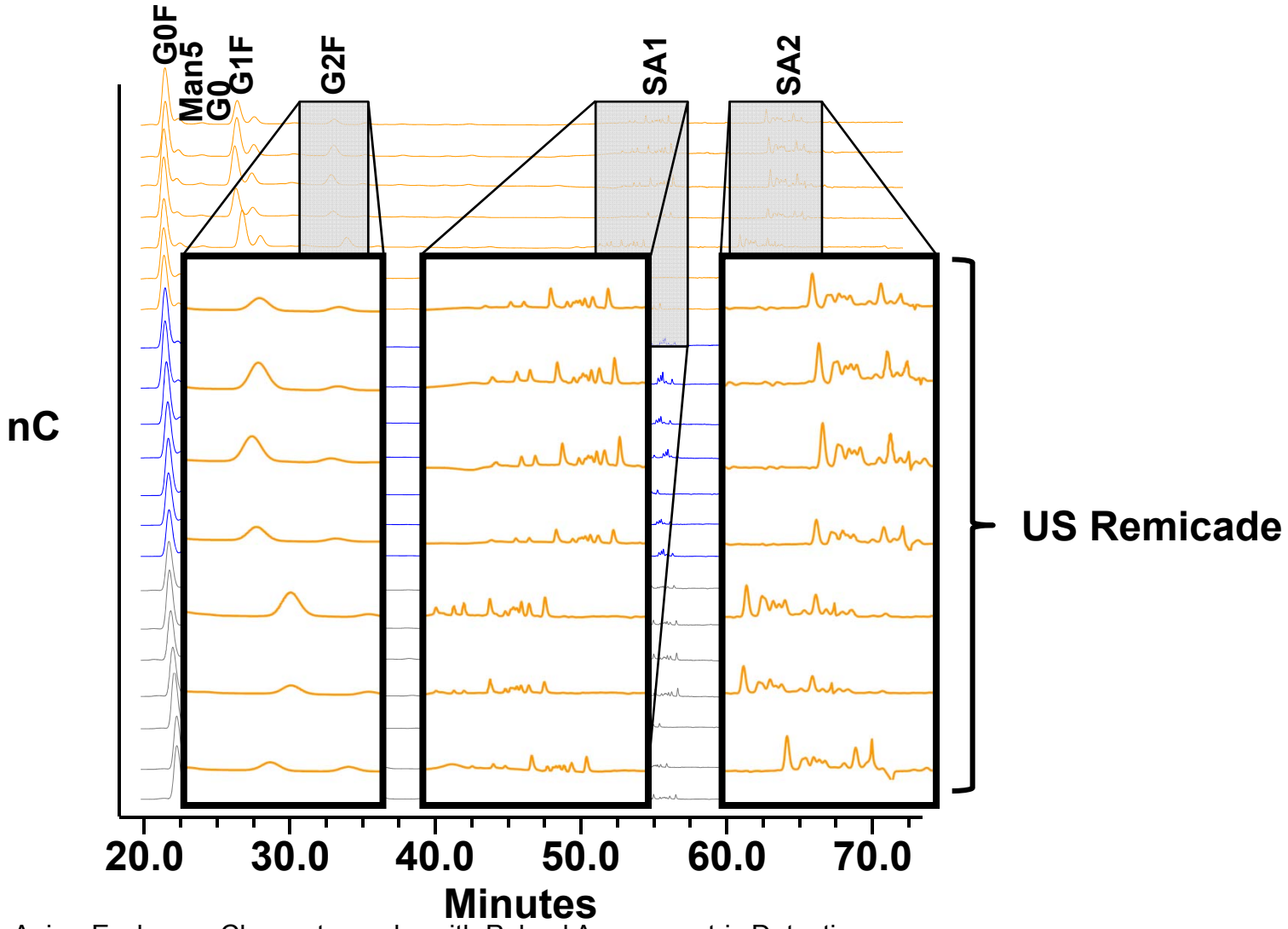
[1] Ion Exchange Chromatography with High Performance Liquid Chromatography

Glycosylation: Oligosaccharide Profiling by HPAEC-PAD[1]



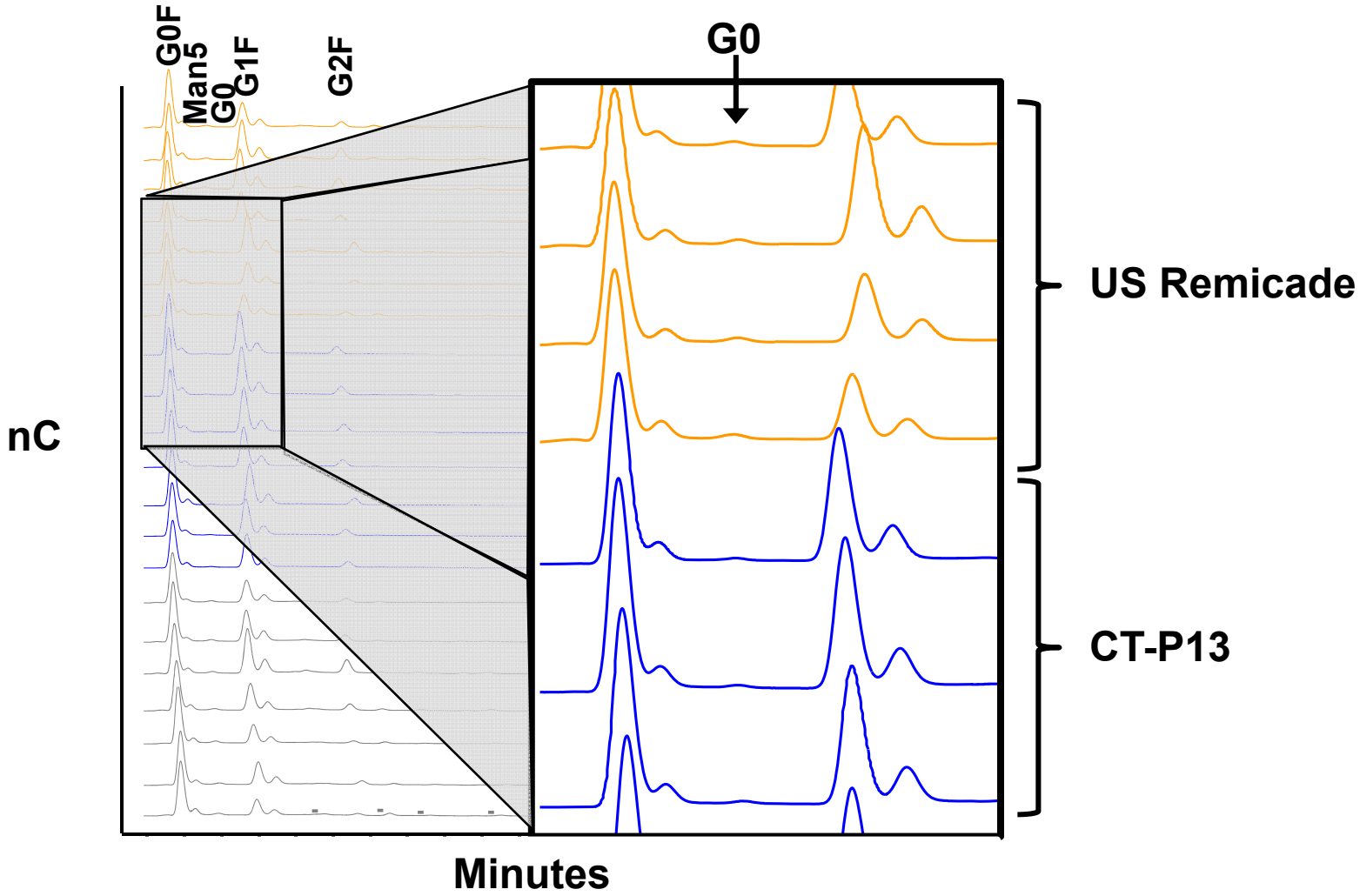
[1] High Performance Anion-Exchange Chromatography with Pulsed Amperometric Detection

Glycosylation: Oligosaccharide Profiling by HPAEC-PAD[1]



[1] High Performance Anion-Exchange Chromatography with Pulsed Amperometric Detection

Glycosylation: Oligosaccharide Profiling by HPAEC-PAD[1]

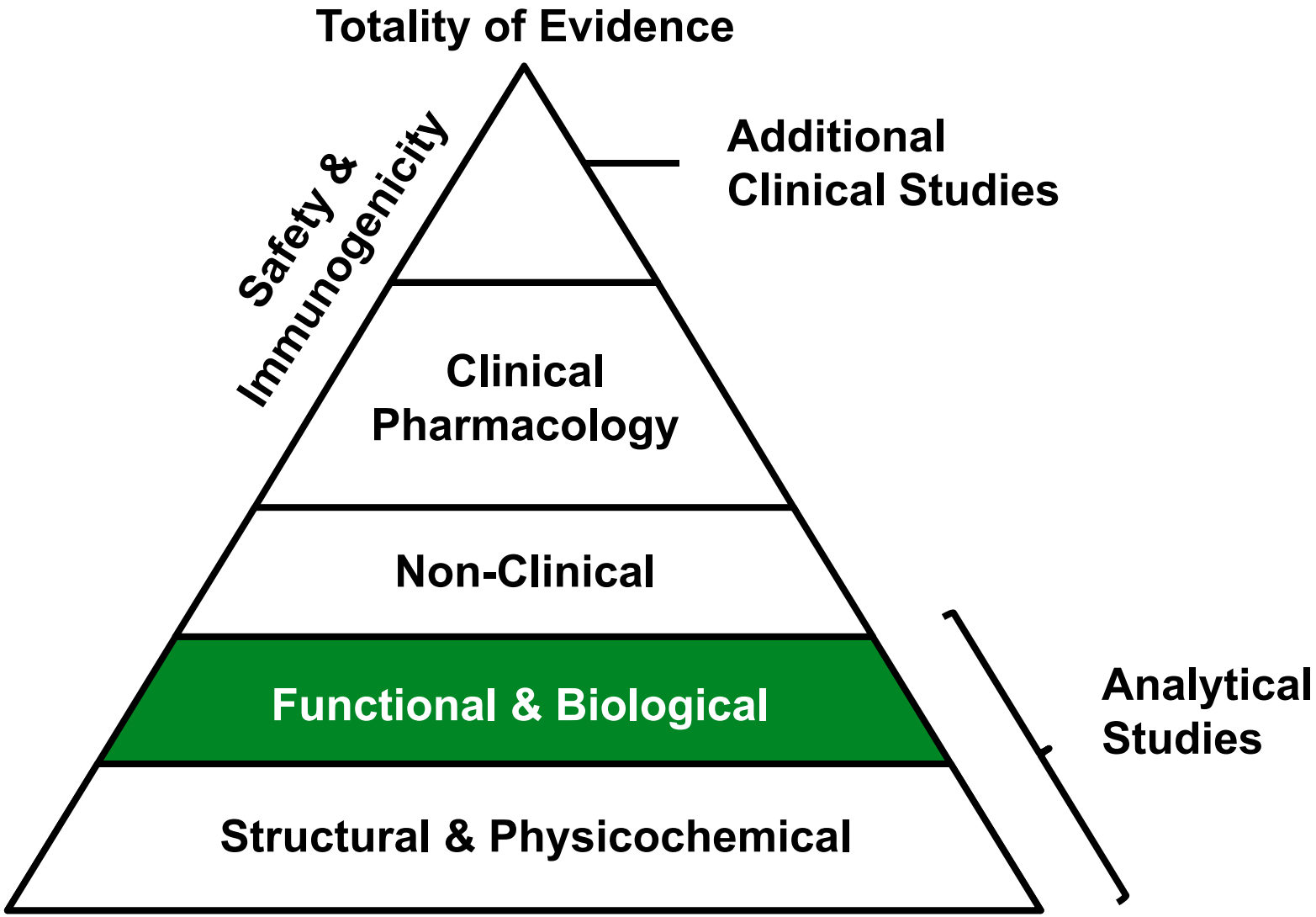


[1] High Performance Anion-Exchange Chromatography with Pulsed Amperometric Detection

Residual Uncertainties Identified from Structural Analyses

Characteristic	Potential Impact	Studies to Address Uncertainty
Intact IgG (H2L2)	**Biologic function**	• Functional assays to compare biological activity
Charge Variants (C-terminal lysine)	**Biologic function**	• *In vitro* and *in vivo* tests • Functional assays to compare biological activity
G0 Content	**Biologic function**	• Functional assays to compare biological activity
Glycation	**Biologic function**	• Functional assays to compare biological activity
High Molecular Weight Forms	**Immunogenicity**	• Assessment of immunogenicity in clinical studies

Functional and Biological Assays



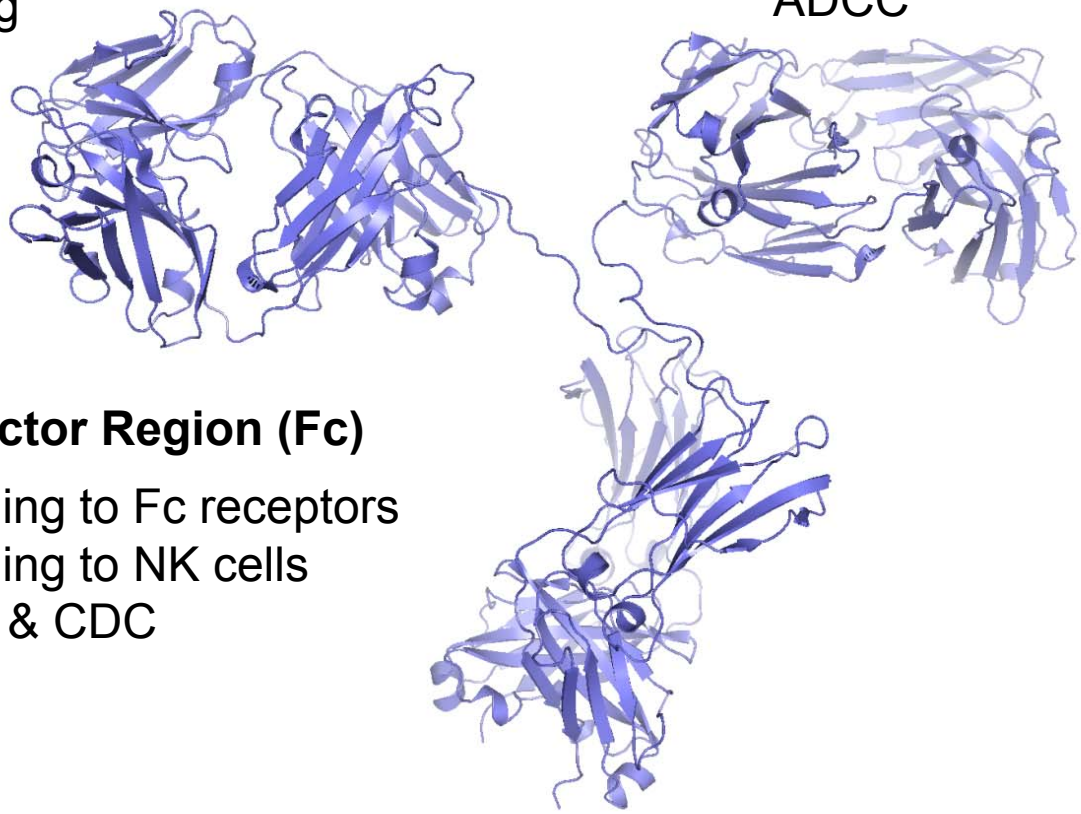
Biological Activities in Similarity Studies

Fab Region

Binding sTNFα
Binding tmTNFα
Reverse signaling

Fab & Fc Binding

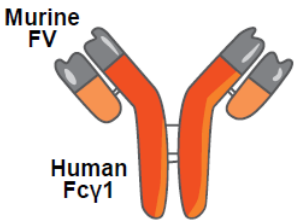
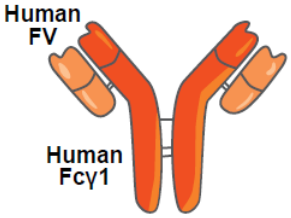
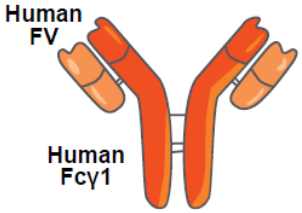
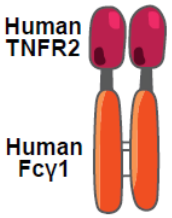
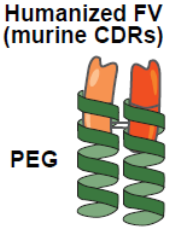
Mixed lymphocyte reaction
Inhibition of T cell proliferation
ADCC



Effector Region (Fc)

Binding to Fc receptors
Binding to NK cells
C1q & CDC

Primary MoA for TNFα Inhibitors: Binding & Neutralization of sTNFα and tmTNFα

	Infliximab (Remicade)	Adalimumab (Humira)	Golimumab (Simponi)	Etanercept (Enbrel)	Certolizumab (Cimzia)
Structure[1]					
US Indications	RA, AS, PsA, Ps, CD, UC	RA, AS, JIA, PsA, Ps, CD, UC	RA, PsA, AS, UC	RA, AS, JIA, PsA, Ps	RA, AS, PsA, CD
sTNFα Binding Affinity (KD) pM	44[2] (25 - 63)	127[2] (99 - 154)	18[2] (9 - 27)	11[2] (10 - 13)	90[3]
sTNFα Neutralization Potency[4]	✓	✓	✓	✓	✓
tmTNFα Binding[5]	✓✓✓	✓✓✓	✓✓✓[6]	✓✓	✓✓✓

These products are licensed TNFα inhibitors. JIA: Juvenile idiopathic arthritis

[1] Adapted from Astrakhantseva *et al*., (2014); [2] Shealy *et al*., (2010); [3] Nesbitt *et al*., 2009; [4] Proposed MoA in USPI and/or EPAR

[5] Tracey *et al*., (2008); [6] Ueda *et al*., (2013)

In Vitro Activities of TNFα Inhibitors

	Infliximab (Remicade)	Adalimumab (Humira)	Golimumab (Simponi)	Etanercept (Enbrel)	Certolizumab (Cimzia)
US Indications	RA, AS, PsA, Ps, CD, UC	RA, AS, JIA, PsA, Ps, CD, UC	RA, PsA, AS, UC	RA, AS, JIA, PsA, Ps	RA, AS, PsA, CD
Apoptosis by Blocking tmTNF-TNFR2[1]	✓✓✓	✓✓✓	No data	No activity	✓✓✓
Cytokine Suppression[2]	✓✓✓	✓✓✓	No data	✓	✓✓✓
Apoptosis[2]	✓✓✓	✓✓✓	✓✓✓[3]	✓	No activity
CDC[2]	✓✓✓	✓✓✓	✓✓✓[3]	✓	No activity
ADCC[2]	✓✓✓	✓✓✓	✓✓✓[3,4]	✓	No activity

These products are licensed TNFα inhibitors.

[1] Atreya *et al*., (2011); [2] Mediated by binding tmTNFα (Tracey *et al*., 2008); [3] Ueda *et al*., (2013); [4] CELLTRION data

Conducted > 20 Tests to Compare CT-P13 and EU vs. US Remicade

Binding to sTNFα
- *In Vitro* TNFα Neutralization
- TNFα Binding Affinity (ELISA)
- Cytokine Suppression (Caco-2)

Binding to tmTNFα
- Cell Based Binding Affinity
- Inhibition of Cytokine Release by Reverse Signaling
- Induction of Apoptosis by Reverse Signaling
- Induction of Regulatory Macrophages
- Suppression of T Cell Proliferation by Regulatory Macrophages
- Wound Healing by Regulatory Macrophages

C1q Binding & CDC
- C1q Binding Affinity
- CDC

Binding to Fc Receptors
- FcRn
- FcγRIIIa (V Type)
- FcγRIIIa (F Type)
- FcγRIIIb
- FcγRIIa
- FcγRIIb
- FcγRI
- *Ex Vivo* Binding in 1% BSA with NK Cells
- *Ex Vivo* Binding in 50% Serum with NK Cells

tmTNFα & Fc Binding
- ADCC using PBMC
- ADCC using NK Cells
- ADCC using LPS-stimulated Monocytes and NK Cells
- Expression Level of tmTNFα on Monocytes/ Macrophages from IBD Patients

Conclusion of Statistical Analysis of Biologic Activities: EU vs. US Remicade

Activity	Assay	EU vs. US (High Similarity)
Binding to sTNFα	*In Vitro* TNFα Neutralization	**Within EM**
	TNFα Binding Affinity (ELISA)	**Within EM**
	Cytokine Suppression (Caco-2)	**Within EM[1]**
Binding to tmTNFα	Cell Based Binding Affinity	**Within EM**
	Inhibition of Cytokine Release by Reverse Signaling	**Within EM[1]**
	Induction of Apoptosis by Reverse Signaling	Yes[1]
	Induction of Regulatory Macrophages	Yes[1]
	Suppression of T Cell Proliferation by Regulatory Macrophages	Yes[1]
	Wound Healing by Regulatory Macrophages	Yes
FcRn Binding	FcRn Binding Affinity (SPR)	**Within EM**
C1q Binding & CDC Activity	C1q Binding Affinity (ELISA)	Yes
	CDC	Yes
Fc Binding	FcγRIIIa V Type Binding Affinity (SPR)	Yes
	FcγRIIIa F Type Binding Affinity (SPR)	Yes
	FcγRIIIb Binding Affinity (SPR)	Yes
	FcγRIIa Binding Affinity (SPR)	Yes
	FcγRIIb Binding Affinity (SPR)	Yes
	FcγRI Binding Affinity (ELISA)	Yes
	Ex Vivo Binding in 1% BSA with NK cells	Yes[1]
	Ex Vivo Binding in 50% serum with NK Cells	Yes[1]
tmTNF & Fc Binding	ADCC using PBMC (Healthy Donor)	Yes
	ADCC using NK Cells (Healthy Donor)	Yes[1]
	ADCC using LPS-stimulated Monocytes and NK Cells (Healthy Donor)	Yes (No activity)

Yes: within quality range
EM: Equivalence margin

[1]Tested at multiple concentrations. Results shown for combined concentrations.

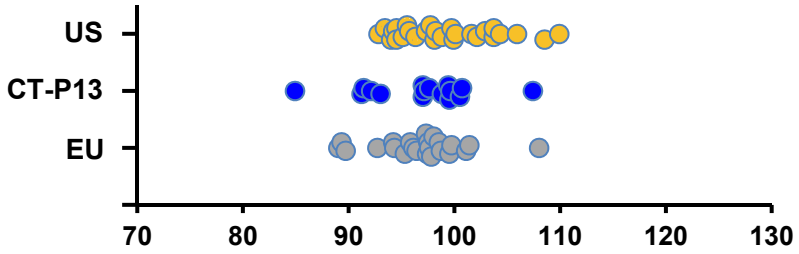
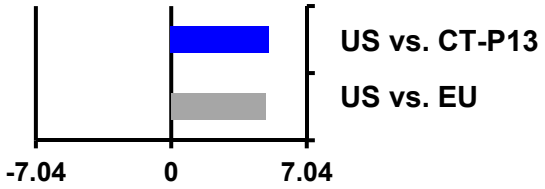
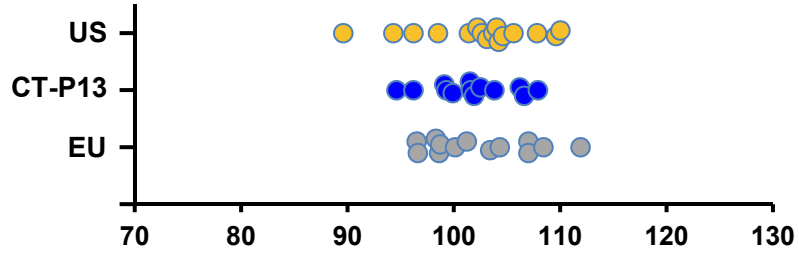
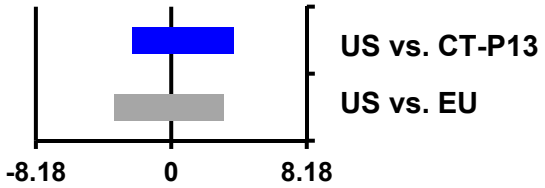
Conclusion of Statistical Analysis of Biologic Activities: CT-P13 vs. US Remicade

Activity	Assay	CT-P13 vs. US (High Similarity)
Binding to sTNFα	*In Vitro* TNFα Neutralization	**Within EM**
	TNFα Binding Affinity (ELISA)	**Within EM**
	Cytokine Suppression (Caco-2)	**Within EM**[1]
Binding to tmTNFα	Cell Based Binding Affinity	**Within EM**
	Inhibition of Cytokine Release by Reverse Signaling	**Within EM**[1]
	Induction of Apoptosis by Reverse Signaling	Yes[1]
	Induction of Regulatory Macrophages	Yes[1]
	Suppression of T Cell Proliferation by Regulatory Macrophages	Yes[1]
	Wound Healing by Regulatory Macrophages	Yes
FcRn Binding	FcRn Binding Affinity (SPR)	**Within EM**
C1q Binding & CDC Activity	C1q Binding Affinity (ELISA)	Yes
	CDC	Yes
Fc Binding	FcγRIIIa V Type Binding Affinity (SPR)	No
	FcγRIIIa F Type Binding Affinity (SPR)	No
	FcγRIIIb Binding Affinity (SPR)	Yes
	FcγRIIa Binding Affinity (SPR)	Yes
	FcγRIIb Binding Affinity (SPR)	Yes
	FcγRI Binding Affinity (ELISA)	Yes
	Ex Vivo Binding in 1% BSA with NK cells	No[1]
	Ex Vivo Binding in 50% serum with NK Cells	Yes[1]
tmTNF & Fc Binding	ADCC using PBMC (Healthy Donor)	Yes
	ADCC using NK Cells (Healthy Donor)	Yes[1]
	ADCC using LPS-stimulated Monocytes and NK Cells (Healthy Donor)	Yes (No activity)
	ADCC using LPMC and NK Cells (IBD patient)	Yes (No activity)

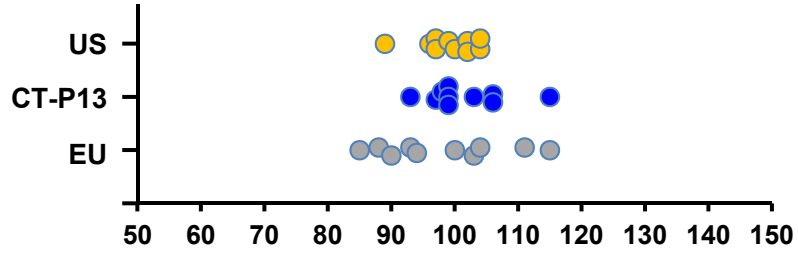
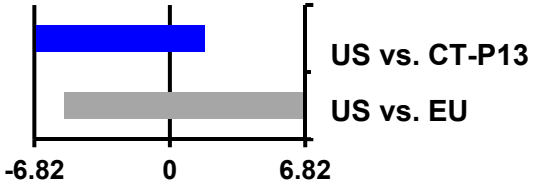
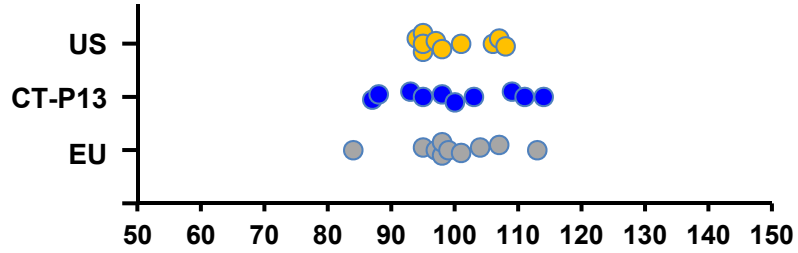
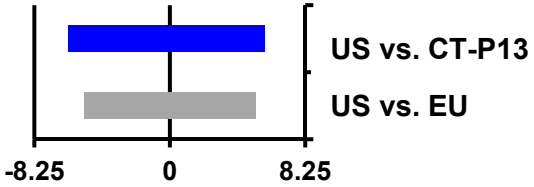
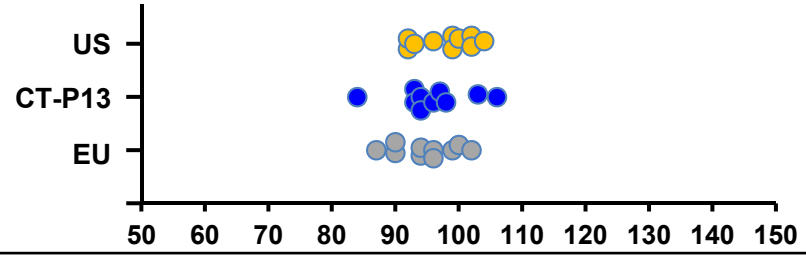
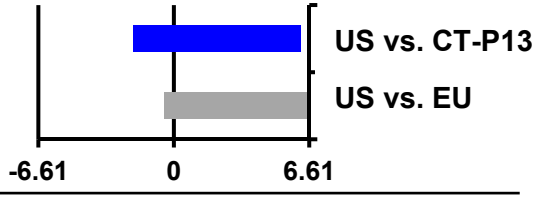
Yes: within quality range
EM: Equivalence margin

[1]Tested at multiple concentrations. Results shown for combined concentrations.

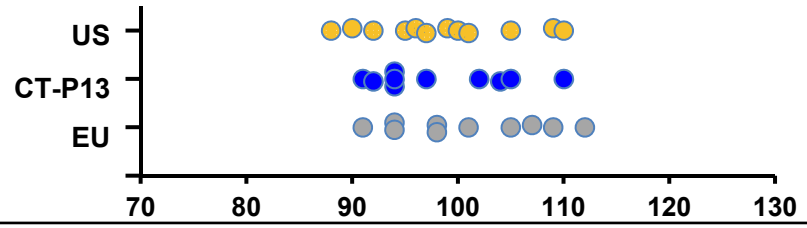
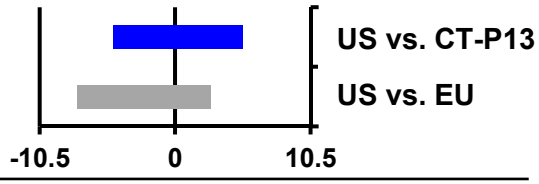
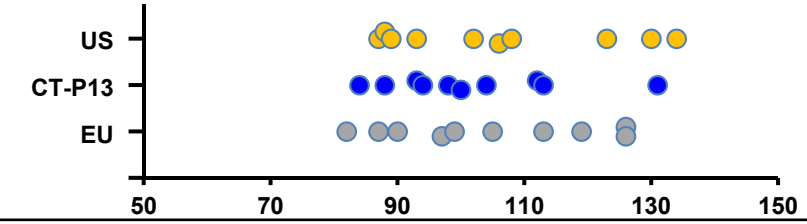
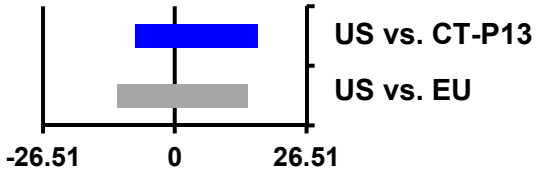
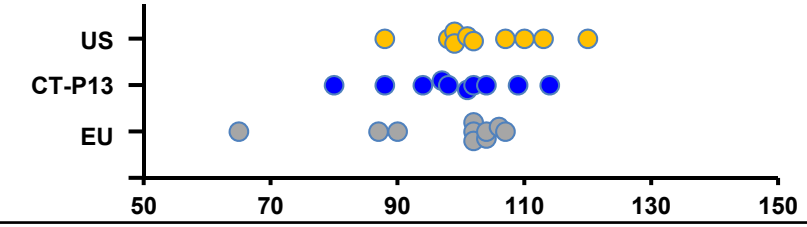
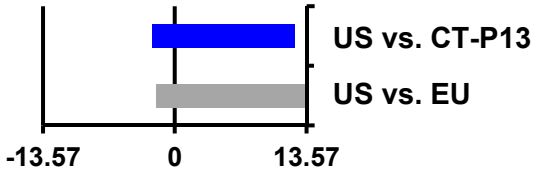
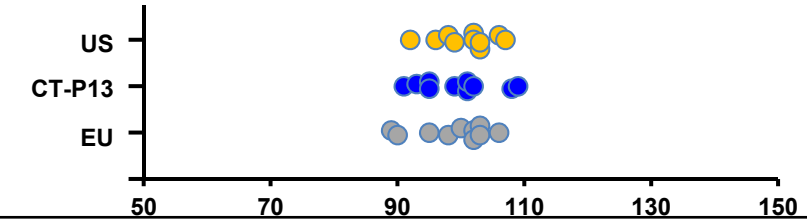
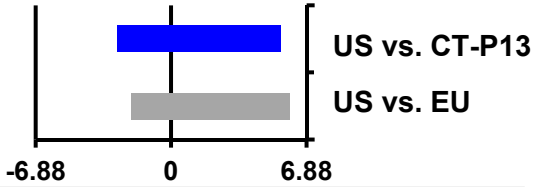
Equivalent sTNFα Binding and Neutralization

Biological Assay	Relative Activity (%)	Equivalence Test Result
TNFα Binding Affinity (ELISA)		
In Vitro TNFα Neutralization		

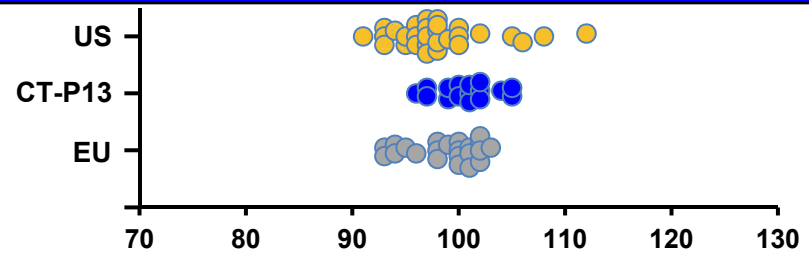
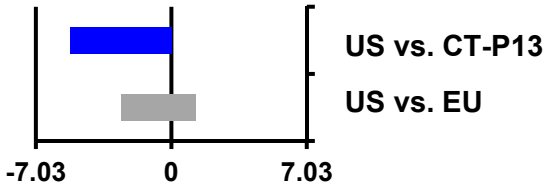
Equivalent sTNFα Neutralization

Biological Assay	Relative Activity (%)	Equivalence Test Result
Cytokine Suppression (Caco-2, 10 µg/mL)		
Cytokine Suppression (Caco-2, 2 µg/mL)		
Cytokine Suppression (Caco-2, 0.4 µg/mL)		

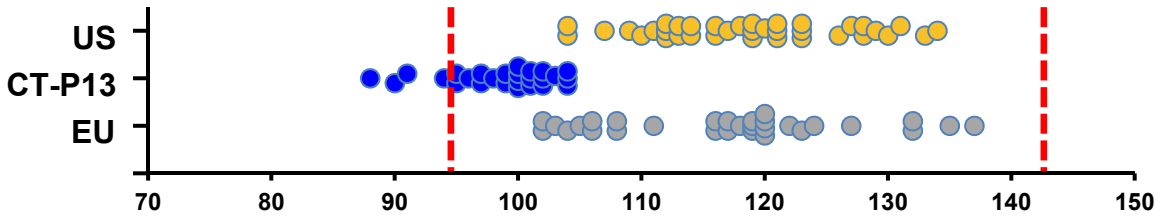
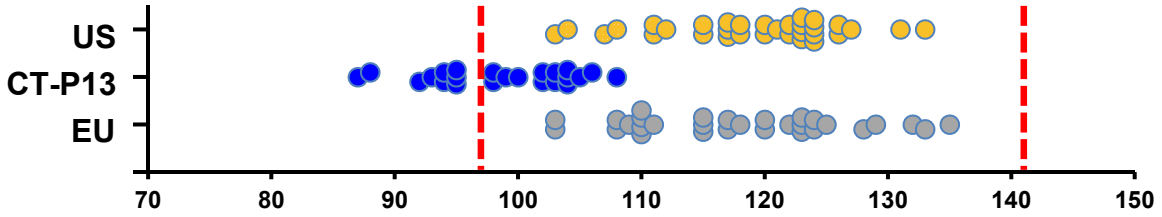
Equivalent tmTNFα Binding and Signaling

Biological Assay	Relative Activity (%)	Equivalence Test Result
Cell Based Binding Affinity		
Inhibition of Cytokine Release by Reverse Signaling (5.3 µg/mL)		
Inhibition of Cytokine Release by Reverse Signaling (2.4 µg/mL)		
Inhibition of Cytokine Release by Reverse Signaling (1.1 µg/mL)		

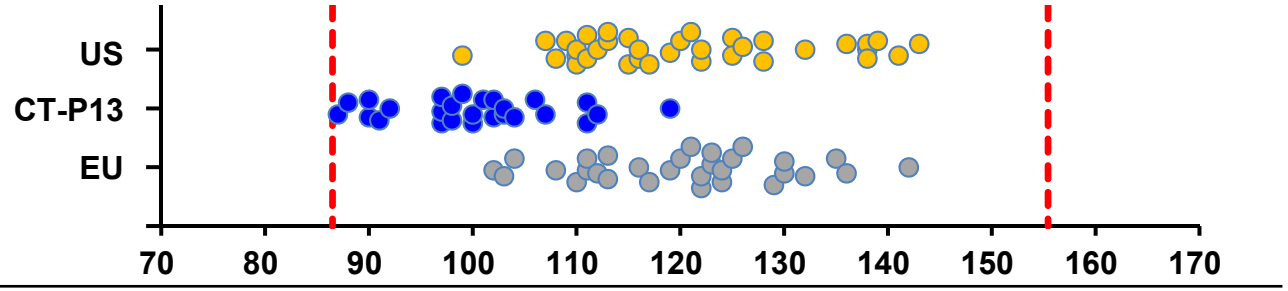
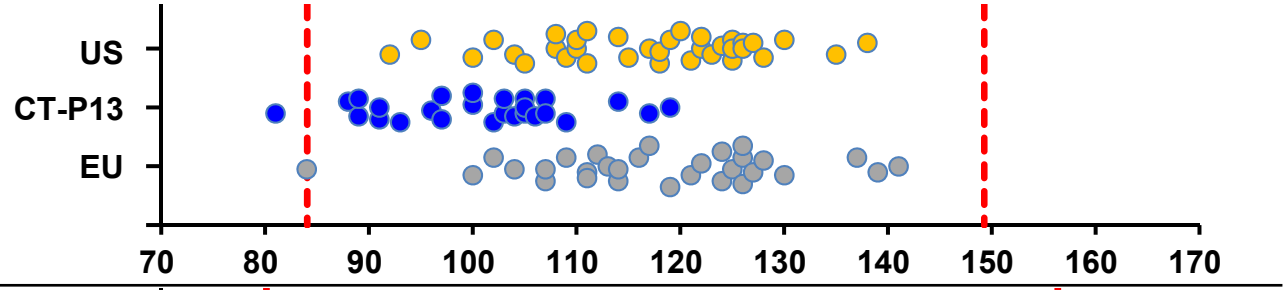
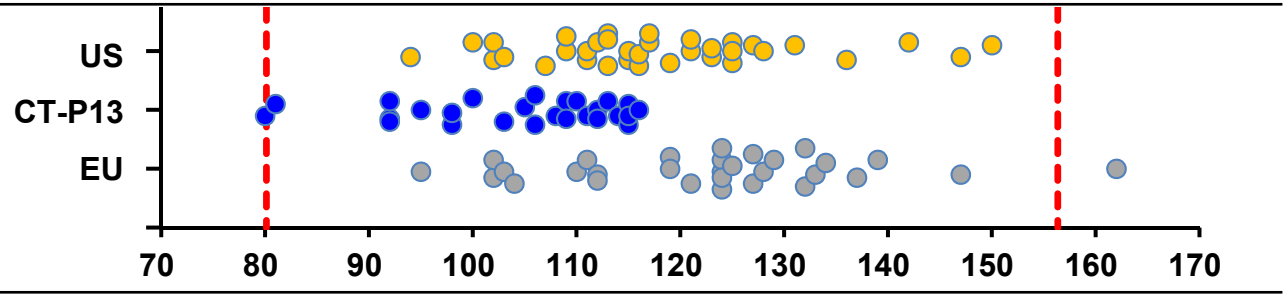
Equivalent FcRn Binding

Biological Assay	Relative Activity (%)	Equivalence Test Result
FcRn Binding Affinity (SPR)		

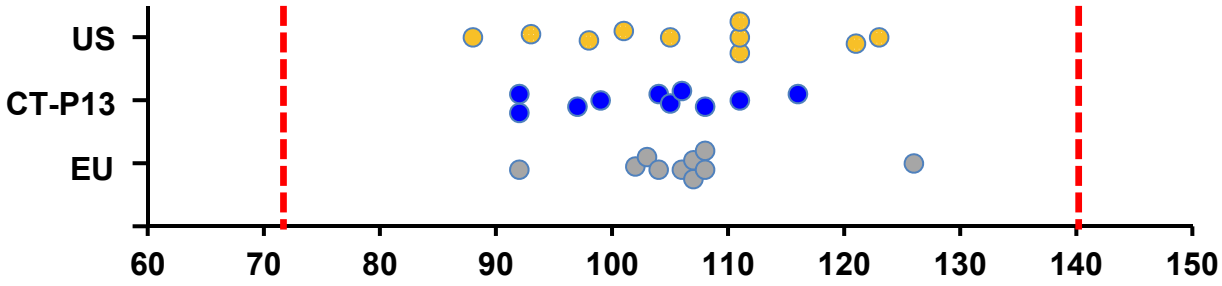
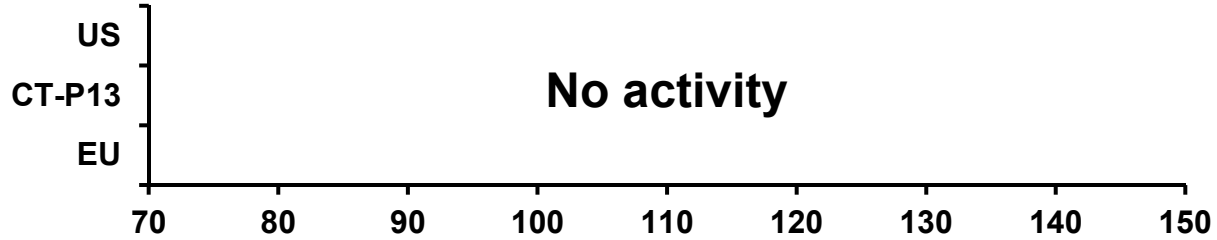
Binding FcγRIIIa

Biological Assay	Relative Activity (%)
FcγRIIIa V type Binding Affinity (SPR)	
FcγRIIIa F type Binding Affinity (SPR)	

tmTNFα-Expressing Jurkat and NK ADCC Activity (Relative Potency)

ADCC Analysis	Relative Potency (%)
8 ng/mL	
4 ng/mL	
2 ng/mL	

High Similarity in ADCC Activity

ADCC Analysis	Relative Activity (%)
tmTNFα-Expressing Jurkat and PBMC	
LPS-Stimulated Monocytes and NK	

Residual Uncertainties Resolved

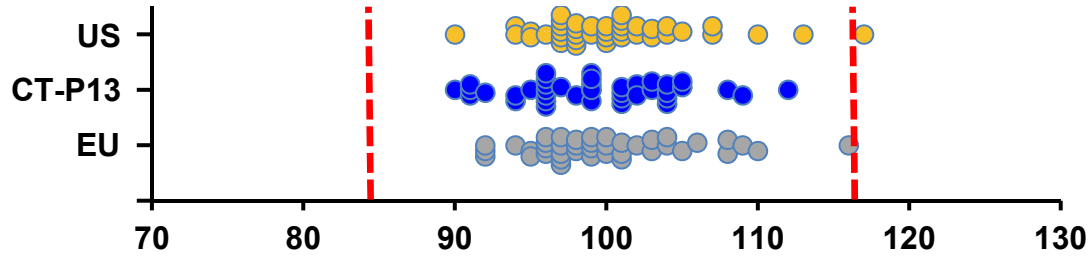
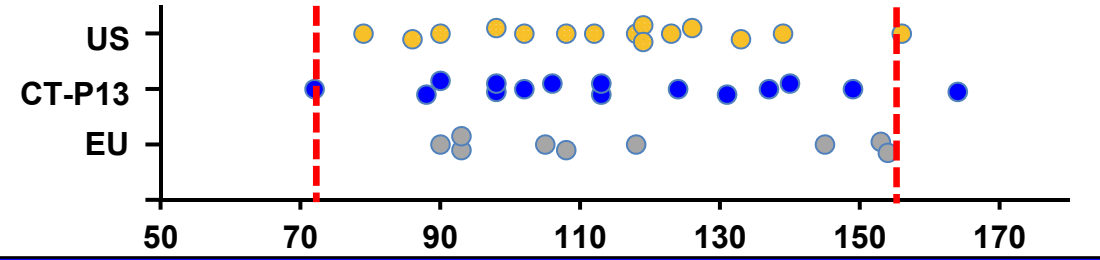
Characteristic	Potential Impact	Conclusions
Intact IgG (H2L2)	**Biologic function**	• Theoretically translates to 1.5% difference in TNFα binding • No impact on biological activities
Charge Variants (C-terminal lysine)	**Biologic function**	• Removed rapidly in serum and *in vivo*
Glycation	**Biologic function**	• Located outside of TNF binding and FcγRIIIa binding regions • No impact on biological activities
G0 Content	**Biologic function**	• FcγRIIIa binding affinity • No impact on binding to NK cells in presence of serum • No impact on ADCC
High Molecular Weight Forms	**Immunogenicity**	• Addressed in clinical studies

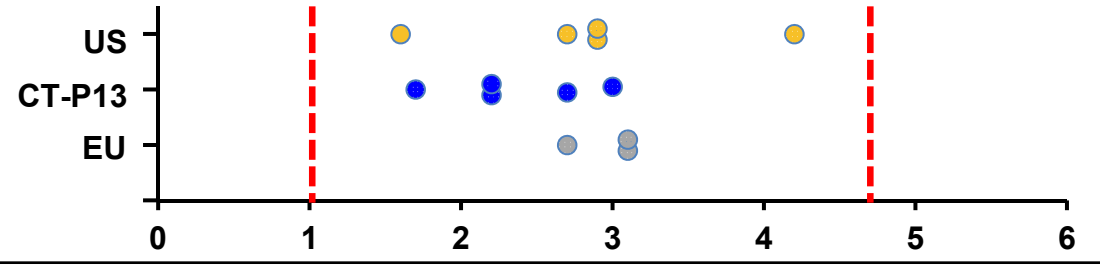
Similarity of Biological Activities Support Extrapolation to IBD Indications

Biological Assay	Target	Cells	Similarity CT-P13 vs. US Remicade	EU vs. US Remicade Bridge
Cytokine Suppression (Caco-2)[1]	**sTNFα**	**Caco-2**	**Within EM**	**Within EM**
Cell Based Binding Affinity	**tmTNFα**	**tmTNFα Jurkat cells**	**Within EM**	**Within EM**
Inhibition of Cytokine Release by Reverse Signaling[1]	**tmTNFα**	**PBMC**	**Within EM**	**Within EM**
Induction of Apoptosis by Reverse Signaling[1]	tmTNFα	tmTNFα Jurkat cells	High	High
Induction of Regulatory Macrophages[1]	tmTNFα-macrophage	Mixed lymphocytes	High	High
Suppression of T Cell Proliferation by Regulatory Macrophages[1]	tmTNFα-macrophage	Mixed lymphocytes	87%	High
Wound Healing by Regulatory Macrophages[2]	tmTNFα-macrophage	HCT 116 & regulatory macrophages	High	High
ADCC[1]	tmTNFα of monocytes-FcγRIIIa of NK cell	LPS stimulated monocytes & NK cells	High (No activity)	High (No activity)
	tmTNFα of LPMC-FcγRIIIa of NK cell	IBD patient-derived LPMC & NK cells	High (No activity)	-

High: ≥ 90% within QR; EM: Equivalence margin
[1] Tested at multiple concentrations. Results shown for combined concentrations; [2] Visual comparison

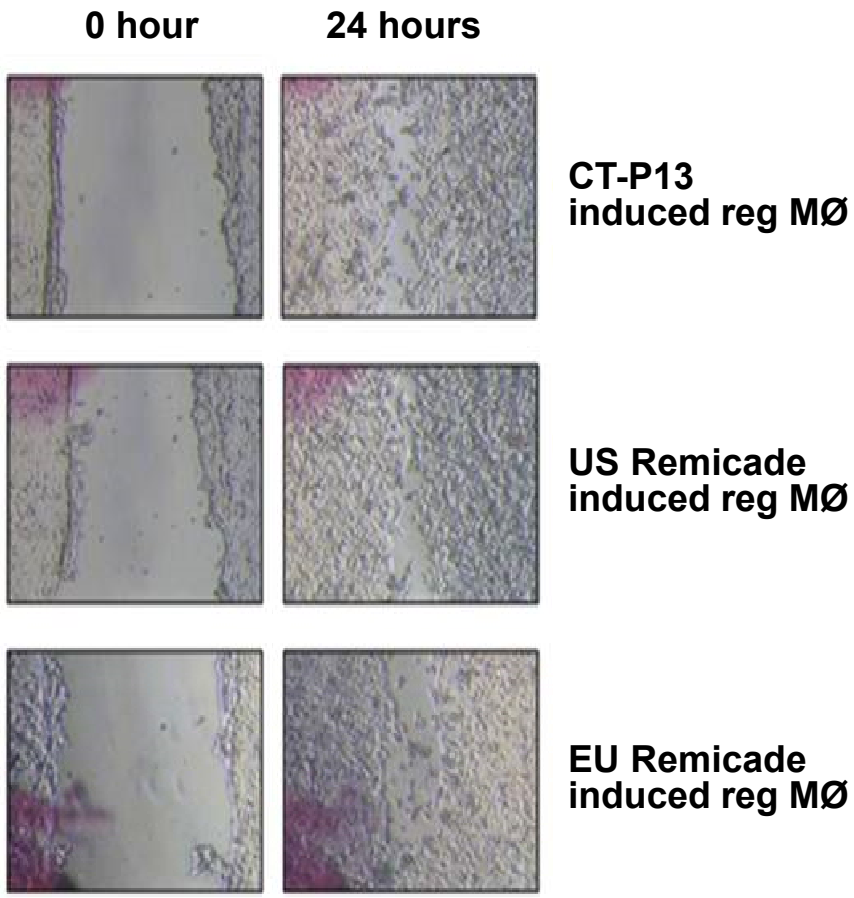
High Similarity in tmTNF or tmTNF-Fc Induced Effects

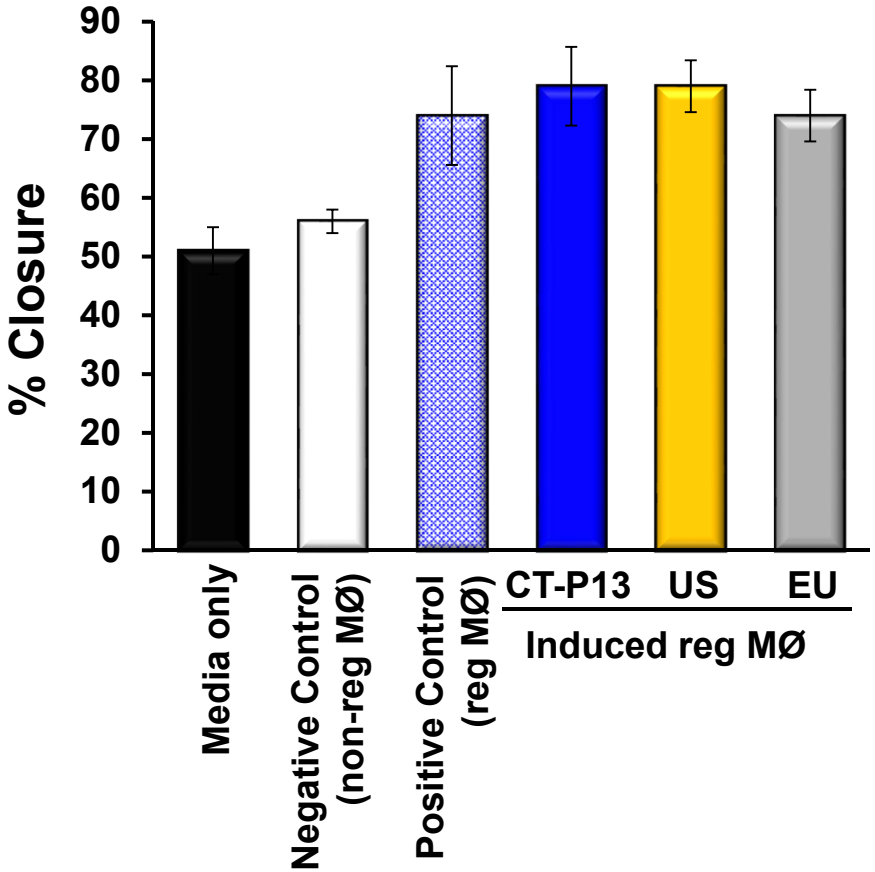
Biological Assay	Relative Activity (%)
Induction of Apoptosis by Reverse Signaling[1]	
Suppression of T Cell Proliferation by Regulatory Macrophages[2]	

Biological Assay	Induced Macrophages from Total PBMC (%)
Induction of Regulatory Macrophages (0.625 µg/mL)[2]	

[1] QR was ± 3SD of US Remicade lots.
[2] QR was ± 2SD of US Remicade lots.

Induces Comparable Wound Healing in Colorectal Cells in Scratch Model

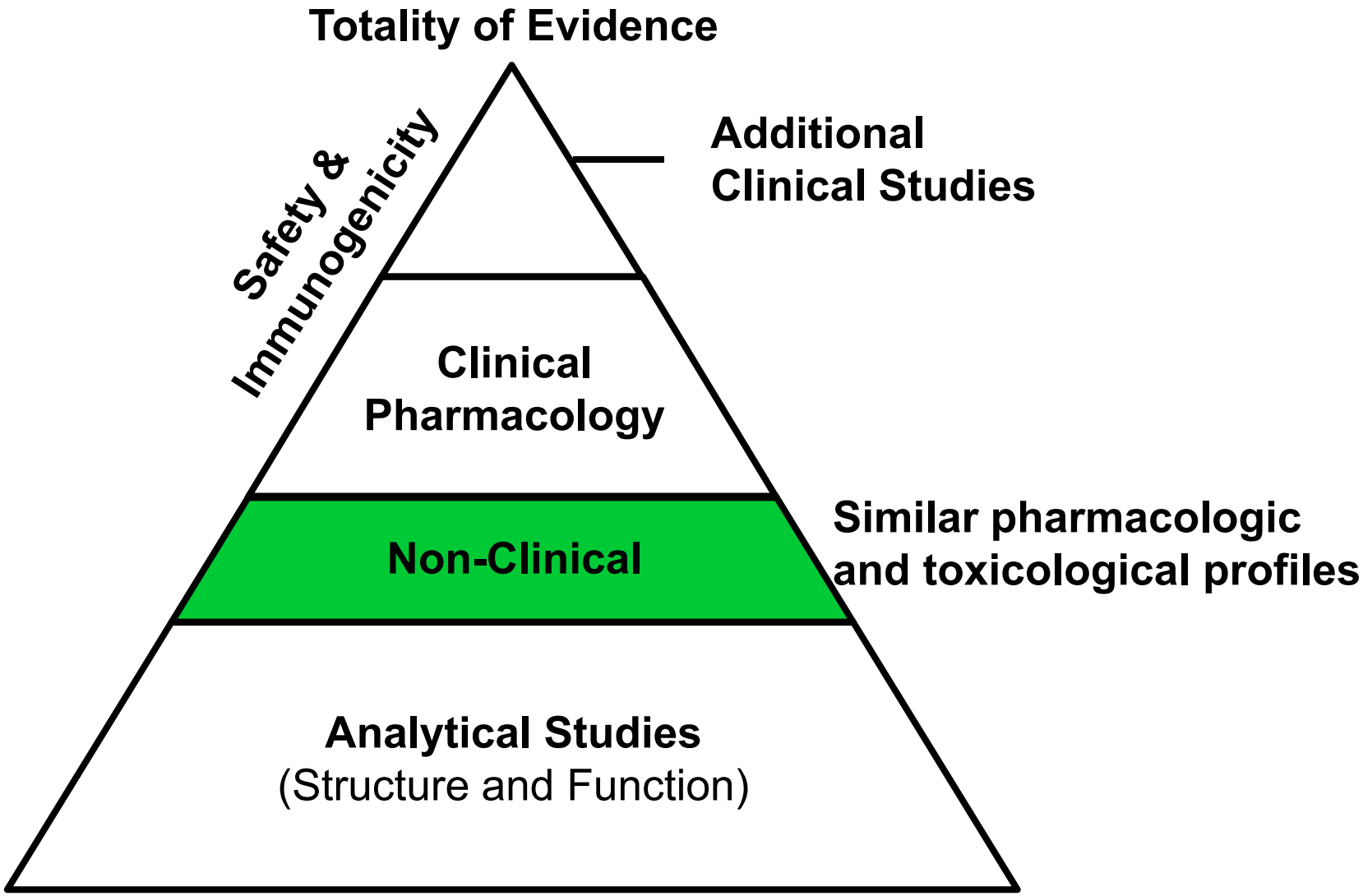




CT-P13 Highly Similar to Remicade and Supports Extrapolation

- High similarity in structural and physicochemical analyses
- High similarity in functional and biological analyses
- EU Remicade data relevant for US Remicade
- Extrapolation is supported by high similarity and mechanism of action
- Totality of evidence supports that products can be expected to perform like Remicade in all indications for which Remicade is licensed

Non-Clinical Profile of CT-P13 Similar to EU Remicade



Clinical Development

Alex Kudrin, MD, PhD, MBA

Vice President

Head of Clinical Development

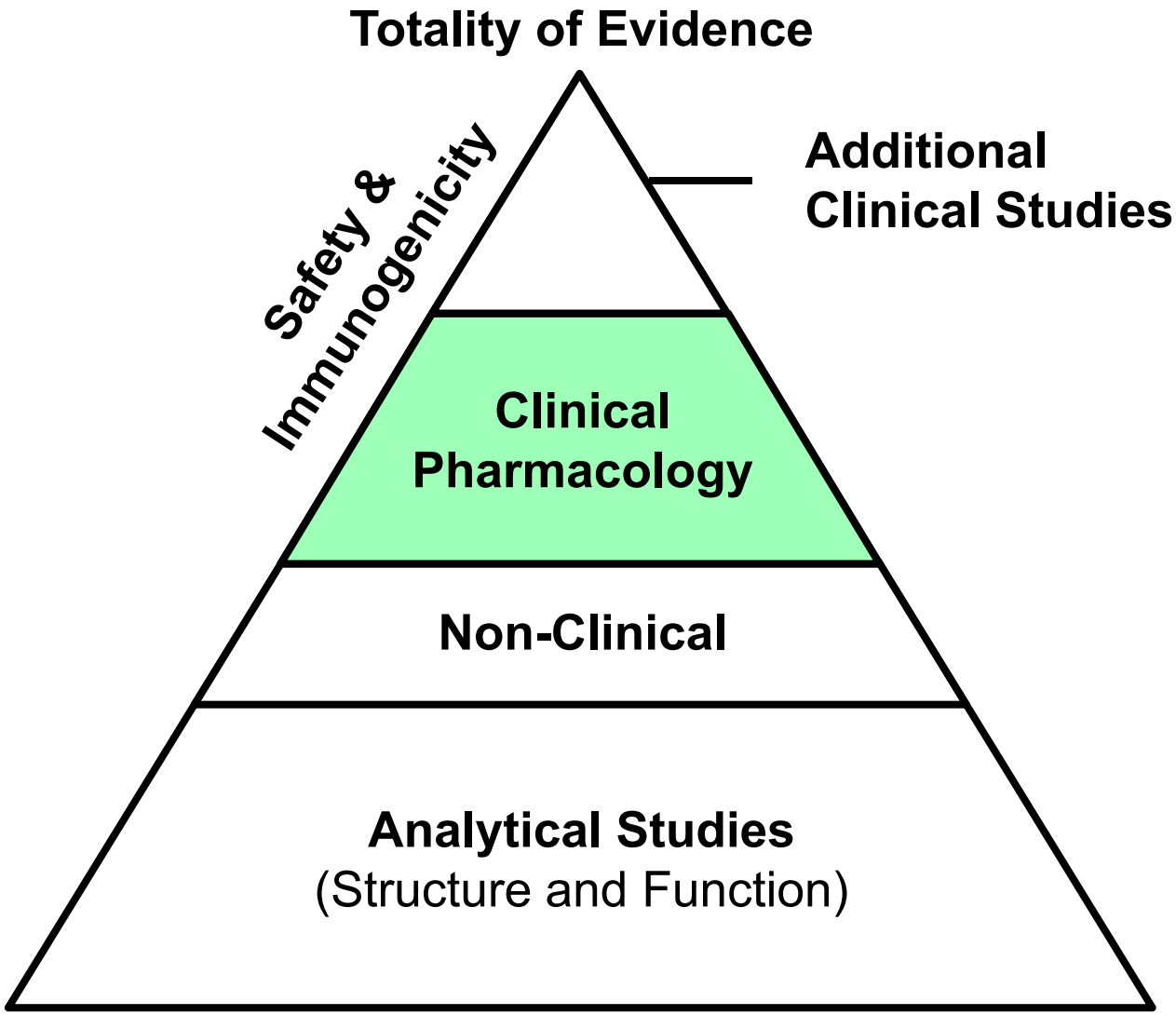
CELLTRION, Inc.

Key CT-P13 Clinical Studies

	AS Study (N = 250)	RA Study (N = 606)	3-way PK (N = 213)
Subjects	AS patients[1]	RA patients[2]	Healthy subjects
Dosing	5 mg/kg at wk 0, 2, 6 → q8wk	3 mg/kg at wk 0, 2, 6 → q8wk	Single dose, 5 mg/kg
Combination Treatment	None	MTX	None
Remicade Reference	EU	EU	US & EU
Primary Endpoints	AUC_T $C_{max,SS}$	ACR20	AUC_{last} AUC_{inf} C_{max}

[1]1984 modified NY classification, [2]1987 ACR classification

Clinical Pharmacokinetics Studies



Studied in Sensitive Populations

- Healthy subjects, immunocompetent
- Ankylosing spondylitis (AS)
  - No background immunosuppression
  - 5 mg/kg dose representative of non-RA indications
- Rheumatoid arthritis (RA)
  - Extensive clinical PK and safety experience with Remicade
  - More immunogenic 3 mg/kg dose
  - Similar comorbidities as PsA and Ps

PK Measurements in Key CT-P13 Clinical Studies

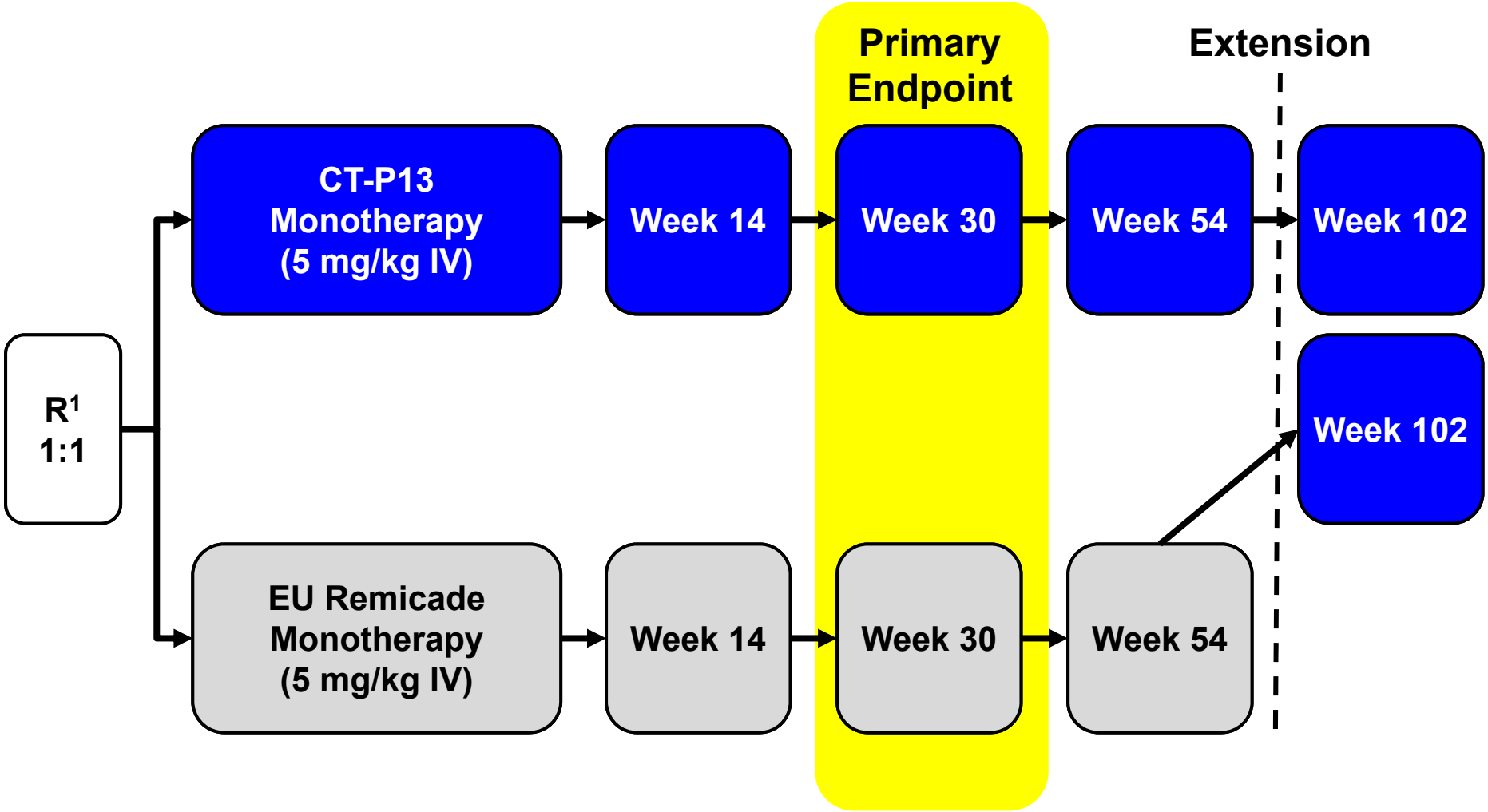
	AS Study (N = 250)	RA Study (N = 606)	3-way PK Study (N = 213)
PK Measurements[1]	AUC_T $C_{max,SS}$	C_{max} C_{min}	AUC_{inf} AUC_{last} C_{max}
Timing of PK Assessment	Baseline Week 2 Week 6 q8w → Week 54	Baseline Week 2 Week 6 q8w → Week 54	Baseline through Week 8

[1] Pre-defined PK Similarity as 80% - 125% in 3-way PK and AS Studies

Pre-Defined PK Similarity Margin of 80% - 125%

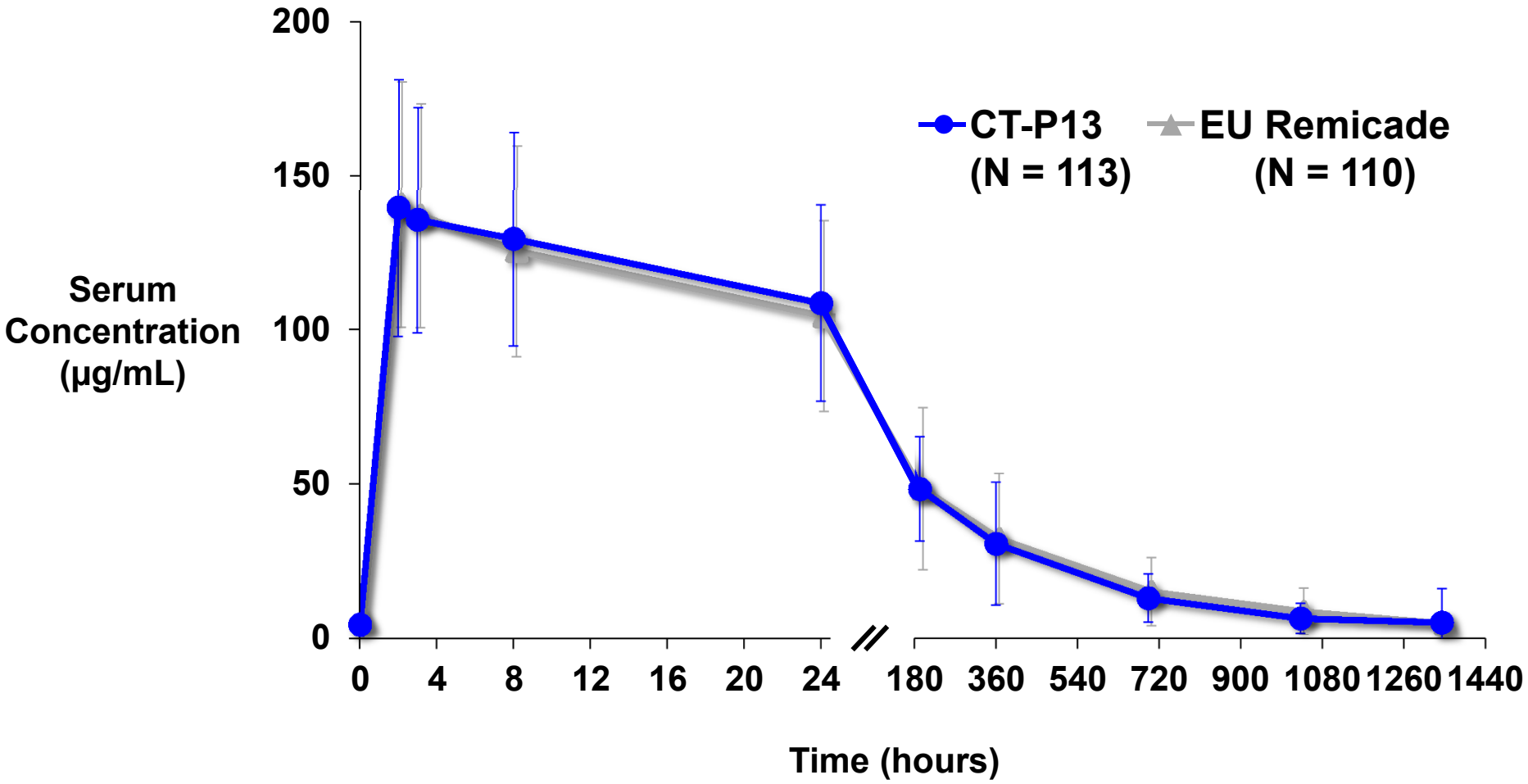
- Linear and well-characterized PK across all indications with doses up to 20 mg/kg
- Broad therapeutic index
- Lack of prominent drug-drug interactions
- Comparable safety profile across indications and wide range of plasma concentrations

Overview of AS Study Design with Extension

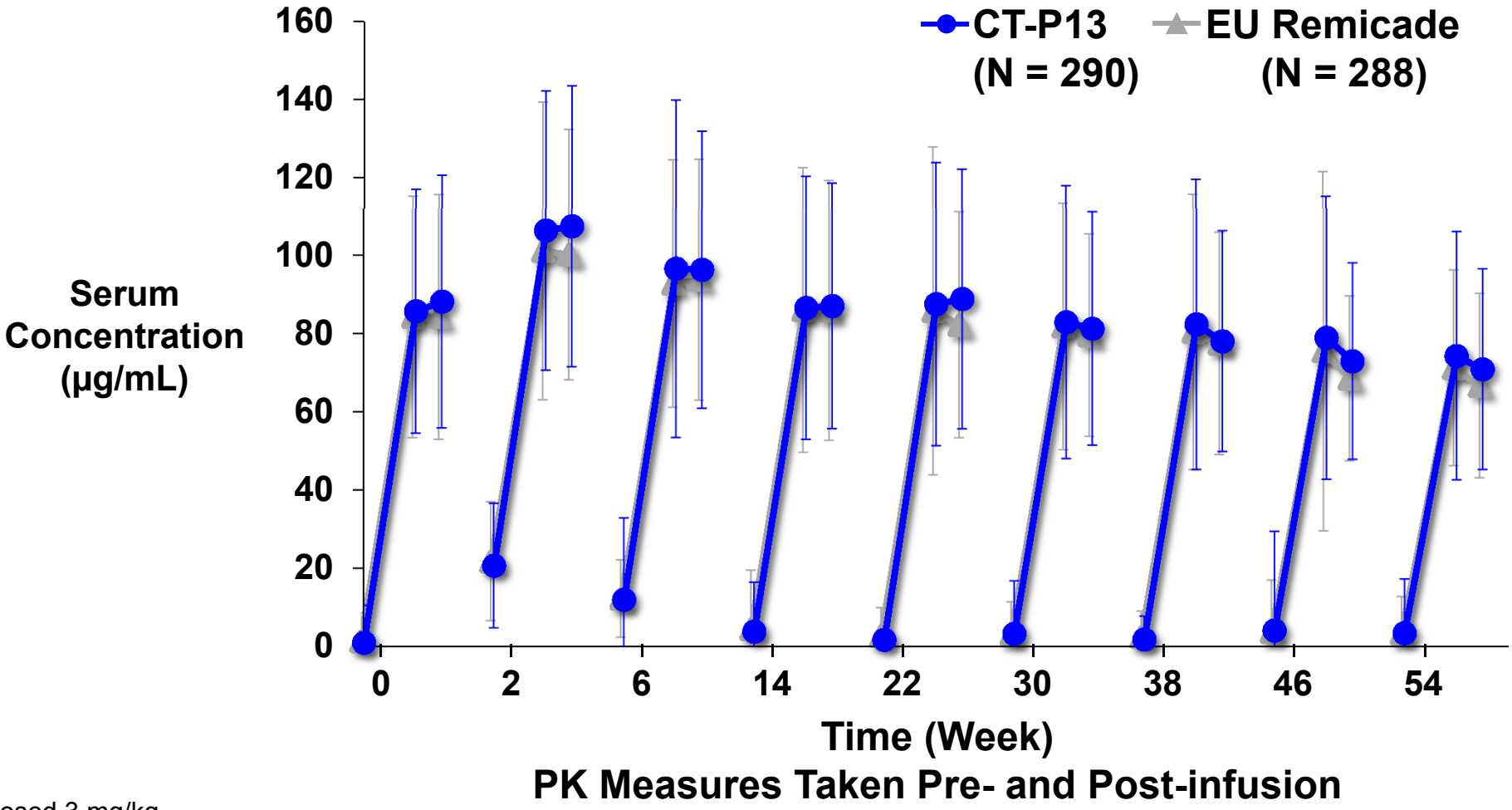


[1] Randomization and stratification by region and BASDAI

AS Study: Similar PK to Remicade between Week 22 and Week 30

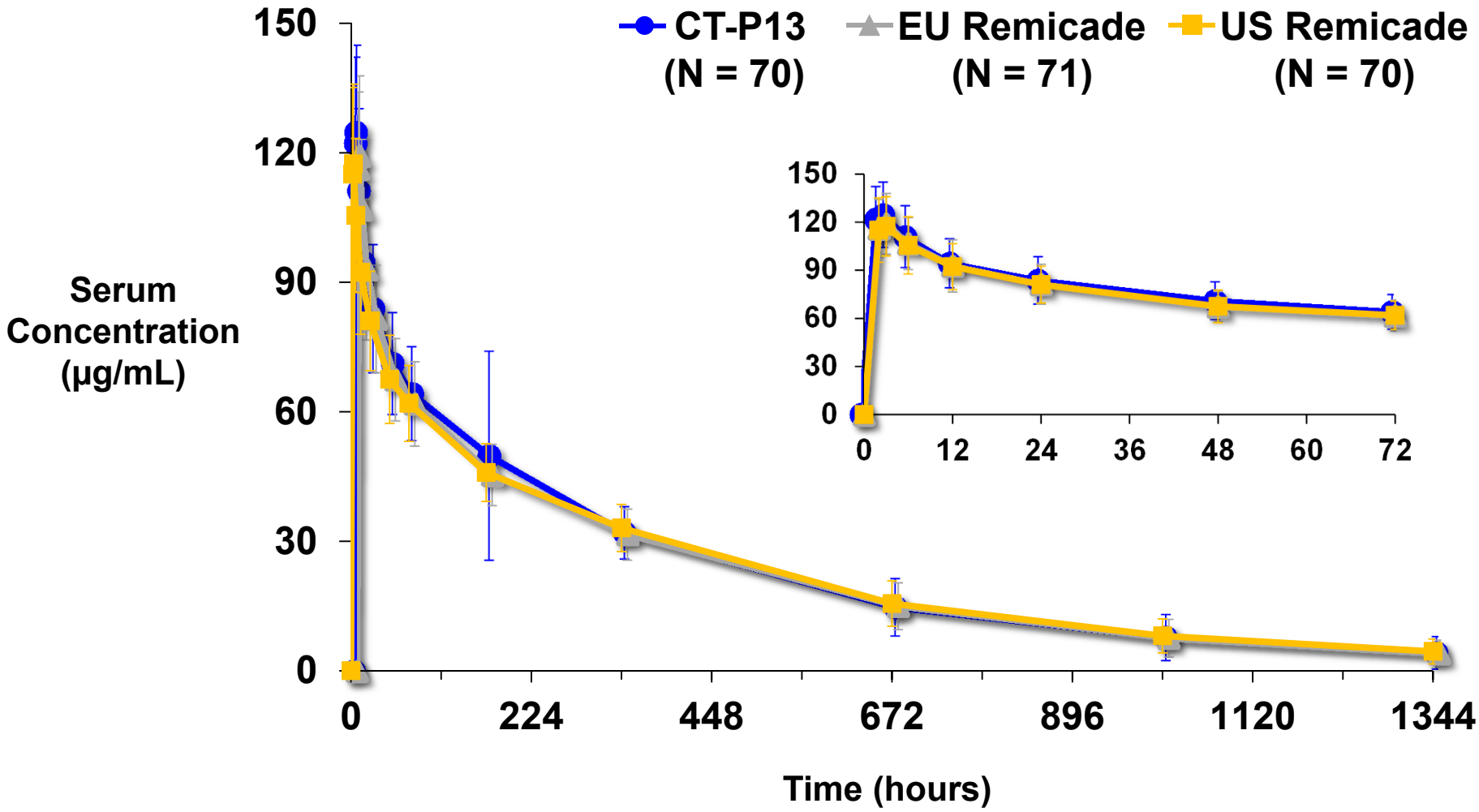


RA Study: Similar Concentration-Dependent PK by Infusion

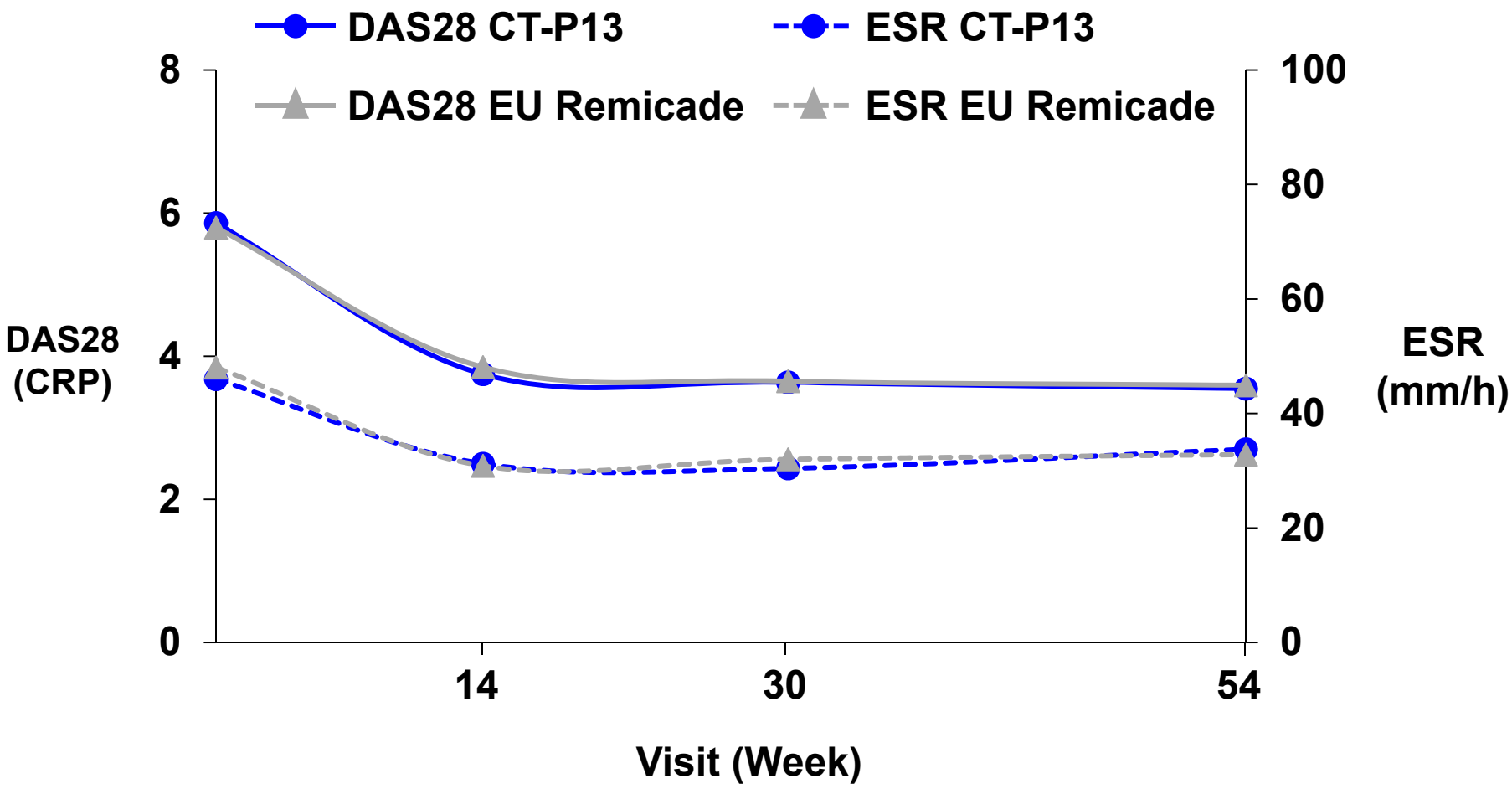


Dosed 3 mg/kg.
PK was collected at 3 time points: 1) pre-dose, 2) the end of infusion, and 3)1 h after the end of infusion

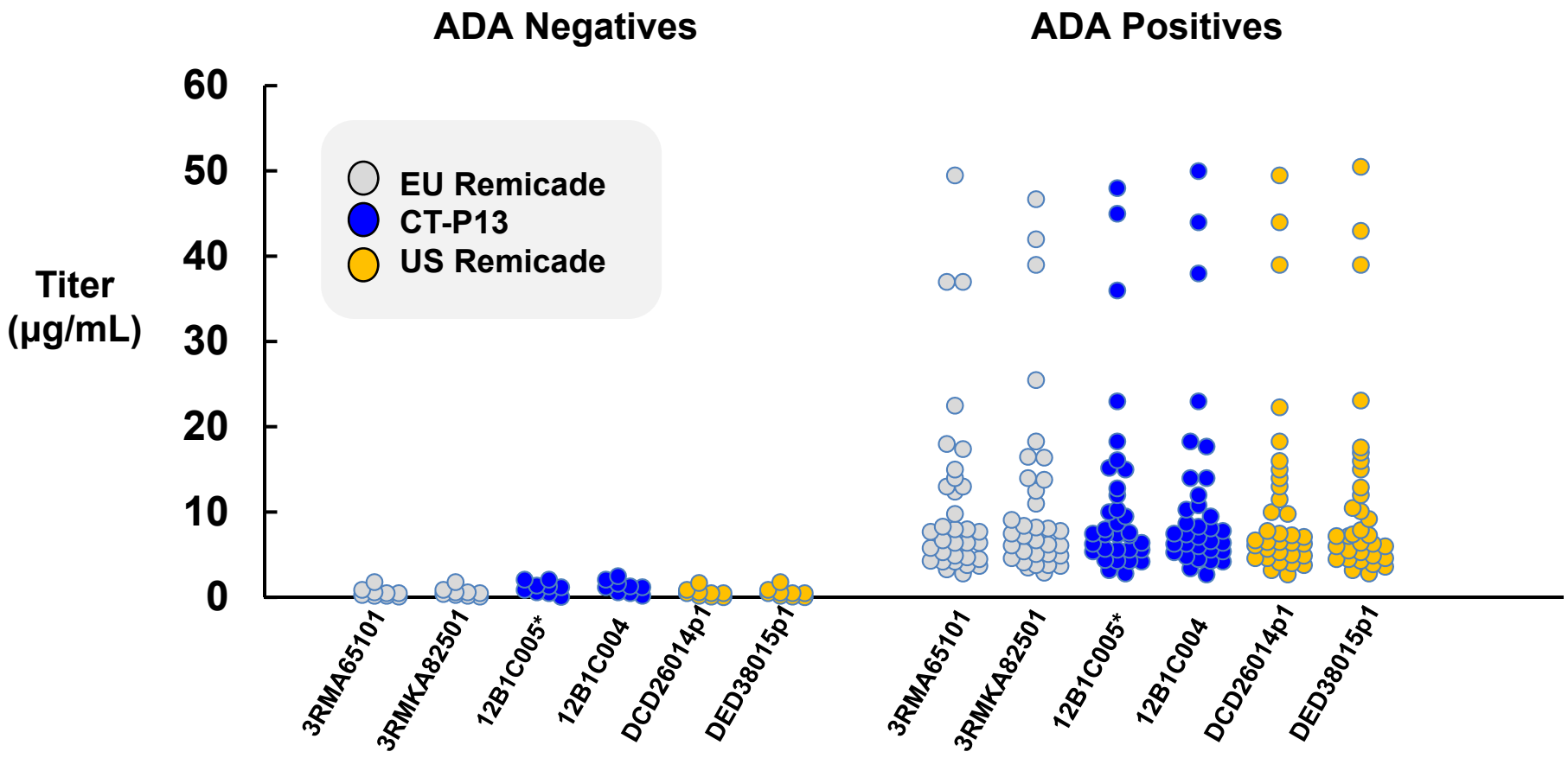
Single-Dose 3-Way PK Study Showed Similar PK over 8 Weeks



Evaluation of ESR and DAS28 (CRP) Response in RA Study



In vitro Evaluation of Cross-Reactivity with Sera from IBD Patients



*CT-P13 lot 12B1C005 was not used in the 3-way PK Study but was included in this study to show consistency between CT-P13 lots.

Similar Immunogenicity Profile between CT-P13 and Remicade in RA and AS Studies

Patients with Positive Antibody Test	RA Study (+MTX)		AS Study (Monotherapy)	
	CT-P13 (N = 302)	EU Remicade (N = 300)	CT-P13 (N = 128)	EU Remicade (N = 122)
Week 14	23%	23%	9%	11%
Week 30	40%	41%	25%	20%
Week 54	41%	36%	20%	23%

- Similar titer levels for ADA and NAb shown through 54 weeks

ADA: Anti-drug antibodies; NAb: Neutralizing antibodies

Consistent Immunogenicity Profile Observed in Extension Studies

Patients with Positive Antibody Test	RA Extension (+MTX)		AS Extension (Monotherapy)	
	Maintained (N = 159)	Switched (N = 143)	Maintained (N = 90)	Switched (N = 84)
Week 78	45%	46%	23%	30%
Week 102	40%	45%	23%	27%

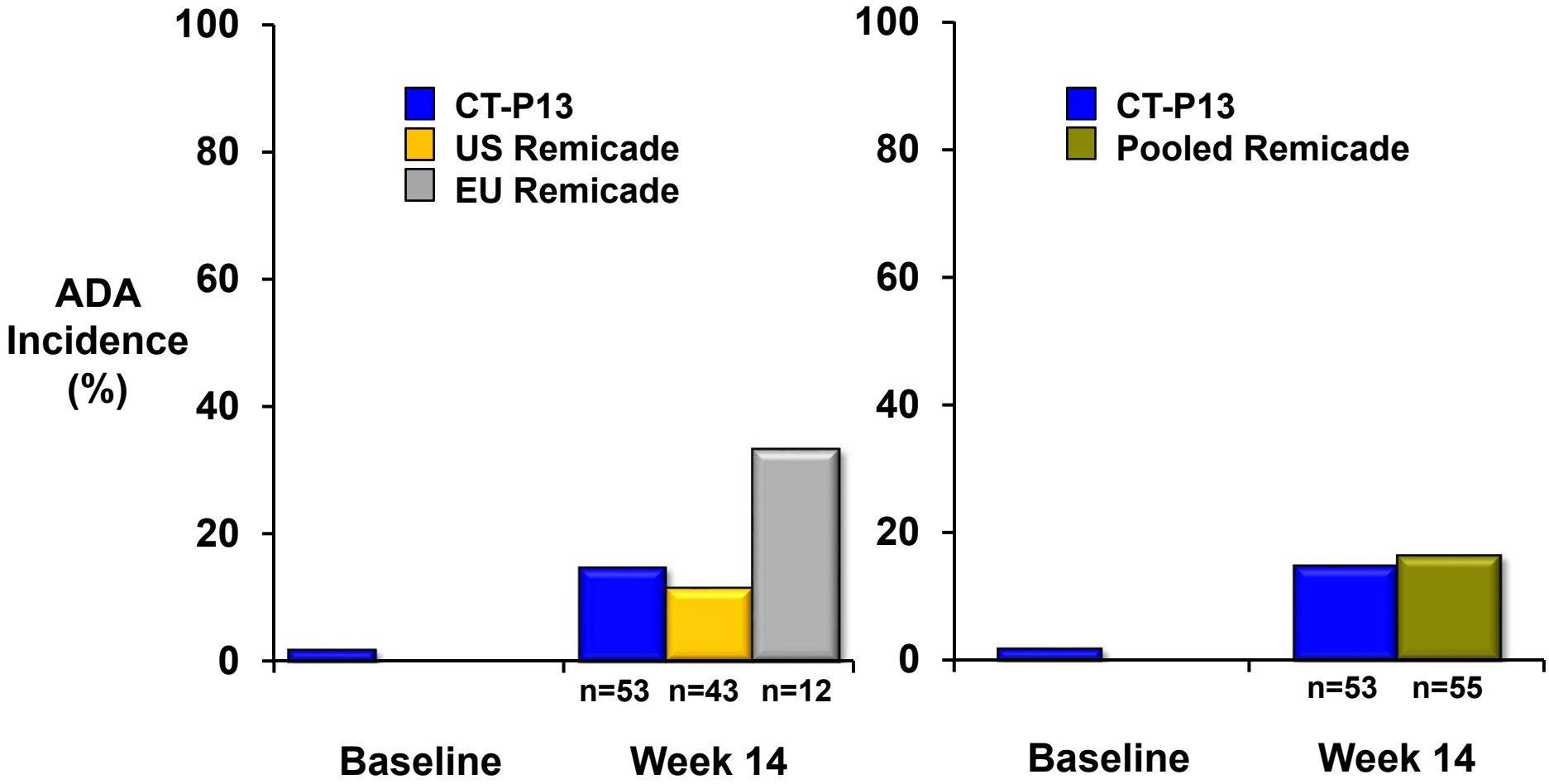
- Immunogenicity profile remains stable following single transition

Infusion-Related Reactions and Anaphylaxis Support Consistent Immunogenicity Profile

Anti-drug Antibody Status	RA Study (+MTX) CT-P13 (N = 302)	RA Study (+MTX) EU Remicade (N = 300)	AS Study (Monotherapy) CT-P13 (N = 128)	AS Study (Monotherapy) EU Remicade (N = 122)
% Reporting Infusion-related AEs				
Antibody Positive	13.6%	21.3%	13.6%	28.2%
Antibody Negative	5.3%	5.9%	6.0%	4.8%
% Reporting Anaphylaxis (Sampson Criteria[1])				
Antibody Positive	2.4%	1.2%	2.3%	7.7%
Antibody Negative	1.5%	1.5%	0	0

[1] Sampson *et al*., (2006)

Similar Immunogenicity between CT-P13 and Remicade in Post-Approval CD Study[1]

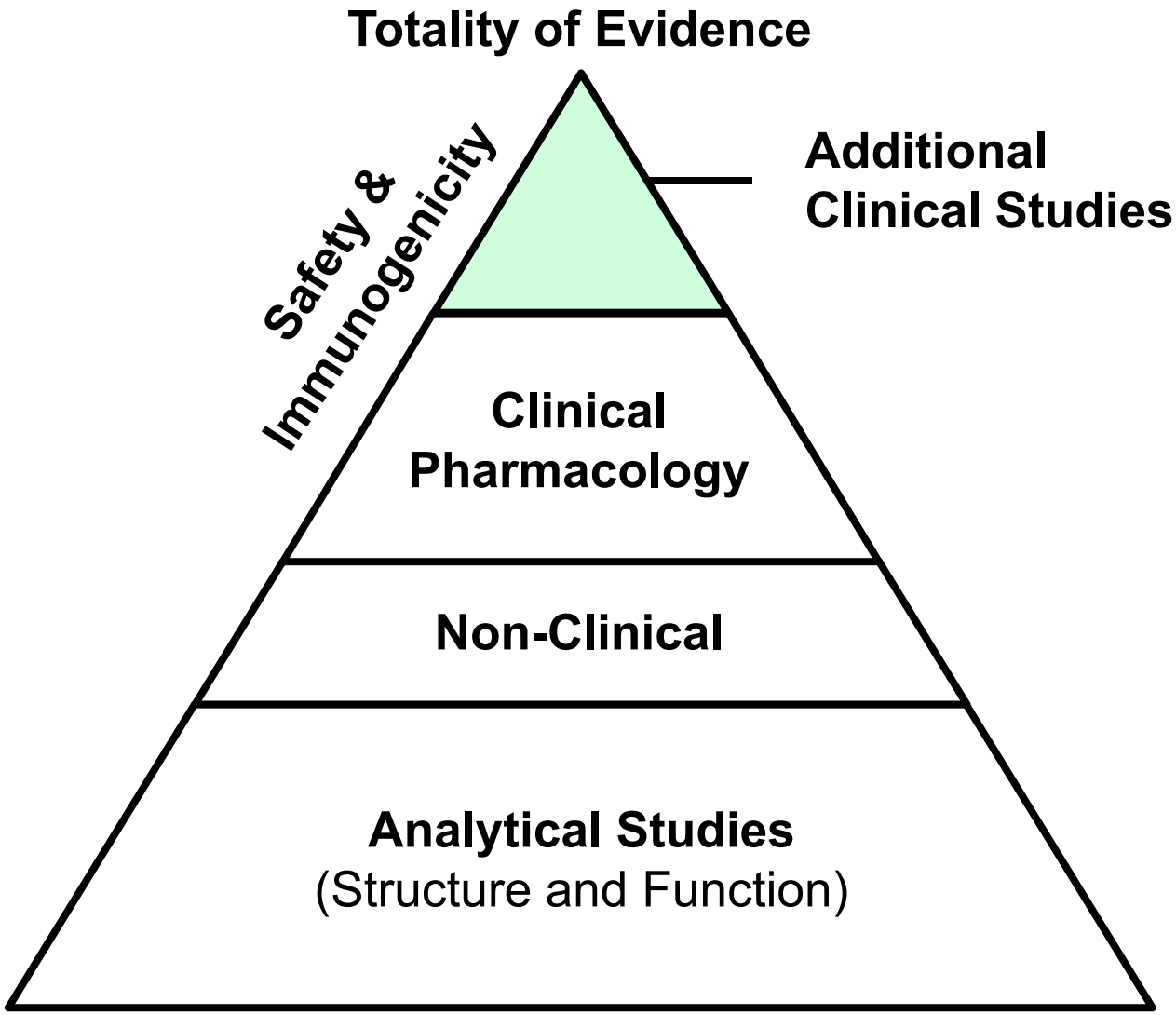


[1] Interim analysis

Evidence for Similar Immunogenicity Profile between CT-P13 and Remicade

- Systematic evaluation using validated state-of-art methods
- Similar proportion of patients developing ADAs to CT-P13 and Remicade in AS, RA, and CD
- Similar impact of ADA on PK and efficacy
- Similar incidence of infusion-related reactions and anaphylaxis

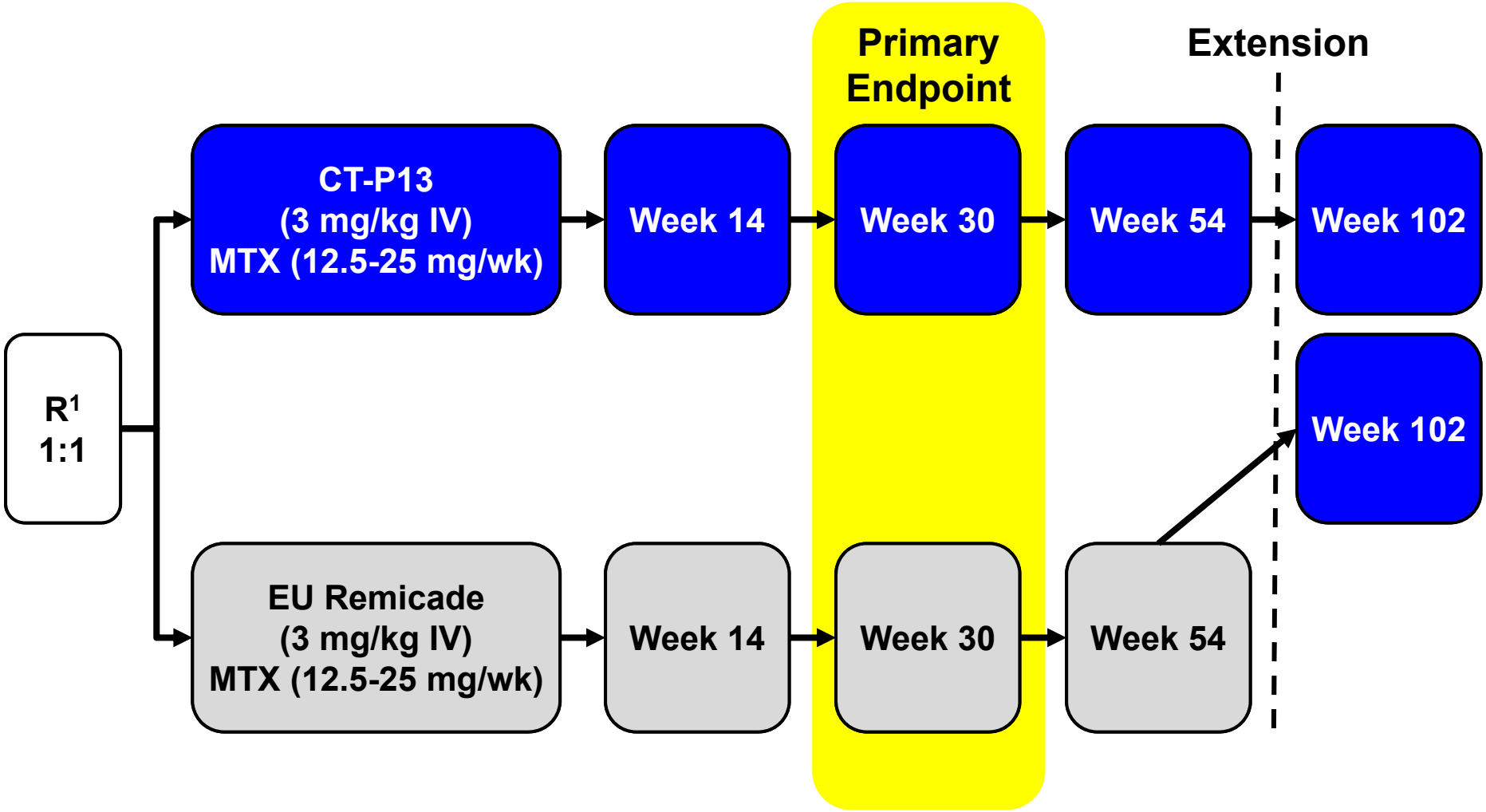
Clinical Efficacy in Rheumatoid Arthritis



Rationale for CT-P13 RA Study

- Designed in line with scientific input from EMA
- Most studied and sensitive indication
- Broad, dose-dependent historical data
- ACR20 used as validated endpoint for equivalence
- Lower and potentially more immunogenic 3 mg/kg dose

Overview of RA Study Design



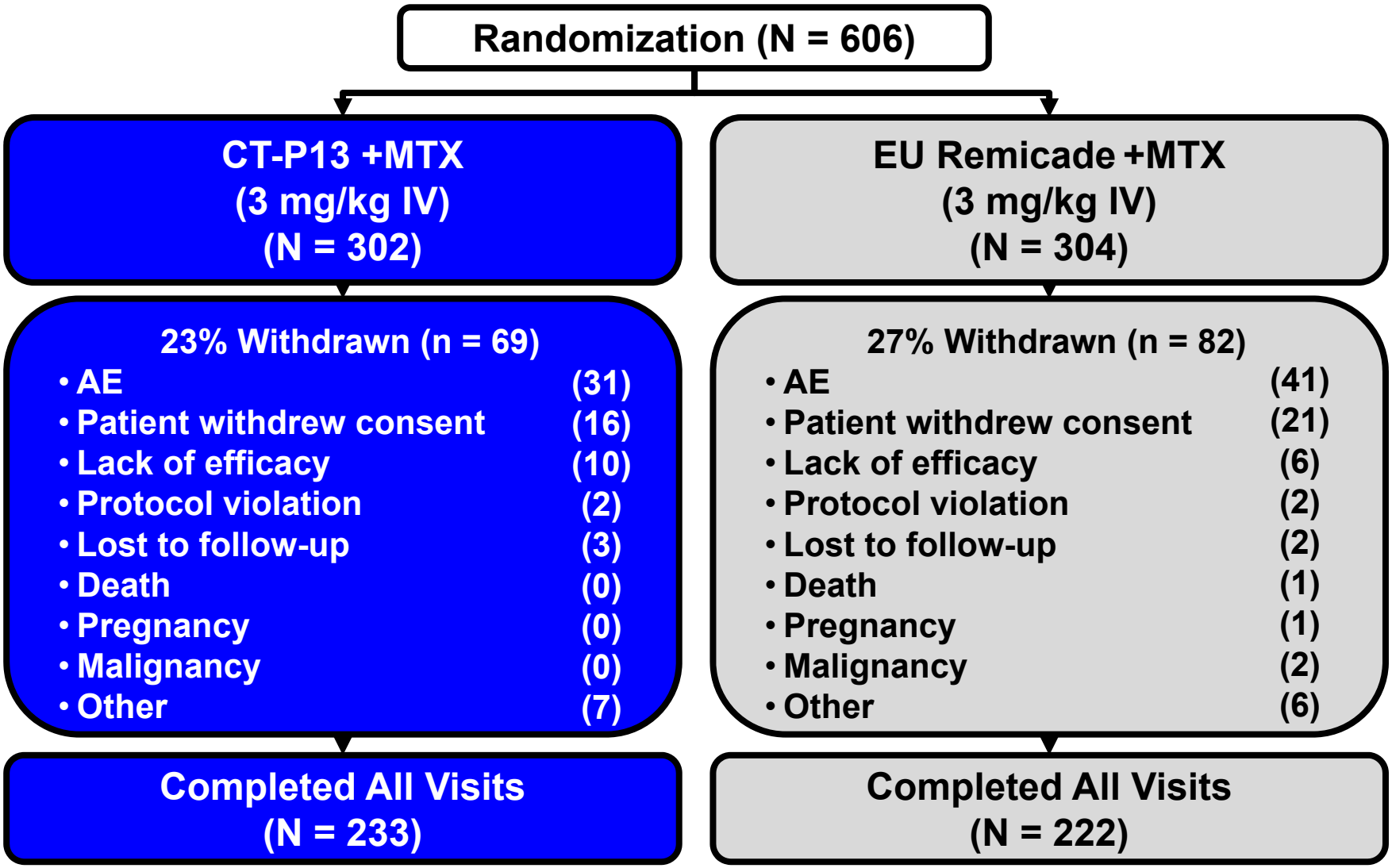
[1] Randomization and stratification by region and CRP

RA Study Statistical Design

- Pre-specified ACR20 equivalence margin = 15%
  - Based on absolute treatment differences from historical Remicade RA studies[1]
  - Power 80%, 95% CI
- FDA suggested margin derived from meta-analysis (RCTs) using CI approach
  - Resulting equivalence margin = 12%
  - Power 83%, 90% CI

[1] Includes ATTRACT study (Matthew SBA)

RA Study Disposition



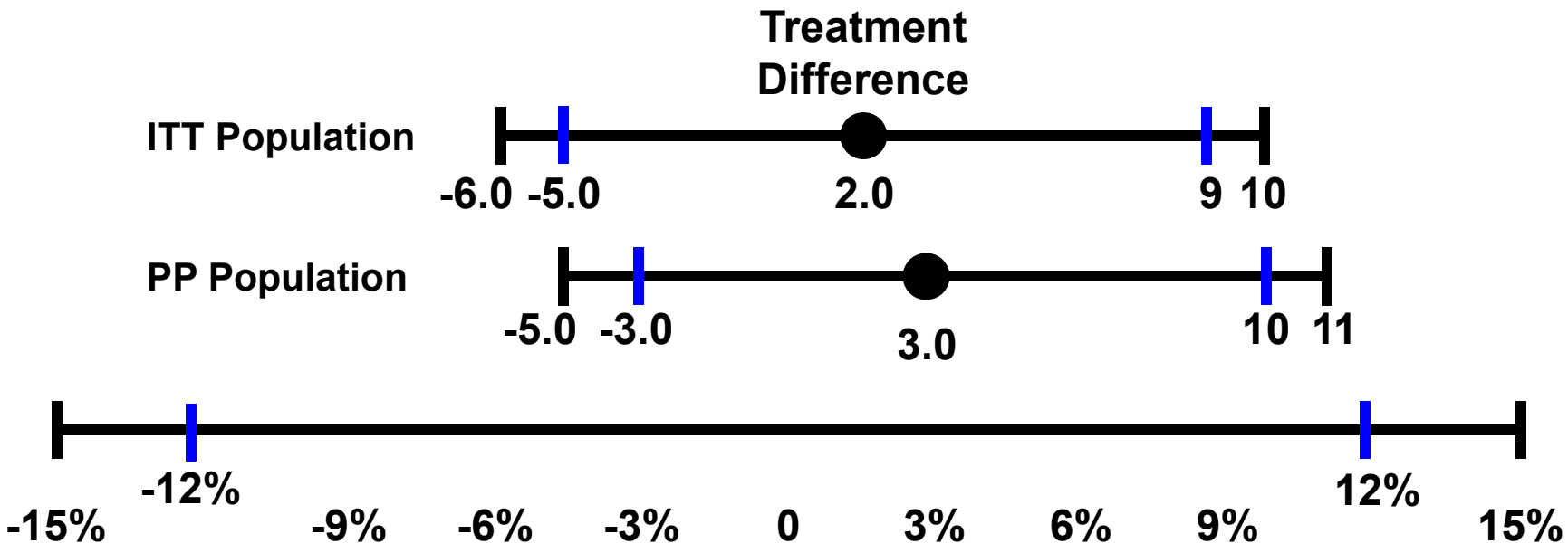
RA Study: Baseline Characteristics

Category		CT-P13 +MTX (N = 302)	EU Remicade +MTX (N = 304)
Age (years)	Mean (SD)	49.0 (12.2)	48.6 (11.5)
Gender	Female	81%	84%
Race	Caucasian	73%	73%
	Black	1%	0.3%
	Asian	11%	12%
	Other	15%	15%
BMI (kg/m^2)	Mean (SD)	26.5 (5.3)	26.3 (5.3)
Serum CRP Concentration	≤ 2 mg/dL	54%	55%
	> 2 mg/dL	46%	45%
MTX Therapy (Duration)	< 1 year	51%	50%
	1 to < 3 years	33%	31%
	≥ 3 years	17%	20%

SD: Standard Deviation, CRP: C-reactive protein

Therapeutic Equivalence of ACR20 at Week 30 Established between CT-P13 and Remicade

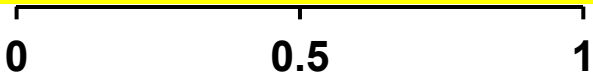
	CT-P13 + MTX	EU Remicade + MTX
ITT Population	60.9%	58.9%
PP Population	73.4%	70.1%



Equivalence pre-specified margin = 15%
FDA suggested equivalence margin = 12%

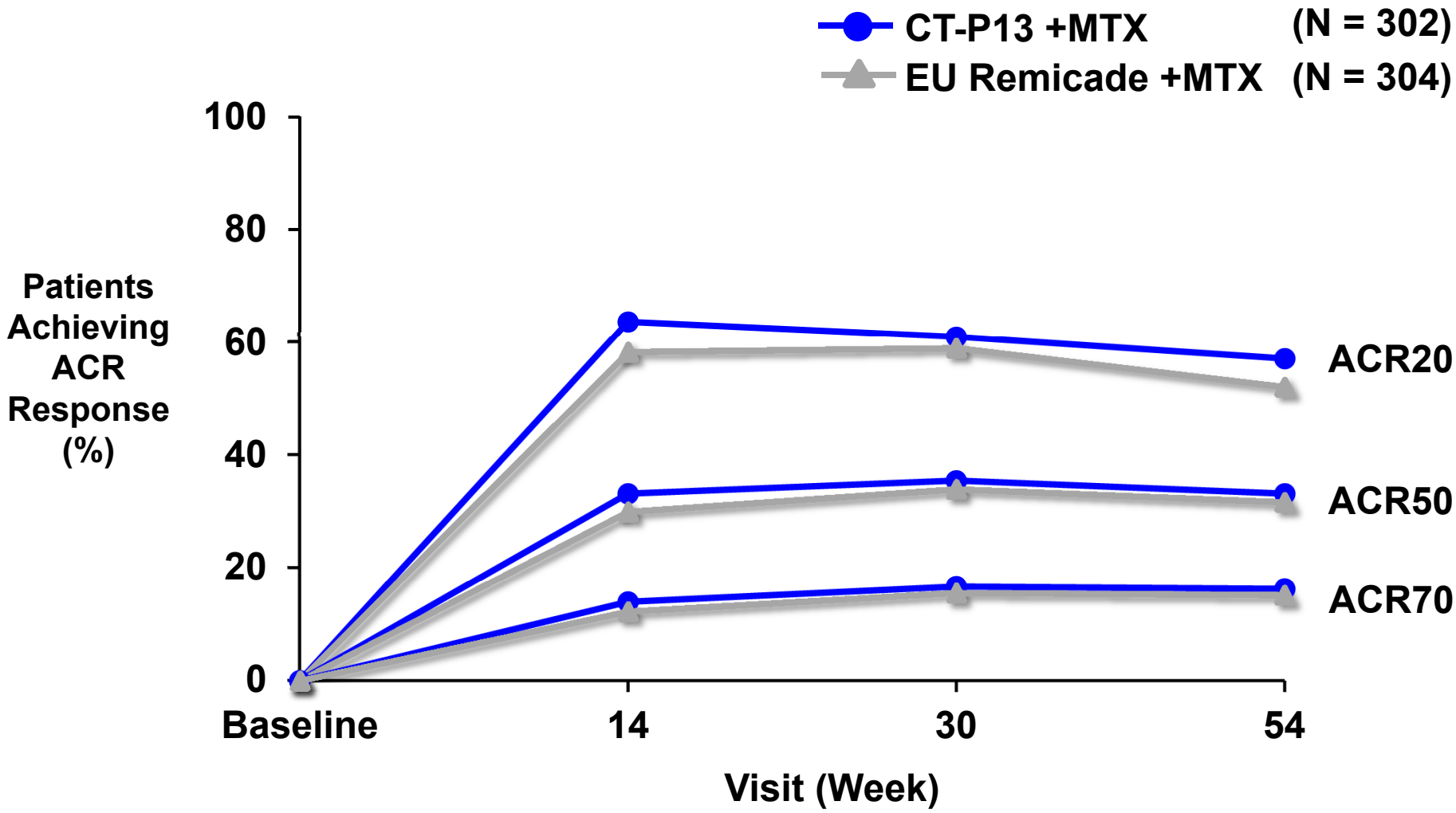
ACR20 Results Align with Historical Remicade Data in MTX-IR[1] RA Patients

Reference	Group	ACR20 n/N	Response Rate (95% CI)
ATTRACT (1999) – Wk 30	Infliximab	43/86	0.50 (0.39, 0.61)
	Placebo	18/88	0.20 (0.13, 0.30)
Westhovens *et al*., (2006) – Wk 22	Infliximab	209/360	0.58 (0.53, 0.63)
	Placebo	87/361	0.24 (0.20, 0.29)
Schiff *et al*., (2008) – Wk 28	Infliximab	97/165	0.59 (0.51, 0.66)
	Placebo	46/110	0.42 (0.32, 0.52)
Zhang *et al*., (2006) – Wk 18	Infliximab	66/87	0.76 (0.65, 0.84)
	Placebo	42/86	0.49 (0.38, 0.60)
Abe *et al*., (2006) – Wk 14	Infliximab	30/49	0.61 (0.46, 0.75)
	Placebo	11/47	0.23 (0.12, 0.38)
RA Study - Wk 30	**EU Remicade**	179/304	0.59 (0.53, 0.64)
	CT-P13	184/302	0.61 (0.55, 0.66)



[1] IR: Incomplete responders

RA Study Demonstrated Similar ACR Response over 54 Weeks



Clinical Safety

Remicade Safety Profile Background

- FDA Guidance (2015)
  - "Biosimilar products…can rely on certain existing scientific knowledge about safety… of the reference product to support licensure"[1]
- > 4.2 million patients exposed to Remicade
- Relatively well-understood and communicated risks
- Comparable AE profile across approved indications[2]

[1] FDA Biosimilar Guidance (2015)
[2] Remicade USPI (2015)

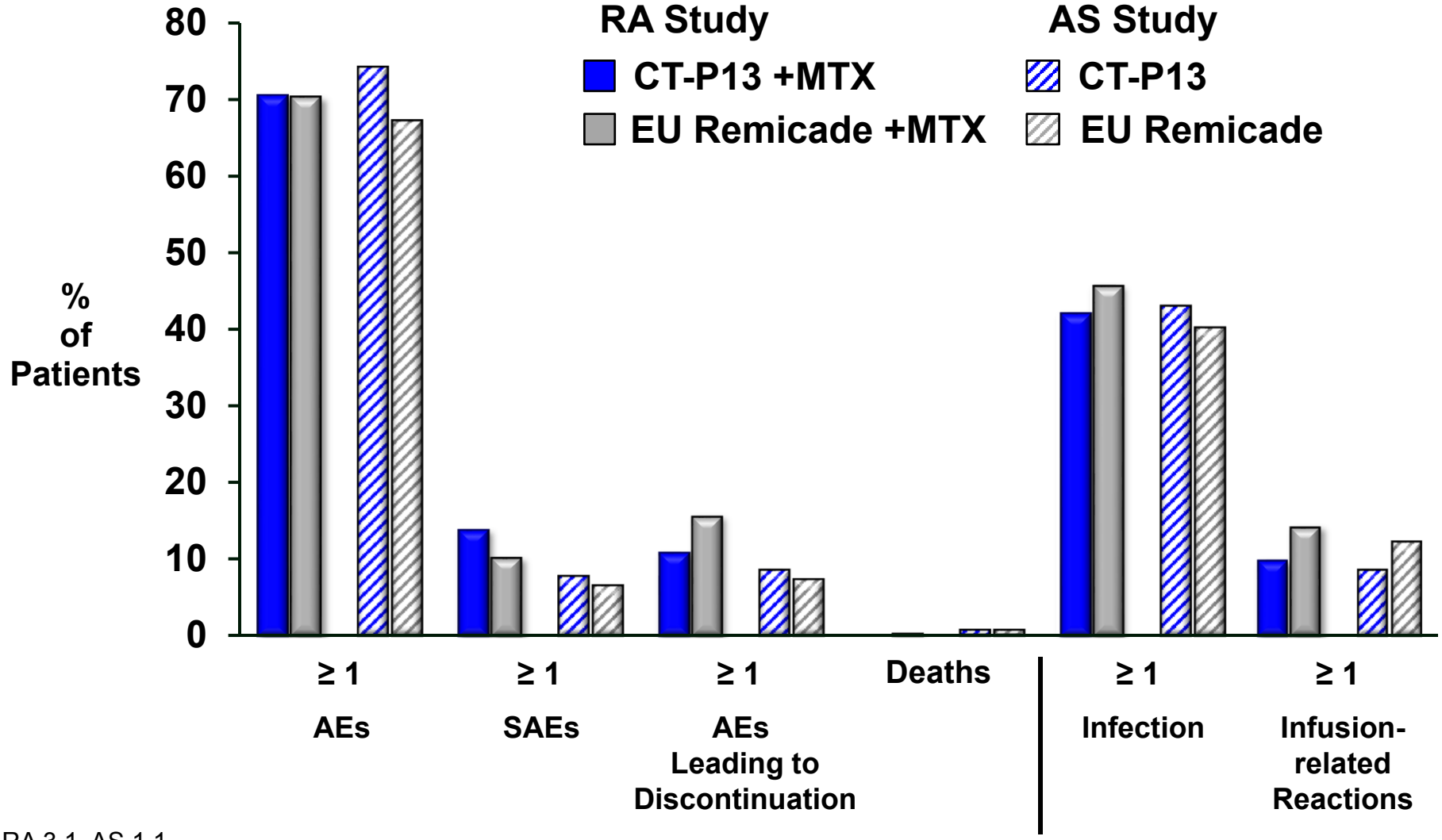
Safety Database Supports Biosimilar Application

- ~1,000 treated with either CT-P13 or Remicade
  - > 800 treated with ≥ 1 dose of CT-P13

	Exposure to CT-P13		
	≥ 6 Months	≥ 1 Year	≥ 2 Years
AS Study	117	109	84
AS Extension Study[1]	79	76	-
RA Study	257	237	141
RA Extension Study[1]	136	128	-
Pilot RA Study	14	13	5
Russia RA Study	6	6	-
Japan RA Study	44	42	-
Total	**653**	**611**	**230**

[1] Single-way transition from Remicade

Safety Overview – RA and AS Studies



RA 3.1, AS 1.1

Deaths

Study	Treatment Group	Days on Therapy	Cause of Death[1]	Related to Treatment
RA (N = 602)	EU Remicade (+MTX)	379	Sudden Death	No
RA Extension (N = 302)	CT-P13 (+MTX)	578	Appendectomy Complication	No
AS (N = 250)	EU Remicade (Monotherapy)	246	Car Accident	No
	CT-P13 (Monotherapy)	423	Car Accident	No

[1] As reported by investigator

RA and AS AEs Leading to Discontinuation

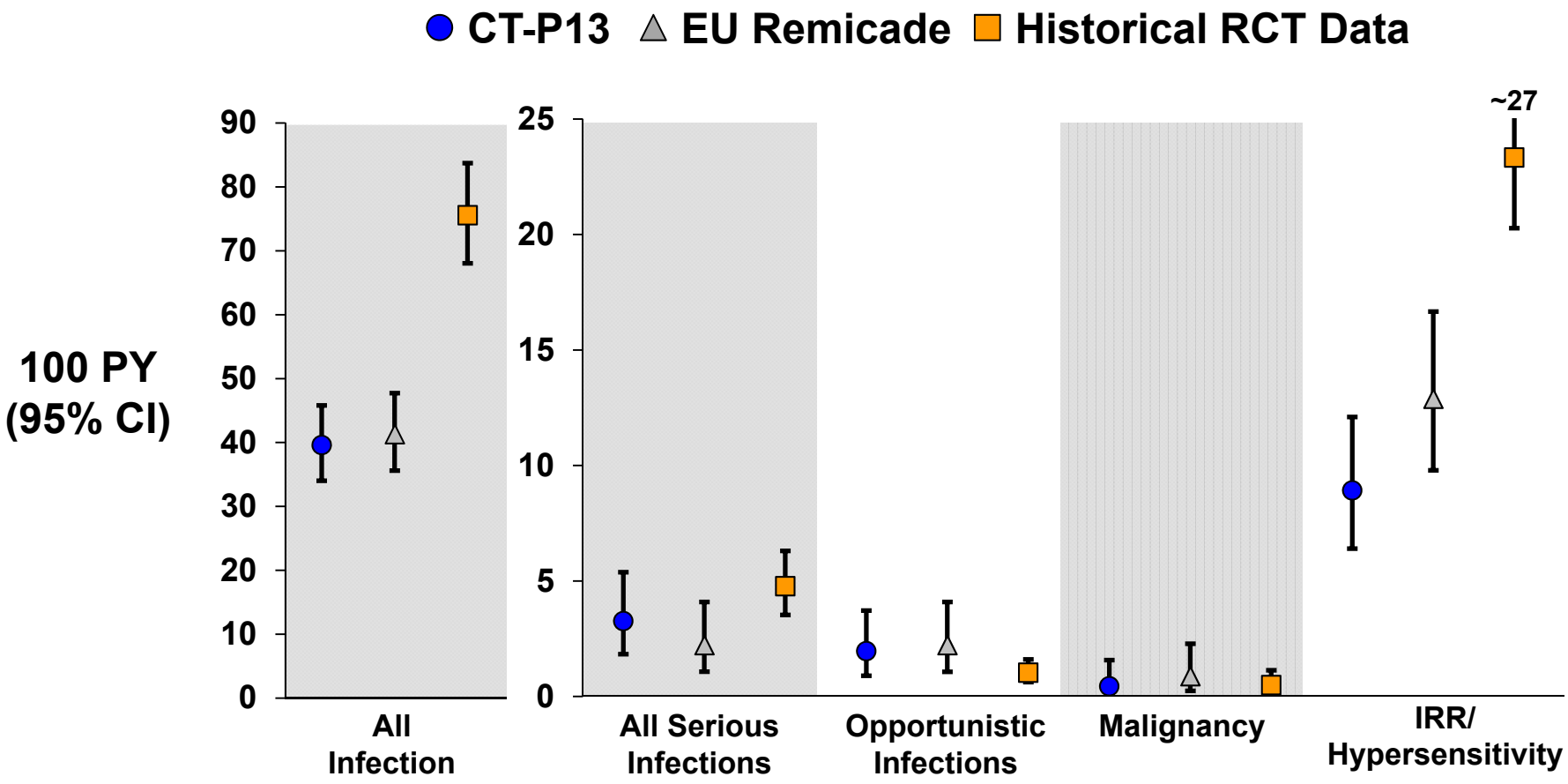
AE Leading to Permanent Study Treatment Discontinuation	RA Study (+MTX)		AS Study (Monotherapy)	
	CT-P13 (N = 302)	EU Remicade (N = 300)	CT-P13 (N = 128)	EU Remicade (N = 122)
Any AE	10.9%	15.7%	8.6%	7.4%
IRR	4.6%	5.7%	0.8%	4.1%
Infection	3.0%	6.0%	2.3%	0.8%

Overall AEs: RA and AS Studies (Preferred Term ≥ 3%)

Preferred Term	RA and AS Studies	
	CT-P13 (N = 430)	EU Remicade (N = 422)
Upper Respiratory Tract Infection	19.3%	16.1%
Latent Tuberculosis	8.8%	7.6%
Alanine Aminotransferase Increased	7.9%	8.5%
Urinary Tract Infection	6.3%	5.7%
Headache	5.6%	7.1%
Aspartate Aminotransferase Increased	5.1%	5.2%
Lower Respiratory Tract Infection	4.4%	5.7%
Hypertension	4.4%	2.6%
Anemia	3.7%	4.3%
Rheumatoid Arthritis	3.7%	2.6%
Diarrhea	3.5%	2.4%
Influenza	3.0%	2.6%
Rash	2.8%	3.8%
Infusion-related Reaction	2.3%	3.6%
Drug Hypersensitivity	1.9%	3.3%
Pyrexia	1.6%	3.8%
Herpes Virus Infection	1.4%	3.6%

RA 3.1, AS 1.1

Incidence Rate of AESI in RA and AS Studies

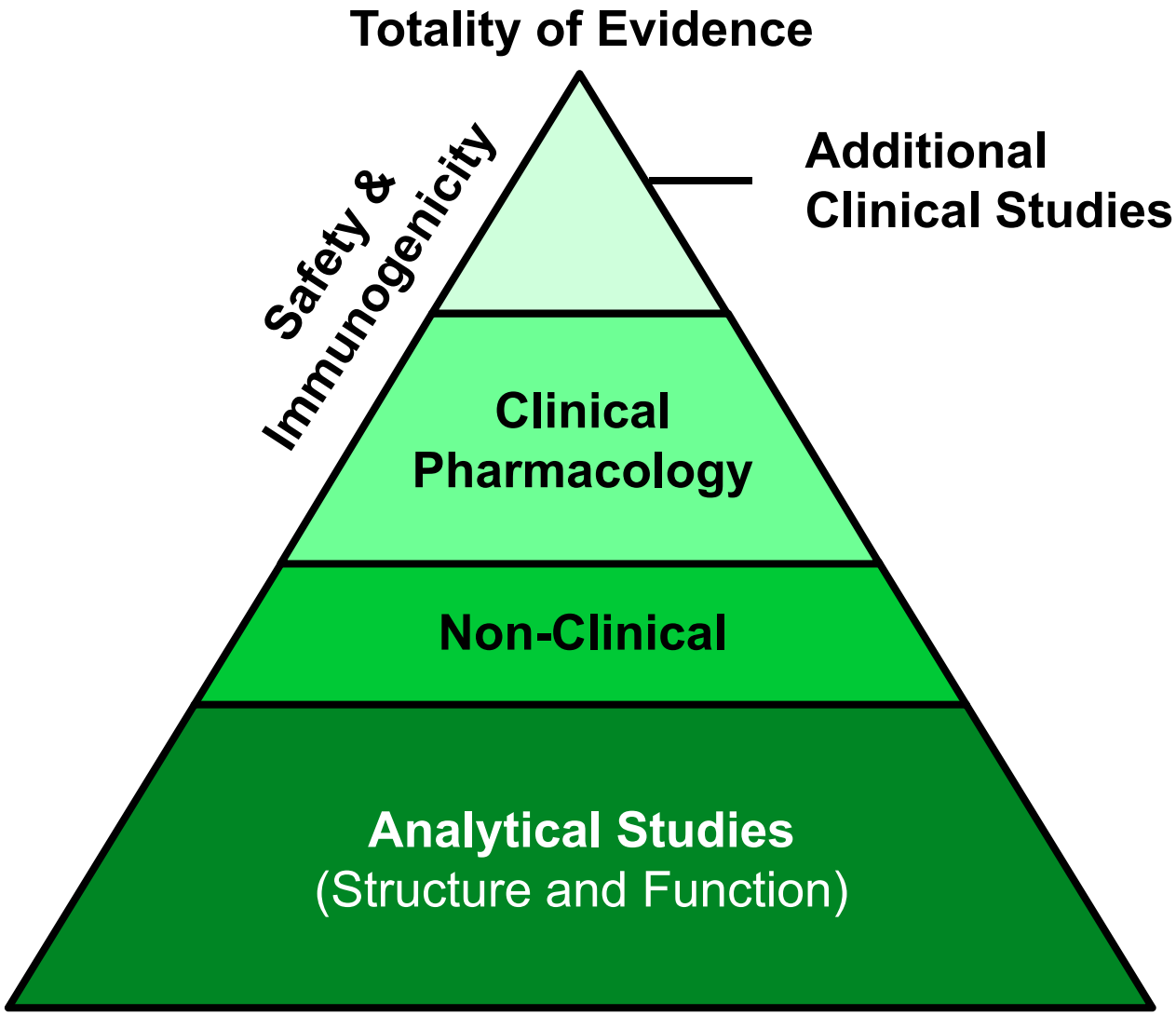


Abe *et al.,* (2006); Braun *et al.,* (2002)*;* Breban *et al.,* (2008); Giardina *et al.,* (2010); Lipsky *et al*., (2000); Maini *et al*., (1999); Marzo-Ortega *et al*., (2005); Quinn *et al.,* (2005); Remicade RMP (2015); Schiff *et al*., (2008); St. Clair *et al.,* (2004); Van Der Heijde *et al*., (2005); Westhovens *et al.*, (2006)
RA 3.1, AS 1.1

Similar Safety Profile as Remicade

- High similarity in structure and function predicts similar clinical safety
- No clinically meaningful differences in relation to overall safety and immunogenicity
- Similar impact of immunogenicity on PK, efficacy and safety across all studies

Totality of Evidence Supports Biosimilarity

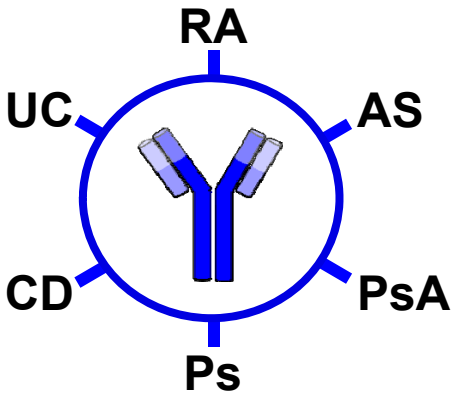


Biological Assays Support Extrapolation to All Indications

Activity	Assay	CT-P13 vs. US (High Similarity)
Binding to sTNFα	*In Vitro* TNFα Neutralization	✓
	TNFα Binding Affinity (ELISA)	✓
	Cytokine Suppression (Caco-2)	✓
Binding to tmTNFα	Cell Based Binding Affinity	✓
	Inhibition of Cytokine Release by Reverse Signaling	✓
	Induction of Apoptosis by Reverse Signaling	✓
	Induction of Regulatory Macrophages	✓
	Suppression of T Cell Proliferation by Regulatory Macrophages	✓
	Wound Healing by Regulatory Macrophages	✓
FcRn Binding	FcRn Binding Affinity (SPR)	✓
C1q Binding & CDC Activity	C1q Binding Affinity (ELISA)	✓
	CDC	✓
Fc Binding	FcγRIIIb Binding Affinity (SPR)	✓
	FcγRIIa Binding Affinity (SPR)	✓
	FcγRIIb Binding Affinity (SPR)	✓
	FcγRI Binding Affinity (ELISA)	✓
	Ex Vivo Binding in 50% Serum with NK Cells	✓
tmTNF & Fc Binding	ADCC using PBMC (Healthy Donor)	✓
	ADCC using NK Cells (Healthy Donor)	✓
	ADCC using LPS-stimulated Monocytes and NK Cells (Healthy Donor)	✓
	ADCC using LPMC and NK Cells (IBD patient)	✓

Common MoA, PK and Safety Supports Extrapolation

1. **Known and potential MoA**
   - ✓ CT-P13 and US Remicade are highly similar for all MoAs involving Fab- and Fc-regions



2. **PK across conditions of use**
   - ✓ Remicade has well-characterized, linear and predictable PK across all indications
   - ✓ CT-P13 and US Remicade have highly similar PK

3. **Similar immunogenicity and comparable safety**
   - ✓ Remicade has comparable immunogenicity and safety profile across all indications
   - ✓ CT-P13 and US Remicade have similar immunogenicity in AS, RA and CD. Comparable safety in AS and RA

Extrapolation to PsA, Ps, CD and UC

CT-P13 Use in Patients with Inflammatory Bowel Disease: Post-Marketing Clinical Studies and Real-World Experience

Peter Lakatos, MD, PhD, FEBG

Associate Professor

Head of Gastroenterology

Semmelweis University, Budapest, Hungary

Experience with CT-P13 in IBD

- Real-world clinical data from studies and cohorts in Korea and several European countries
- Prospective nationwide observational study from Hungary
- Data submitted to FDA

Practicing Gastroenterologist for > 15 Years Treating CD and UC Patients

- Conducted clinical studies and registries at national level
- European Crohn's and Colitis Organization
  - Head of Epidemiology Committee
  - Member of Educational Committee
  - National Representative of Hungary
- Founded Hungarian IBD Study Group

Disclosures

- Speaker and/or advisory board member
  - AbbVie, EGIS, Falk Pharma GmbH, Ferring, Genetech, Kyowa Hakko Kirin Pharma, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka, Pharmacosmos, Pfizer, Roche and Takeda
- Unrestricted research grants
  - AbbVie, MSD and Pfizer
- No financial stake in CELLTRION or Pfizer

Hungarian IBD Study is Prospective, Uncontrolled Observational Study[1]

- Nationwide, open-label, observational multi-center study enrolling unselected and consecutive patients
- Initiated May 2014 following Hungarian launch
  - EU approval for all infliximab indications
- New patients
  - Infliximab naive
  - Patients who previously responded to Remicade with drug holiday for ≥ 12 months
- Evaluations: Week 14, and every 3 months
- Planned investigational period ≥ 54 weeks

[1] Gecse *et al*., (2015)

Baseline Characteristics

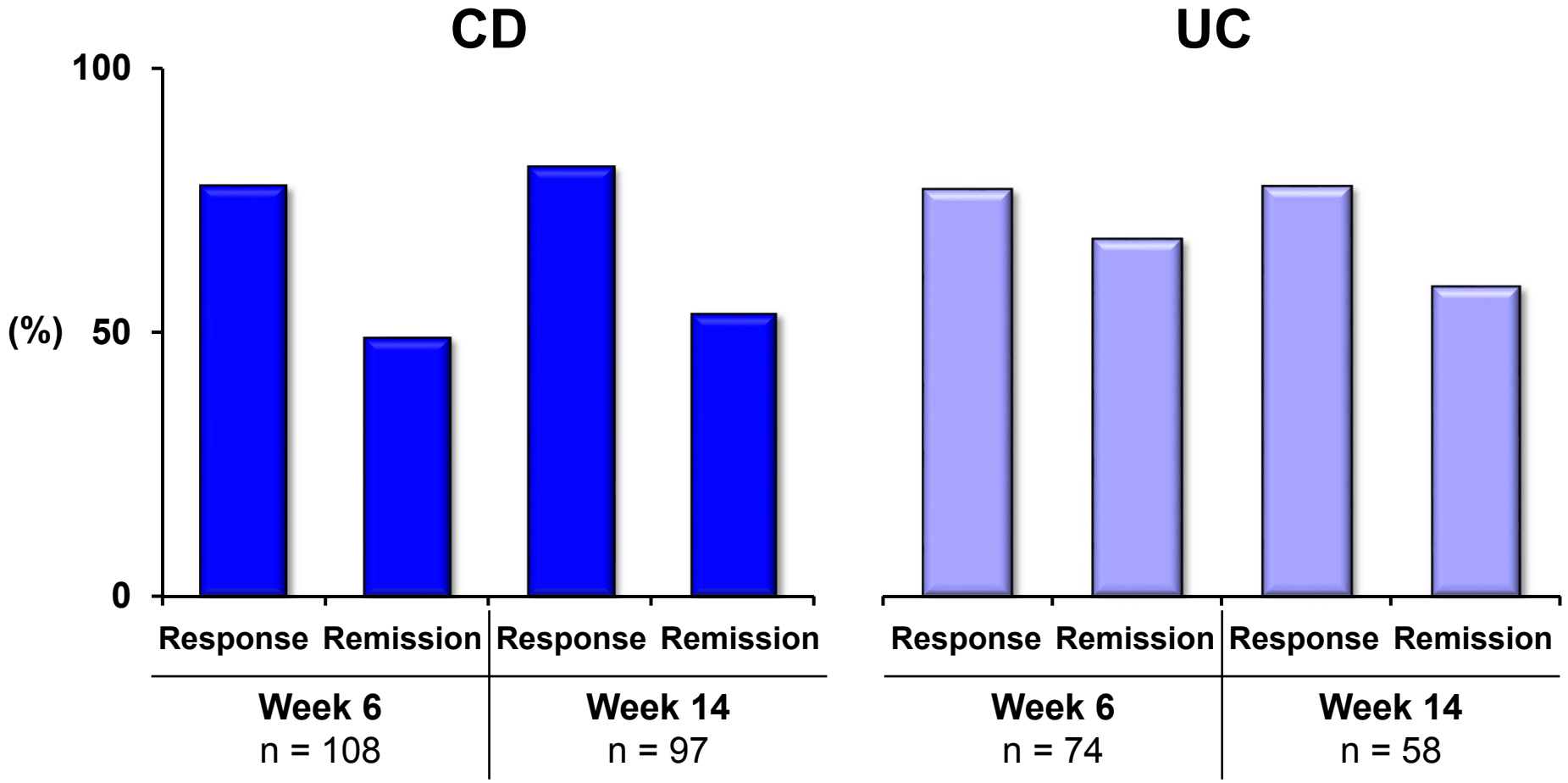
	CD (N = 126)	UC (N = 84)
Male/Female	**56 / 70**	**47 / 37**
Age at Onset, Median (IQR)	**24 (19-35) yrs**	**27 (22-37) yrs**
Duration, Median (IQR)	**6 (3-11) yrs**	**4 (2-12) yrs**
Baseline Activity, Median (IQR)	**CDAI:** 324 (310-353) n = 93 **PDAI:** 10 (IQR: 9-11) n = 33	**MAYO:** 9 (IQR: 8-11) **pMAYO:** 7 (IQR: 5-9)
Location (L1/L2/L3/L4/all L4)[1]	**17% / 40% / 42% / 2% / 9%**	-
Extent of Colitis (E1/E2/E3)[1]	-	**7% / 36% / 57%**
Behavior (B1/B2/B3)[1]	**58% / 22% / 20%**	-
Perianal	**33%**	-
Previous Surgery	**26%**	-

[1] L1: Ileal, L2: Colonic, L3: Ileocolon, L4: Upper GI, E1: Proctitis, E2: Left-sided colitis, E3: Extensive colitis, B1: Inflammatory, B2: Stenotic, B3: Penetrating

Prior and Concomitant Use of Anti-Inflammatory and Immunomodulatory Agents

	CD (N = 126)	UC (N = 84)
Prior Treatments		
5ASA (Local UC)	85%	92% (52%)
Steroids	82%	92%
AZA	87%	77%
CSA	-	10%
TNFα (IFX/ADA)	26% (22% / 4%)	19% (11% / 6%)
Concomitant Immunomodulators		
Steroids	48%	64%
AZA	63%	57%

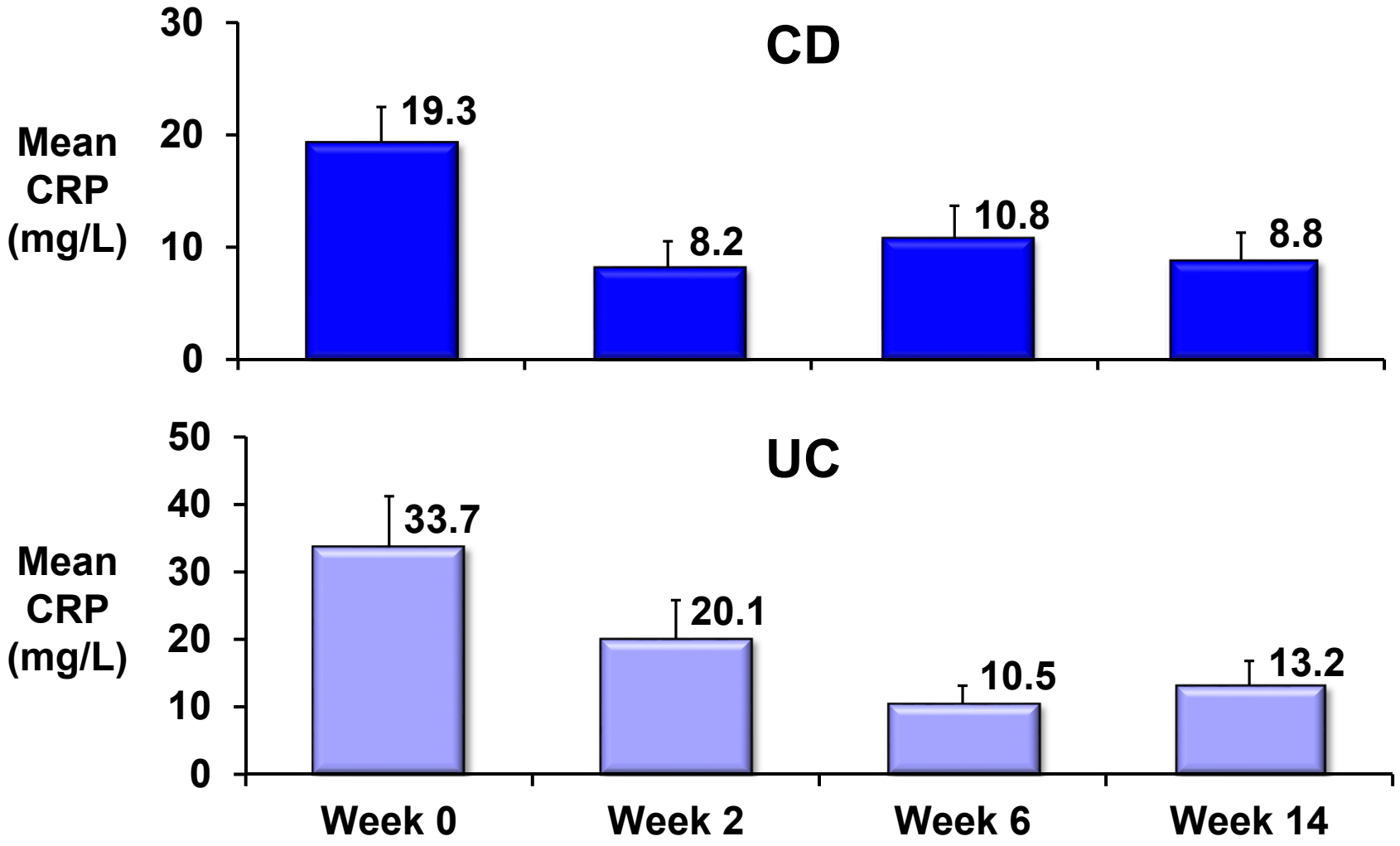
Early Clinical Response and Remission with CT-P13



Response: CD = CDAI Δ > 70 points or fistula drainage Δ > 50%, UC = pMAYO Δ > 3
Remission: CD = CDAI < 150 or no fistula drainage reported, UC = pMAYO < 3

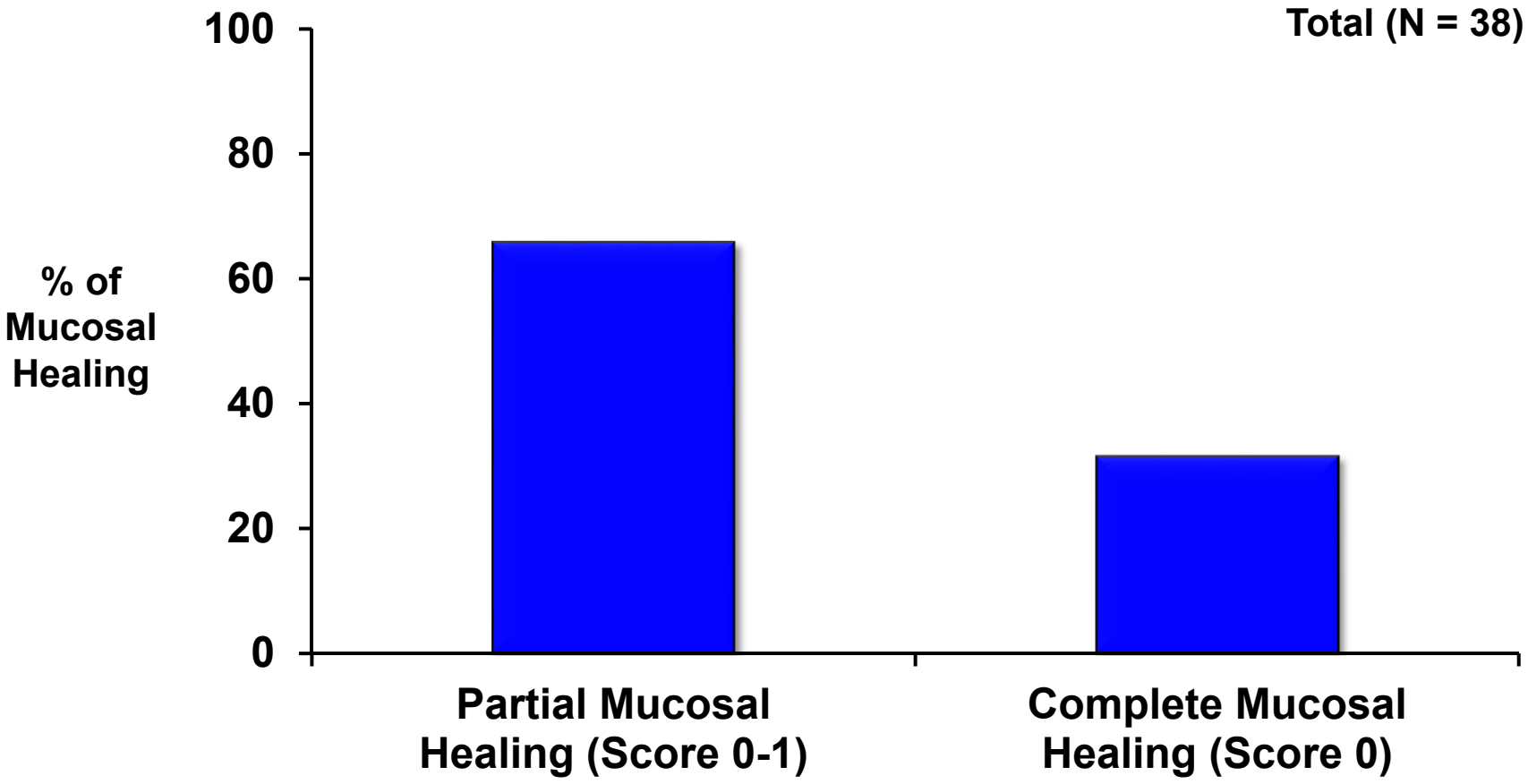
Hungarian IBD Study Group

Early Biomarker Response in IBD



Hungarian IBD Study Group

Early Mucosal Healing in UC by Week 14



Compared to baseline; Molnar *et al.,* 2015 UEGW P1605
Mucosal healing was defined as Mayo endoscopic subscore of 0 or 1.
Complete mucosal healing was defied as Mayo endoscopic subscore of 0.

Early ADA Positivity in IBD Patients Treated with CT-P13

	Infliximab Naive	Previous Infliximab Exposure	Total
	Number of Patients with ADA Positivity (%)		
Total IBD Patients			
Baseline	5/130 (4%)	10/37 (27%)	15/167 (9%)
Week 14	15/80 (19%)	8/23 (35%)	23/103 (22%)
CD Patients			
Baseline	3/75 (4%)	6/24 (24%)	9/99 (9%)
Week 14	8/48 (17%)	5/13 (39%)	13/61 (21%)
UC Patients			
Baseline	2/55 (4%)	4/13 (31%)	6/68 (9%)
Week 14	7/32 (22%)	3/10 (30%)	10/42 (24%)

CT-P13 Post-Approval Studies

Other (AS, RA, PsA, Ps) Indications

CELLTRION Studies

- Korean PMS Study in AS, RA, PsA, Ps — N = 890
- Observational Cohort Study in RA — N = 108
- Observational Cohort Study in AS — N = 95

IBD (CD, UC) Indication

CELLTRION Studies

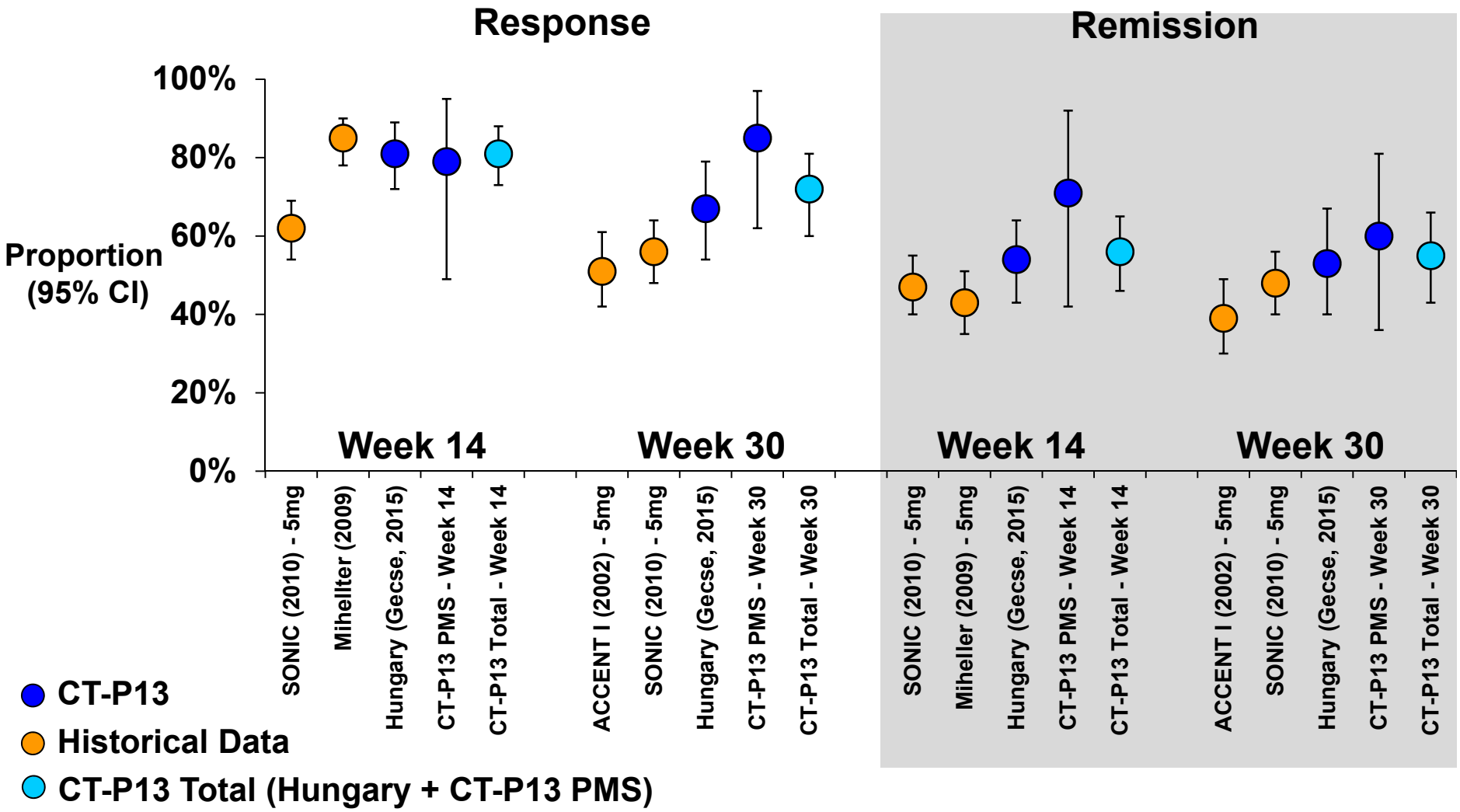
- Post-approval study (CD) up to Week 54 — N = 220
- Korean PMS Study in IBD — N = 173
- Open-label, Single-arm Study in IBD — N = 10
- Observational Single-arm Study in IBD — N = 63

Real-world Studies

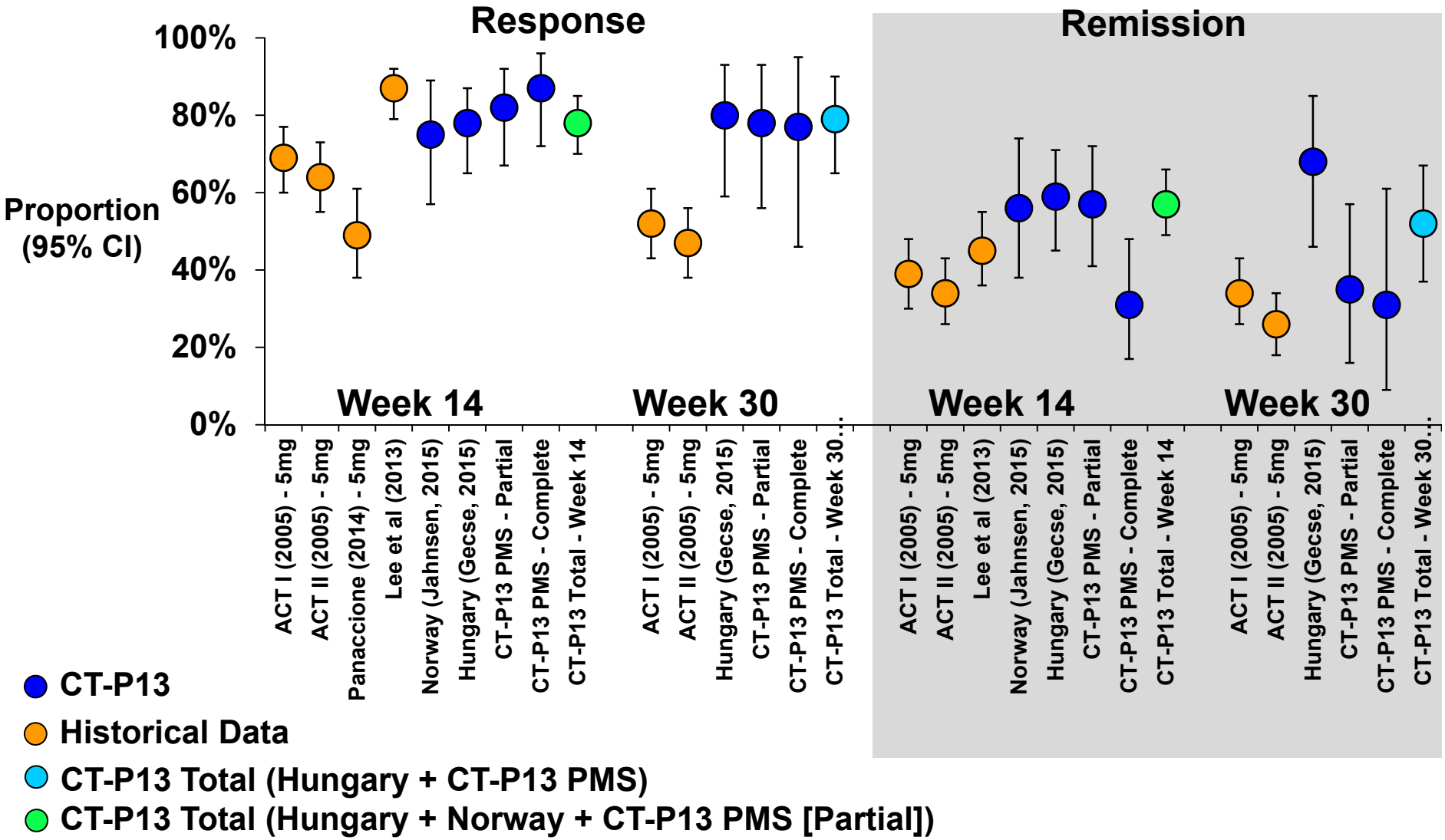
- Hungarian Nationwide IBD Study — N = 210
- Norwegian IBD Study — N = 78
- Other Published Sources in IBD — N = 773

Blue: Controlled study (CT-P13, EU Remicade and US Remicade)
Orange: Post-marketing study (CT-P13 and other anti-TNFs cohorts)

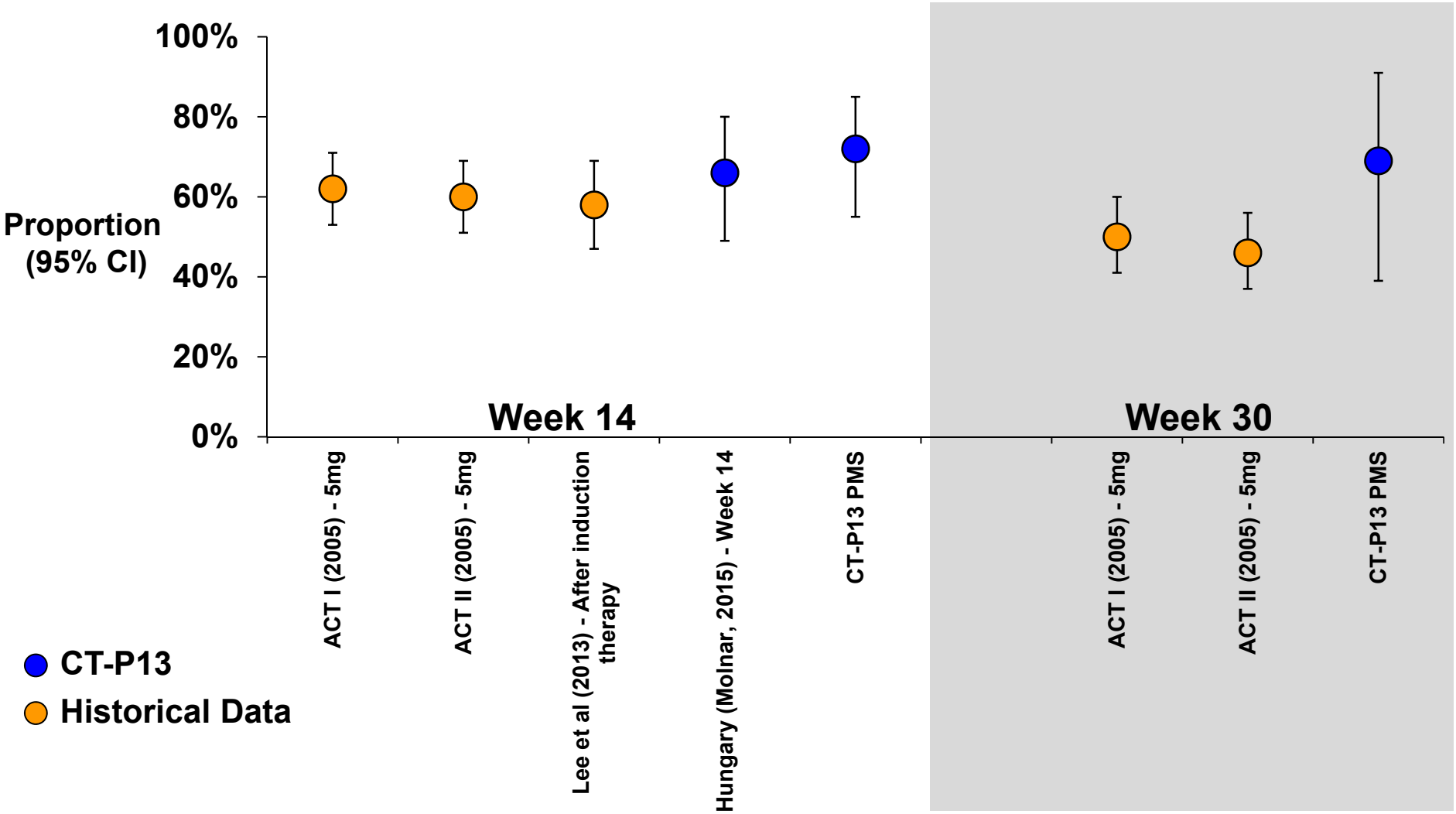
Comparison of Clinical Response/ Remission with Historical CD Data



Comparison of Clinical Response/ Remission with Historical UC Data



Comparison of Mucosal Healing with Historical Data in UC Patients



Post-Marketing Data Support CT-P13 Effective in IBD

- Response, remission and mucosal healing rates consistent with those reported with Remicade
  - EU and South Korean cohorts
- Drug trough and ADA levels in Hungary consistent with Remicade use in IBD
- Data collected to date suggest CT-P13 is biosimilar to Remicade in CD and UC patients

Totality of Evidence of CT-P13: Clinical Perspective

Vibeke Strand, MD, MACR, FACP
Adjunct Clinical Professor
Division of Immunology / Rheumatology
Stanford University

Disclosures

- Consultant, Clinical and Scientific Advisory Boards

AbbVie	Crescendo	Pfizer
Amgen	EMDSerono	Regeneron
Anthera	Genentech/Roche	Sandoz
AstraZeneca	GSK	Sanofi
BiogenIdec	Incyte	Takeda
BMS	Janssen	UCB
CELLTRION	Lilly	
Corrona	Novartis	

- I hold no stock or options

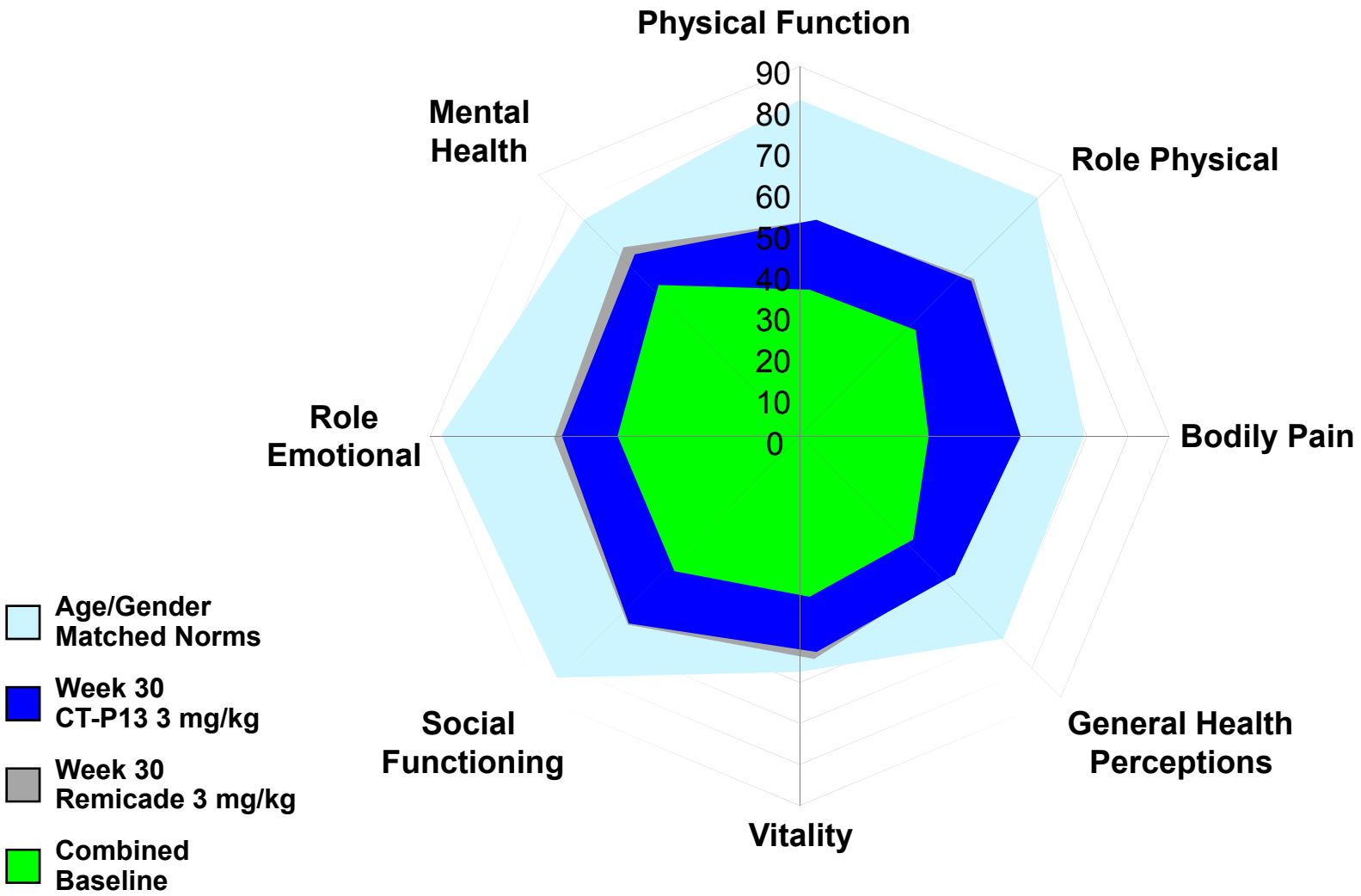
Emergence of Biosimilars is an Important Next Step

- Increased access to effective, expensive therapies
- Lowered cost to society of chronic debilitating diseases
- Filgrastim allowed broader use of effective doses to prevent febrile neutropenia
- Confident in biosimilarity pathway
- Does not require large randomized controlled trials
- Small residual differences can be assessed in context of variability of currently available biologic therapies

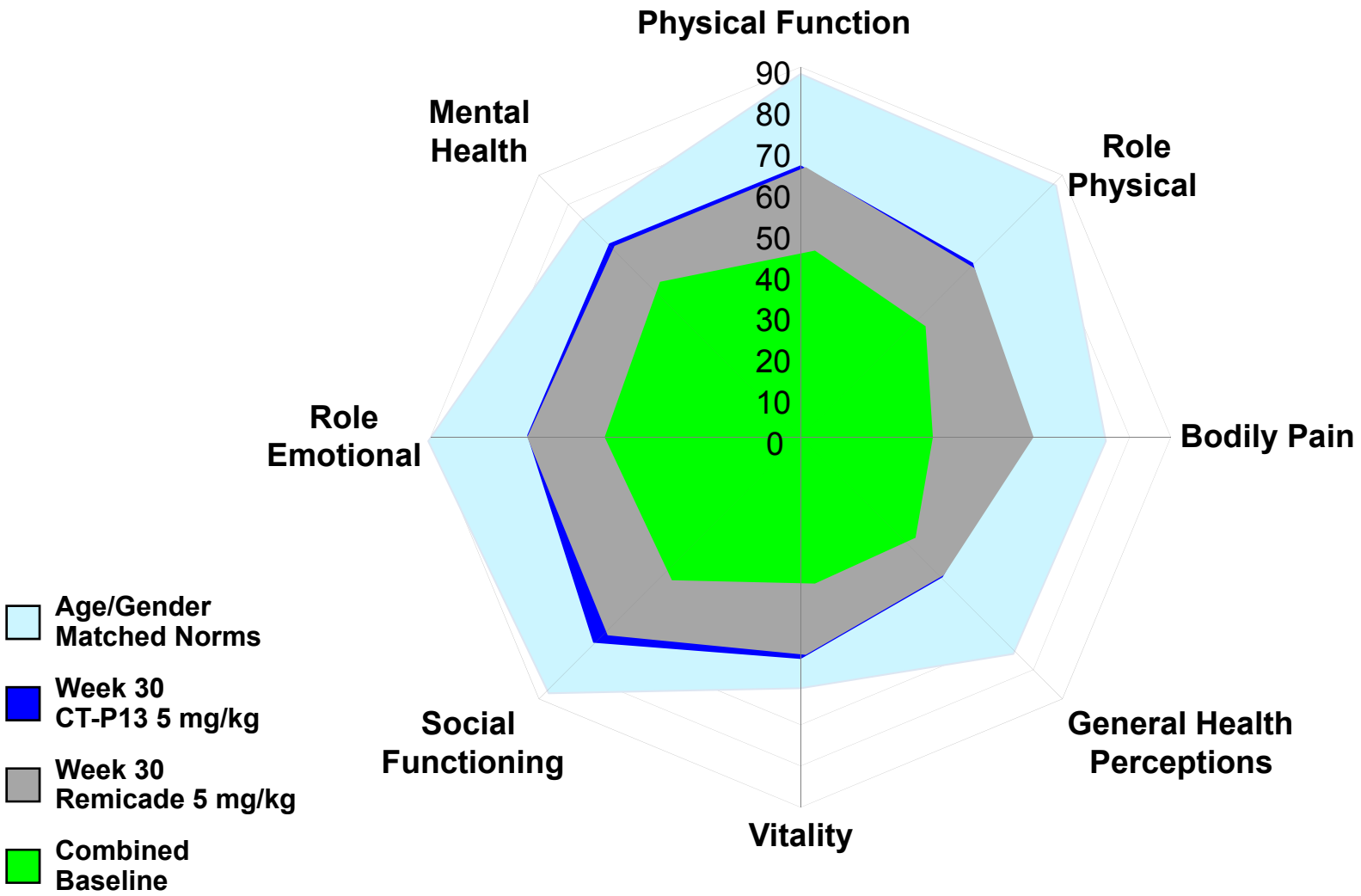
How I Evaluate this Biosimilar

- Equivalent structural and functional characteristics to originator
- Similar efficacy, immunogenicity and comparable safety profiles

SF-36 Domain Scores: CT-P13 vs. Remicade vs. Age/Gender Norms – BL and Week 30 (RA Study)



SF-36 Domain Scores: CT-P13 vs. Remicade vs. Age/Gender Norms – BL and Week 30 (AS Study)



How I Evaluate this Biosimilar

- Equivalent structural and functional characteristics to originator
- Similar efficacy, immunogenicity and comparable safety profiles
- Clinical performance is aligned with reference product

Extrapolation Scientifically Justified across All Indications

- Extrapolation further supported by real-world use in other countries
- Anti-TNF agents of different structures are effective/approved in Ps/PsA
  - Inhibition of sTNF and tmTNF primary MoA of infliximab
- Comparable immunogenicity profile between Ps/PsA and RA
- Comparable use of MTX and other immunomodulatory therapies across RA and PsA

Totality of Evidence Demonstrates Favorable CT-P13 Biosimilar Profile

- CT-P13 demonstrated to be highly similar to reference product
  - Structure and function
  - Efficacy, immunogenicity and comparable safety
- Supports licensure as a biosimilar to Remicade
- Supports extrapolation to all other clinical indications
- Approval would improve access and reduce costs

CT-P13 (Infliximab Biosimilar)

Arthritis Advisory Committee

February 9, 2016

CELLTRION, Inc.

Backup Slides Shown

RA Study Comparison with Historical Data

	PLANETRA Study	ATTRACT Study[1] (1999)	Westhovens *et al*., (2006)
ACR20 Rate	60.9% at Wk30	50% at Wk30	58% at Wk22
Dosing Schedule	3 mg/kg, Week 0, 2, 6, then every 8 weeks		
MTX[2]	12.5 – 25 mg/wk (Med 15 [n.r.]; Mean 15.6 ± 3.1)	10 – 35 mg/wk (Med 15 [12.5,17.5])	n.r. – 25 mg/wk (Med 15 [10,18])
Inclusion Criteria	≥ 6 tender joints ≥ 6 swollen joints plus any two of: 1) morning stiffness ≥ 45 min 2) ESR > 28 mm/hr and CRP > 2 mg/dL	≥ 6 tender joints ≥ 6 swollen joints plus any two of: 1) morning stiffness ≥ 45 min 2) ESR > 28 mm/hr and CRP > 2 mg/dL	≥ 6 swollen joints and ≥ 6 tender joints
Tender Joints[2]	25.6 ± 13.9 22.0 [n.r.]	32 ± 18 32 [16,46]	22 [15,31]
Swollen Joints[2]	16.2 ± 8.7 15.0 [n.r.]	22 ± 12 19 [13,30]	15 [11,21]
CRP (mg/dL)[2]	1.9 ± 2.5 1.1 [n.r.]	3.9 ± 3.4 3.1 [1.3,5.3]	1.6 [1,3]
Steroid	66.2%	63%	59.2%

n.r: Not reported. [1] Maini *et al*., (1999), Matthews *et al*., (1999), [2] (mean ± SD) OR (Med [IQR])

RA Study Comparison with Historical Data

	PLANETRA Study	Zhang *et al*., (2006) [3]	Abe *et al*., (2006)
ACR20 Rate	60.9% at Wk30	75.9% at Wk18	61.2% at Wk14
Dosing Schedule	3 mg/kg, Week 0, 2, 6, then every 8 weeks		
MTX[2]	12.5 – 25 mg/wk (Med 15 [n.r.]; Mean 15.6 ± 3.1)	7.5 – 20 mg/wk[2]	≥ 6 mg/wk (Mean 7.1 ± 1.9)
Inclusion Criteria	≥ 6 tender joints ≥ 6 swollen joints plus any two of: 1) morning stiffness ≥ 45 min 2) ESR > 28 mm/hr and CRP > 2.0 mg/dL	≥ 8 tender joints ≥ 3 swollen joints plus any two of: 1) morning stiffness ≥ 45 min 2) ESR > 28 mm/hr and CRP > 1.5 mg/dL	≥ 6 tender joints ≥ 6 swollen joints plus any two of: 1) morning stiffness ≥ 45 min 2) ESR > 28 mm/hr and CRP > 2.0 mg/dL
Tender Joints[2]	25.6 ± 13.9 22.0 [n.r.]	n.r.	19.0 ± 11.8
Swollen Joints[2]	16.2 ± 8.7 15.0 [n.r.]	n.r.	15.1 ± 9.0
CRP (mg/dL)[2]	1.9 ± 2.5 1.1 [n.r.]	n.r.	4.2 ± 3.1
Steroid	66.2%	n.r.	85.7%

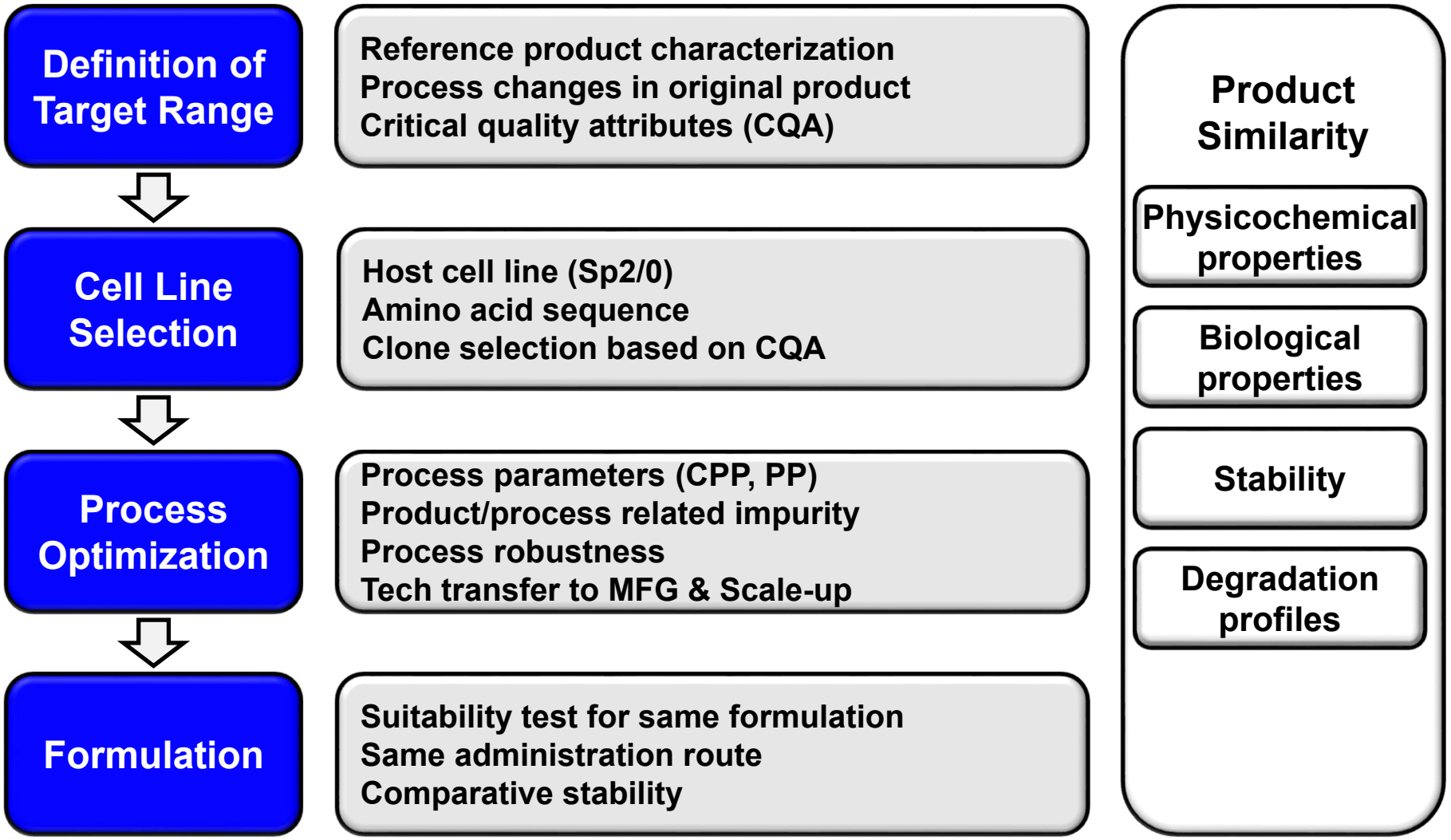
[1] (mean ± SD) OR (Med [IQR]), [2] Inclusion criteria; n.r. (not reported) [3] Dosing Schedule: At 0,2,6, and 14 weeks.

RA Study Comparison with Historical Data

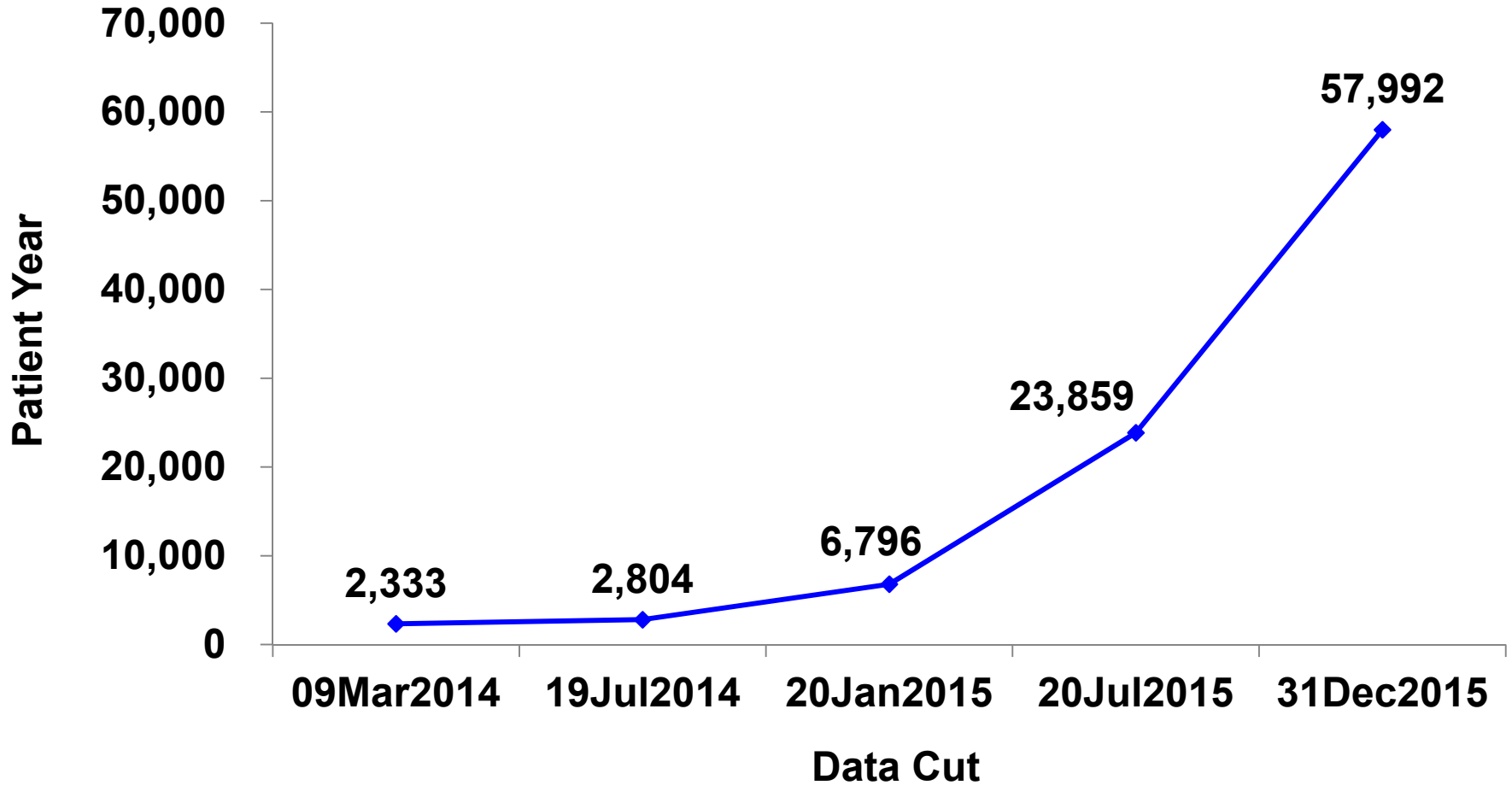
	PLANETRA Study	Schiff *et al.*, (2008)
ACR20 Rate	60.9% at Wk30	59.4% at Wk28
Dosing Schedule	3 mg/kg, Week 0, 2, 6, then every 8 weeks	
MTX[2]	12.5 – 25 mg/wk (Med 15 [n.r.]; Mean 15.6 ± 3.1)	≥ 15 mg/wk (Mean 16.3 ± 3.6)
Inclusion Criteria	≥ 6 tender joints ≥ 6 swollen joints plus any two of: 1) morning stiffness ≥ 45 min 2) ESR > 28 mm/hr and CRP > 2.0 mg/dL	≥12 tender joints ≥10 swollen joints and CRP ≥ 1 mg/dL
Tender Joints[2]	25.6 ± 13.9 22.0 [n.r.]	31.7 ± 14.5
Swollen Joints[2]	16.2 ± 8.7 15.0 [n.r.]	20.3 ± 8.0
CRP (mg/dL)[2]	1.9 ± 2.5 1.1 [n.r.]	3.3 ± 3.2
Steroid	66.2%	71.5%

[1] (mean ± SD) OR (Med [IQR]), [2] Inclusion criteria; n.r. (not reported)

CT-P13 Product Development Strategy



Cumulative Exposure to CT-P13 in Post-marketing Experience

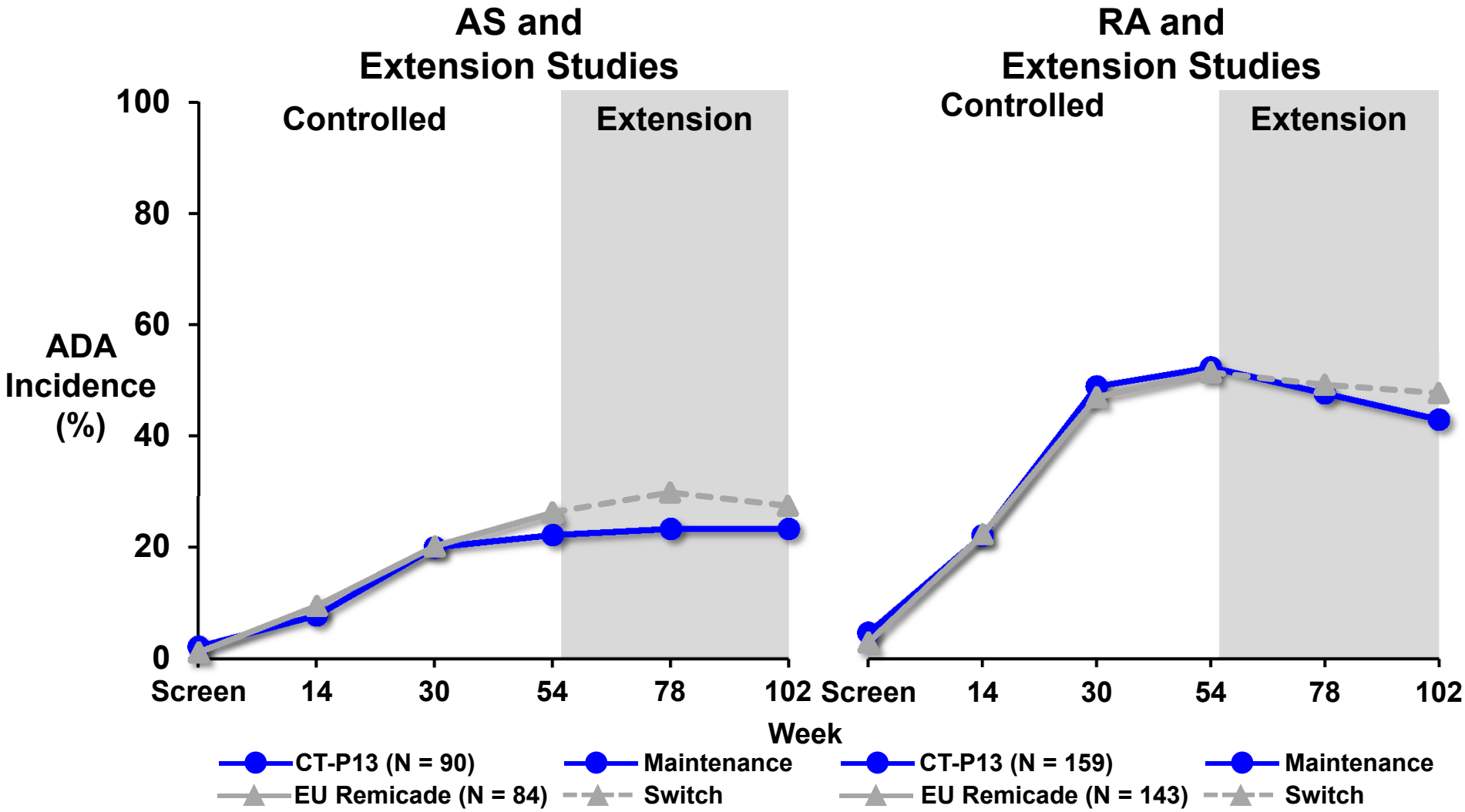


FDA and EMA Guideline: Statistical Recommendation on PK Assessment

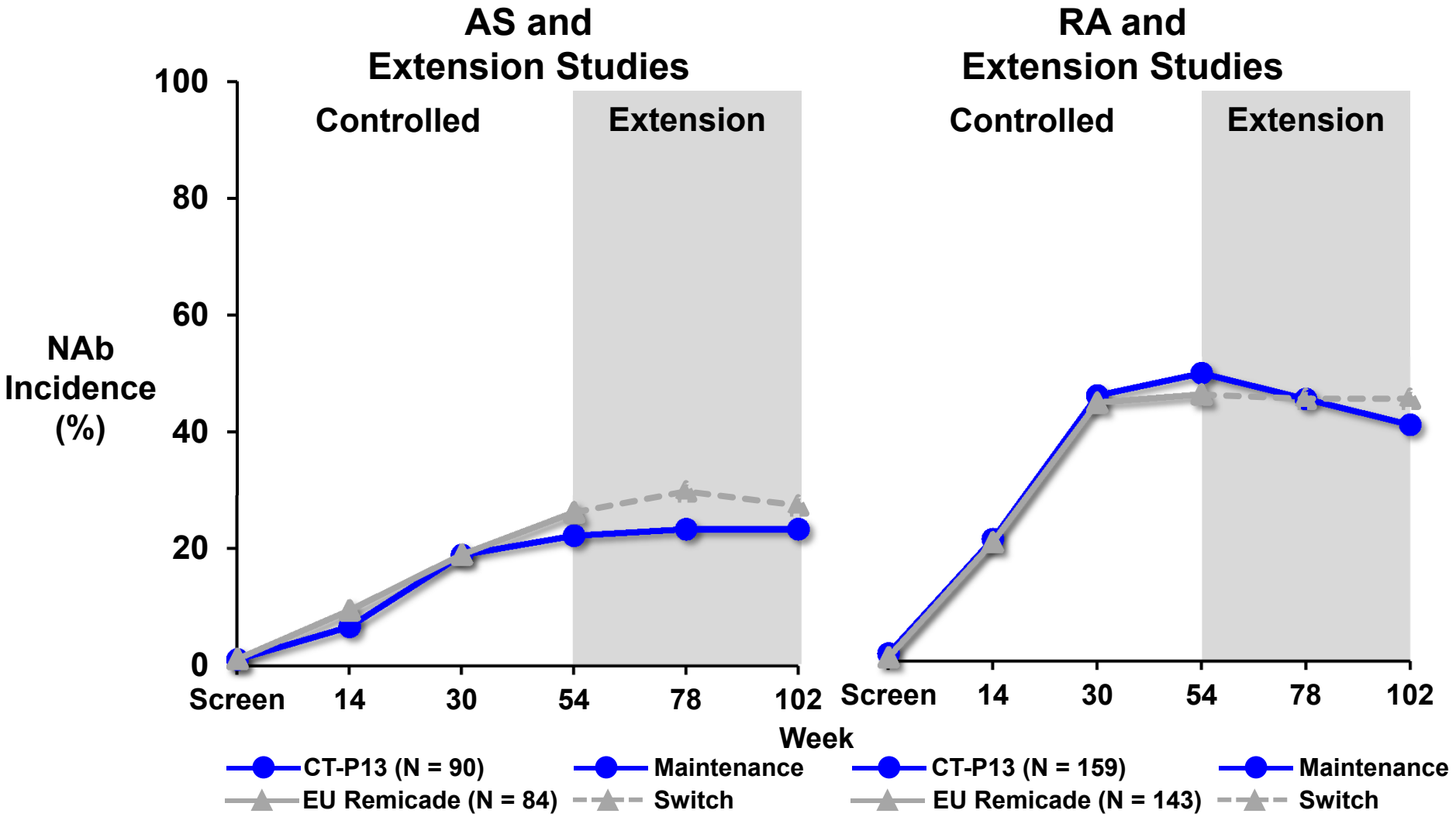
FDA	EMA
■ Acceptable confidence interval: 80 - 125%	■ Thorough justification required for equivalence margin beyond 80 - 125% for primary parameters
■ **90% CI for mean ratio between proposed biosimilar product and reference product**	■ **No acceptance range needs to be defined for secondary parameters** ▪ CIs for ratios or differences can be presented together with descriptive statistics

FDA Guidance for Industry, Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (May 2014)
EMA Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (May 2012)

ADA Incidence Rates in AS and RA Studies (over 2-year)

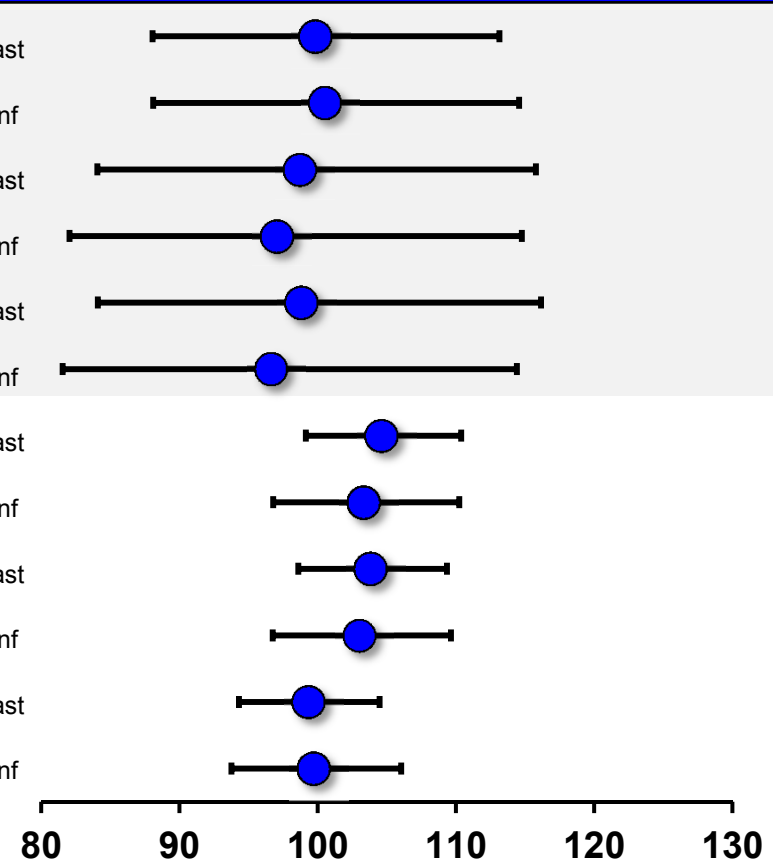


NAb Incidence Rates AS and RA Studies (over 2-year)

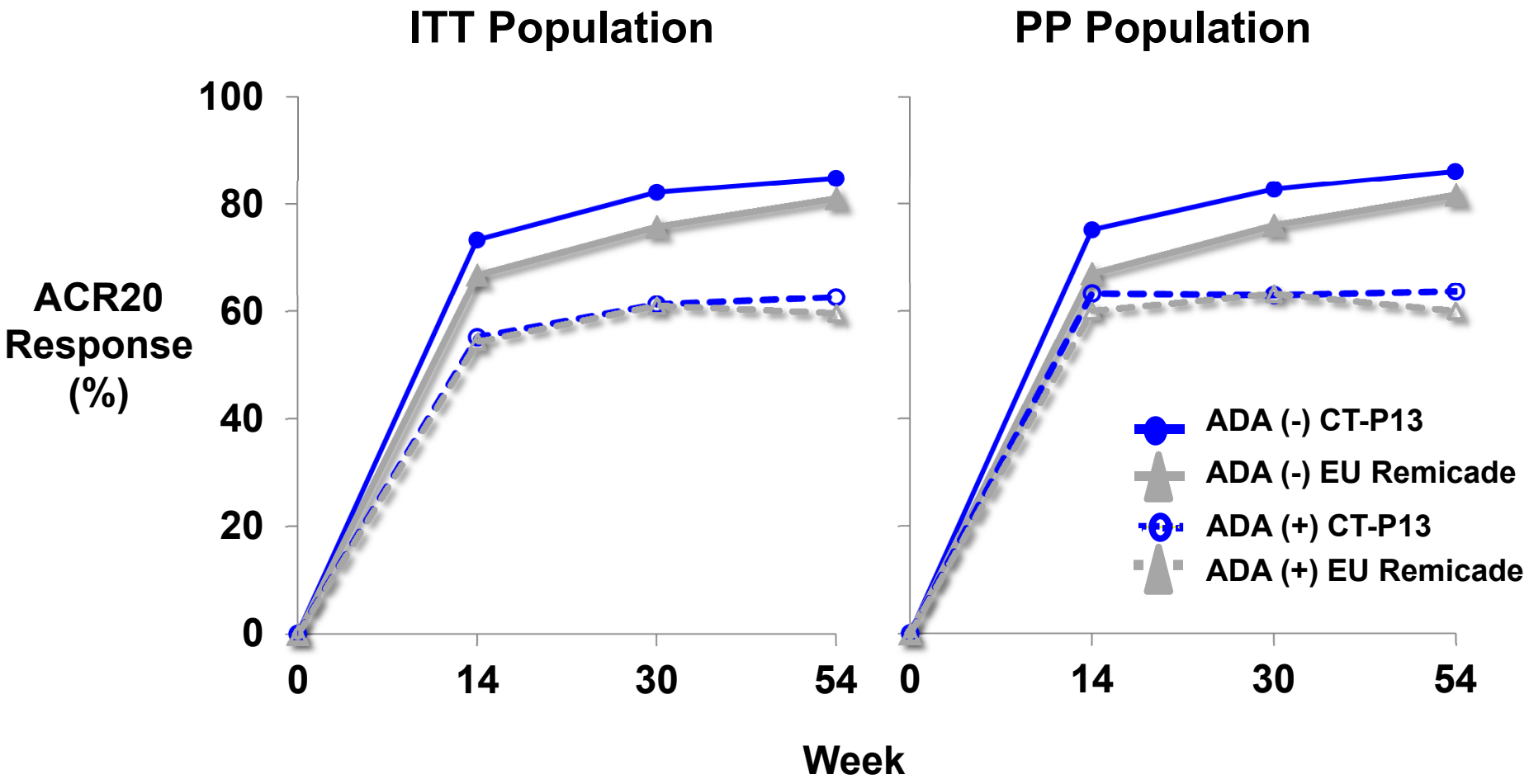


Primary PK Parameters by ADA Subset in 3-way PK Study

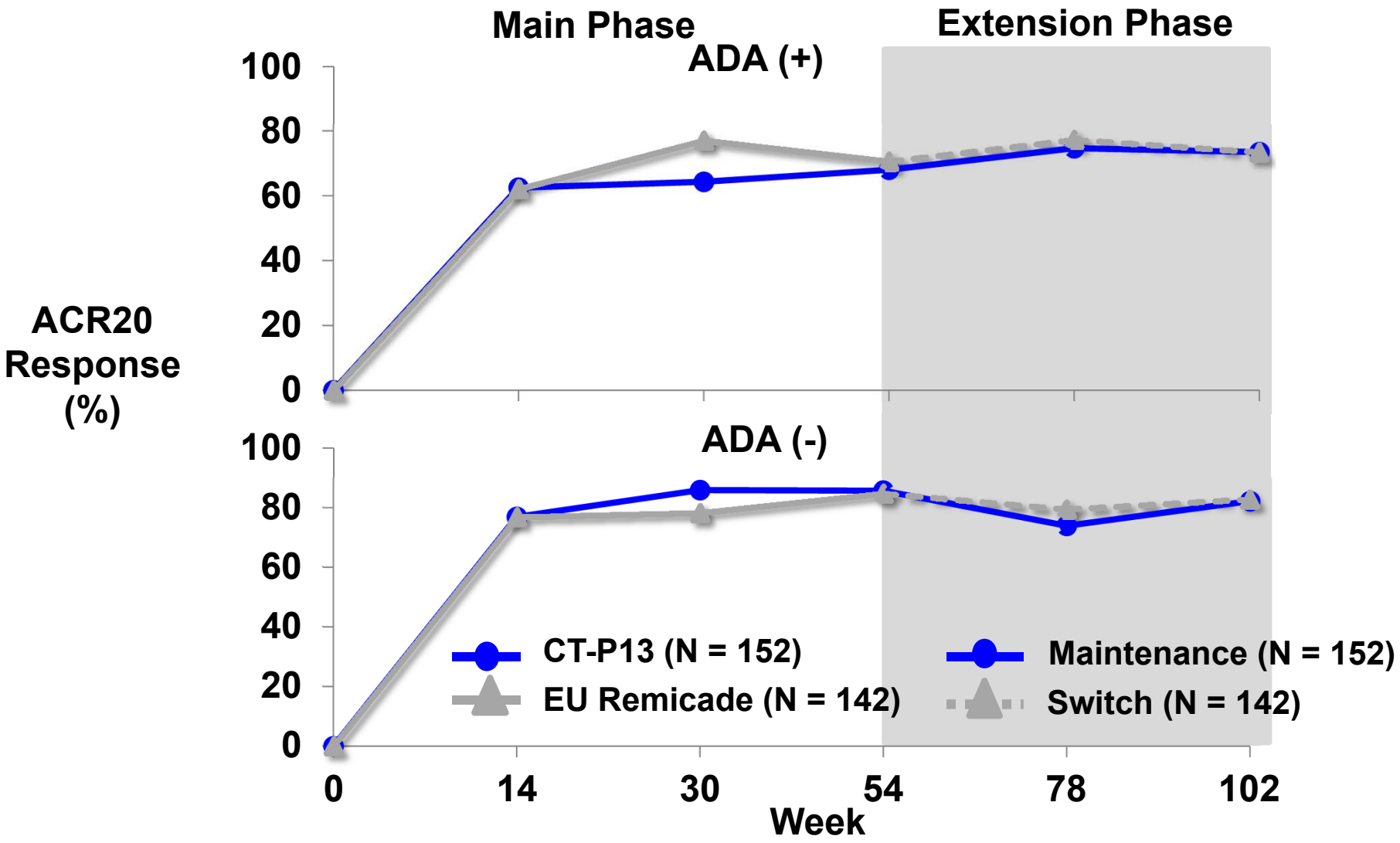
ADA Subset		PK Parameter	Ratio (90% CI)
ADA Positive	CT-P13 vs. EU Remicade	AUC_{last}	99.8 (88.06, 113.15)
		AUC_{inf}	100.5 (88.10, 114.57)
	CT-P13 vs. US Remicade	AUC_{last}	98.7 (84.06, 115.79)
		AUC_{inf}	97.0 (82.05, 114.77)
	EU Remicade vs. US Remicade	AUC_{last}	98.8 (84.10, 116.16)
		AUC_{inf}	96.6 (81.55, 114.41)
ADA Negative	CT-P13 vs. EU Remicade	AUC_{last}	104.6 (99.14, 110.38)
		AUC_{inf}	103.3 (96.78, 110.24)
	CT-P13 vs. US Remicade	AUC_{last}	103.8 (98.60, 109.35)
		AUC_{inf}	103.0 (96.75, 109.64)
	EU Remicade vs. US Remicade	AUC_{last}	99.3 (94.31, 104.48)
		AUC_{inf}	99.7 (93.76, 106.04)



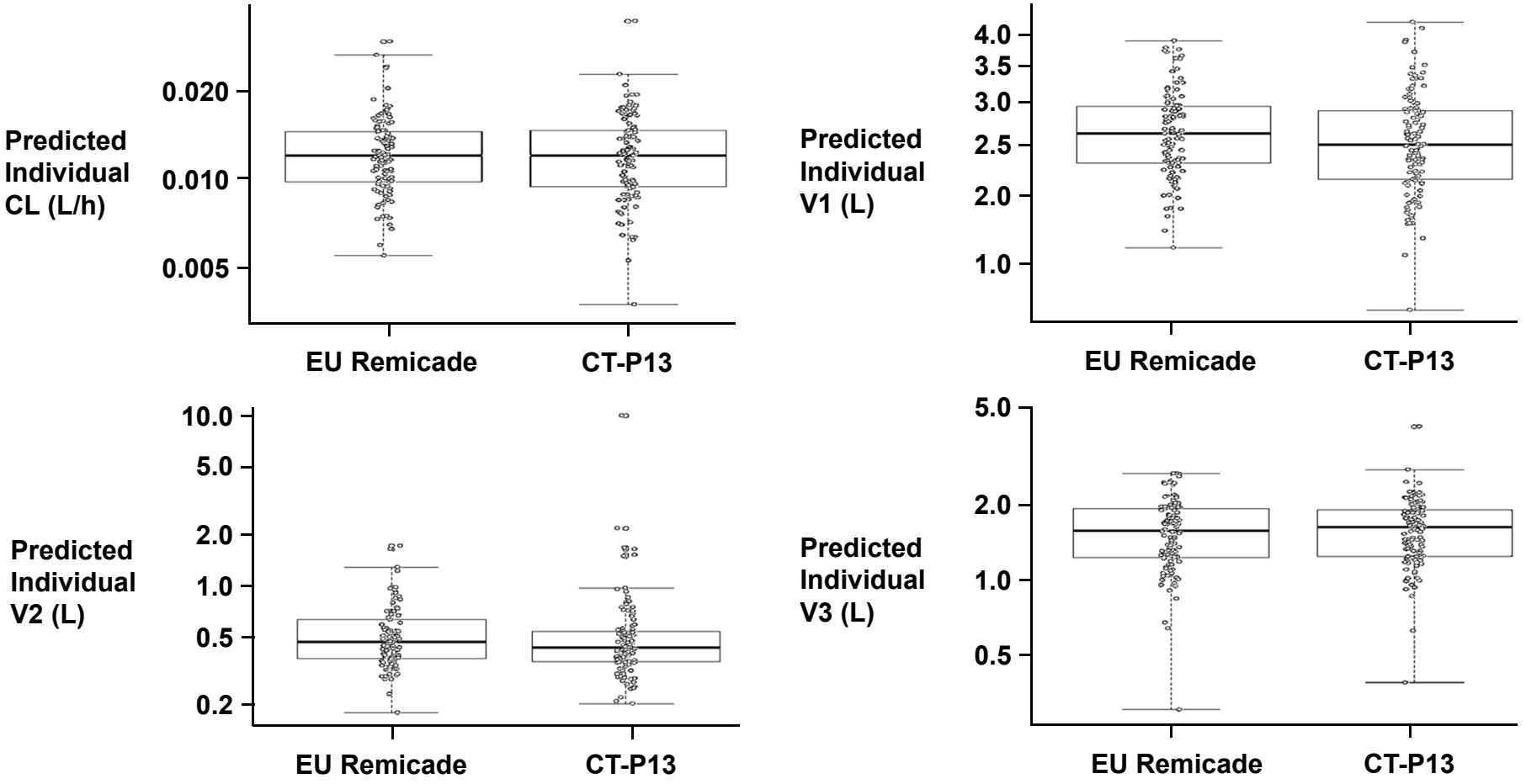
ADA Impact on ACR20 in RA Study



ADA Impact on ACR20 in RA Main and Extension Studies - Over 2-year (Efficacy Population)

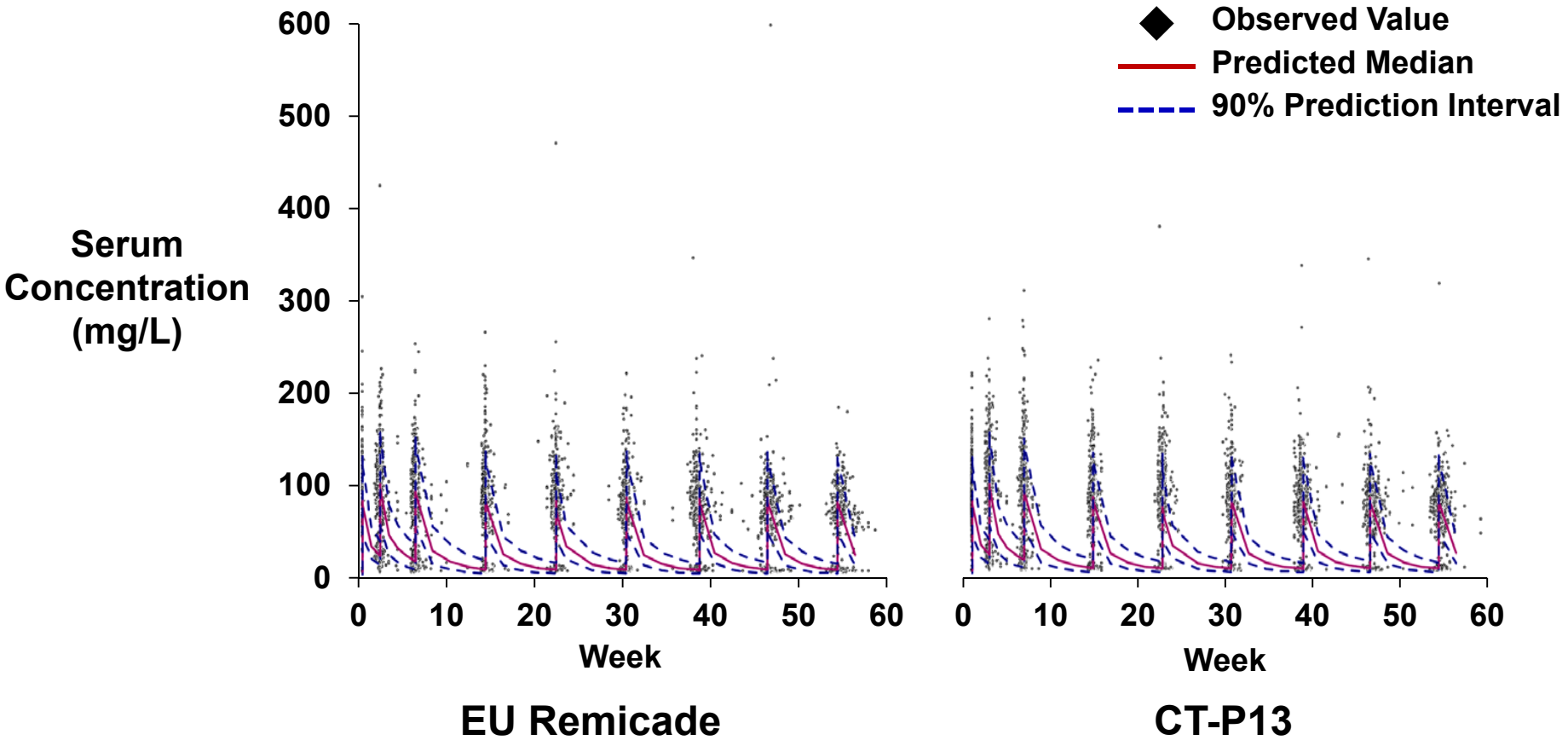


PK Modeling in AS Study



The final population PK model was a three-compartment model with inter−individual variability estimated for CL, V1, V2 and V3.

PK Linearity in RA Study



External Validation from AS Study

Predicted PK Curve of CT-P13 under 10 mg/kg

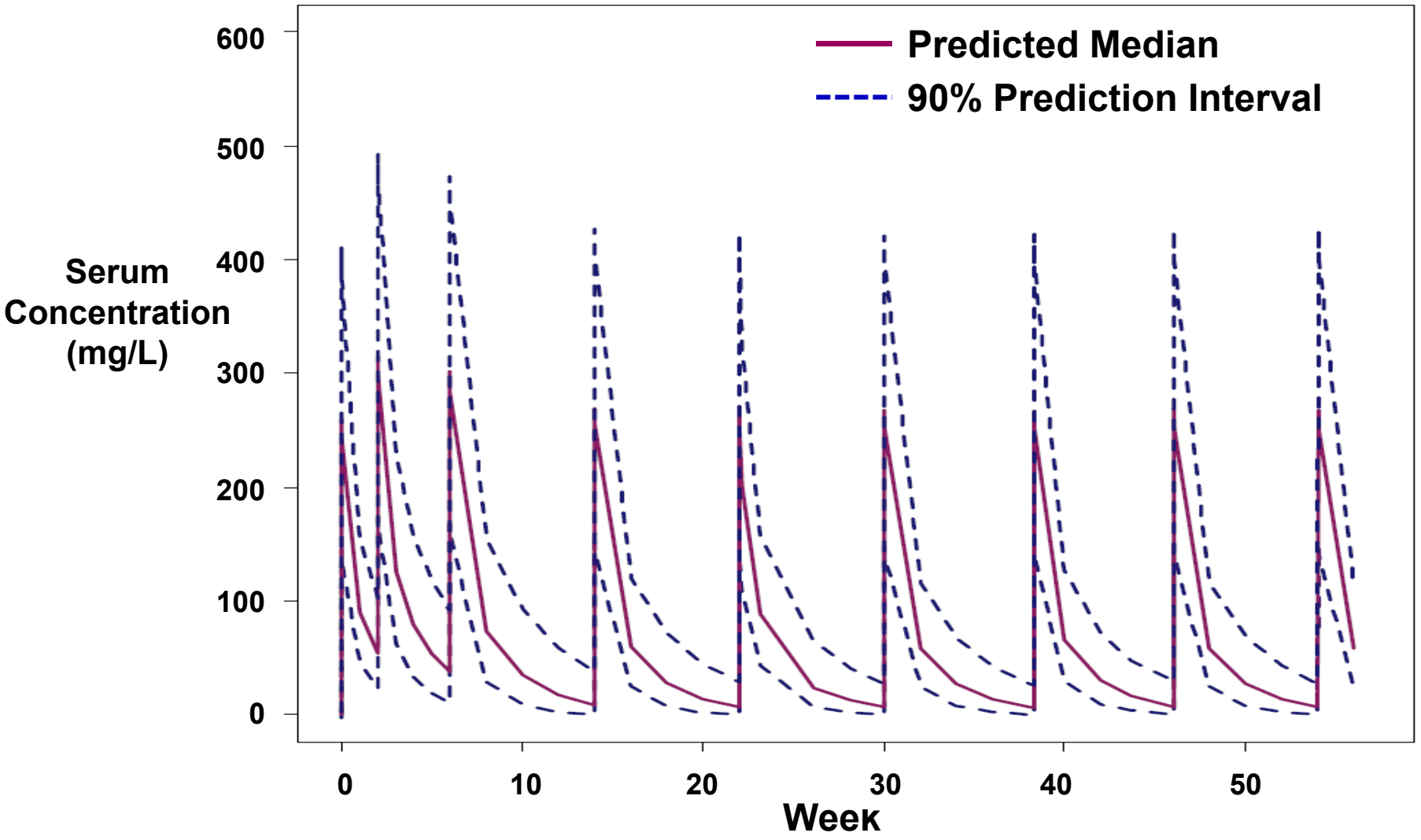


Table 42: Treatment-Emergent Adverse Events of Infusion-Related Reactions and Anaphylaxis by Seroconversion Groups in Controlled Studies (Safety Population)

TEAE	Seroconversion Subgroup	AS Study		RA Study		Total	
		CT-P13 5 mg/kg (N=128)	EU Remicade 5 mg/kg (N=122)	CT-P13 3 mg/kg (N=302)	EU Remicade 3 mg/kg (N=300)	CT-P13 (N=430)	EU Remicade (N=422)
		n/N' (%)	n/N' (%)	n/N' (%)	n/N' (%)	n/N' (%)	n/N' (%)
Infusion-Related Reaction	Seroconversion	6/44 (13.6)	11/39 (28.2)	23/169 (13.6)	35/164 (21.3)	29/213 (13.6)	46/203 (22.7)
	Non-seroconversion	5/84 (6.0)	4/83 (4.8)	7/133 (5.3)	8/135 (5.9)	12/217 (5.5)	12/218 (5.5)
Anaphylaxis	Seroconversion	1/44 (2.3)	3/39 (7.7)	4/169 (2.4)	2/164 (1.2)	5/213 (2.3)	5/203 (2.5)
	Non-seroconversion	0/84	0/83	2/133 (1.5)	2/135 (1.5)	2/217 (0.9)	2/218 (0.9)

(%) = n/N'*100.

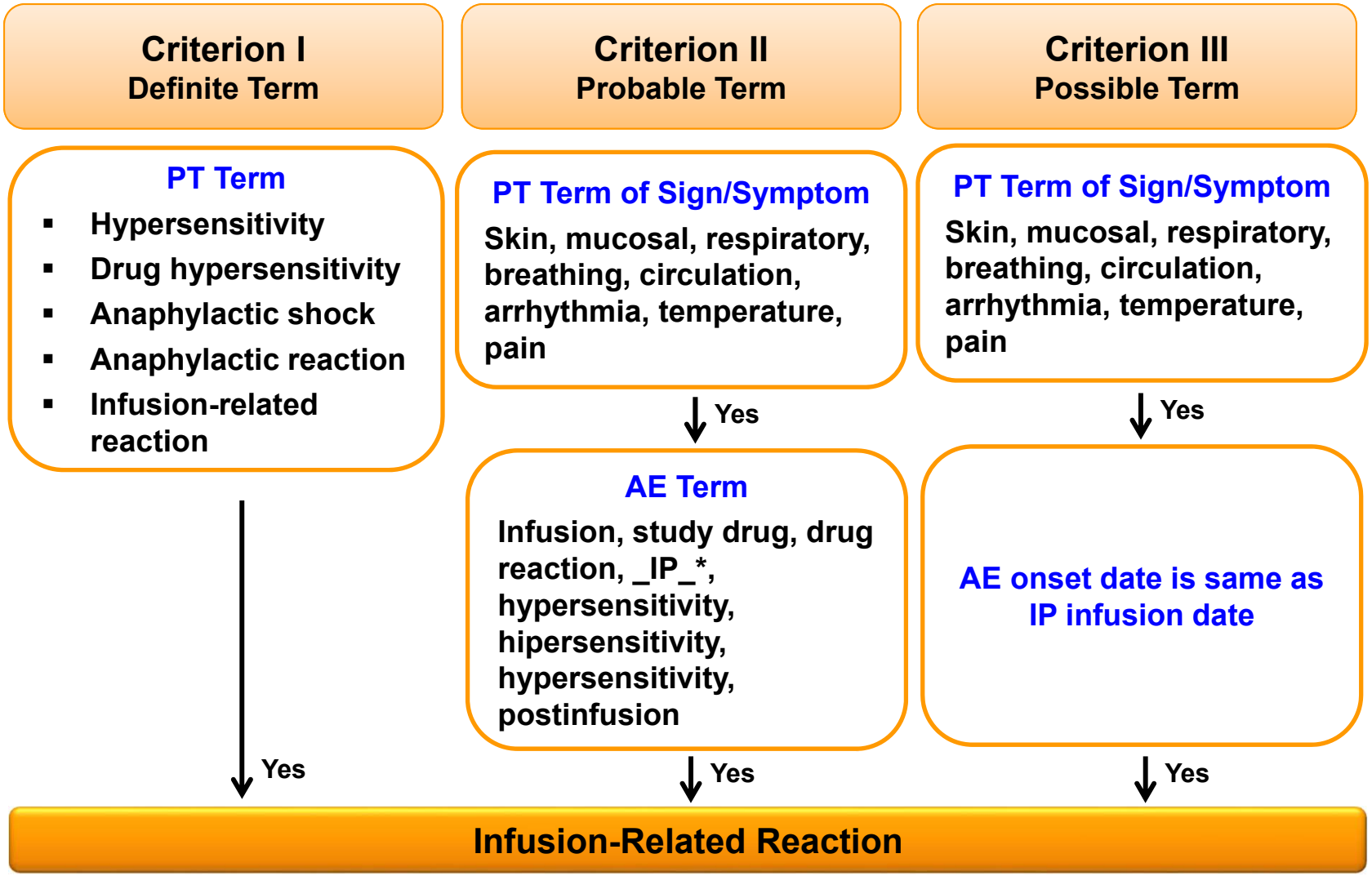
AS: Ankylosing spondylitis, N': the number of patients in each seroconversion subgroup of each treatment. n: the number of patients with Infusion-related reaction/Anaphylaxis, RA: Rheumatoid arthritis, TEAE: Treatment emergent adverse event

Infusion-related Reaction: All CT-P13 Studies

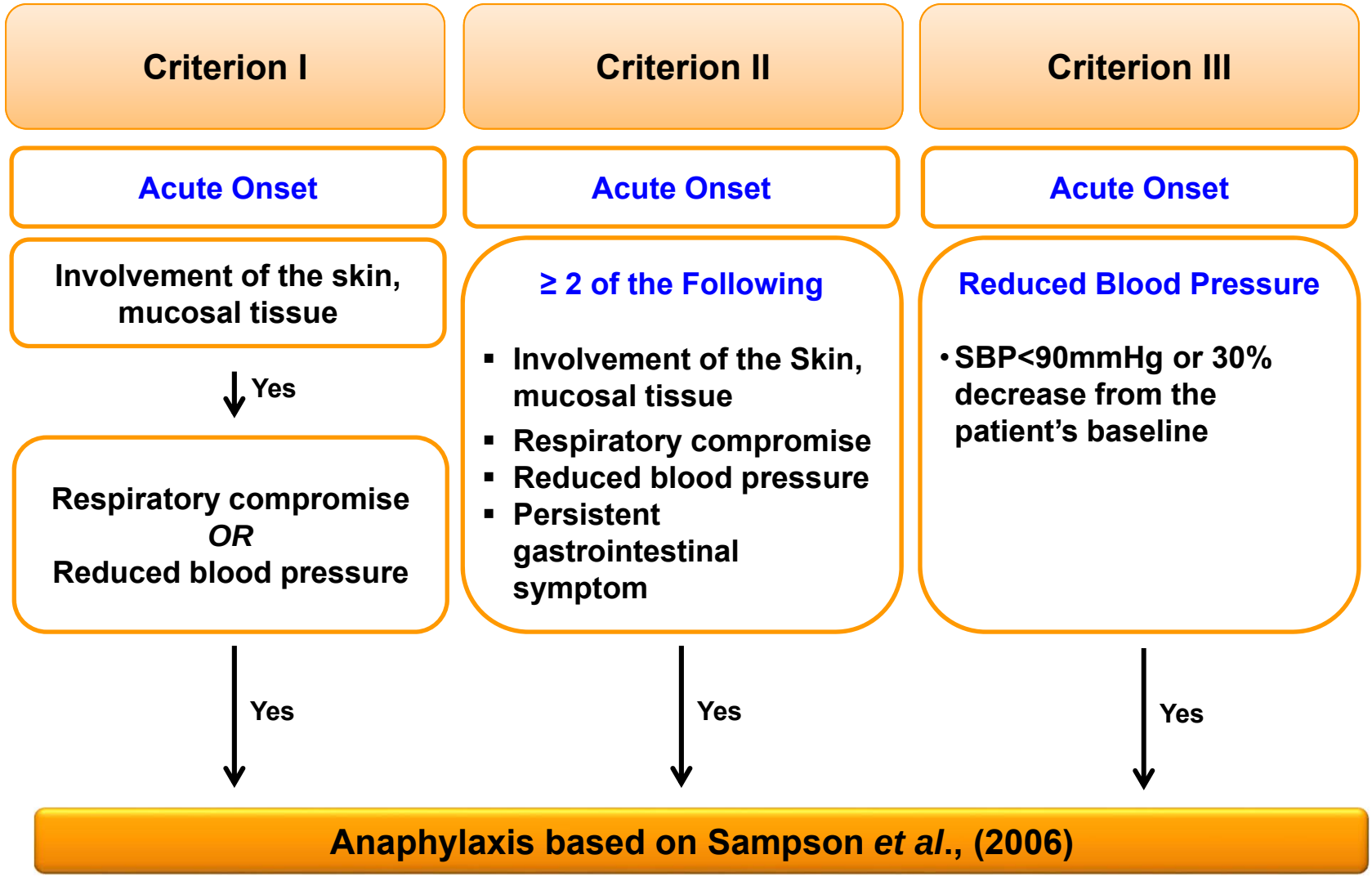
Number of Patients (%)	Controlled		Extension	
	CT-P13 (N = 446)	EU Remicade (N = 440)	Maintenance (N = 257)	Switch (N = 235)
IRR	41 (9.2)	59 (13.4)	18 (7.0)	10 (4.3)
Serious or Severe IRR	9 (2.0)	9 (2.0)	2 (0.8)	1 (0.4)
Anaphylaxis (Sampson)	7 (1.6)	7 (1.6)	1 (0.4)	0
IRR Leading to Discontinuation	15 (3.4)	23 (5.2)	8 (3.1)	2 (0.9)
IRR Leading to Death	0	0	0	0

RCT: RA 3.1, AS 1.1, Pilot RA 1.2, Russia RA 3.3
OLE: RA 3.2, AS 1.3, Pilot RA 1.2 Ext.

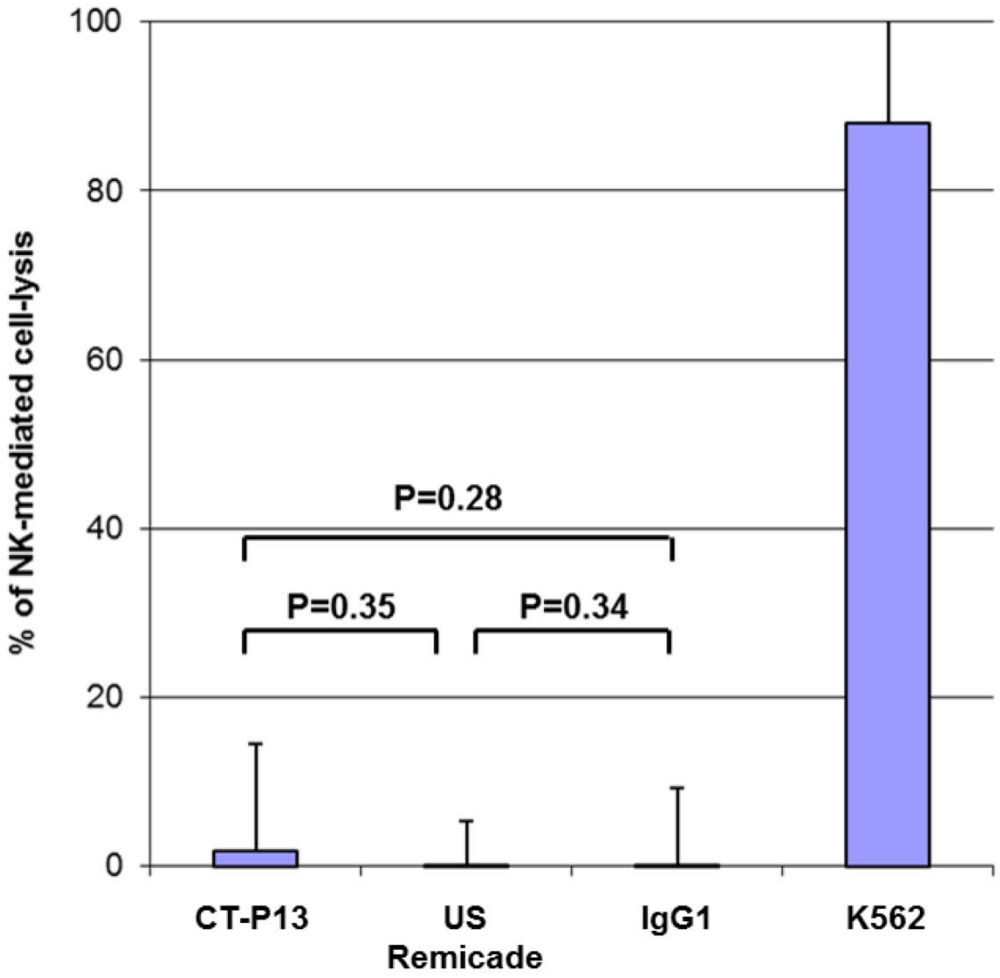
Capture Rules for Infusion-related Reaction



Capture Rules for Anaphylaxis Based on Sampson Criteria



ADCC Using Intestinal Cells (LPMC) from IBD Patients



K562 cell line shows the natural cytotoxicity of the patient NK cells (% cell lysis).

Published Data on Impact of Demographic Factors on PK of Remicade

- Age
  - No significant impact of age on Remicade PK[1]
- Gender
  - In Women, 33% lower clearance, 16% lower volume distribution is shown[2].
  - Effect of gender is negated by weight-based dosing.
- Race/Ethnicity
  - No information on Race/Ethnicity is provided[1]

[1]Remicade USPI (2015), [2]Fasanmade *et al.,* (2009)

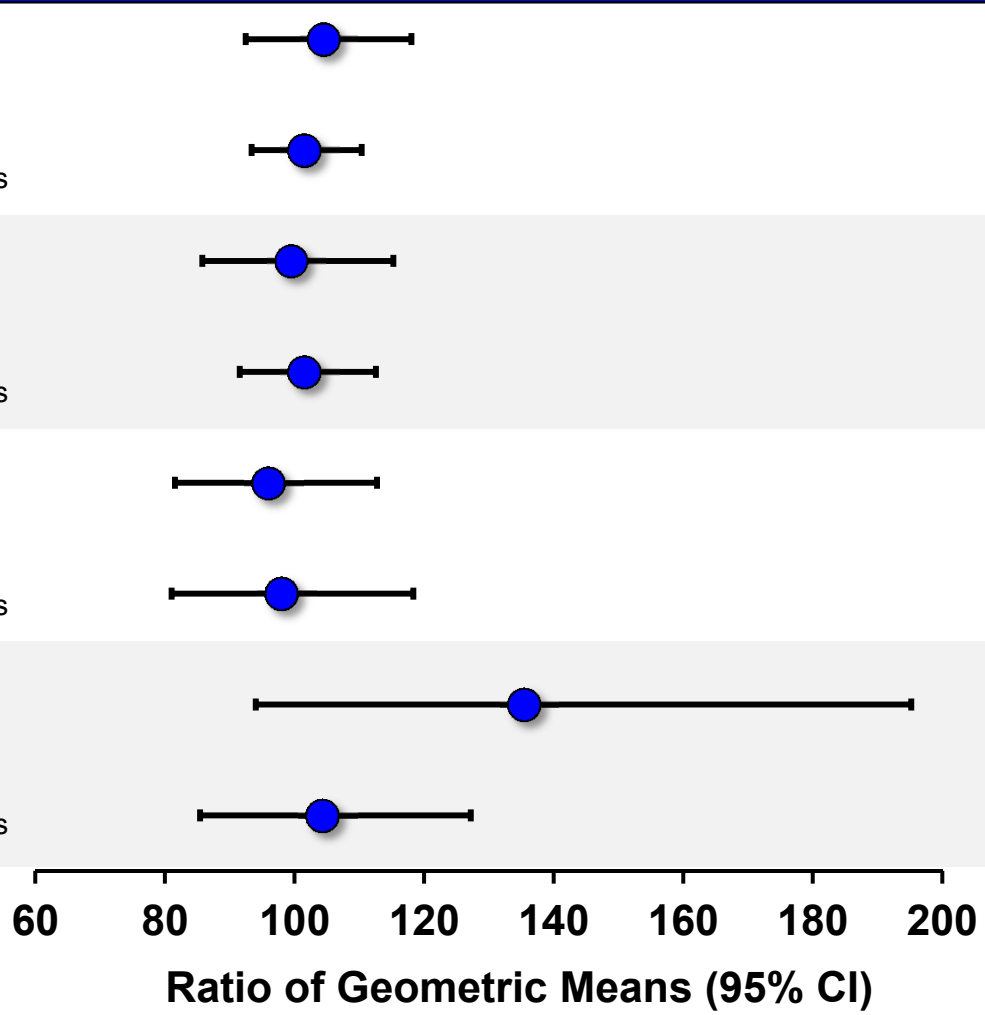
Baseline Characteristics in AS Study

Characteristic		CT-P13 (N = 125)		EU Remicade (N = 125)	
		n	%	n	%
Gender	Female	26	20.8	22	17.6
	Male	99	79.2	103	82.4
BASDAI	< 8	92	73.6	95	76.0
	≥ 8	33	26.4	30	24.0
Race	White	97	77.6	92	73.6
	Asian	16	12.8	13	10.4
	Other	12	9.6	20	16.0
Region	Europe	87	69.6	86	68.8
	Latin America	22	17.6	27	21.6
	Asia	16	12.8	12	9.6

Only 2 patients in each group are ≥ 65 years.

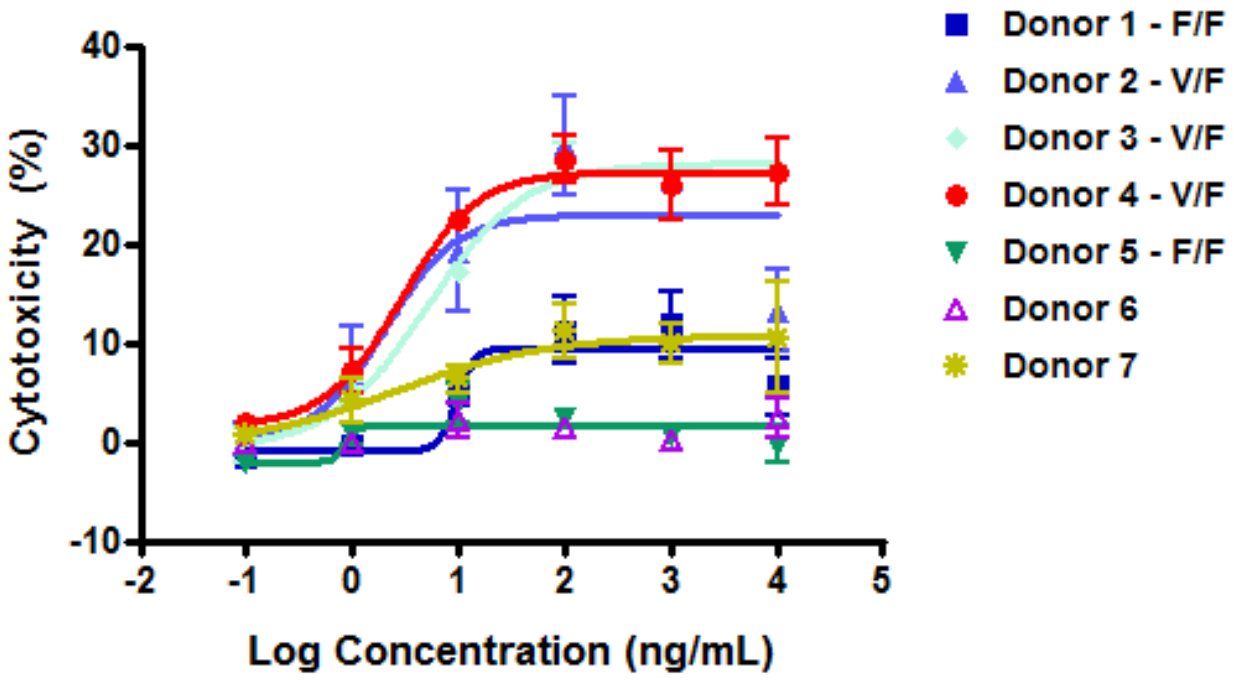
Primary PK Parameters in AS Study - by Race

Race	Parameter	Ratio (95% CI)
Total	AUC_T	104.48 (92.47, 118.06)
	$C_{max,ss}$	101.53 (93.40, 110.37)
White	AUC_T	99.44 (85.78, 115.28)
	$C_{max,ss}$	101.53 (91.56, 112.59)
Asian	AUC_T	95.90 (81.57, 112.74)
	$C_{max,ss}$	97.94 (81.04, 118.36)
Other	AUC_T	135.48 (94.03, 195.20)
	$C_{max,ss}$	104.26 (85.44, 127.23)

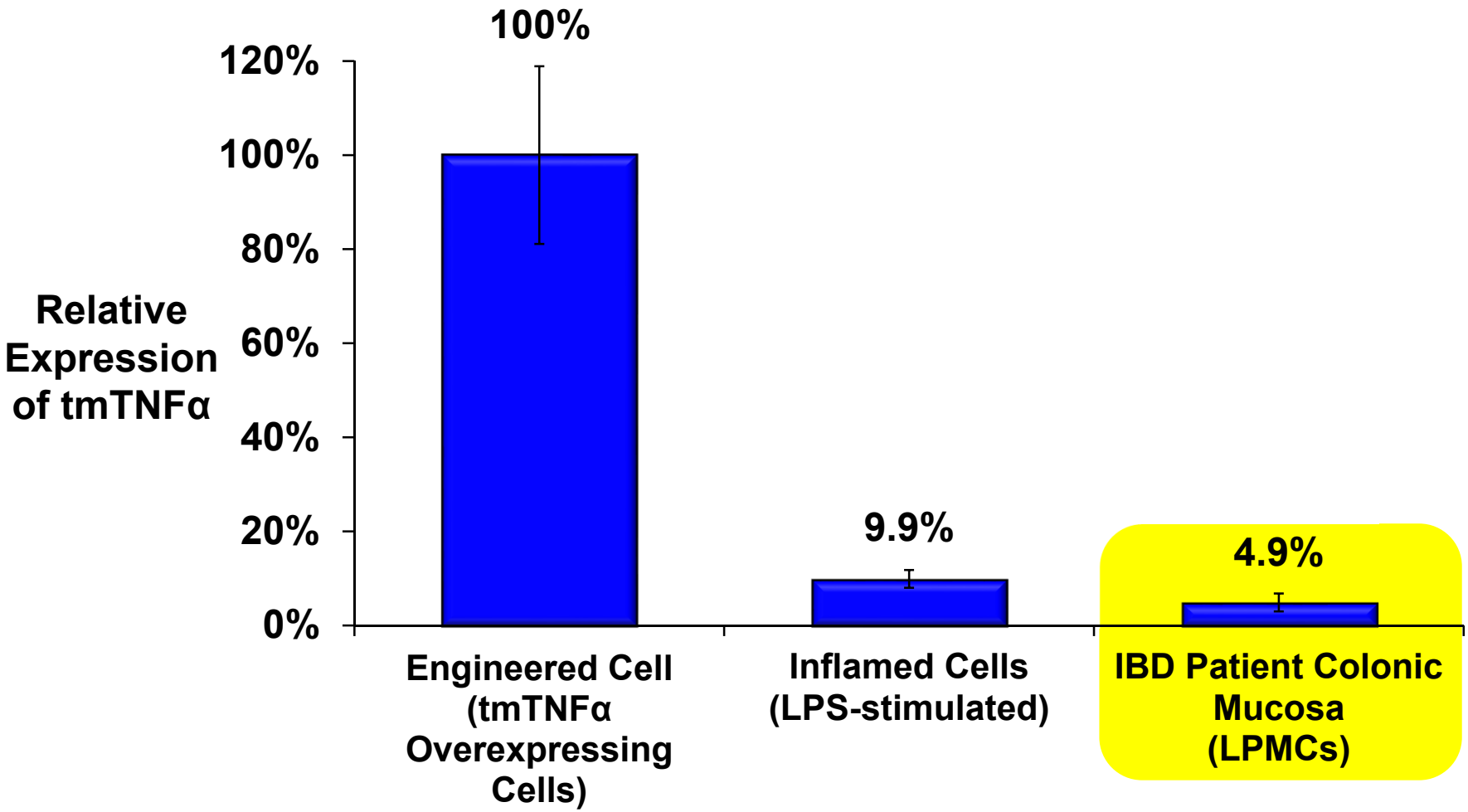


Natural Variation in Cytotoxicity of PBMC from Different Donors

- Donor 4 was selected for ADCC assays

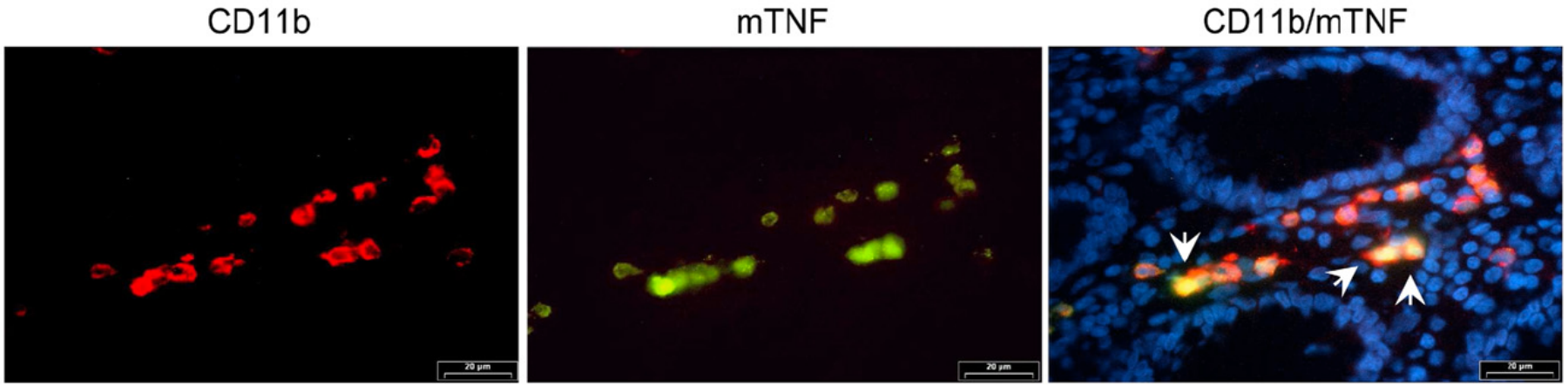


ADCC Activity Requires Overexpression of tmTNFα



Blocking tmTNF Appears an Important MoA in IBD

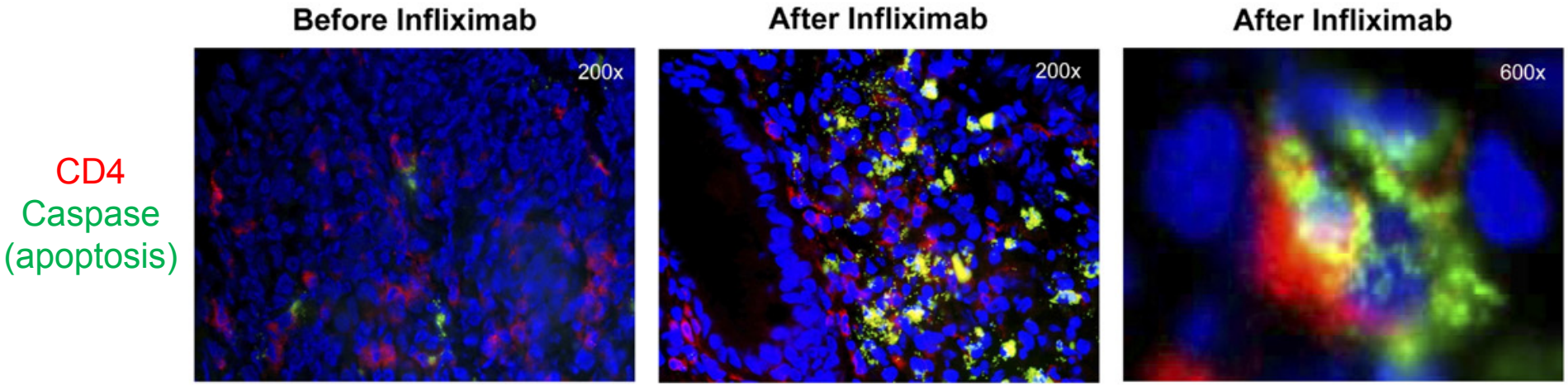
- In the IBD intestine, monocytes (CD11b+) are predominant tmTNF-expressing cell, whereas T cells (CD4+) express TNFR2.
- The T cells rather than the myeloid cells are the cells that die during infliximab therapy.



Atreya *et al*., (2011)

Blocking tmTNF Appears an Important MoA in IBD

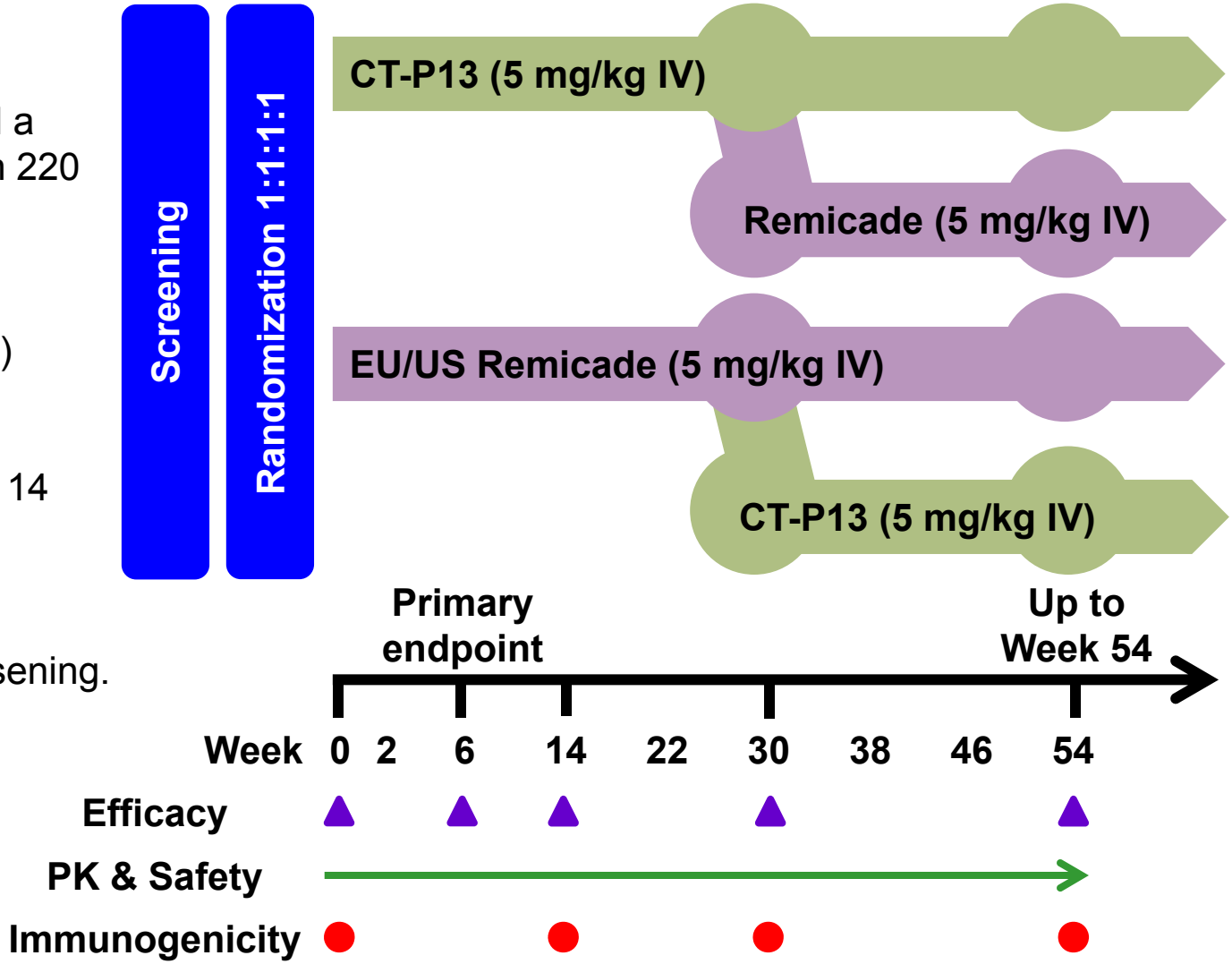
- Administration of infliximab and adalimumab results in apoptosis in the intestinal lamina propria, mostly restricted to CD4+ T cells.
- T cells from IBD patients do not undergo apoptosis in the presence of clinically effective anti-TNFα antibodies (infliximab, adalimumab, and certolizumab) unless co-cultured with tmTNFα-expressing CD14+ intestinal macrophages. Etanercept was ineffective in these co-cultures.



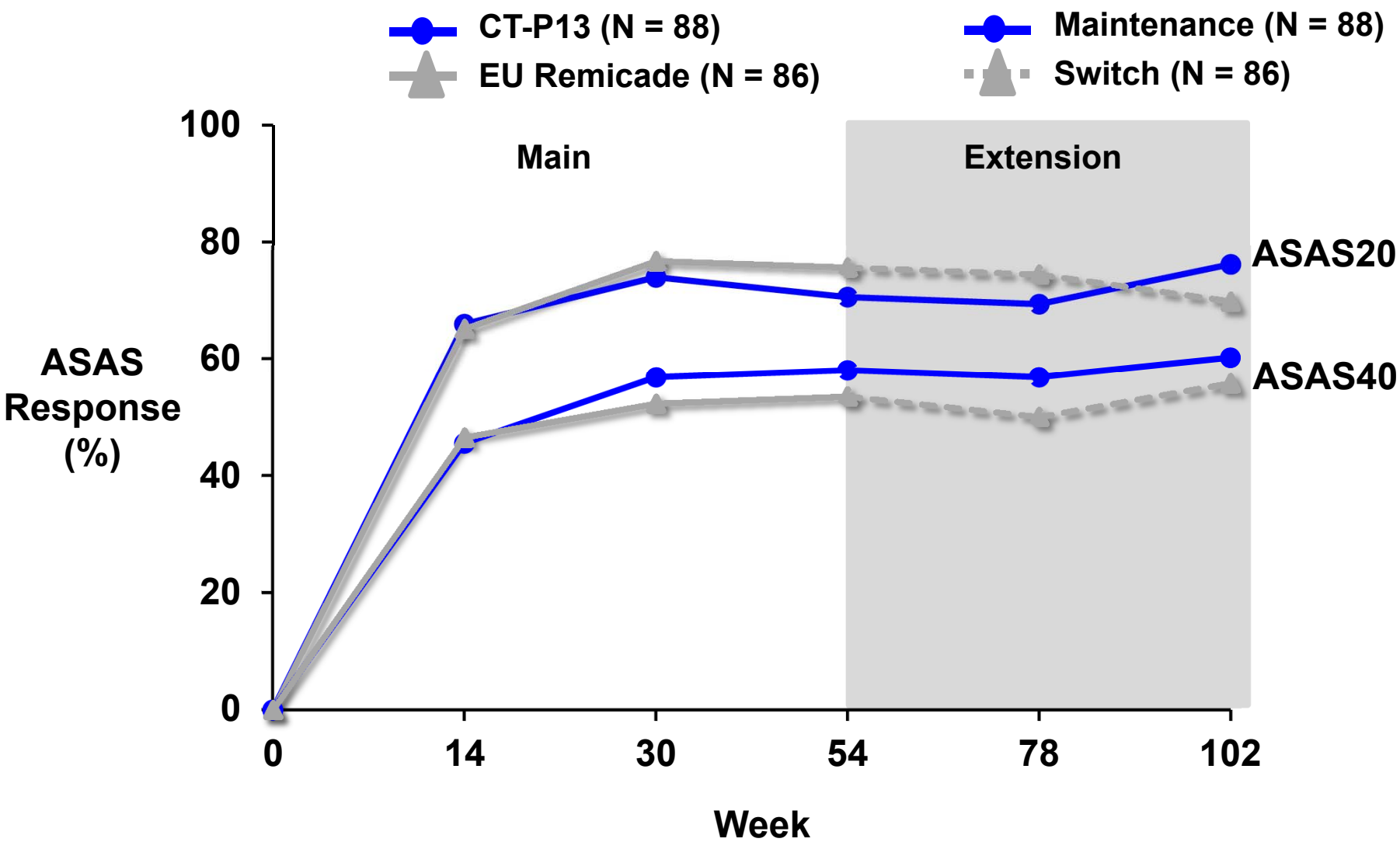
Atreya *et al*., (2011)

CT-P13 CD Study

- **Study population:** patients with active Crohn's disease and a CDAI score between 220 and 450 points
- **Primary endpoint:** CDAI-70 (at week 6)
- **Non-responder withdrawal** at week 14
- **Dose escalation:** 10 mg/kg is allowed from week 22 if worsening.
- **Sample size**: 220



ASAS20/ASAS40 Responses over 2 Years in Patients of AS Extension Study

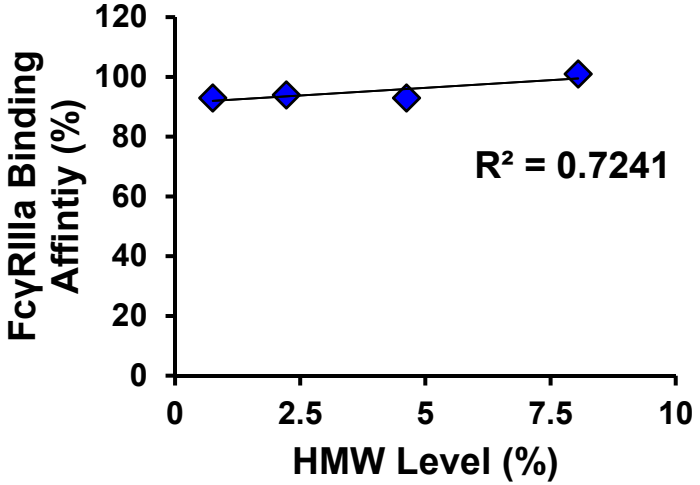


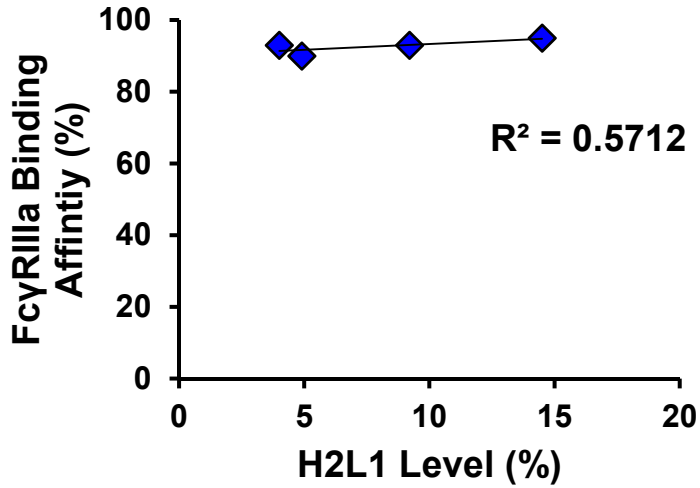
Efficacy Assessment Plan in AS Study

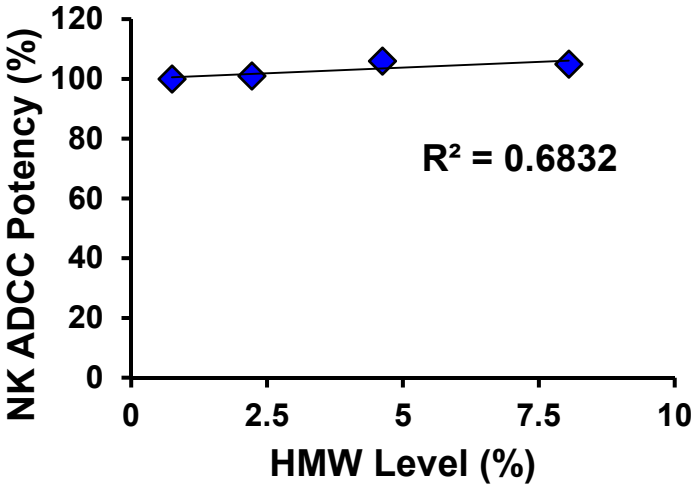
	Screening	Week 0	Week 14	Week 30	Week 54	EOS[1]
ASAS response	✓	✓	✓	✓	✓	✓
Global Assessment Score (VAS)	✓	✓	✓	✓	✓	✓
Spinal Pain Score (VAS)	✓	✓	✓	✓	✓	✓
BASDAI Score	✓	✓	✓	✓	✓	✓
BASFI Score	✓	✓	✓	✓	✓	✓
BASMI Score	✓	✓	✓	✓	✓	✓
Chest Expansion	✓	✓	✓	✓	✓	✓
SF-36 (Quality-of-Life Questionnaire)	✓	✓	✓	✓	✓	✓

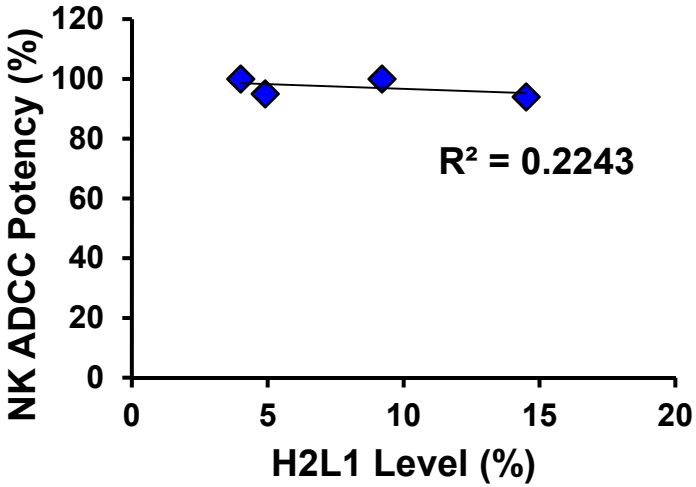
[1] EOS efficacy assessments only need to be completed if the patient withdraws prior to Week 54. If the patient has EOS efficacy assessments at Week 54, efficacy assessments are not required at EOS.

FcγRIIIa Binding Affinity and ADCC Activity are not Affected by HMW or H2L1 Levels





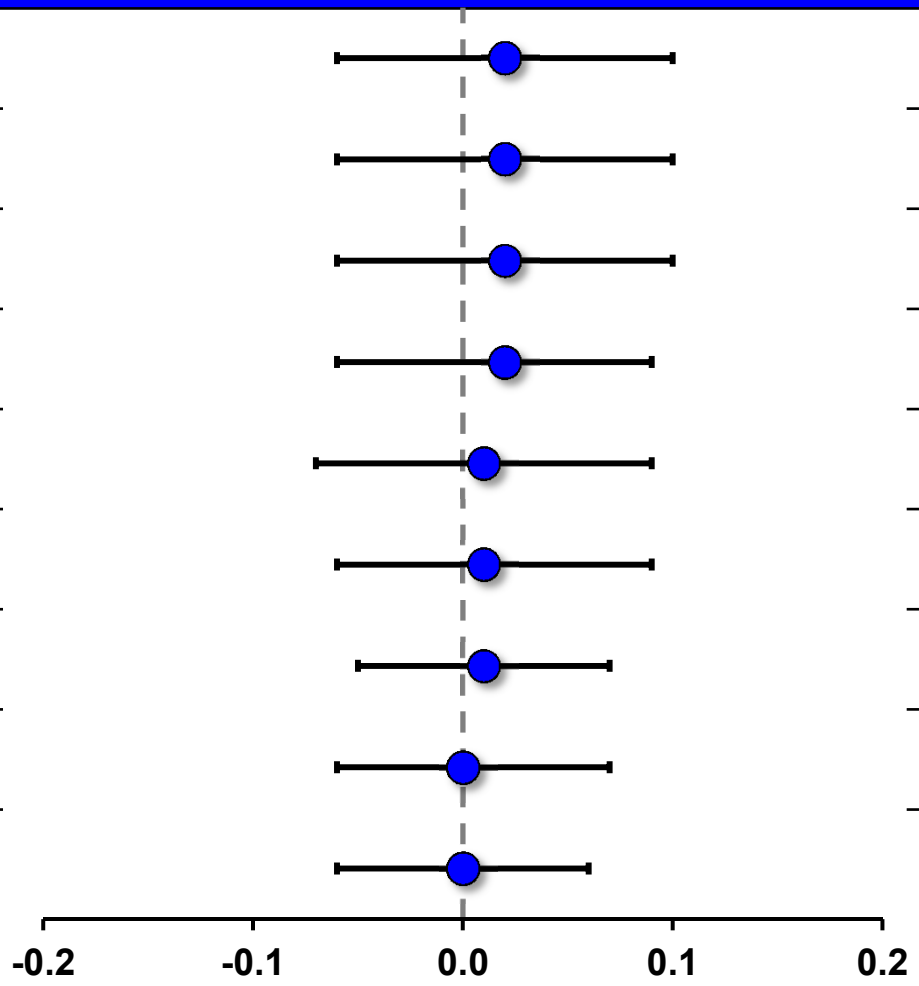




HMW: High Molecular Weight forms, H: Heavy chain, L: Light chain

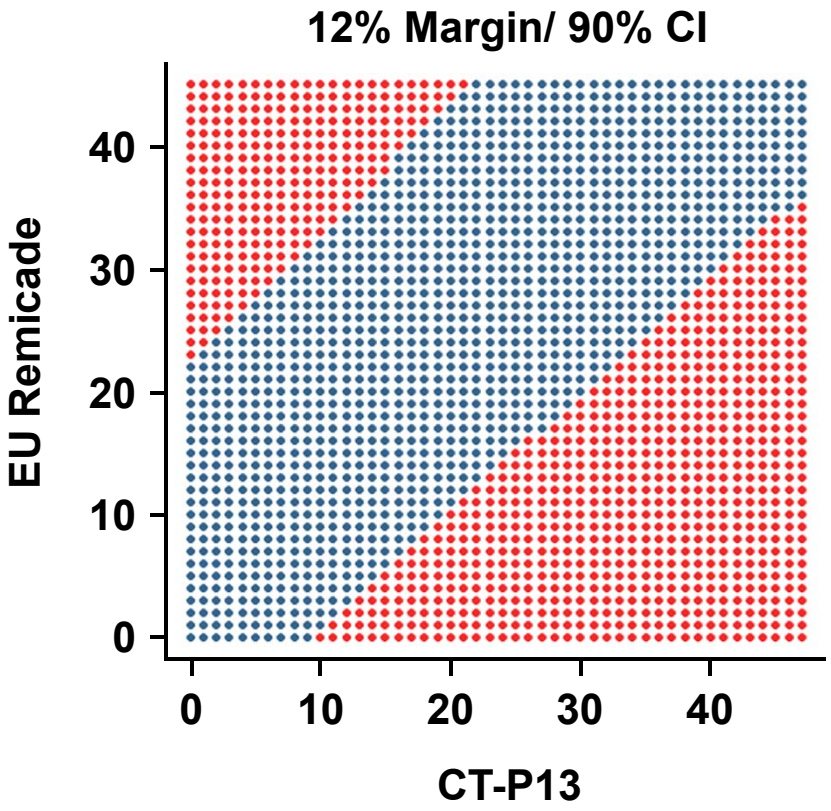
Sensitivity Analysis with Discontinued Patients for ACR20 at Week 30 (ITT)

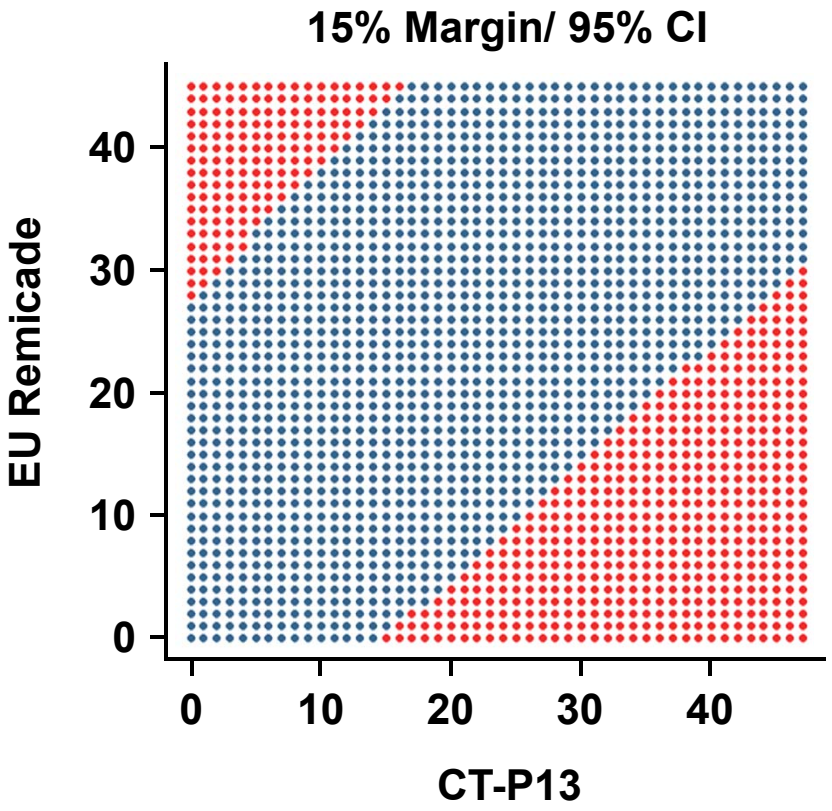
	Methods	(95% CI)
ACR20	Original[1]	(-0.06, 0.10)
	Method A[2]	(-0.06, 0.10)
	Method B[3]	(-0.06, 0.10)
ACR50	Original[1]	(-0.06, 0.09)
	Method A[2]	(-0.07, 0.09)
	Method B[3]	(-0.06, 0.09)
ACR70	Original[1]	(-0.05, 0.07)
	Method A[2]	(-0.06, 0.07)
	Method B[3]	(-0.06, 0.06)



[1] Using non-responder imputation [2] Using LOCF [3] Using LOCF and non-responder imputation

Tipping Point Analysis with Missing Data for ACR20 at Week 30





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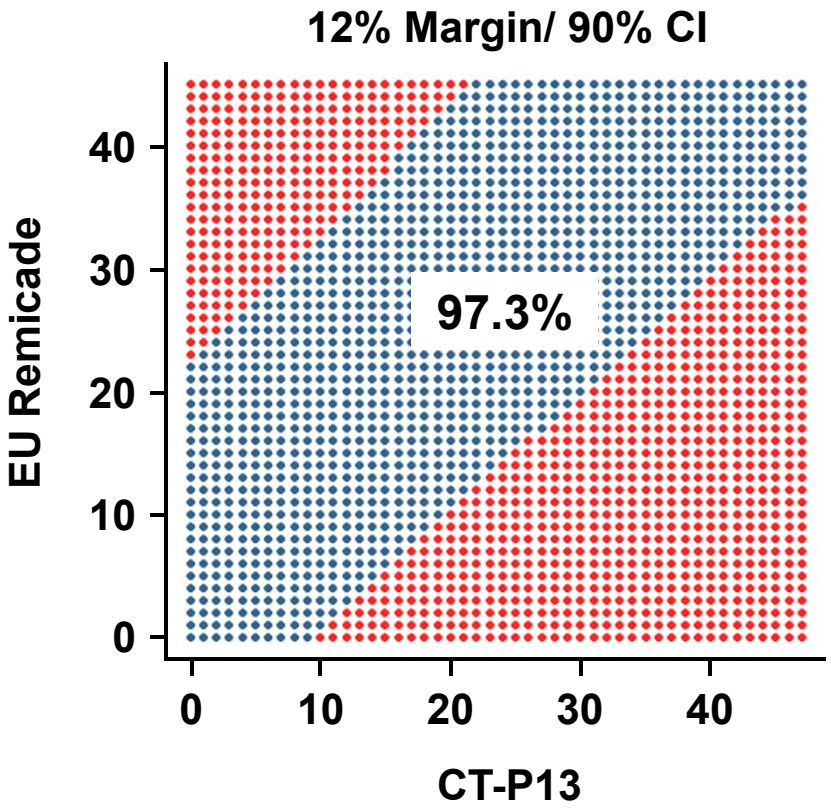
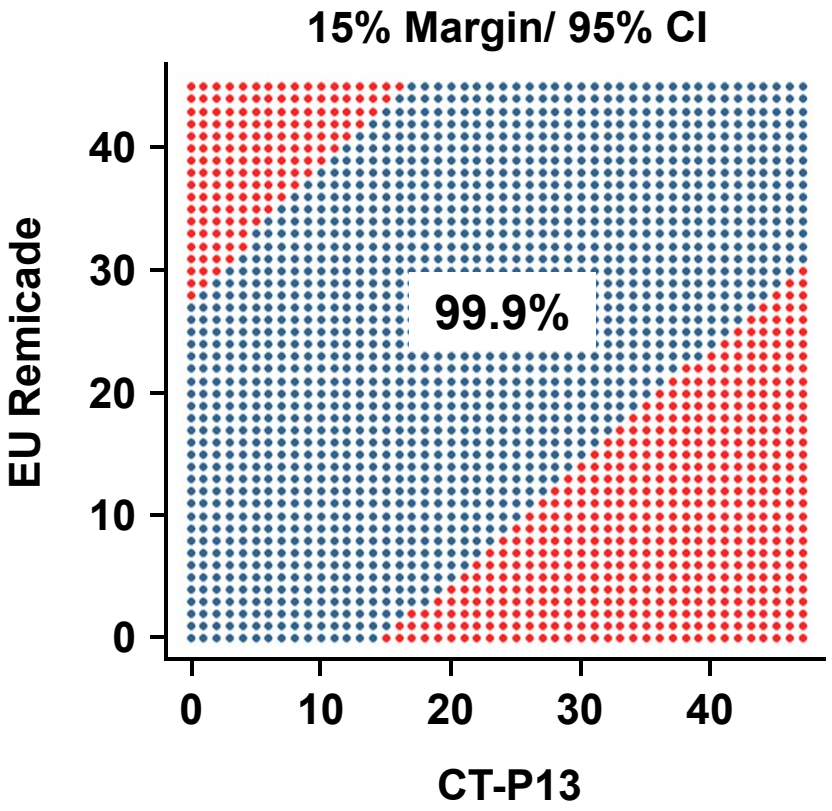
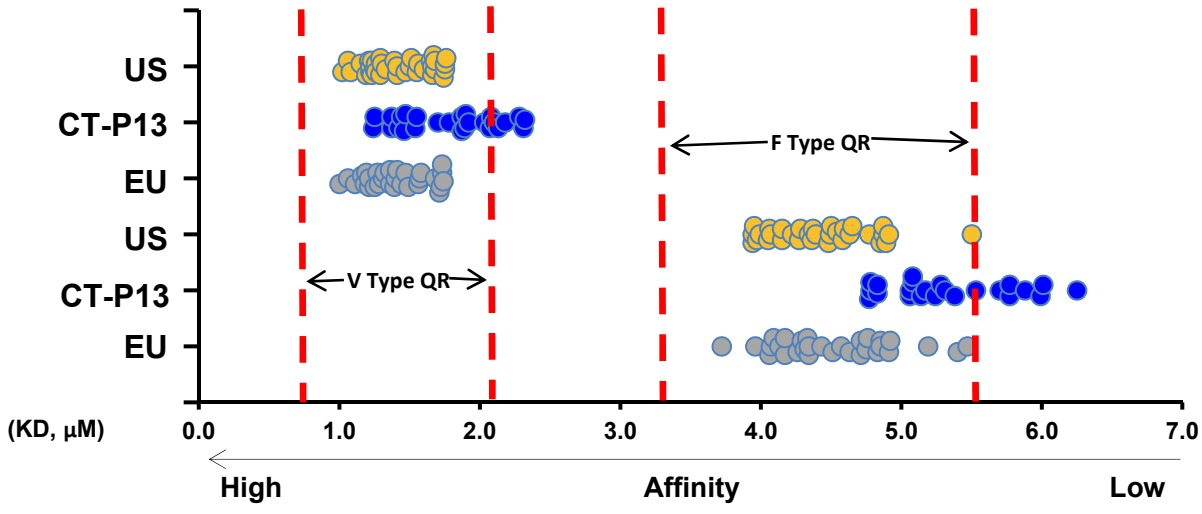




Comparative FcγRIIIa Binding Affinity

Biological Analysis	Binding Affinity (KD, μM)[1]
FcγRIIIa Binding Affinity (SPR)	

[1]The lower the KD value, the higher the binding affinity

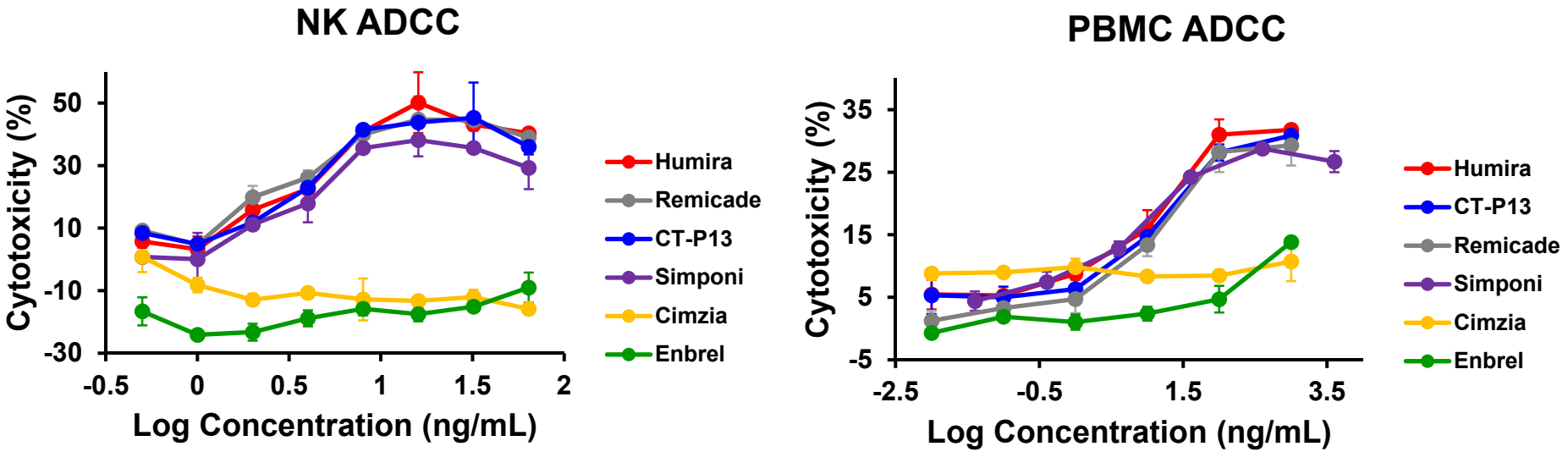
FcγRIIIa Role in Efficacy Not Confirmed

- FcγRIIIa genotypes have different IgG binding affinity[1]
- No differences in clinical responses based on different FcγRIIIa genotypes in clinical studies of Remicade in CD[2], RA[3], and PsA[4]
- Greater difference in binding of Remicade to FcγRIIIa receptors of different allotype

[1] Bruhns *et al., (*2009); Gillis *et al*., (2014)
[2] Louis *et al*., (2006); Papamichael *et al*., (2011); Tomita *et al*., (2010)
[3] Kastbom *et al*., (2007); Sarsour *et al*., (2013)
[4] Tutuncu *et al*., (2005); Morales-Lara *et al*., (2010); Ramirez *et al*., (2012)

CT-P13 ADCC is Comparable to Levels Induced by Remicade, Humira and Simponi

Comparison of ADCC by CT-P13 and Various TNFα Inhibitors



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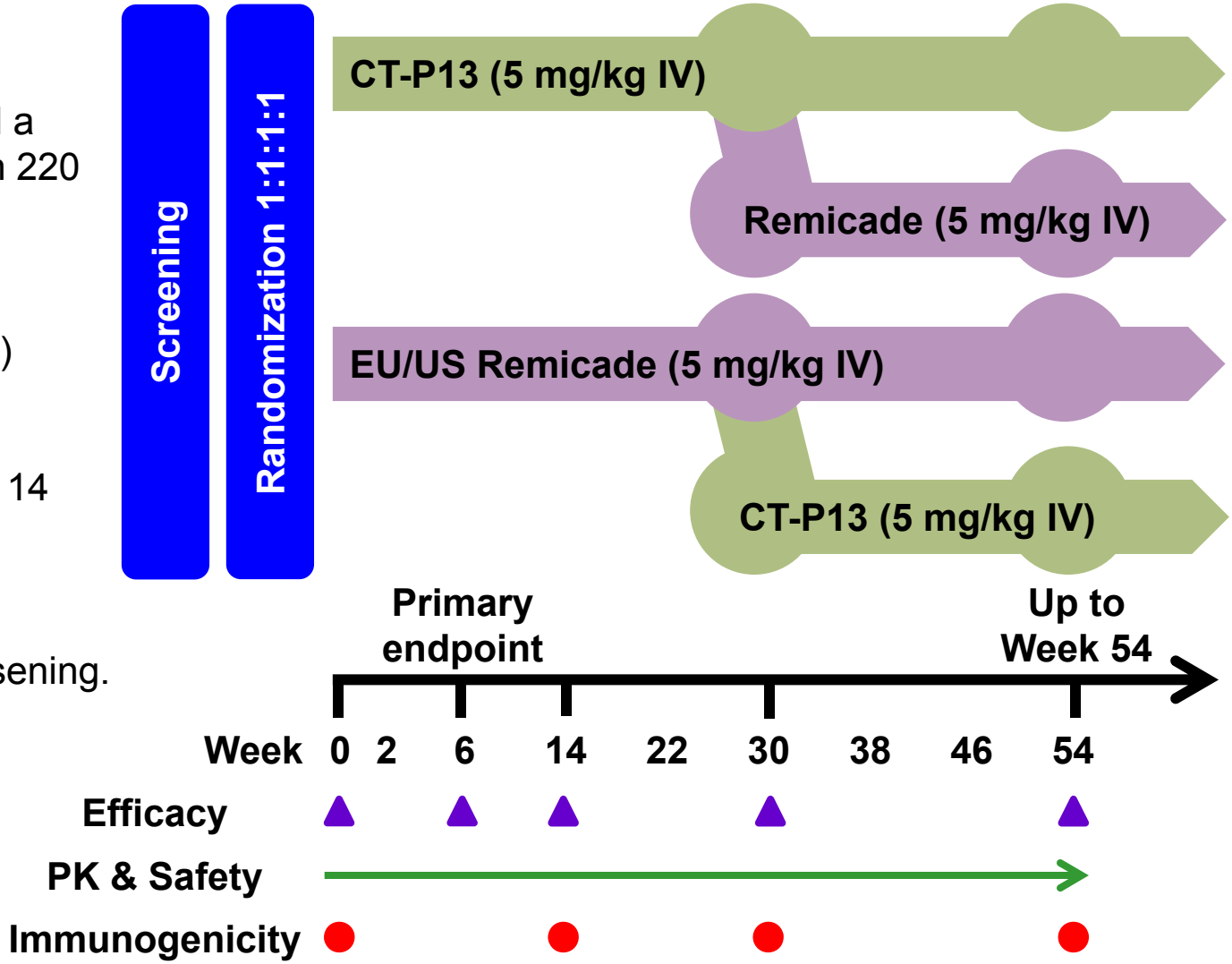

Is the company aware of data presented at ECCO by an Irish medical center describing reports of potential lack of efficacy in IBD?

- Hospira/Pfizer and Celltrion have rigorous PV processes in place. This includes collecting and reviewing safety data from multiple sources such as but not limited to:
  - spontaneous reports from HCPs, patients, and consumers, etc.
  - data from clinical studies
  - routine review of scientific literature
- Hospira/Pfizer has received 13 reports of suspected lack of efficacy involving Inflectra from a pharmacist in Ireland and is aware of data presented at ECCO IBD that included information from this Irish medical center. These reports are included in our safety database
- Infliximab literature supports that up to 40% of patients do not respond to induction therapy (primary non-response), and among initial responders, response wanes over time in approximately 23-46% of patients (secondary LOR). [1]
- From EU marketing authorization in September 2013 to date, no safety data has been collected that is inconsistent with the safety information that was known at the time of EU authorization and is currently reflected in the EU Inflectra label

[1] Ben-Horin S, *et al*. Optimizing anti-TNF treatments in inflammatory bowel disease. Autoimmunity Reviews, 2014; 13:24-30