ABP 501 – Biosimilar Candidate to Adalimumab

FDA Arthritis Advisory Committee

12 July 2016

Introduction

Richard Markus, MD, PhD

Global Development, Amgen

Agenda

Introduction	**Richard Markus, MD, PhD** Global Development, Amgen
Analytical and Nonclinical Similarity	**Simon Hotchin** Regulatory Affairs, Amgen
Clinical Similarity and Extrapolation to All Indications	**Richard Markus, MD, PhD** Global Development, Amgen
Conclusion	**Steven Galson, MD, MPH** Regulatory Affairs and Safety, Amgen

External Experts

Stanley Cohen, MD

Clinical Professor, Department of Internal Medicine

University of Texas Southwestern Medical School, Dallas, TX

Kim Papp, MD, PhD, FRCPC

Probity Medical Research, Ontario Canada

Walter Reinisch, MD

Professor, Division of Gastroenterology, Department of Medicine

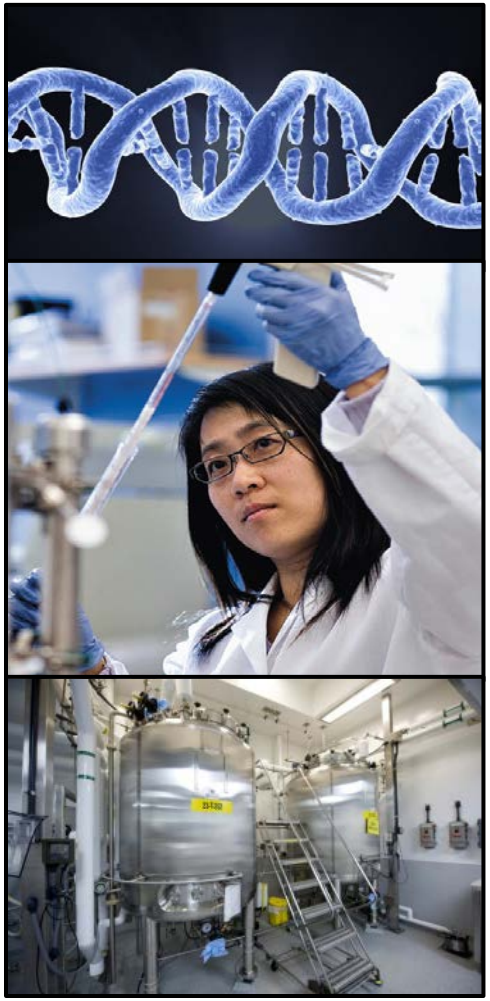
McMaster University, Ontario, Canada

Associate Professor, Gastroenterology

Medical University of Vienna, Austria

Amgen: A Biotechnology Pioneer

- More than 35 years of experience
- Capability to discover, develop, and manufacture complex biologics
- Broad pipeline of innovative medicines, and now also biosimilars
- Same scientists and laboratories to develop our biosimilars
- Same manufacturing network and quality systems to produce our biosimilars



ABP 501 and Adalimumab IgG1 Molecules that Bind and Inhibit TNFα

Primary mechanism: *Neutralization* of TNFα

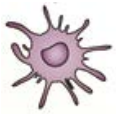
Apoptosis

Proliferation (keratinocytes, fibroblasts)

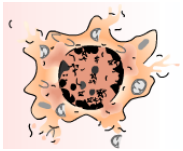
Cytokine and chemokine release

Adhesion molecule expression

DC maturation

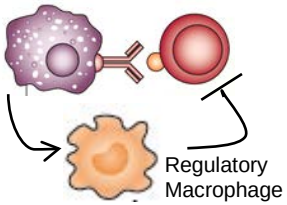


Non-apoptotic cell death

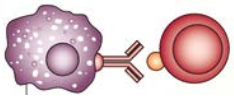


Additional activities: *Induced* by mbTNFα engagement

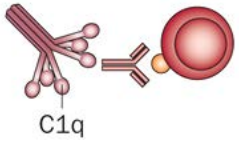
Induce regulatory macrophages/Inhibit T cell proliferation in MLR



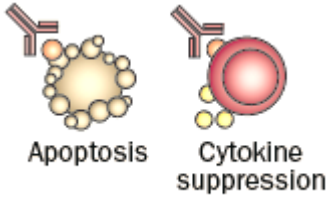
Antibody-dependent cellular cytotoxicity (ADCC)



Complement-dependent cytotoxicity (CDC)

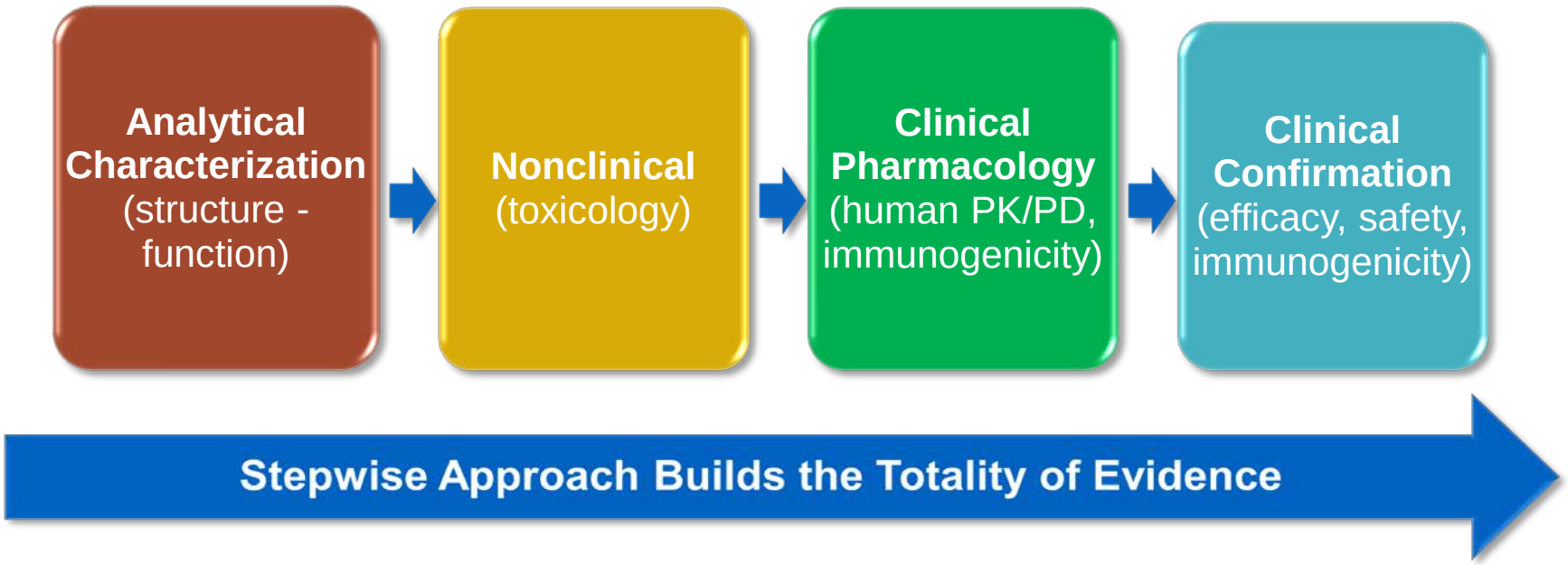


Reverse signaling

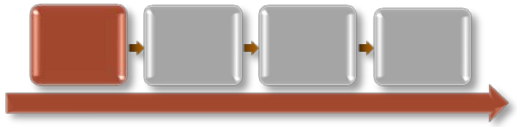


Adapted from Vande Casteele and Sandborn, *Nature Reviews Gastro & Hepat* 12:373 (2015).

Biosimilar Development and Approval Is Based on the Totality of Evidence



ABP 501
Analytical Characterization



Analytical Characterization (structure - function)

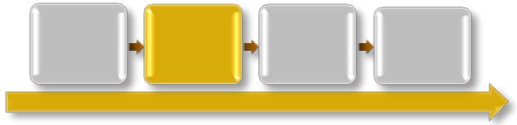
- Same amino acid sequence
- Same potency and strength

- Similar structure with minor differences

- Similar binding and functions

Analytical Characterization Shows Similar Structure and Function

ABP 501
Nonclinical Assessments



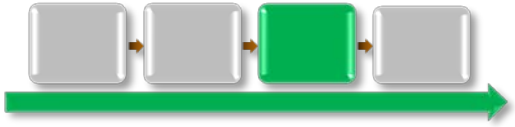
Nonclinical
(toxicology)

- Similar toxicokinetics

- Similar toxicology

Nonclinical Assessments Support Similarity

ABP 501
Clinical Pharmacology



Clinical Pharmacology (human PK/PD, immunogenicity)

- Similar PK
- No specific PD markers predictive of efficacy available for anti-TNFs

- Similar Immunogenicity

Pharmacology Shows Similar Drug Exposure

ABP 501
Clinical Confirmation

Clinical Confirmation (efficacy, safety, immunogenicity)

Similar Efficacy
- Rheumatoid Arthritis 6 month study
- Psoriasis 1 year study

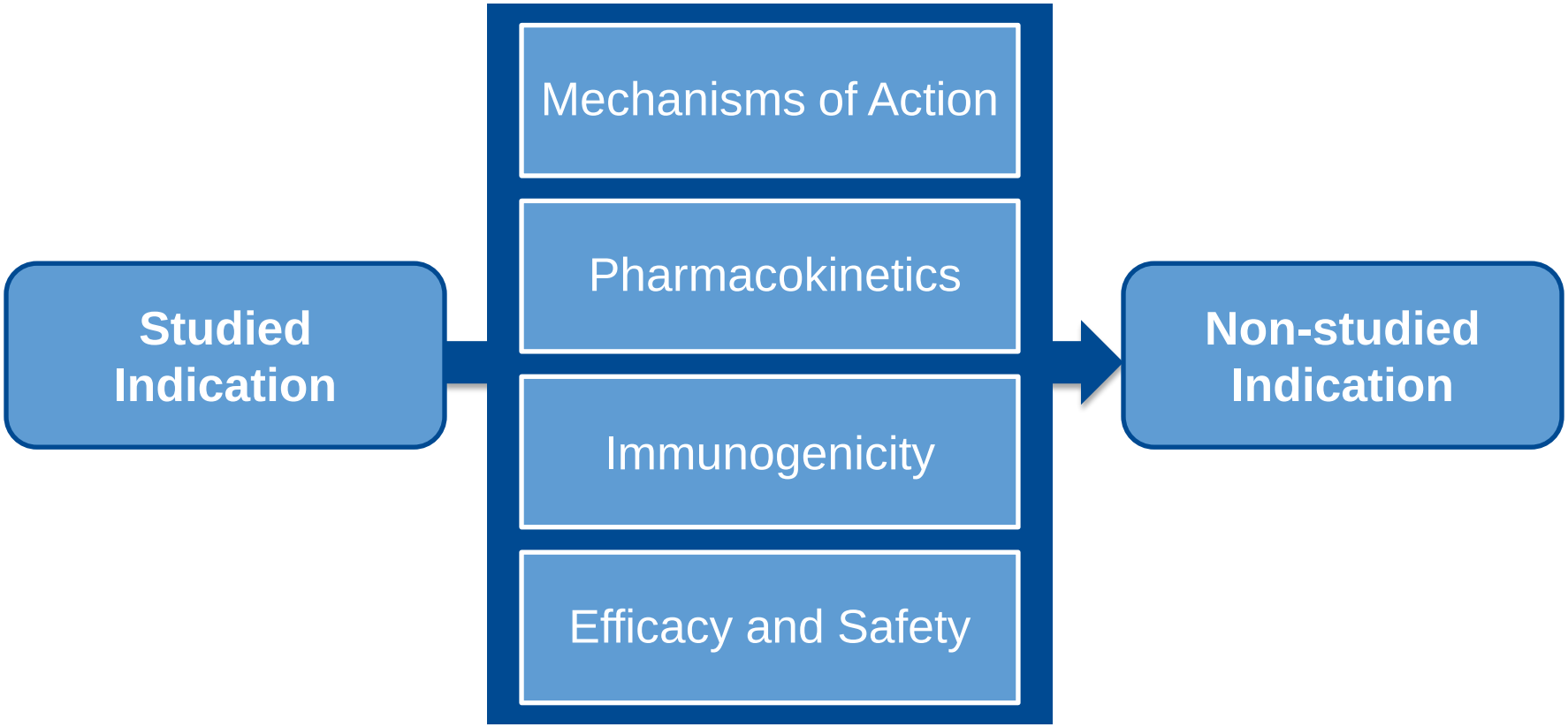
Similar Safety
- Rheumatoid Arthritis – with methotrexate
- Psoriasis – without methotrexate

Similar Immunogenicity
- Rheumatoid Arthritis and Psoriasis
- Psoriasis includes transition to ABP 501

Equivalent Efficacy and Similar Safety and Immunogenicity

Extrapolation to Additional Populations

Extrapolation of **overall similarity** informing clinical safety and efficacy to non-studied indication



Proposed Indications of Use

Arthridities

- Rheumatoid Arthritis
- Juvenile Idiopathic Arthritis (≥4 yrs)
- Psoriatic Arthritis
- Ankylosing Spondylitis

Dermatologic

- Plaque Psoriasis

Inflammatory Bowel Disease

- Crohn’s Disease
- Ulcerative Colitis

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Analytical and Nonclinical Similarity to Adalimumab

Simon Hotchin

Regulatory Affairs, Amgen

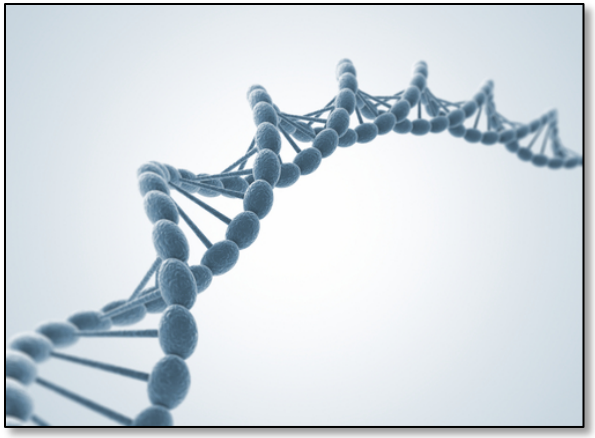
Overview

- **ABP 501 product and process design**
- **Design of the analytical similarity assessment**
- **Analytical similarity results and conclusions**
  - Structural and purity attributes
  - Functional activities
- **Nonclinical results and conclusions**

ABP 501 Product and Process Design

ABP 501 Cell Line Development

- Each biosimilar requires a new expression construct, transfection, clone selection, and cell bank
- Amgen carefully designed the ABP 501 cell line, screening a large number of clones
- Matched amino acid sequence and critical attributes of the reference product



ABP 501 Process Design

- Process developed with multiple controls to ensure similarity
- Commercial manufacturing process established at the outset of development
- Same cell line used throughout development

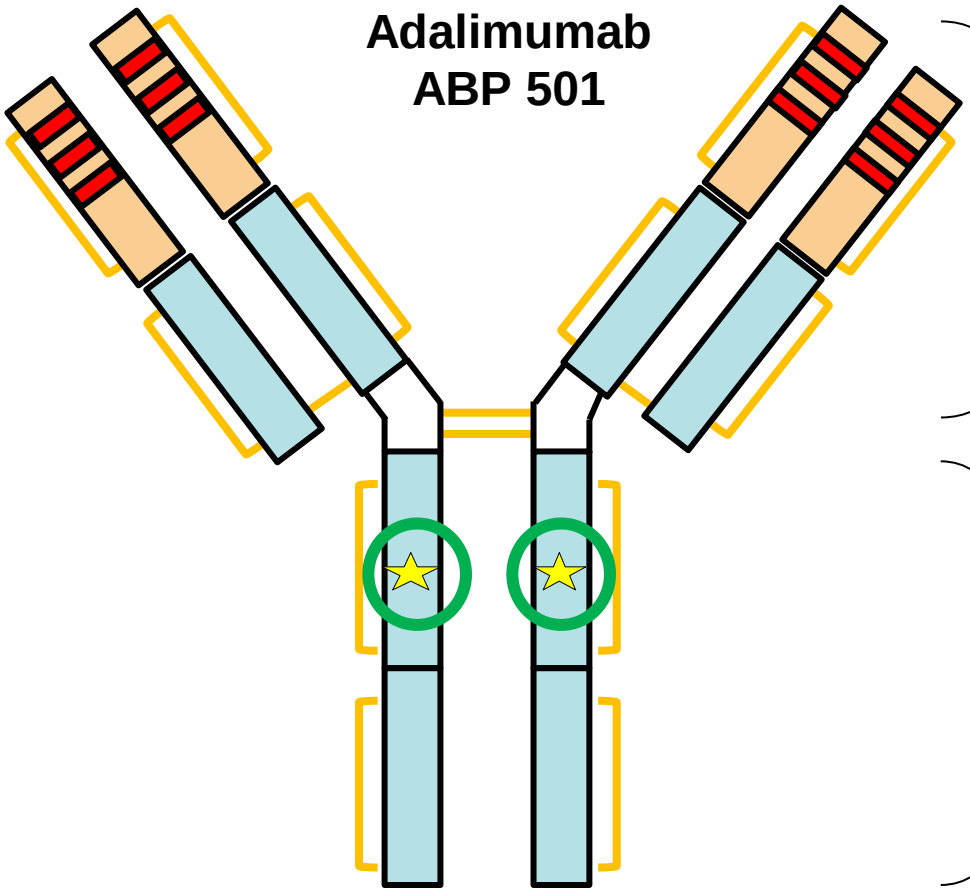
ABP 501 Presentations and Formulation

- **Three drug product presentations:**
  - Prefilled syringe, 20 mg
  - Prefilled syringe, 40 mg
  - Prefilled syringe / autoinjector, 40 mg

- **Formulation based on Amgen experience**
- **Excipients commonly used in injectable products**
- **Formulation differences shown to not impact similarity**

Design of the Analytical Similarity Assessment

Design Considerations: Activities Relevant to the Mechanisms of Action



Functional Activities

Fab-mediated activities

- TNFα binding
- TNFα neutralization

Fc-mediated activities

- FcγR binding
- FcRn binding
- C1q binding

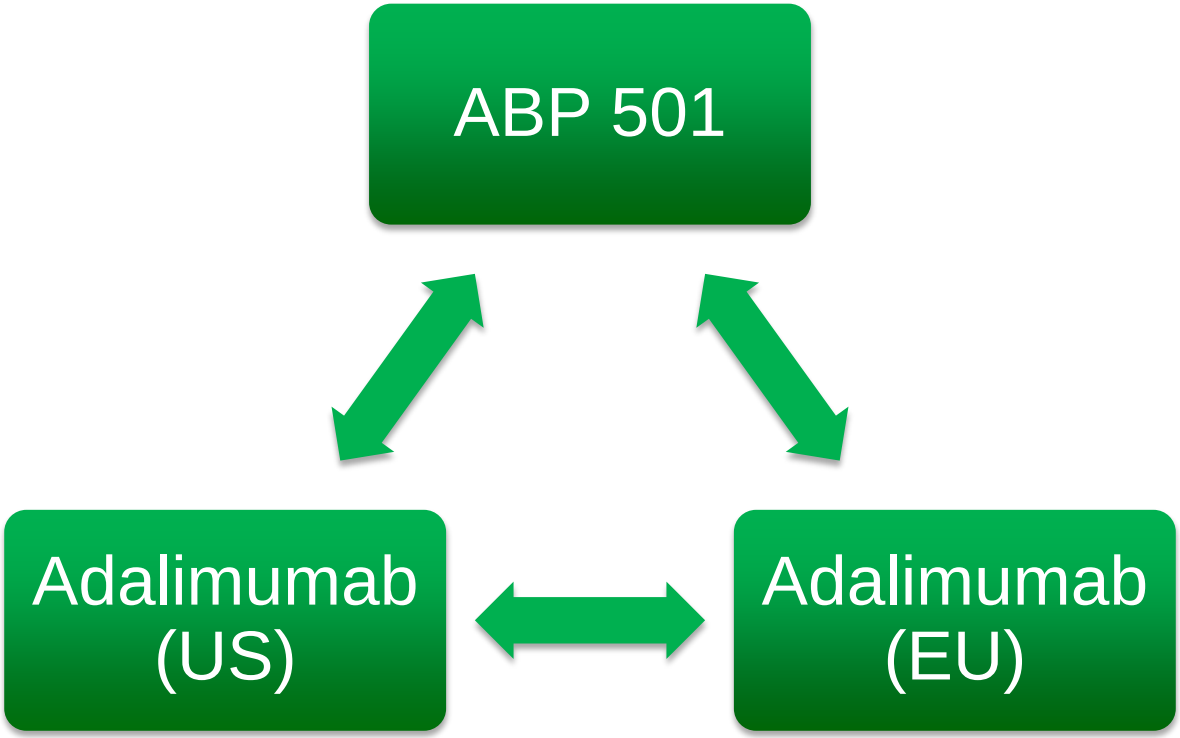
Fab- and Fc-mediated activities

- Effector functions
- Inhibition of proliferation in a mixed lymphocyte reaction (MLR)

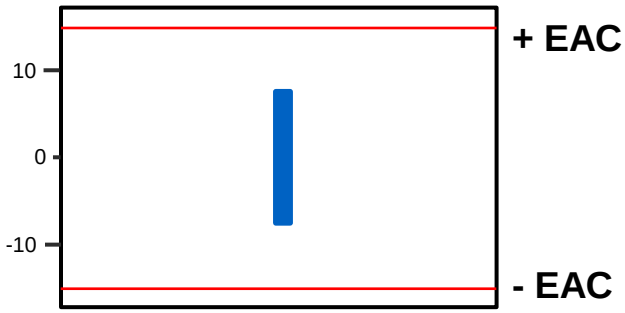
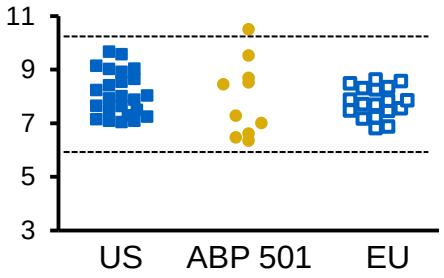
Design Considerations: Lots Used

- **Multiple lots were procured to facilitate the analysis**
  - Adalimumab: 24 US and 18 EU lots procured over 6 years
  - ABP 501: 10 lots manufactured over a similar period
- **The number of lots tested for a given method depended on the expected impact of the process on the attribute**

Design Considerations: Reference Product Bridging



Design Considerations: Assessment Criteria

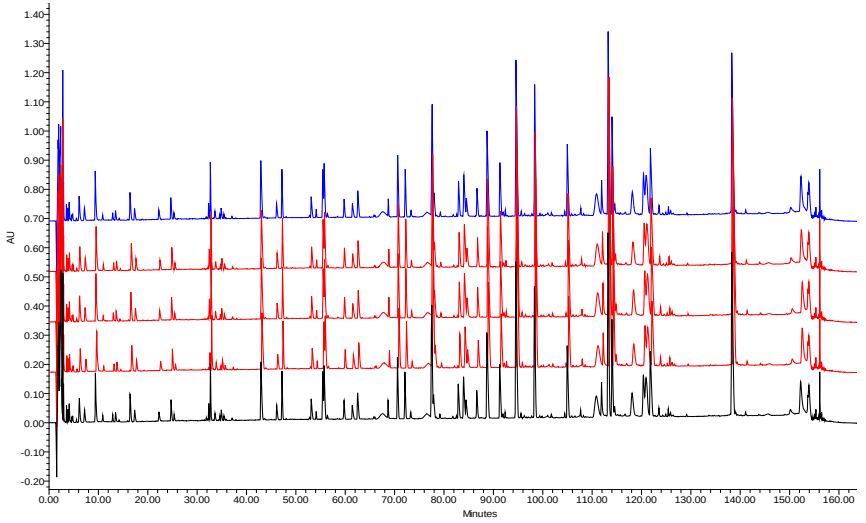
Considerations and Criteria		Results
Tier 1	Attributes with the highest risk to clinical outcomes and includes assay(s) that evaluate clinically relevant primary mechanism(s) of action Similarity is concluded when the 90% confidence interval around difference in means (blue bar) within ± 1.5 times the standard deviation of the US reference product lots tested	 EAC = equivalence acceptance criteria
Tier 2	Attributes with relatively lower risk to clinical outcomes Similarity is concluded when 90% of the ABP 501 lots are within a quality range set at mean ± 3 times the standard deviation of the US reference product lots tested	
Tier 3	Attributes with the lowest risk to clinical outcomes or non-quantitative data Similarity is based on qualitative comparisons	

Evaluation of Structural and Purity Attributes

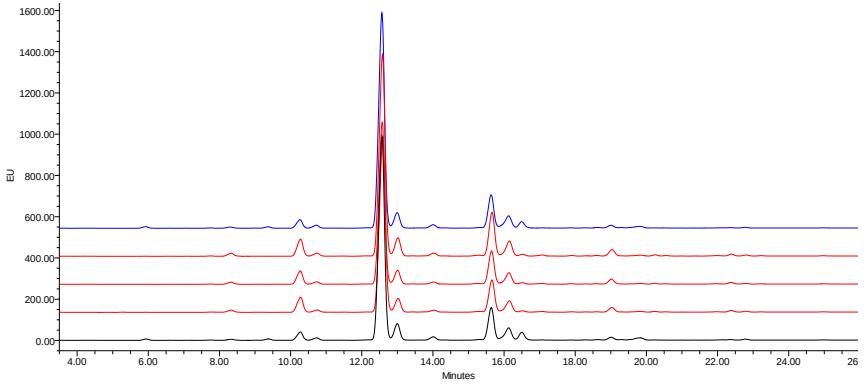
Primary Structure Similarity Results

Primary Structure	Similarity Outcome
Intact whole mass	✓
Reduced deglycosylated molecular mass	✓
Reduced peptide map	✓
Nonreduced peptide map	✓
Glycan map	Minor quantitative differences
cIEF	✓
Extinction coefficient	✓
Identity by ELISA	✓

Reduced Peptide Map



Glycan Map



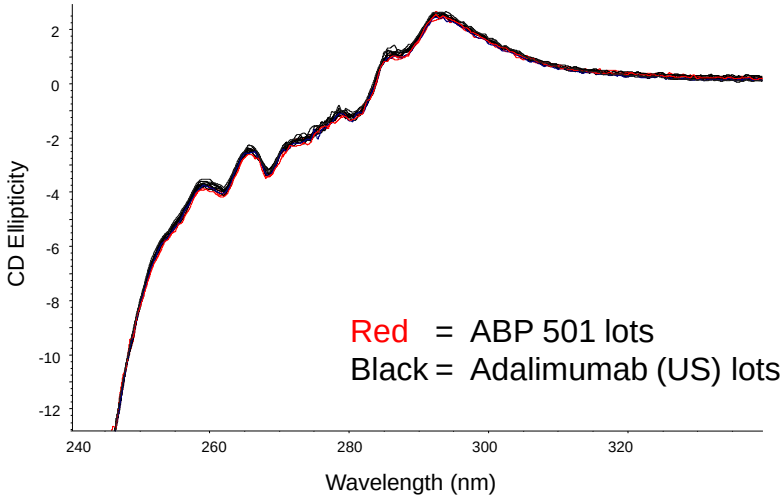
Blue = Adalimumab (EU) lots
Red = ABP 501 lots
Black = Adalimumab (US) lots

Higher Order Structure and Particles and Aggregates Similarity Results

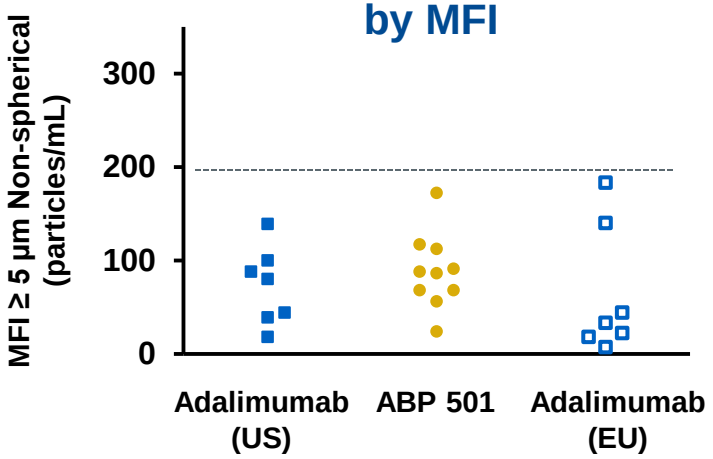
Higher Order Structure	Similarity Outcome
FTIR	✓
Near UV circular dichroism	✓
DSC	✓

Particles and Aggregates	
Microflow imaging (MFI)	✓
Subvisible particle counts by HIAC	✓
Field flow fractionation	✓
Dynamic light scattering	✓
AUC sedimentation velocity	✓
SE-HPLC with light-scattering	✓

Near UV Circular Dichroism



Proteinaceous Particles by MFI

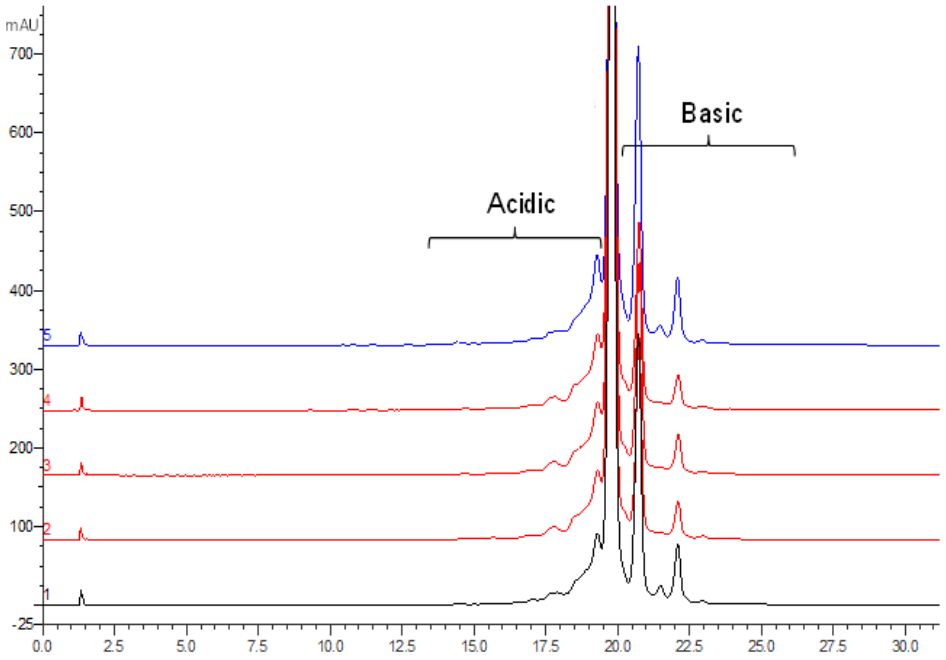


Product-related Substances and Impurities Similarity Results

Product-related Substances and Impurities	Similarity Outcome
SE-HPLC	✓
rCE-SDS	Minor quantitative differences
nrCE-SDS	Minor quantitative differences
CEX-HPLC	Minor quantitative differences

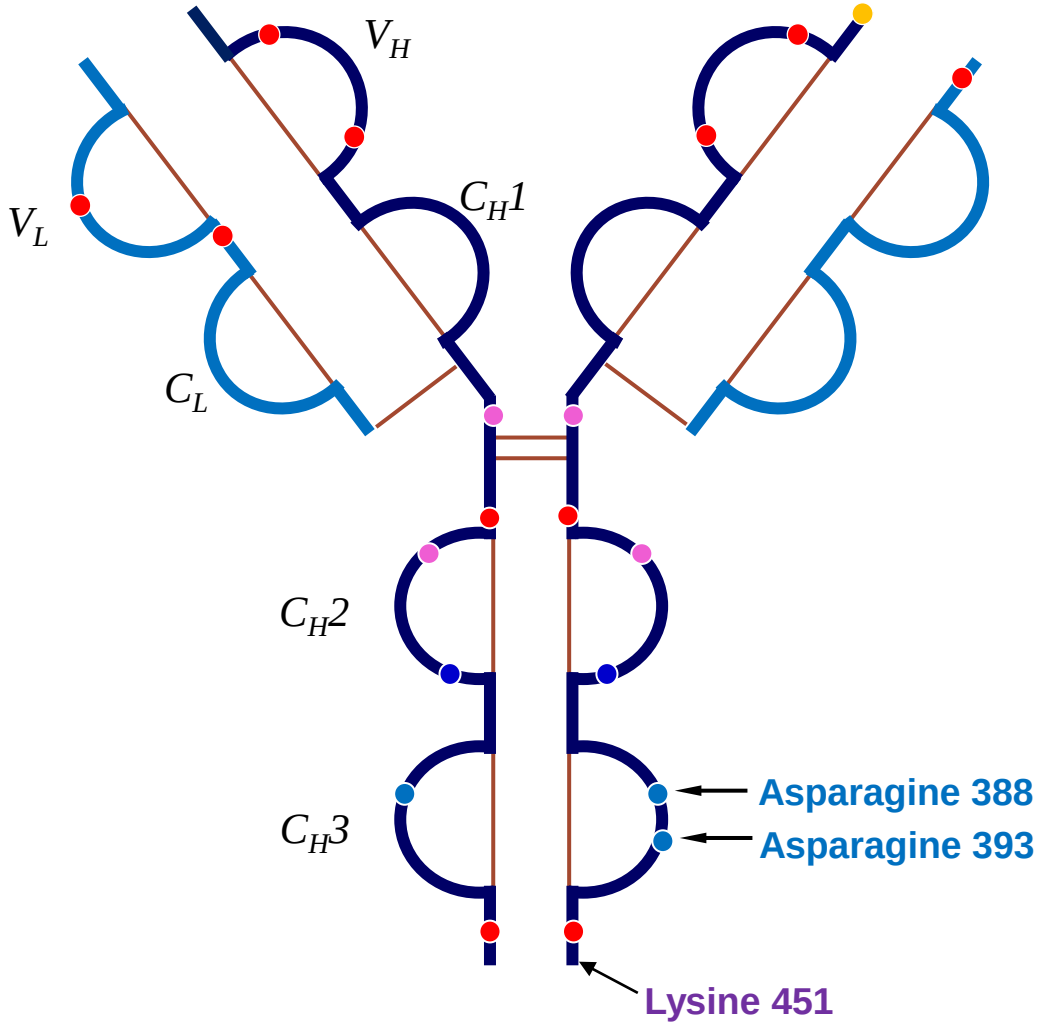
- **No new species observed**
- **No impact on functional activities**

CEX-HPLC



Blue = Adalimumab (EU) lots
Red = ABP 501 lots
Black = Adalimumab (US) lots

Assessment of Charge Profile Differences

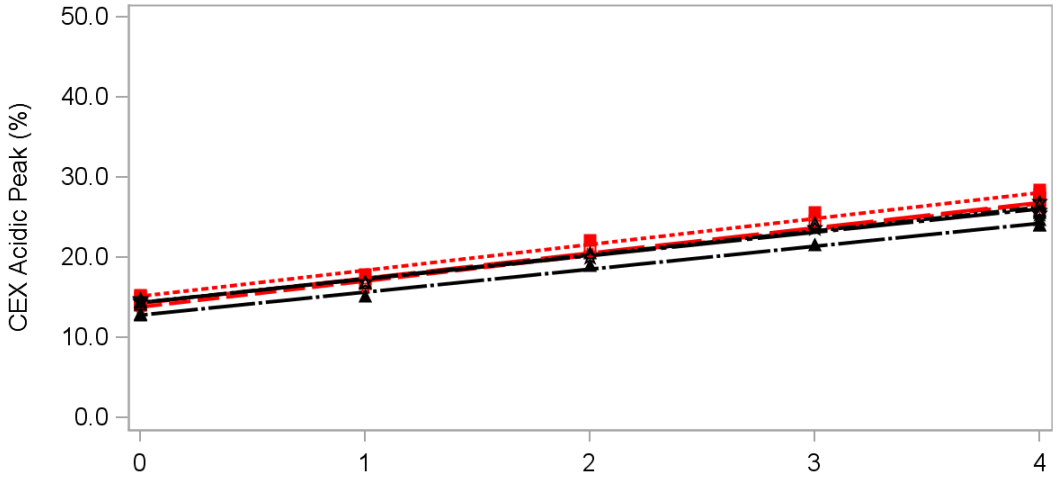


- Basic peak area differences due to differences in levels of C-terminal lysine (451)
- Acidic peak area differences due to differences in levels of deamidation at two asparagine sites (388 and 393)
- Same variants present in the reference product
- Modifications are not within the antigen, Fc receptor, or C1q binding domains
- Unlikely to impact PK, efficacy, safety, or immunogenicity

Thermal Forced Degradation Similarity Results

Thermal Forced Degradation	Similarity Outcome
50°C Forced degradation	✓
40°C Accelerated stability	✓
25°C Accelerated stability	✓

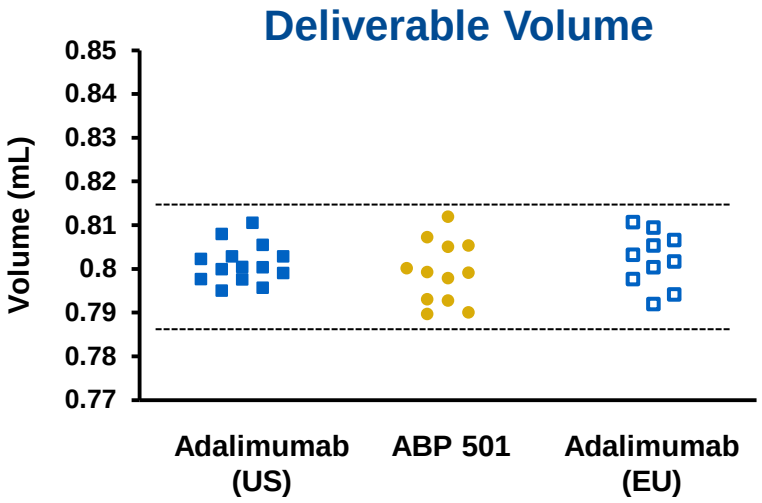
Degradation Rate Plot for CEX-HPLC Acidic Peaks at 50°C

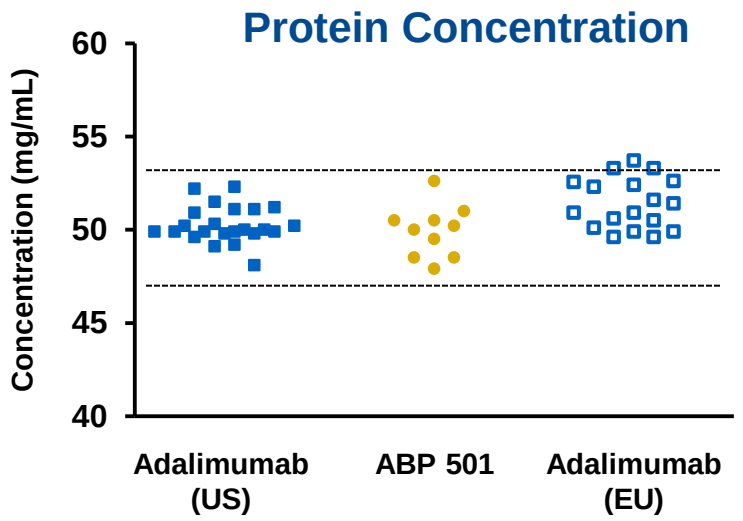


Red = ABP 501 lots
Black = Adalimumab (US) lots

General Properties Similarity Results

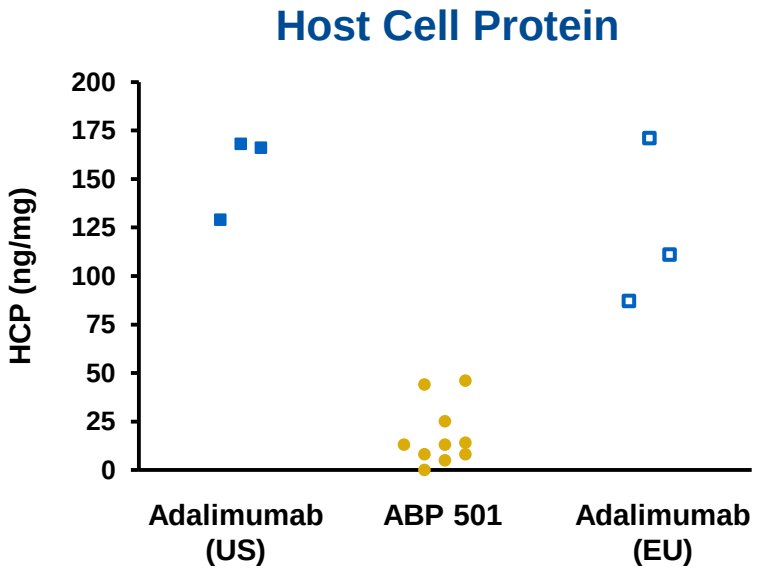
General Properties	Similarity Outcome
Appearance	✓
Color	✓
Clarity	✓
pH	✓
Osmolality	✓
Volume	✓
Polysorbate	✓
Protein concentration	✓





Process-related Impurities Similarity Results

Process-related Impurities	Similarity Outcome
Host cell protein (HCP) - ELISA	✓
HCP analysis by 2D differential in gel electrophoresis	✓
Protein A – ELISA	✓
Residual DNA – qPCR	✓

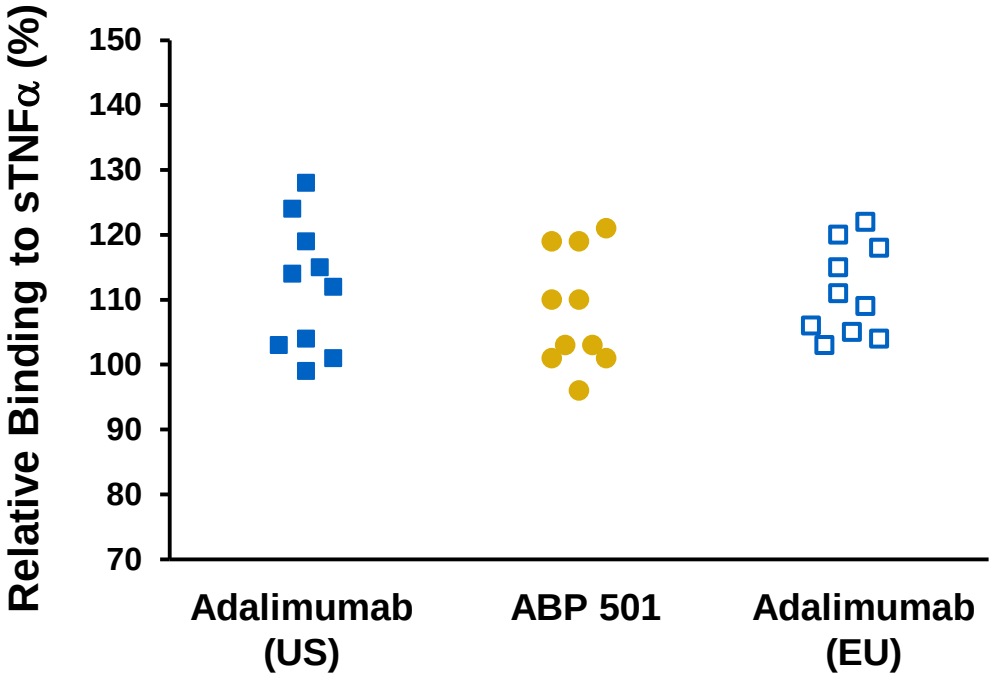


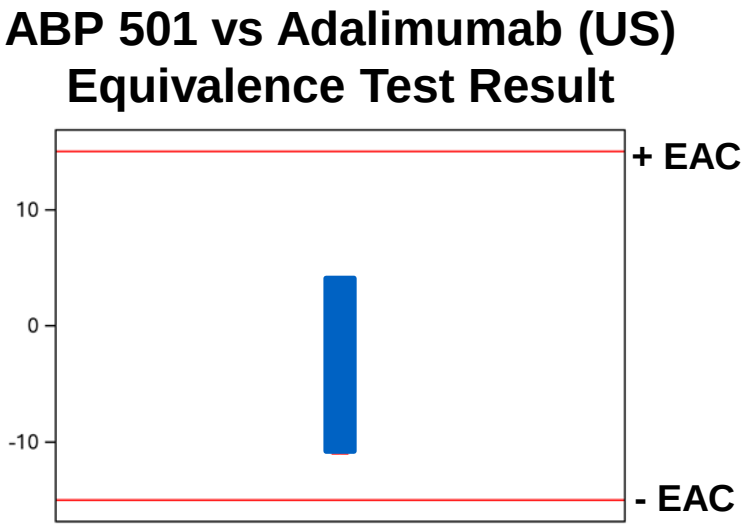
Evaluation of Functional Activities

Similarity was Demonstrated in All Functional Activities Evaluated

Fab-mediated Activities		Fc-mediated Activities		Fab and Fc-mediated Activities	
Apoptosis inhibition bioassay (Potency)	✓	FcγRIIIa (158V) binding	✓	Inhibition of proliferation in a mixed lymphocyte reaction (MLR)	✓
sTNFα binding	✓	FcγRIIIa (158V) + TNFα binding	✓	ADCC	✓
Binding kinetics to sTNFα	✓	FcγRIa binding	✓	CDC	✓
Inhibition of sTNFα-induced IL-8 in HUVEC	✓	FcγRIIa (131H) binding	✓		
Inhibition of sTNFα- induced cell death in L929 cells	✓	FcγRIIIa (158F) binding	✓		
Inhibition of sTNFα-induced chemokines in whole blood	✓	FcRn binding	✓		
Specificity against LTα in a HUVEC assay	✓	C1q binding	✓		
Binding to mbTNFα	✓				

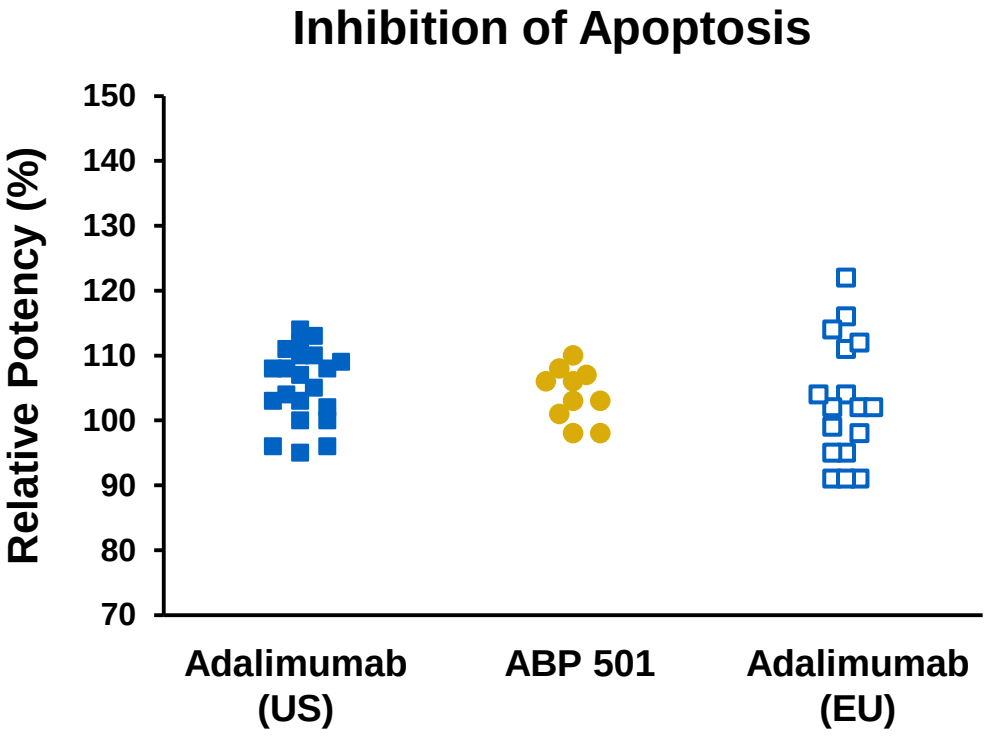
Similar Binding to Soluble TNFα

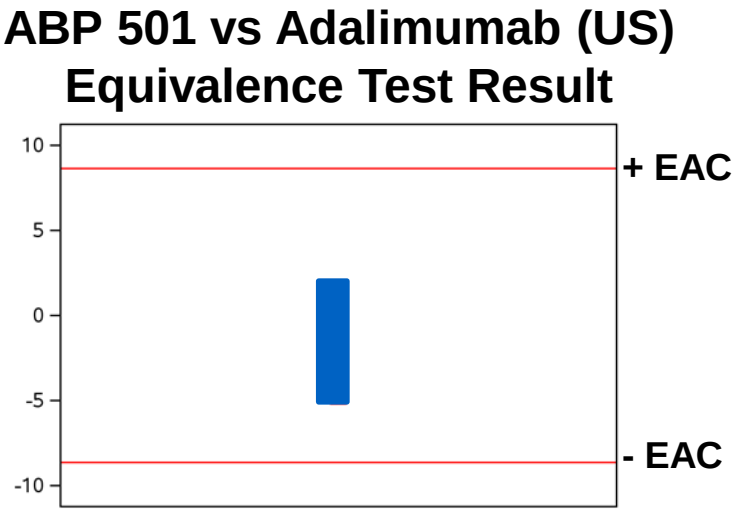




Blue bar = 90% confidence interval

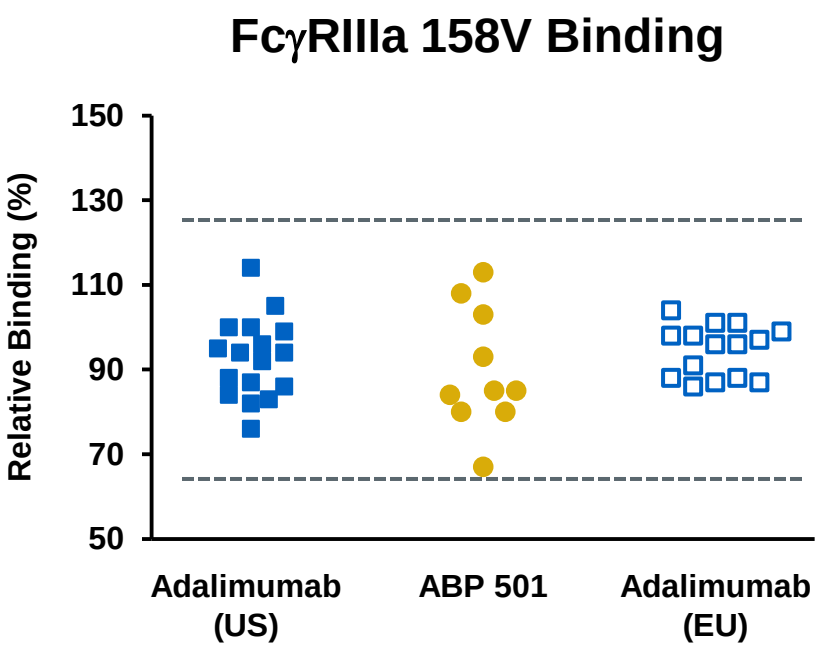
Similar TNFα Neutralization

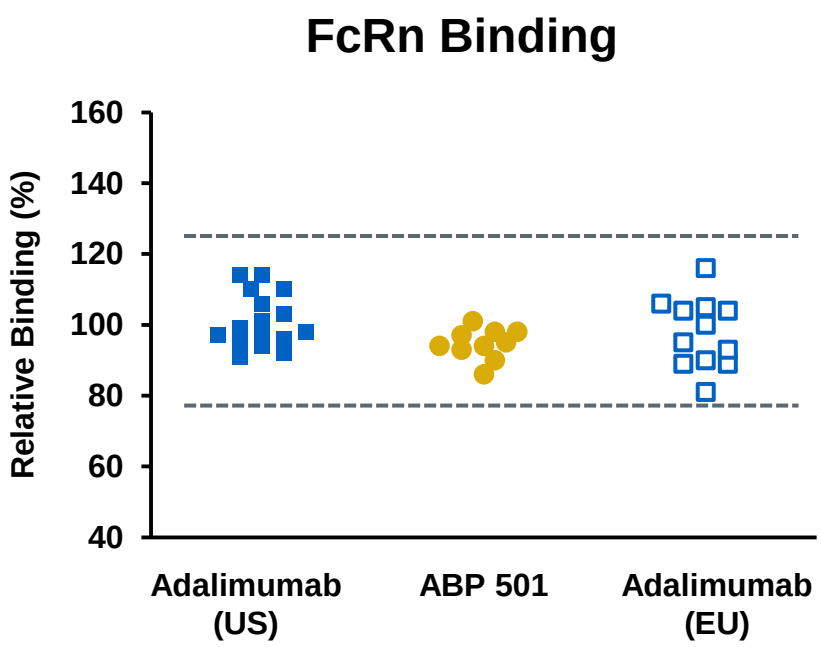




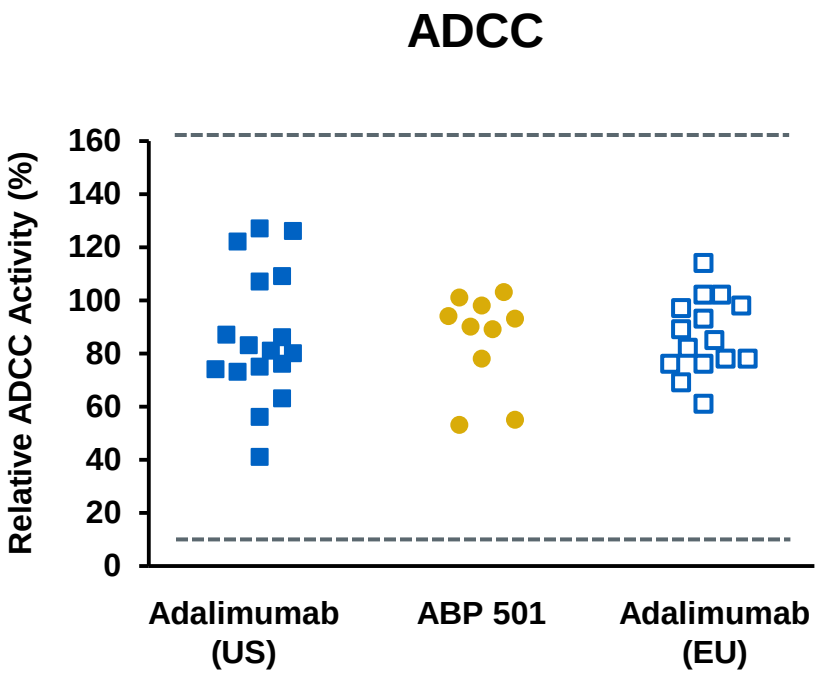
Blue bar = 90% confidence interval

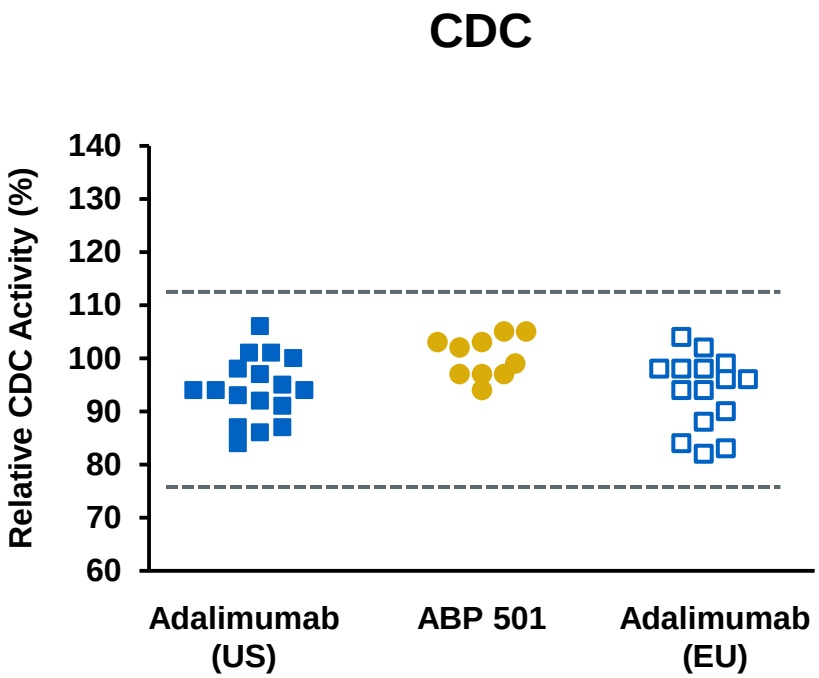
Similar Fc-mediated Activities



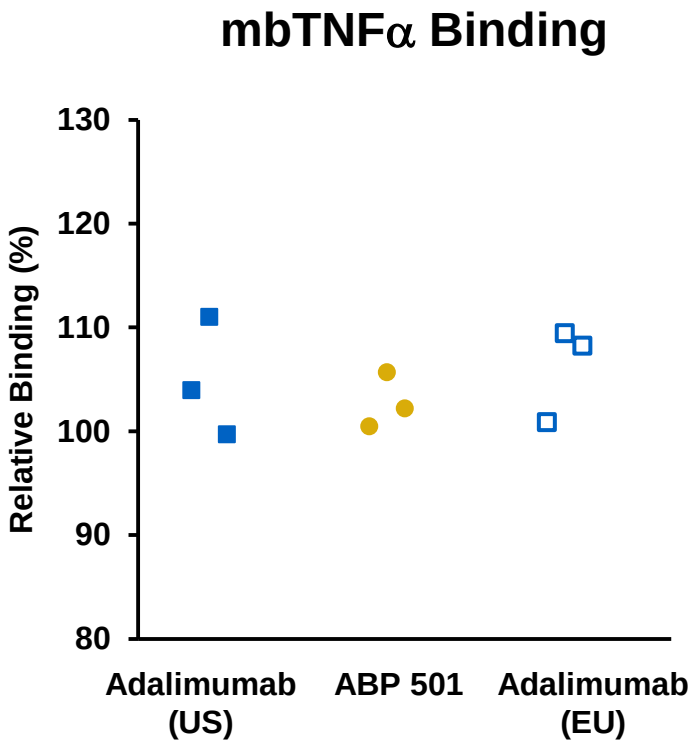


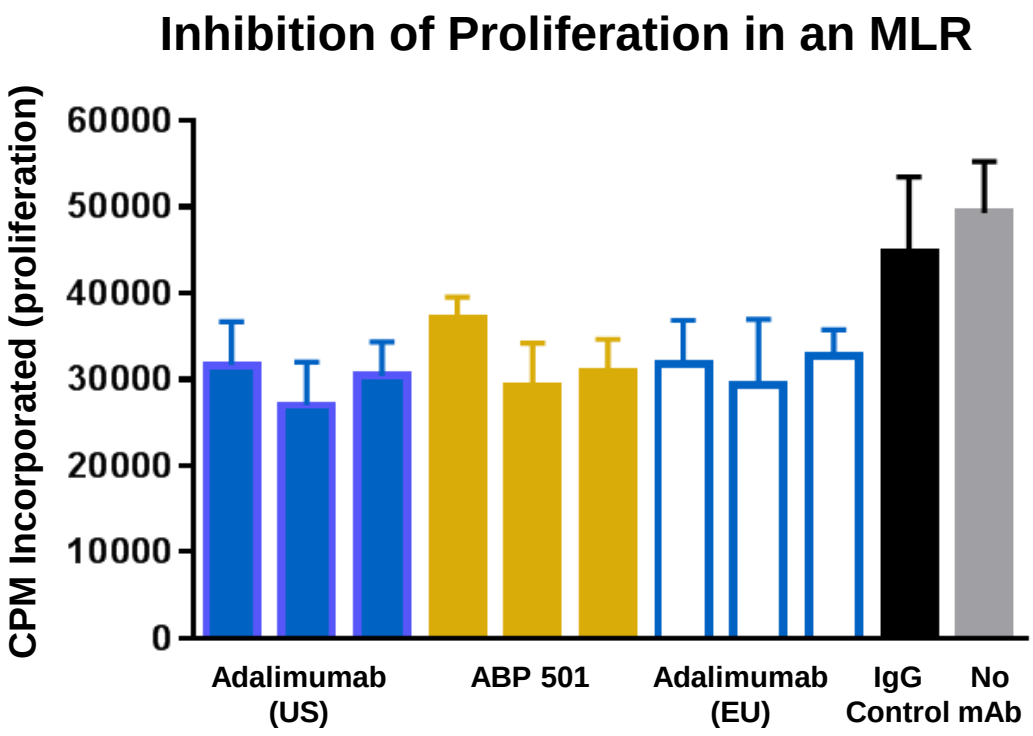
Similar Effector Functions





Similar mbTNFα Binding and Activity





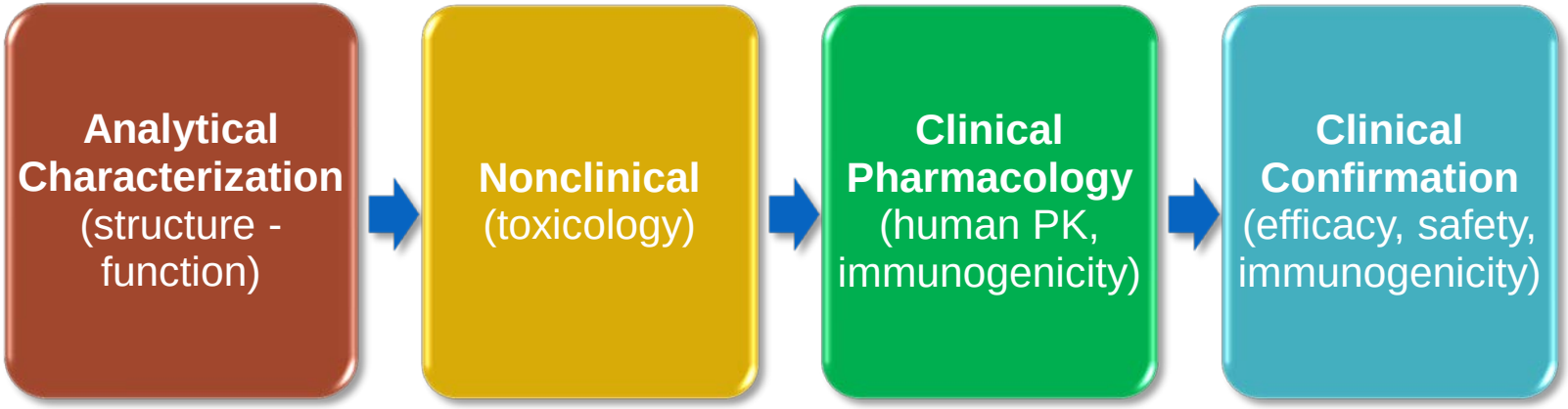
- Each bar represents a single lot tested (5 replicates per assay) with the standard deviation

Extrapolation Based on Similarity in All Mechanisms of Action

Functional Similarity is Demonstrated in All Known and Plausible Mechanisms of Action

Mechanism of Action	Arthritides: RA, JIA, AS, PsA	Dermatologic: Ps	IBD: CD, UC	Functional Activity	Similarity Outcome
Primary					
Soluble TNFα binding	known	known	known	Relative binding to sTNFα	✓
				Binding kinetics by SPR	✓
Soluble TNFα neutralization	known	known	known	Inhibition of apoptosis	✓
				Neutralization of TNFα-induced cytokine in HUVEC	✓
				Inhibition of cytotoxicity	✓
				Inhibition of chemokine induction in blood	✓
Additional MOAs					
Membrane-bound TNFα binding	--	--	plausible	mbTNFα binding	✓
Effector functions	--	--	plausible	CDC	✓
				ADCC	✓
Modulation of Immune cells expressing mbTNFα	--	--	plausible	Inhibition of proliferation in an MLR	✓

Analytical Characterization Supports Biosimilarity

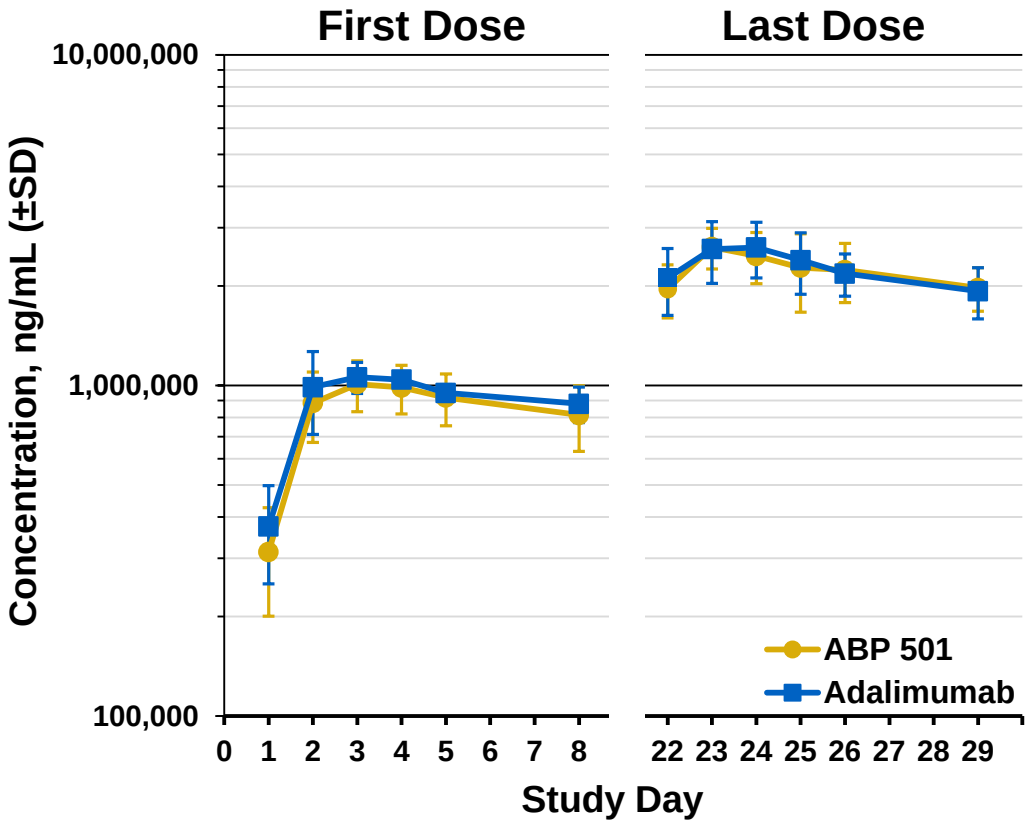


- **Comprehensive analytical characterization was conducted**
- **Results demonstrate similarity, notably all functional activities matched the reference product**
- **ABP 501 is highly analytically similar to adalimumab**
- **Analytical similarity results form the foundation of the scientific justification for extrapolation**

Nonclinical Results and Conclusions

Nonclinical: Toxicology

- ABP 501 vs adalimumab vs vehicle
- Four weeks: 157 mg/kg/wk dosed subcutaneously
- 3 male and 3 female cynomolgus monkeys/group

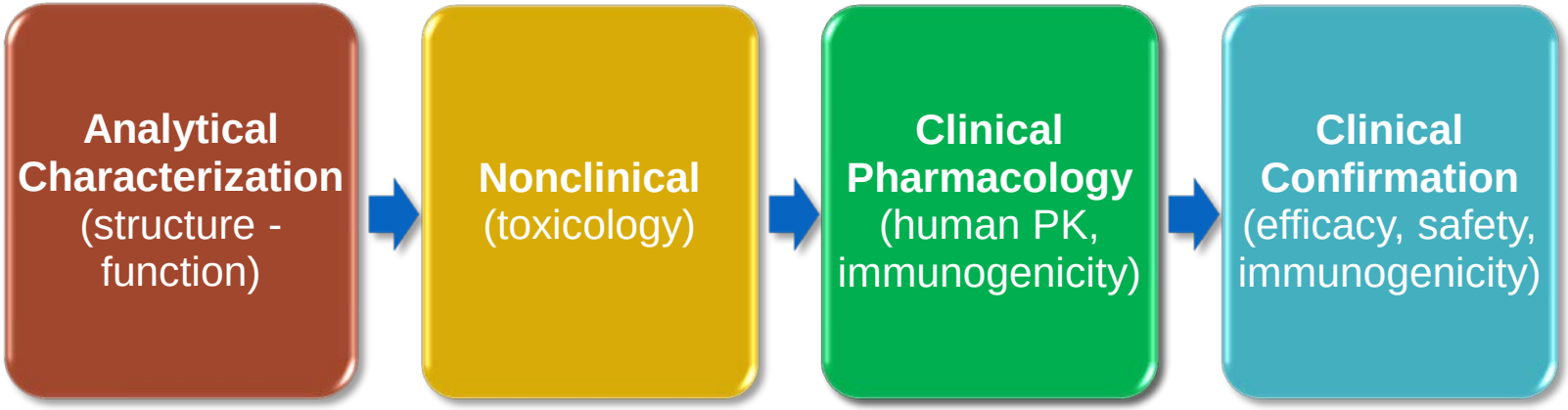


Similar toxicology findings between treatment groups

Toxicity findings were limited to the expected effects on the immune system:

- Decreased B cells in the follicular germinal centers of spleen, tonsil, and lymph nodes

Nonclinical Data Supports Biosimilarity



- **ABP 501 and adalimumab had similar toxicokinetics**
- **ABP 501 and adalimumab both induced the expected lymphoid changes in cynomolgus monkey studies**

Agenda

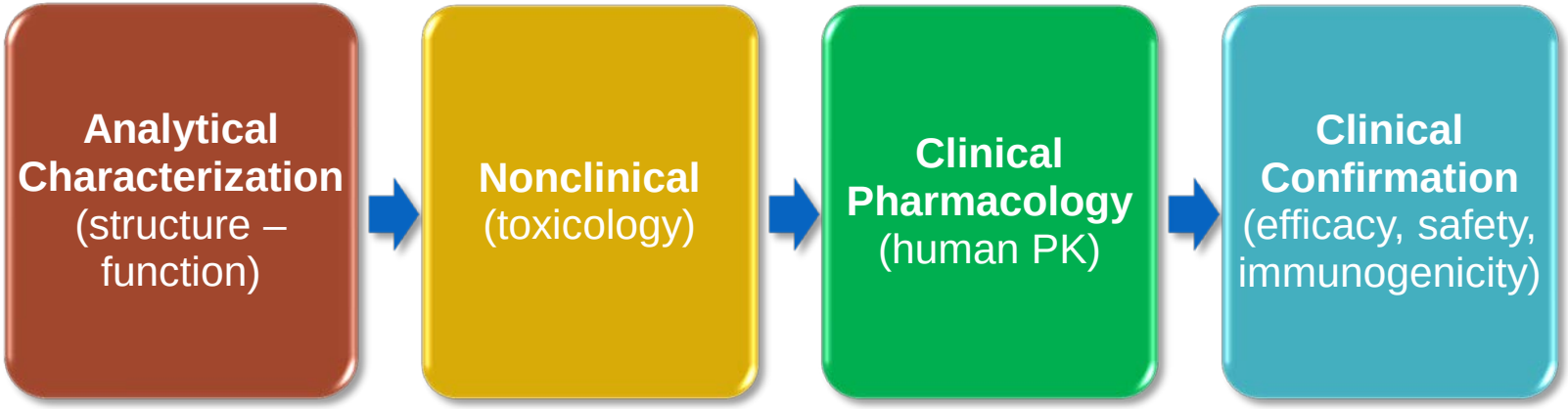
Introduction	**Richard Markus, MD, PhD** Global Development, Amgen
Analytical and Nonclinical Similarity	**Simon Hotchin** Regulatory Affairs, Amgen
Clinical Similarity and Extrapolation to All Indications	**Richard Markus, MD, PhD** Global Development, Amgen
Conclusion	**Steven Galson, MD, MPH** Regulatory Affairs and Safety, Amgen

ABP 501 Clinical Similarity

Richard Markus, MD, PhD

Global Development, Amgen

Clinical Pharmacology is Next in Stepwise Development



- **Same amino acid sequence**
- **Same strength**
- **Highly similar structure and function**

- **Similar kinetics**
- **Similar toxicology**

Clinical Studies

Subject Population	Type of Study	Number of Subjects	Study Duration	Primary Endpoint
Healthy subjects	PK similarity	203 randomized	Single dose	AUC_{inf} and C_{max}
Rheumatoid arthritis	Efficacy, Safety, Immunogenicity	526 randomized	26 weeks	ACR20 at week 24
	Long-term Extension Study	467 enrolled	72 weeks	Safety, ACR20, DAS28-CRP
Plaque psoriasis	Efficacy, Safety, Immunogenicity	350 randomized	52 weeks	PASI % improvement from baseline at week 16

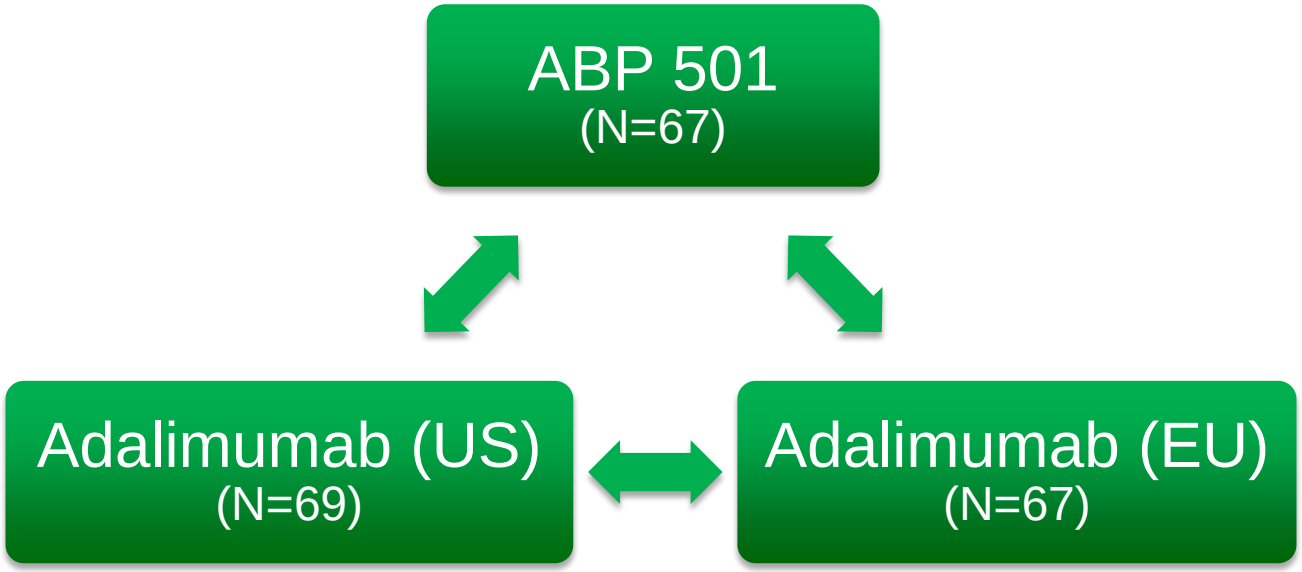
Clinical Pharmacology – PK Similarity

Design:

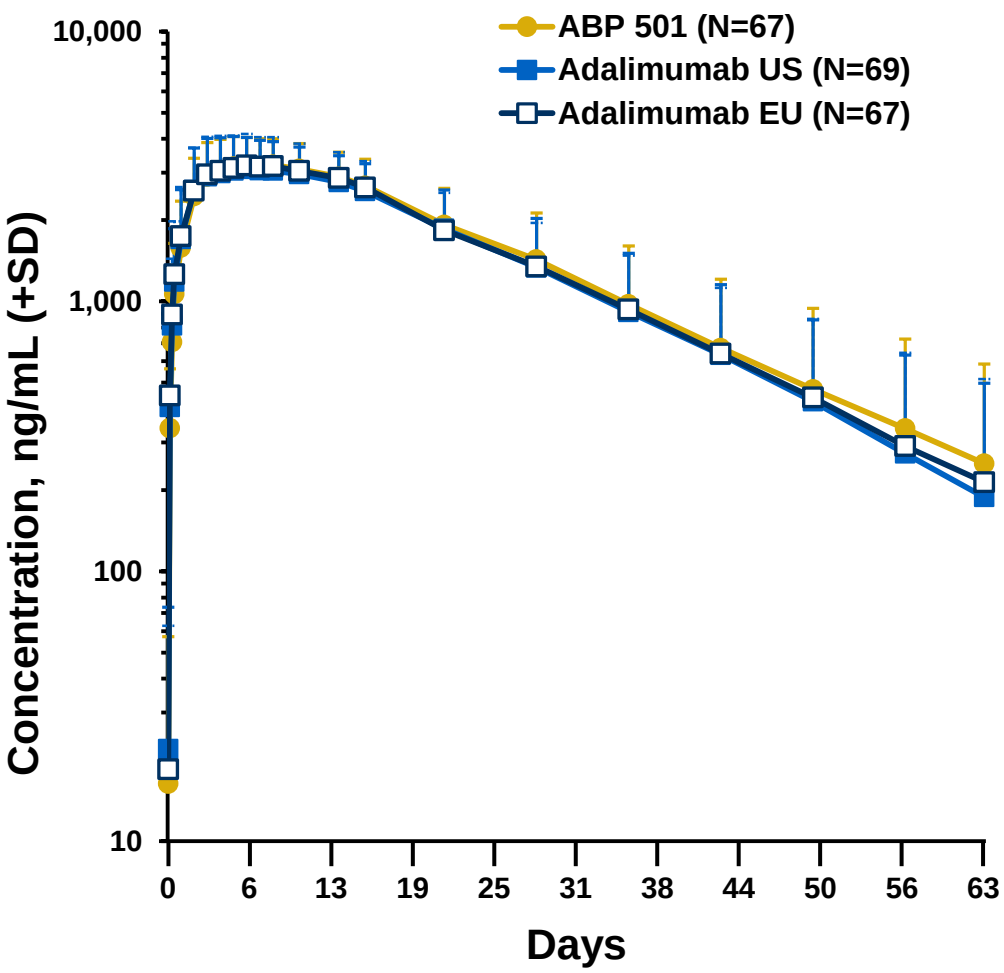
- **Healthy subjects**
- **Single 40 mg subcutaneous dose**
- **63 days follow-up**

Endpoints:

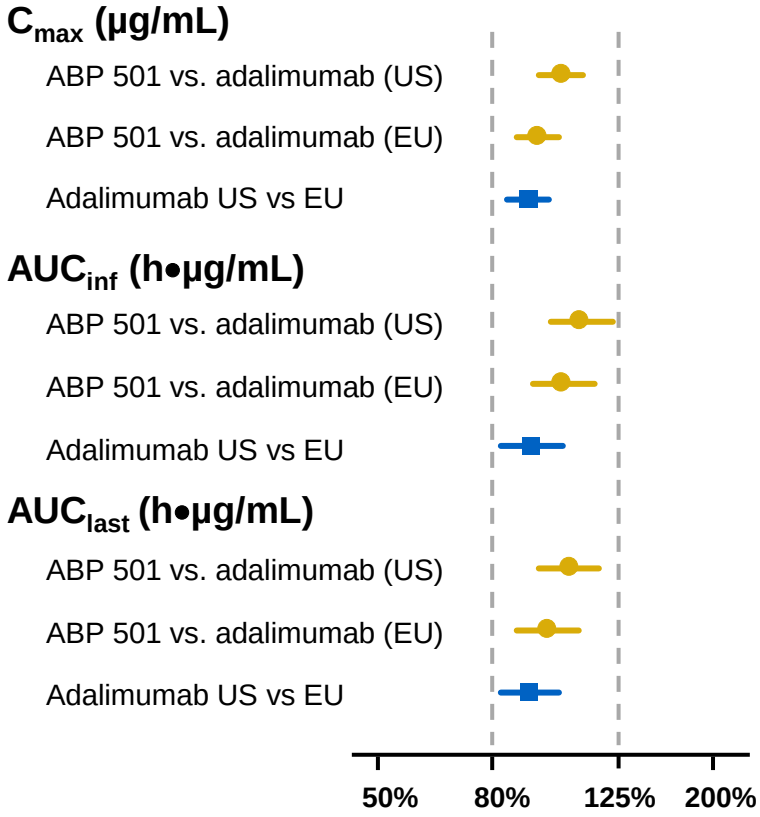
- **C_{max}, AUC_{inf}, AUC_{last} (Margin 80-125%)**
- **Safety**
- **Immunogenicity**



ABP 501 Pharmacokinetic Similarity with Adalimumab



Ratio of Adjusted LS Geometric Means with 90% CI



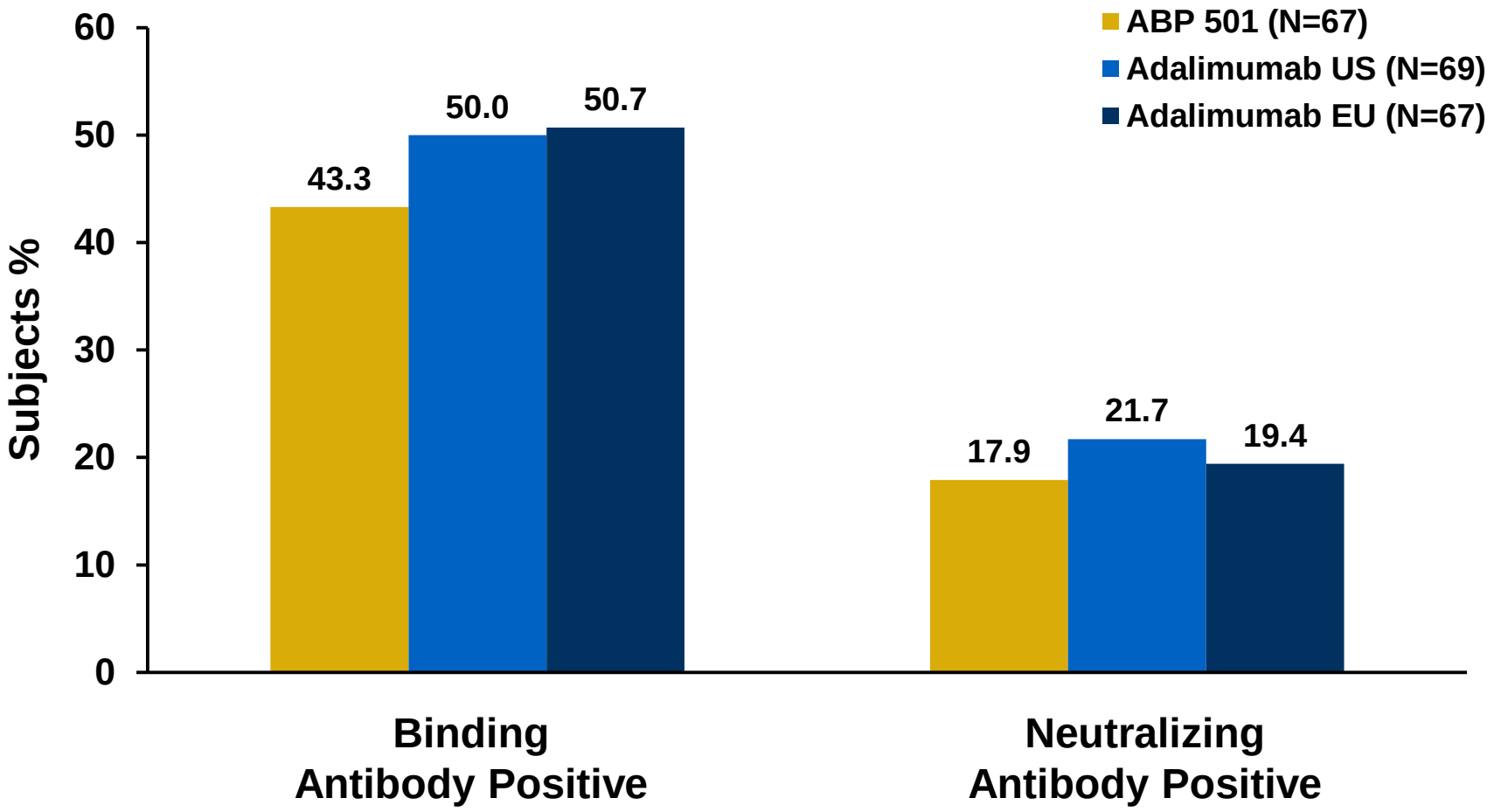
- **All assessments met the predefined equivalence criteria with 90% CI within 80-125%**

PK Study: Treatment-emergent Adverse Events Reported in >5% of Subjects in Any Treatment Group

Preferred Term	ABP 501 N=67 n (%)	Adalimumab (US) N=69 n (%)	Adalimumab (EU) N=67 n (%)
Headache	19 (28.4)	16 (23.2)	13 (19.4)
Oropharyngeal pain	6 (9.0)	6 (8.7)	3 (4.5)
Sinus congestion	6 (9.0)	6 (8.7)	0
Nasopharyngitis	4 (6.0)	0	7 (10.4)
Nausea	5 (7.5)	2 (2.9)	4 (6.0)
Diarrhea	1 (1.5)	1 (1.4)	8 (11.9)
Vomiting	1 (1.5)	2 (2.9)	5 (7.5)
Back pain	1 (1.5)	1 (1.4)	5 (7.5)
Dizziness	1 (1.5)	1 (1.4)	4 (6.0)
Dysmenorrhea	1 (1.5)	4 (5.8)	1 (1.5)
Nasal congestion	1 (1.5)	4 (5.8)	0

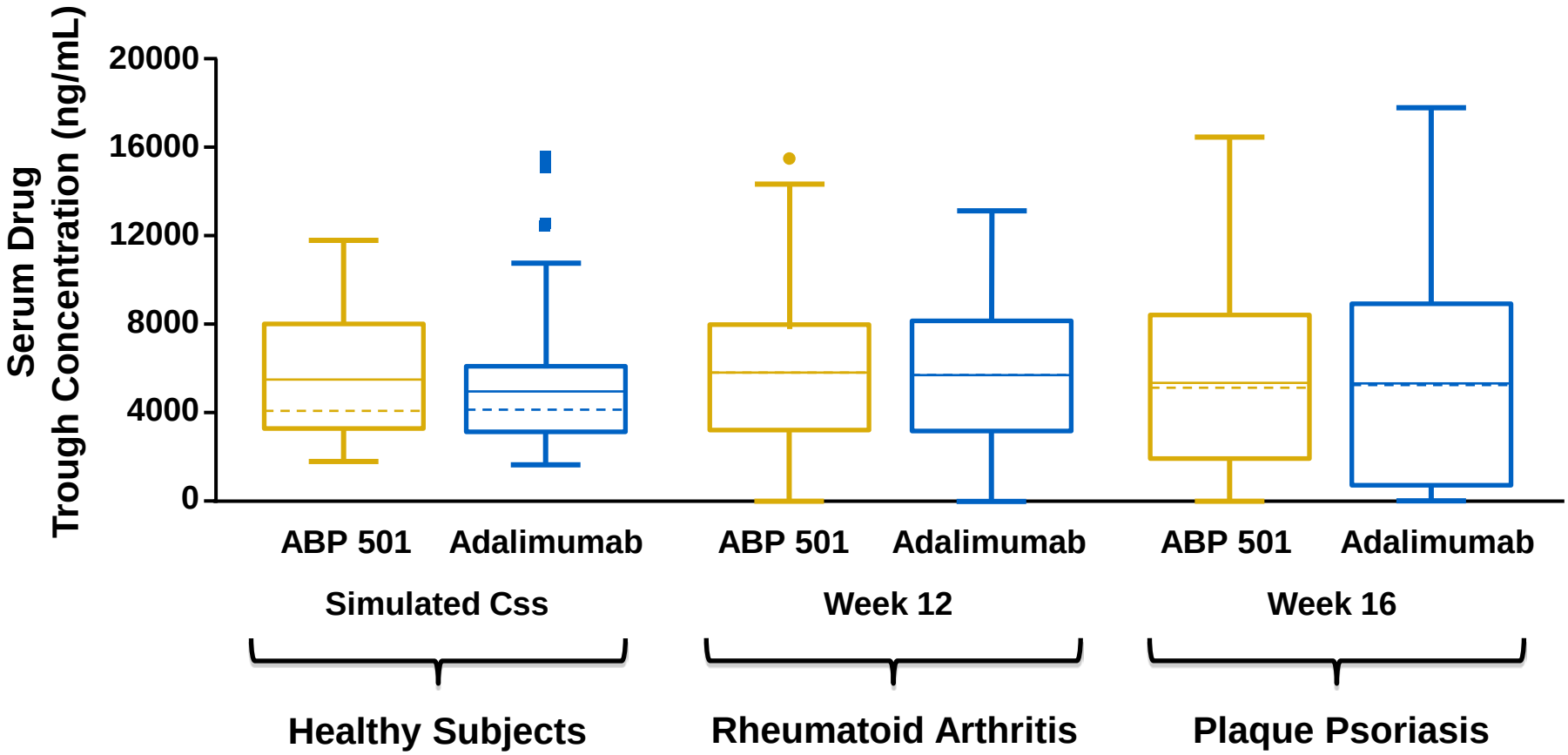
- **1 SAE reported: Ruptured dermoid cyst in subject receiving adalimumab (EU)**

PK Study: Similar Rates of Anti-drug Antibodies



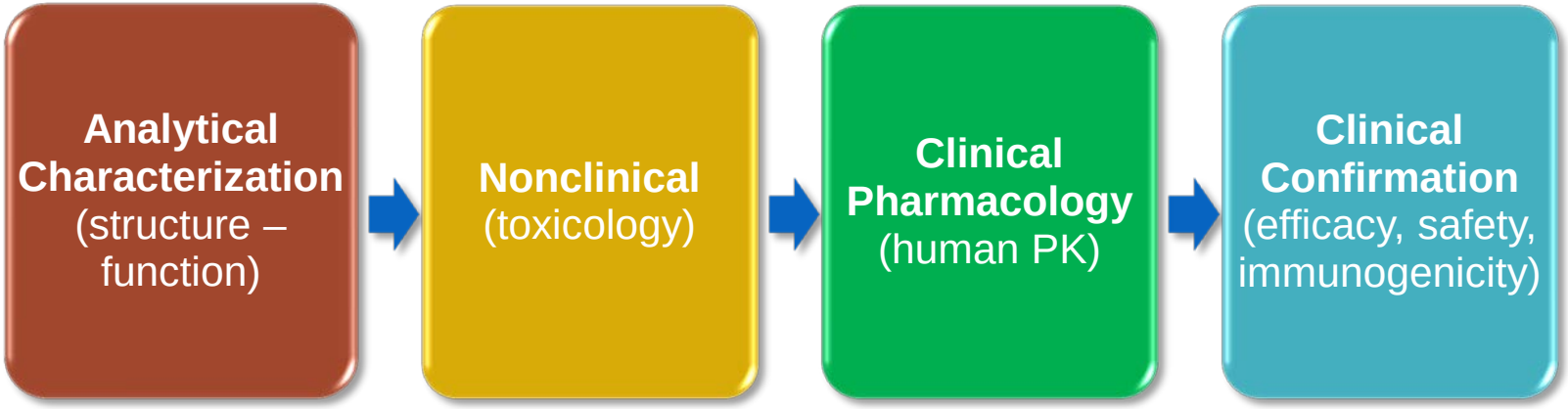
Subjects with binding or neutralizing anti-drug antibodies at end of study.

Pharmacokinetics Similar in 3 Populations



Css = steady-state concentration.

Clinical Confirmation is Next in Stepwise Development



- **Same amino acid sequence**
- **Same strength**
- **Highly similar structure and function**

- **Similar kinetics**
- **Similar toxicology**

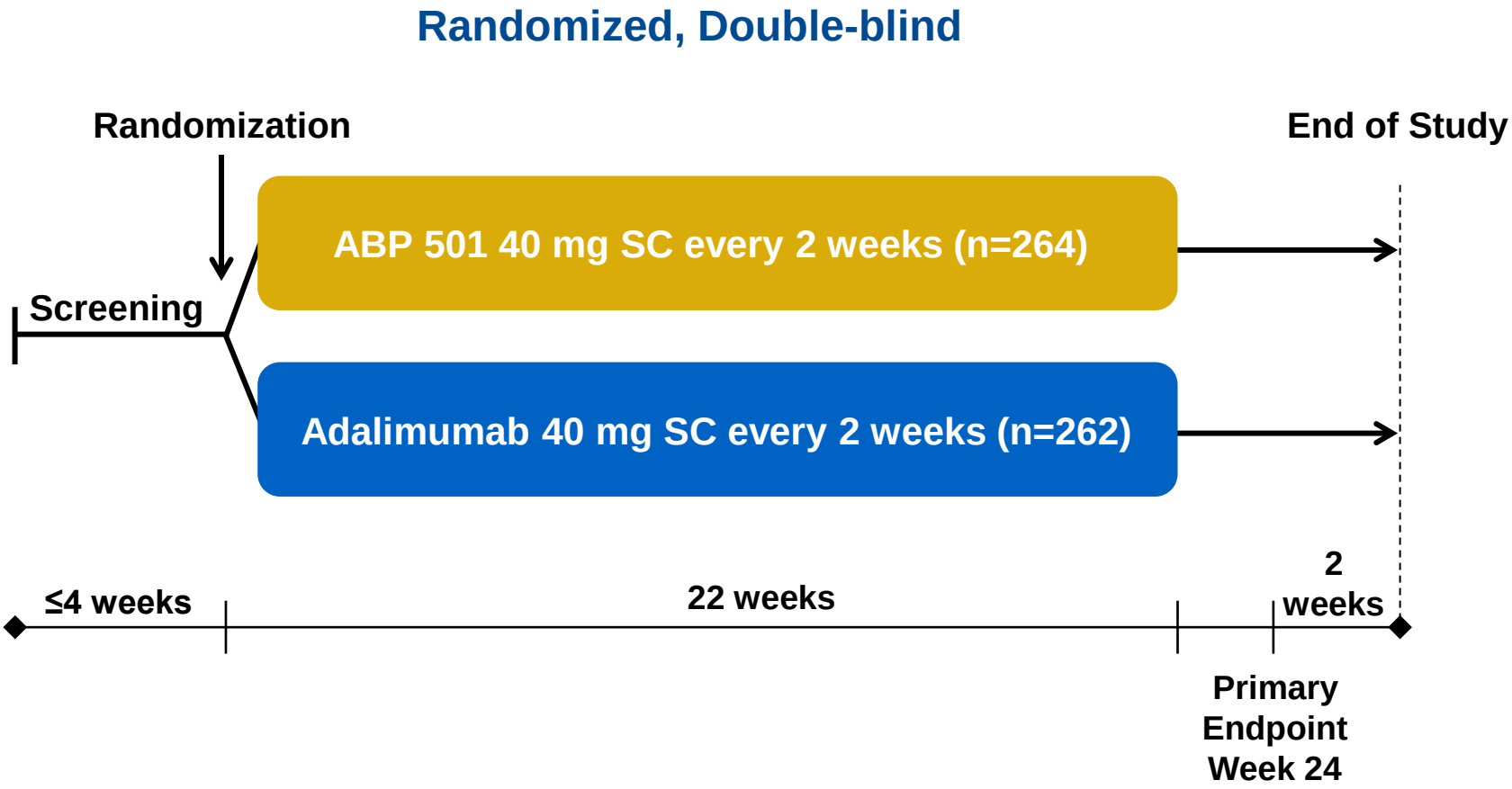
- **PK similarity shown in 3-way study**

Clinical Outline

- RA Efficacy
- Psoriasis Efficacy
- Safety
- Immunogenicity

Rheumatoid Arthritis Study Efficacy

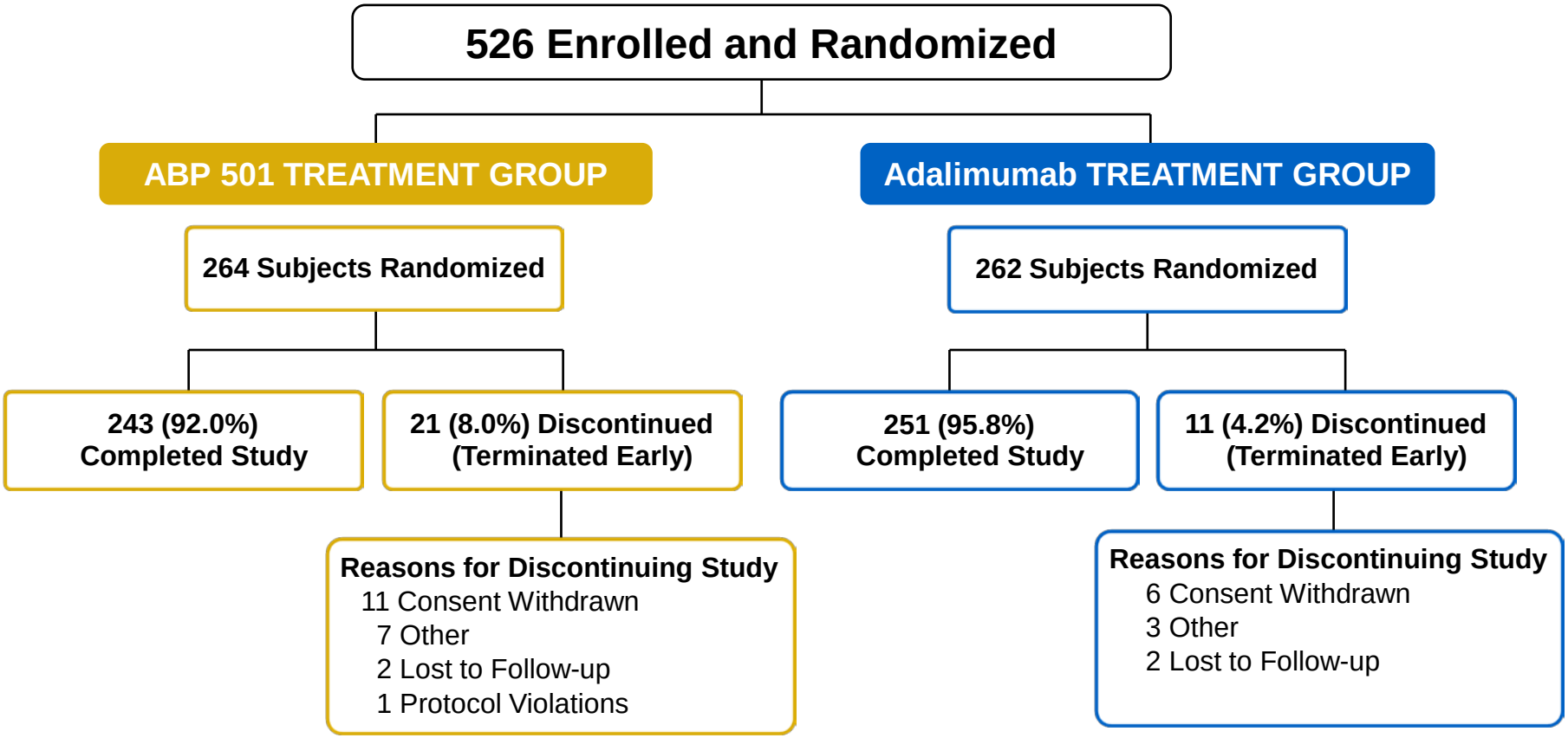
Rheumatoid Arthritis Study Design



RA Study: Primary Analysis

- **Ratio of ACR20 at Week 24**
- **Pre-specified margin followed FDA guidance for non-inferiority studies**
  - Determined effect size (ACR20 responses) based on adalimumab historical studies
  - Equivalence margin = (0.738, 1.355)
    - » Confidence interval must be entirely within equivalence margin
- **Post hoc analysis (FDA recommendation)**
  - Risk difference of ACR20 within (-12%, 12%)
  - Observed difference of <5% to confirm equivalence

RA Study: Subject Disposition



RA Study: Baseline Disease Characteristics

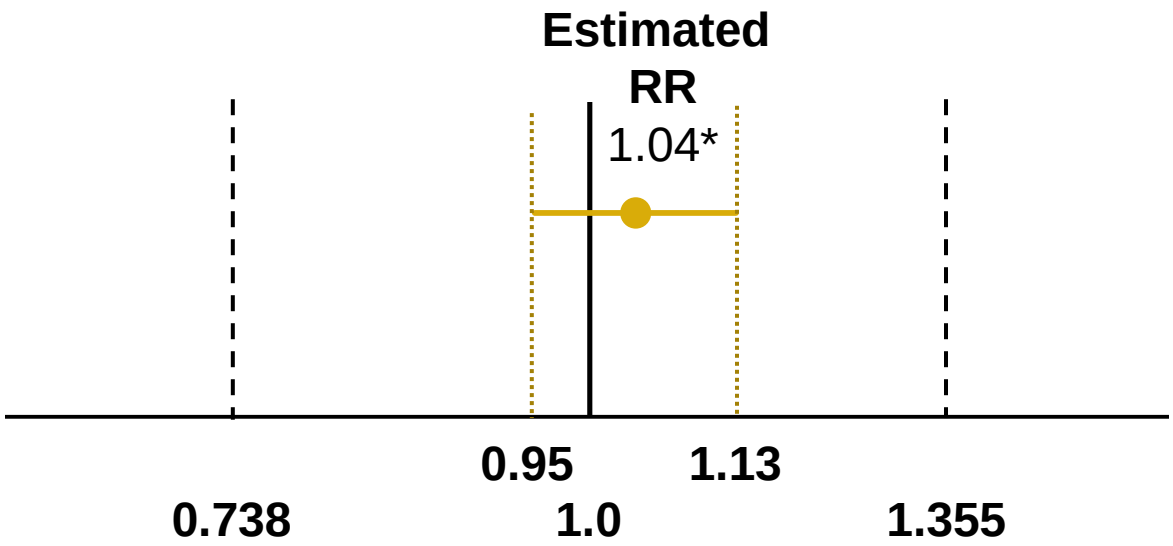
	ABP 501 N=264	Adalimumab N=262
DAS28-CRP, mean (SD)	5.66 (0.92)	5.68 (0.91)
CRP, mg/L, mean (SD)	13.9 (20.7)	14.7 (19.4)
Swollen joint count, mean (SD)	14.7 (9.05)	14.1 (7.98)
Tender joint count, mean (SD)	24.3 (14.4)	23.9 (13.5)
Subject global health assessment, 0-10 scale, mean (SD)	6.5 (1.92)	6.6 (1.86)
Investigator global health assessment, 0-10 scale, mean (SD)	6.8 (1.29)	6.7 (1.59)
Subject assessment of disease related pain, 100 mm VAS, mean (SD)	58.3 (21.8)	60.6 (22.4)
HAQ-DI, mean (SD)	1.48 (0.62)	1.50 (0.65)
Duration of RA, years, mean (SD)	9.41 (8.08)	9.37 (8.05)
Rheumatoid factor status positive, n (%)	243 (92.0)	240 (91.6)
Anti-cyclic citrullinated peptide status positive, n (%)	212 (80.3)	230 (87.8)
Prior biological use for RA, n (%)	71 (26.9)	74 (28.2)
Use of oral corticosteroid, n (%)	134 (50.8)	130 (49.6)
Use of NSAID, n (%)	159 (60.2)	168 (64.1)
Baseline methotrexate dose, mg/week, mean (SD)	16.9 (4.81)	16.6 (4.93)

HAQ-DI = health disease assessment questionnaire disability index (range 0-3).

RA Primary Endpoint: Risk Ratio (RR) of ACR20 at Week 24

ABP 501 ACR20 Response Rate: 74.6%
Adalimumab ACR20 Response Rate: 72.4%

Risk Ratio (adjusted*): 1.04 (0.95, 1.13)

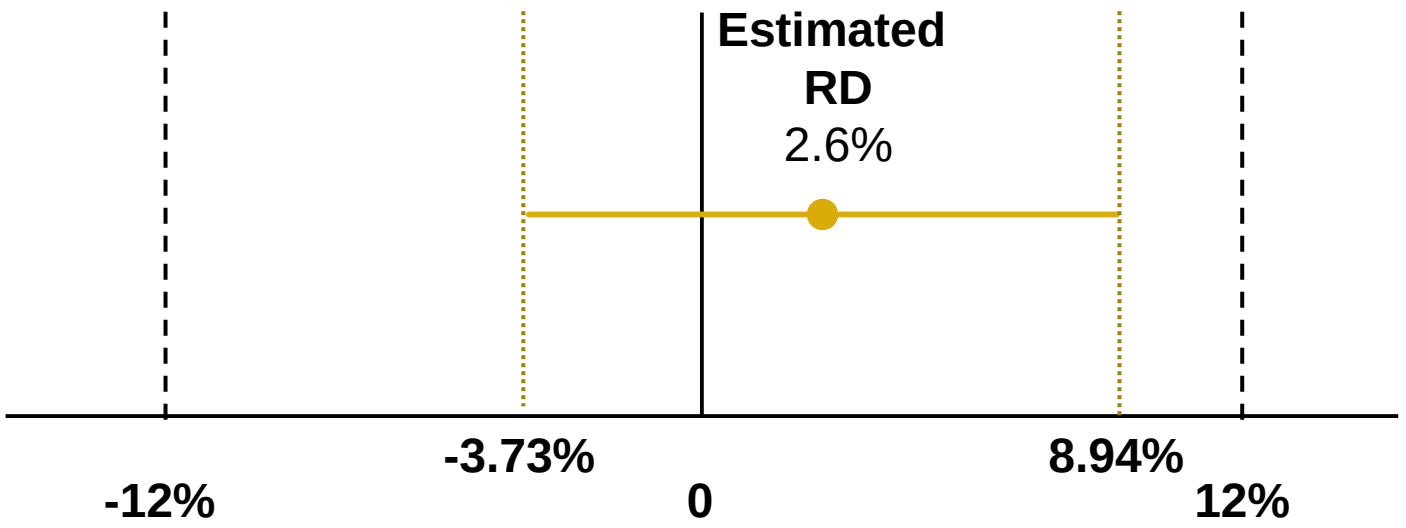


*ACR20 rsk ratio and its confidence interval were estimated with a statistical model adjusted for covariates.
Full analysis set with LOCF.

RA Secondary Endpoint: Risk Difference (RD) of ACR20 at Week 24

ABP 501 ACR20 Response Rate: 74.6%
Adalimumab ACR20 Response Rate: 72.4%

Risk Difference (adjusted*): 2.6% (-3.73%, 8.94%)

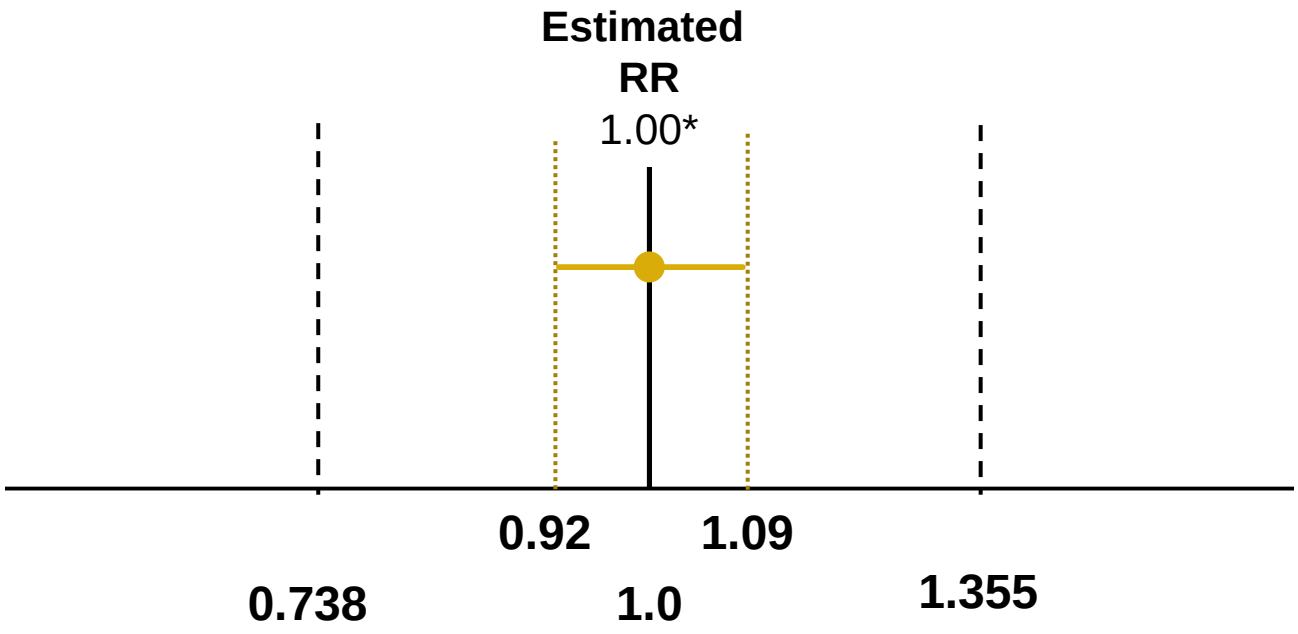


*ACR20 risk difference and its confidence interval were estimated with a statistical model adjusted for covariates.
Full analysis set with LOCF.

RA Sensitivity Analysis: Non-responder Imputation of ACR20 at Week 24

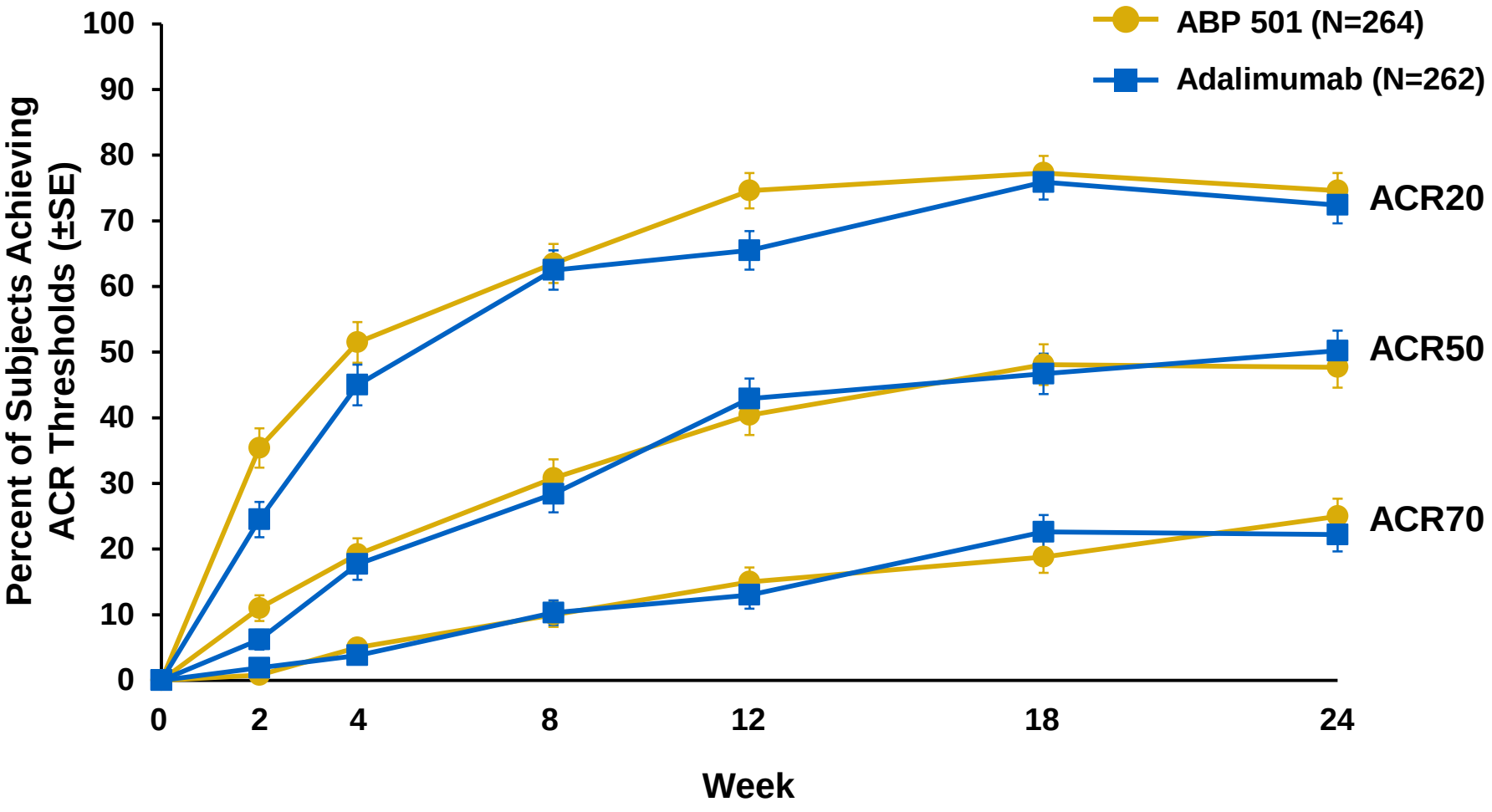
ABP 501 ACR20 Response Rate: 71.2%
Adalimumab ACR20 Response Rate: 72.1%

Risk Ratio (adjusted*): 1.00 (0.92, 1.09)



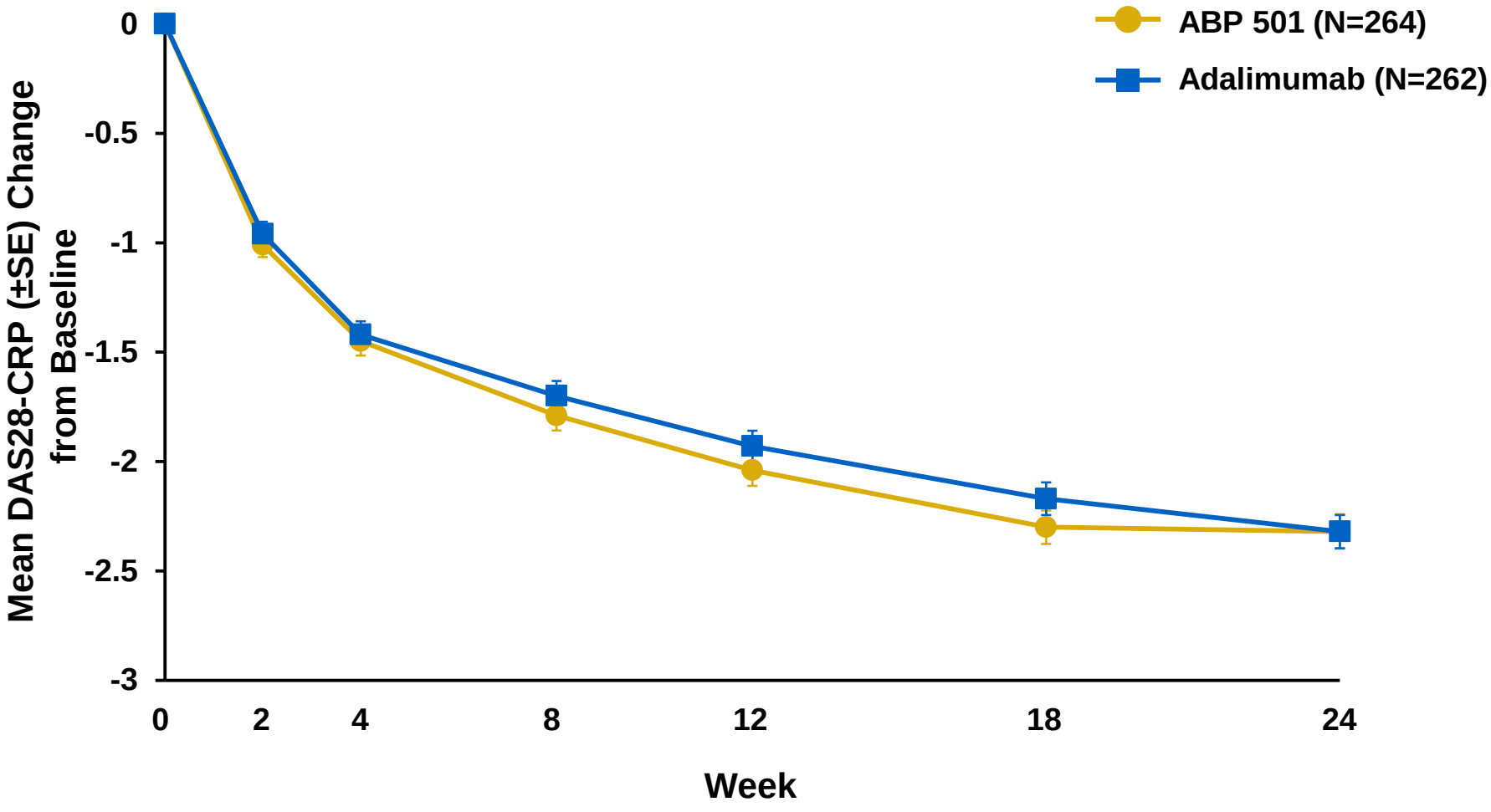
*ACR20 risk ratio and its confidence interval were estimated with a statistical model adjusted for covariates.

RA Study: Percent of Subjects Achieving ACR Thresholds



Full analysis set, LOCF.

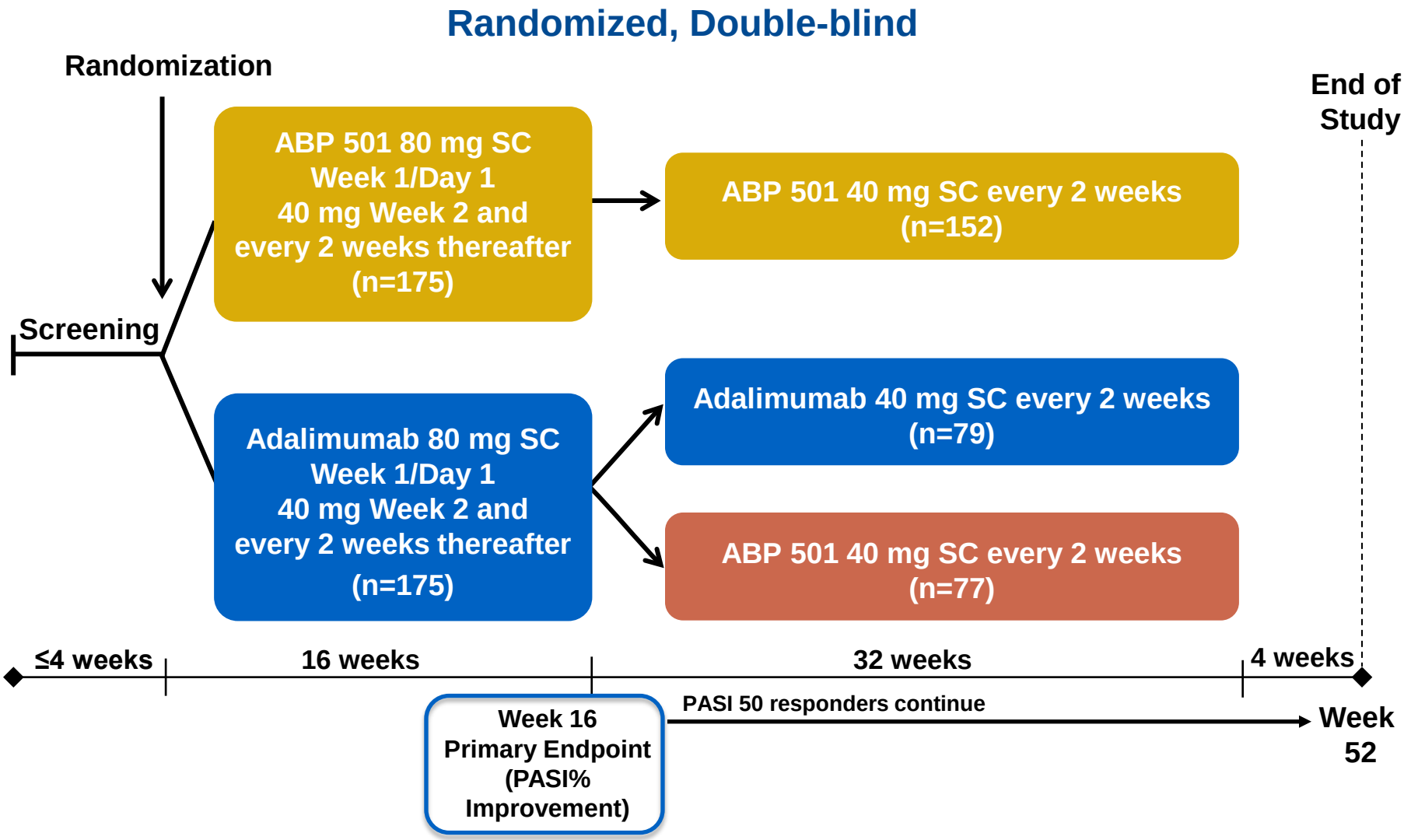
RA Study: DAS28-CRP Change From Baseline



Full analysis set, as observed.

Psoriasis Study Efficacy

Plaque Psoriasis Study Design



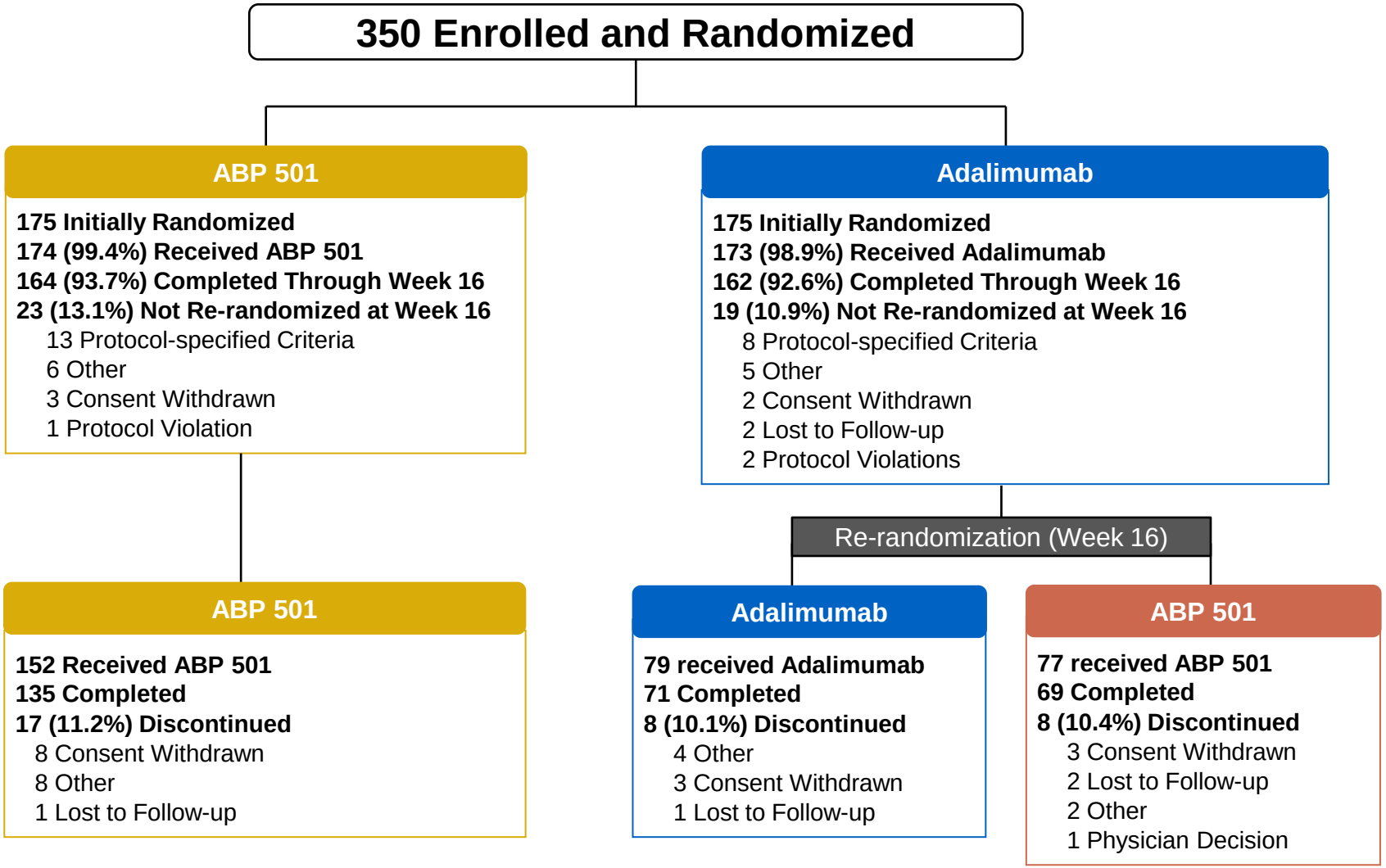
Psoriasis Study: Primary Endpoint

- **Primary endpoint: PASI percent improvement from baseline at Week 16**
  - Continuous measure of PASI percent improvement is most sensitive evaluation and includes full spectrum of responses
- **Additional binary PASI outcomes also assessed:**
  - PASI 50, PASI 75, PASI 90, PASI 100

Psoriasis Study: Primary Analysis

- **Followed FDA guidance for non-inferiority studies**
  - Determined effect size (PASI % improvement) based on meta analysis of published clinical studies
  - Statistical methodology set the margin at ±29
- **We reduced the margin to ±15 for additional clinical rigor in showing no clinically meaningful differences**
  - Confidence interval of mean difference must be entirely within the equivalence margin
  - Observed mean difference of <8 to confirm equivalence

Psoriasis Study: Subject Disposition



Psoriasis Study: Baseline Demographics and Disease Characteristics

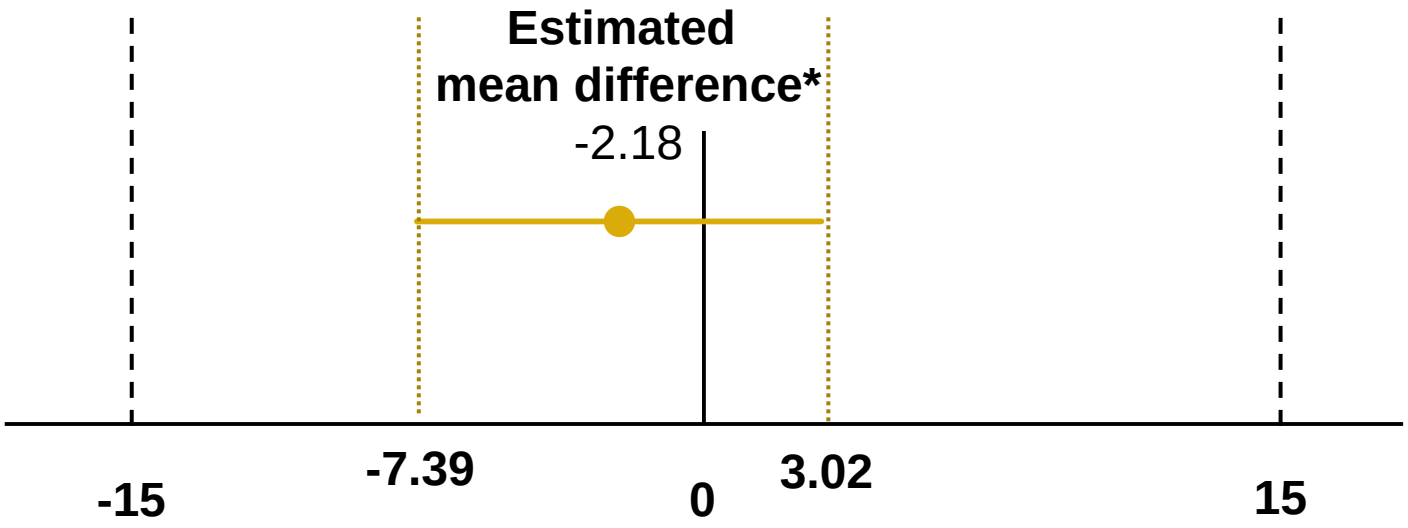
CD-26

Characteristic		ABP 501 N=175	Adalimumab N=175
Sex, male, n (%)		112 (64.0)	116 (66.3)
Age, y, mean (SD)		45.1 (12.95)	44.0 (13.68)
Caucasian, n (%)		167 (95.4)	157 (89.7)
Weight, kg, mean (SD)		88.85 (23.64)	89.33 (19.39)
BMI, kg/m^2, mean (SD)		29.7 (6.57)	29.7 (5.83)
Duration of psoriasis, years, mean (SD)		19.85 (11.87)	20.34 (13.48)
Prior use of biologics for psoriasis, n (%)		33 (18.9)	30 (17.1)
Prior use of systemic or photo therapies, n (%)		128 (73.1)	135 (77.1)
BSA percent affected by psoriasis, mean (SD)		25.3 (15.02)	28.5 (16.82)
sPGA, n (%)	Moderate	106 (60.6)	102 (58.3)
	Severe	61 (34.9)	61 (34.9)
	Very severe	7 (4.0)	10 (5.7)
PASI score, mean (SD)		19.68 (8.10)	20.48 (7.88)

Psoriasis Study Primary Endpoint: PASI Percent Improvement at Week 16

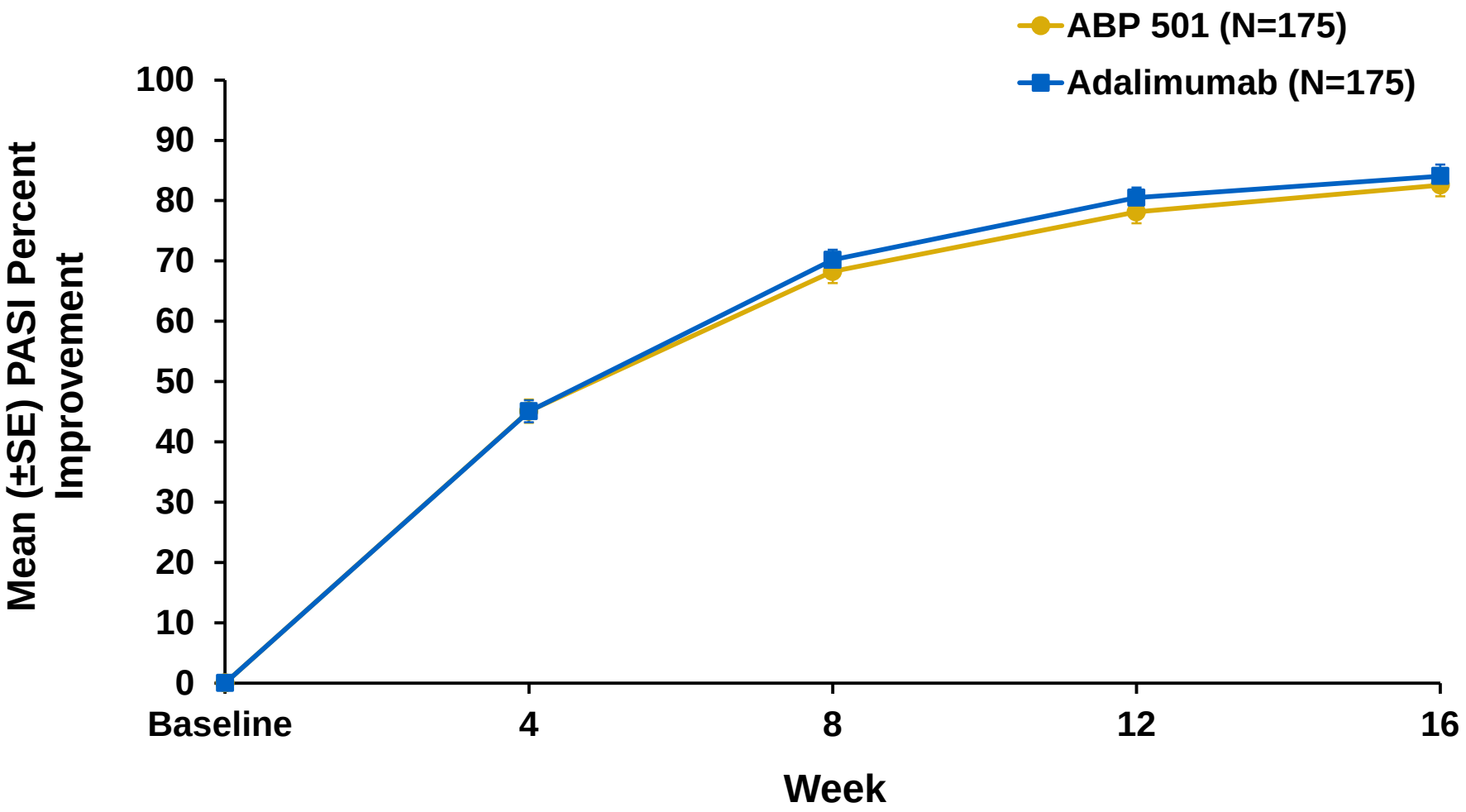
ABP 501 PASI % Improvement: 80.9
Adalimumab PASI % Improvement: 83.1

Mean Difference (adjusted*): -2.18 (-7.39, 3.02)



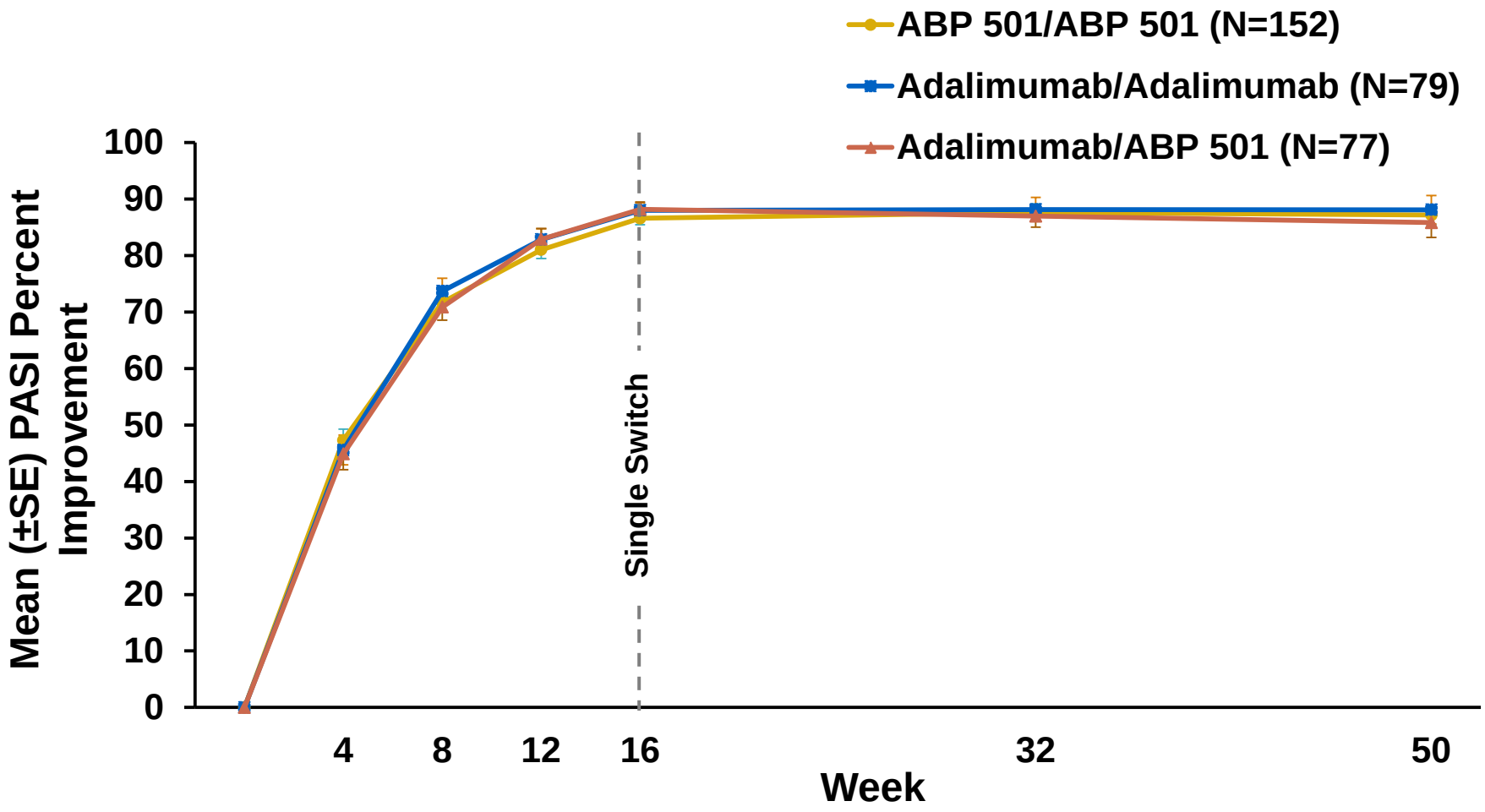
*Mean difference and CI were calculated with a statistical model adjusted for covariates.
Full analysis set, LOCF.

PASI Percent Improvement



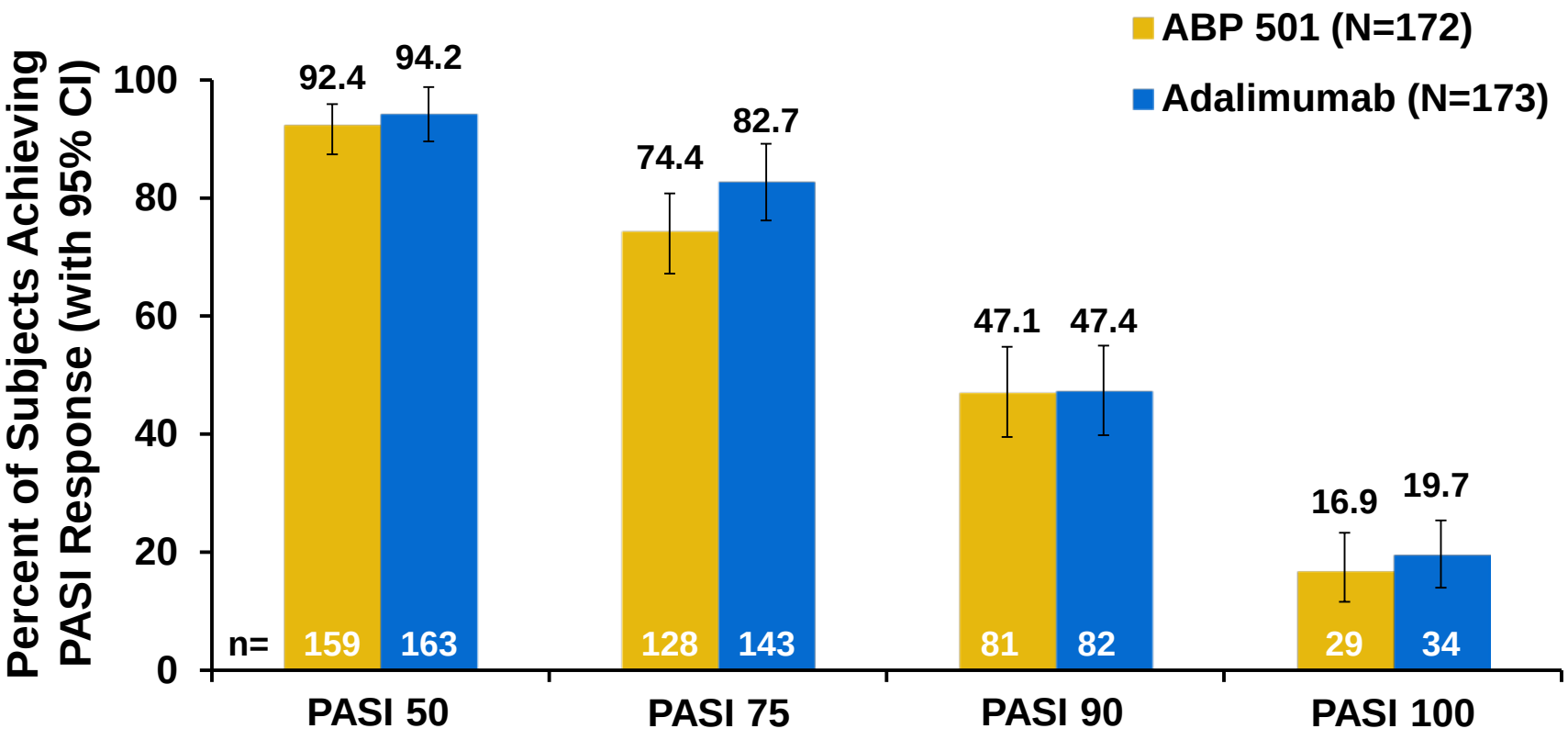
Full analysis set, LOCF.

Mean PASI Percent Improvement Including Post-Switch Week 16-50



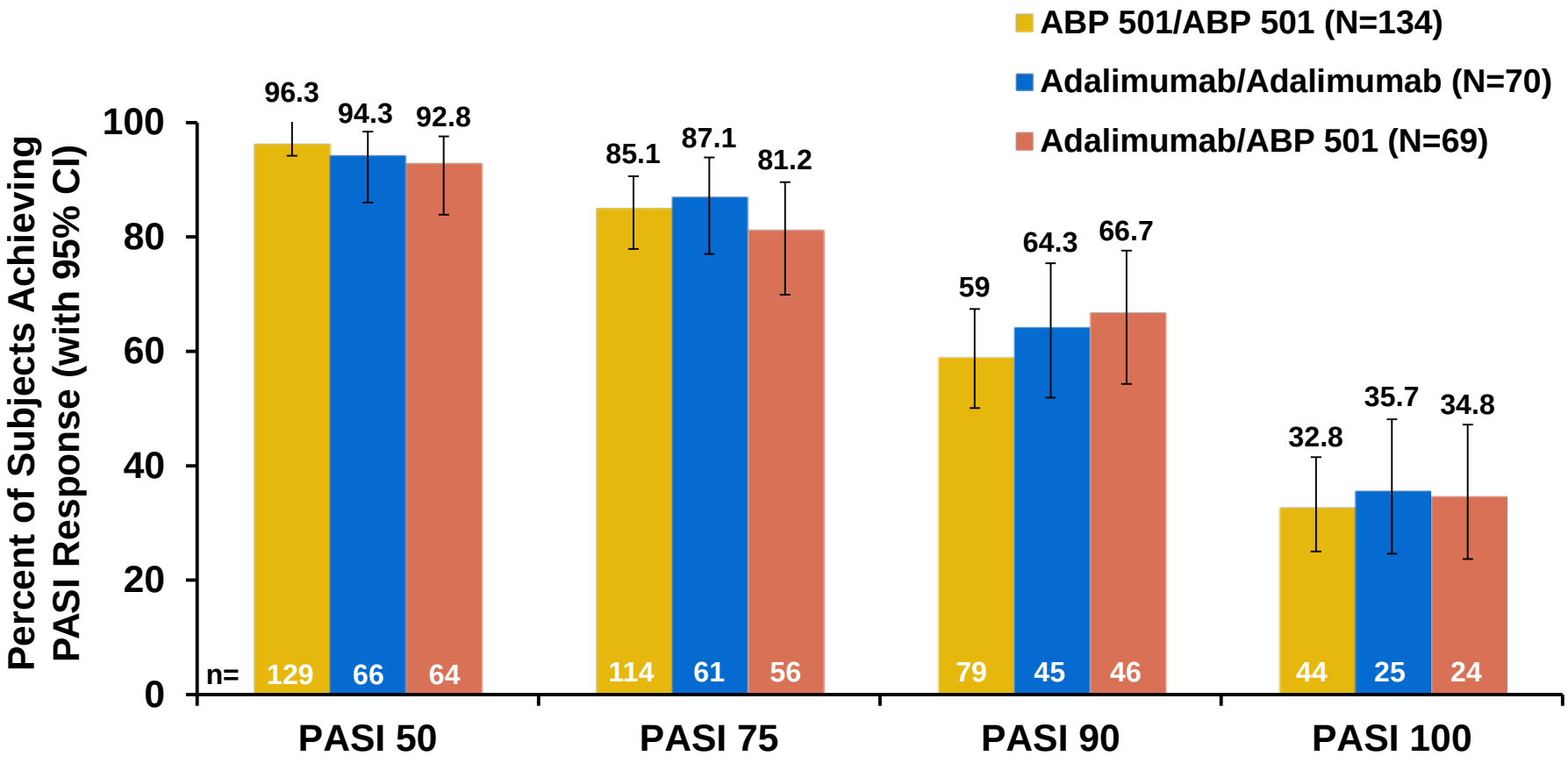
Re-randomized analysis set, as observed.

Additional PASI Assessments at Week 16



Full analysis set, LOCF.

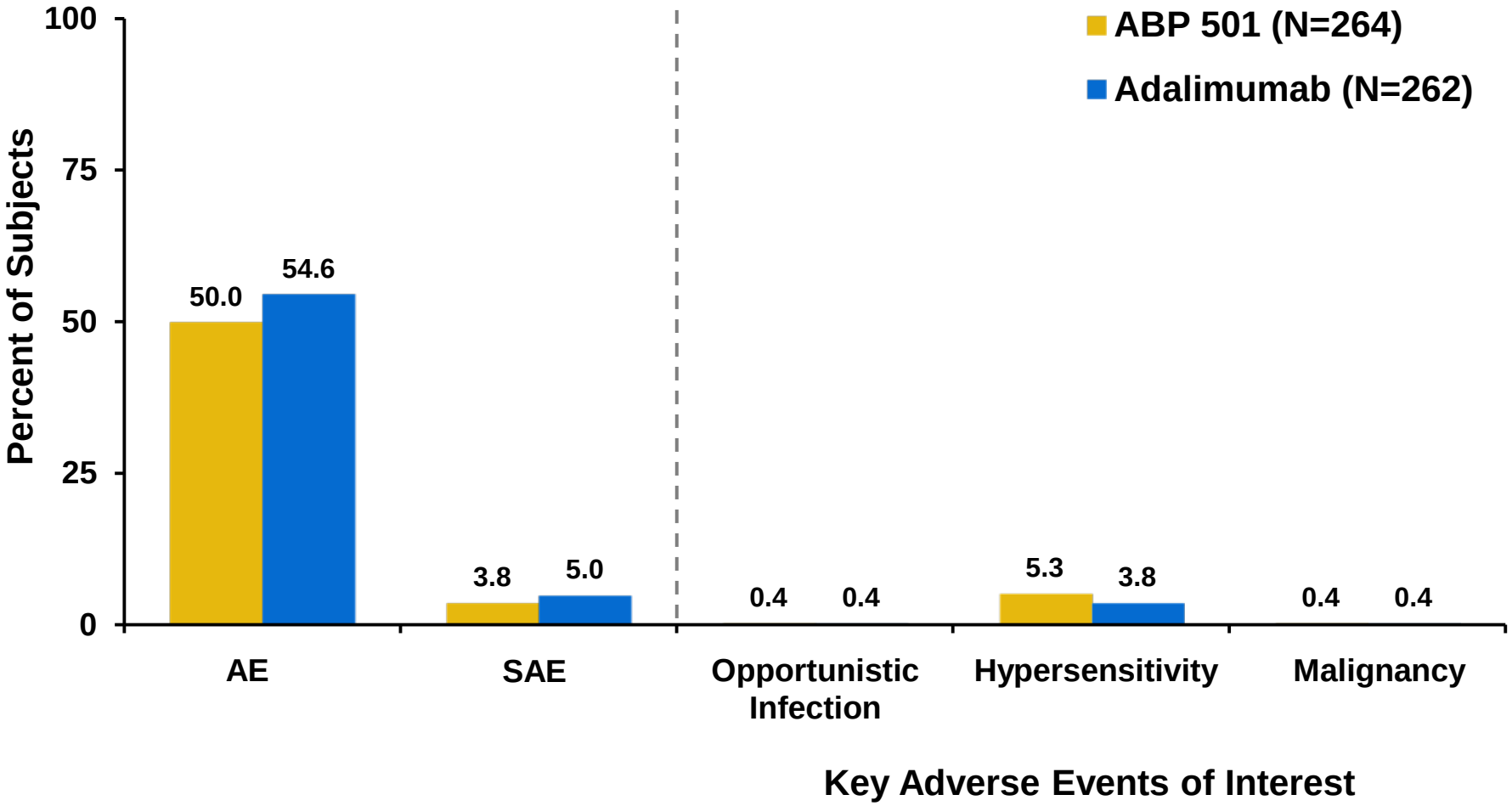
Additional PASI Assessments at Week 50



Re-randomized analysis set, as observed.

Clinical Safety

RA Study: Summary of Adverse Events

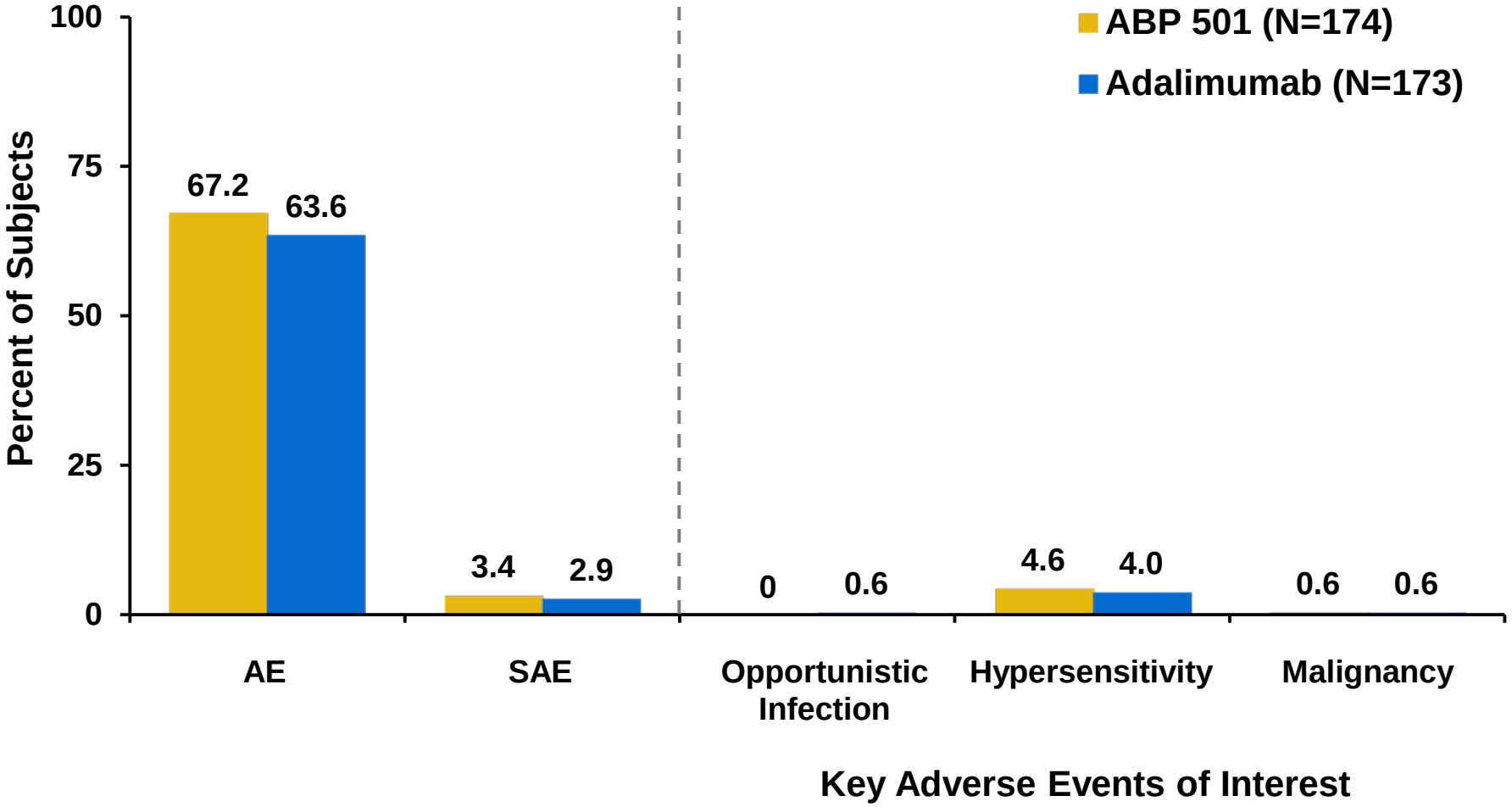


AE = Adverse events; SAE = Serious adverse events.

RA Study: Serious Adverse Events

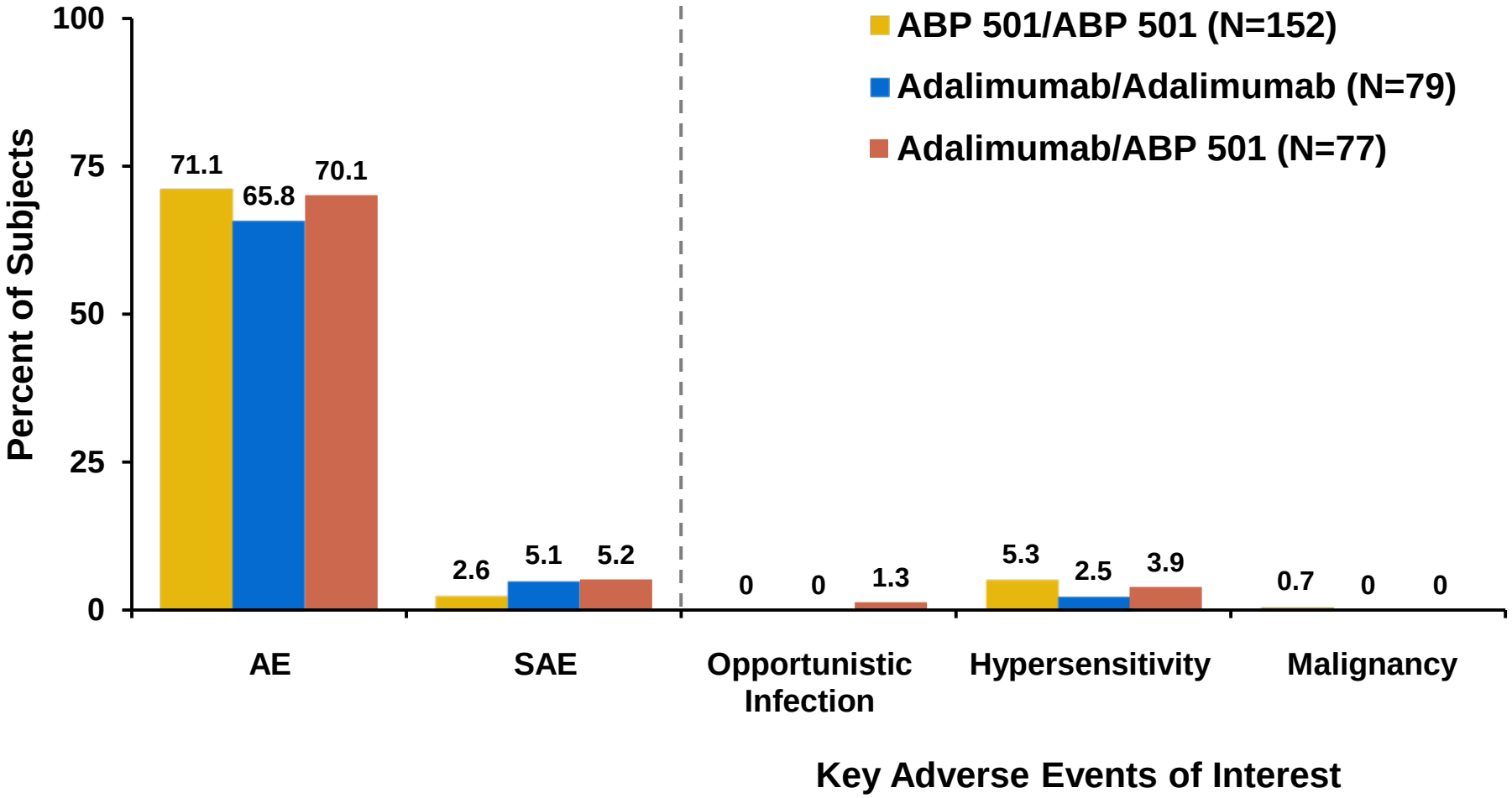
System Organ Class, n (%)	ABP 501 N=264	Adalimumab N=262
Any Serious Adverse Event	**10 (3.8)**	**13 (5.0)**
Cardiac disorders	1 (0.4)	4 (1.5)
Infections and infestations	2 (0.8)	3 (1.1)
Injury, poisoning and procedural complications	2 (0.8)	1 (0.4)
Musculoskeletal and connective tissue disorders	0	3 (1.1)
Gastrointestinal disorders	1 (0.4)	1 (0.4)
Immune system disorders	1 (0.4)	1 (0.4)
Vascular disorders	2 (0.8)	0
Blood and lymphatic system disorders	1 (0.4)	0
Nervous system disorders	1 (0.4)	0

Psoriasis Study: Summary of Adverse Events Through Week 16



AE = Adverse events; SAE = Serious adverse events.

Psoriasis Study: Summary of Adverse Events Weeks 16 – 52



AE = Adverse events; SAE = Serious adverse events.

Psoriasis Study: Serious Adverse Events

Event Category, n (%)	Through Week 16		Weeks 16 – 52		
	ABP 501 N=174	Adalimumab N=173	ABP 501/ ABP 501 N=152	Adalimumab/ Adalimumab N=79	Adalimumab/ ABP 501 N=77
Any serious adverse event	**6 (3.4)**	**5 (2.9)**	**4 (2.6)**	**4 (5.1)**	**4 (5.2)**
Infections and infestations	2 (1.1)	1 (0.6)	1 (0.7)	0	2 (2.6)
Cardiac disorders	2 (1.1)	0	1 (0.7)	0	0
Musculoskeletal and connective tissue disorders	0	2 (1.2)	1 (0.7)	1 (1.3)	0
Immune system disorders	1 (0.6)	0	0	0	0
Neoplasms benign, malignant and unspecified	1 (0.6)	0	0	0	0
Nervous system disorders	0	1 (0.6)	1 (0.7)	2 (2.5)	1 (1.3)
Reproductive system and breast disorders	0	1 (0.6)	0	0	1 (1.3)
Respiratory, thoracic and mediastinal disorders	1 (0.6)	0	0	0	0
Hepatobiliary disorders	0	0	1 (0.7)	0	0
Metabolism and nutritional disorders	0	0	1 (0.7)	0	0
Psychiatric disorders	0	0	0	1 (1.3)	0

RA and Psoriasis Studies: Infection

Infection Adverse Event, n (%)	RA		Psoriasis				
			Through Week 16		Weeks 16 – 52		
	ABP 501 N=264	Adalimumab N=262	ABP 501 N=174	Adalimumab N=173	ABP 501/ ABP 501 N=152	Adalimumab/ Adalimumab N=79	Adalimumab/ ABP 501 N=77
Any infection AE	61 (23.1)	68 (26.0)	59 (33.9)	58 (33.5)	67 (44.1)	29 (36.7)	37 (48.1)
Serious infection	2 (0.8)	3 (1.1)	2 (1.1)	1 (0.6)	1 (0.7)	0	2 (2.6)
Opportunistic infection	1 (0.4)	1 (0.4)	0	1 (0.6)	0	0	1 (1.3)
Events leading to discontinuation	2 (0.8)	0	0	1 (0.6)	0	0	1 (1.3)

RA and Psoriasis Studies: Hypersensitivity

Hypersensitivity Adverse Event, n (%)	RA		Psoriasis				
			Through Week 16		Weeks 16 – 52		
	ABP 501 N=264	Adalimumab N=262	ABP 501 N=174	Adalimumab N=173	ABP 501/ ABP 501 N=152	Adalimumab/ Adalimumab N=79	Adalimumab/ ABP 501 N=77
Any hypersensitivity AE	14 (5.3)	10 (3.8)	8 (4.6)	7 (4.0)	8 (5.3)	2 (2.5)	3 (3.9)
Serious reactions	1 (0.4)	0 (0.0)	1 (0.6)	0	0	0	0
Anaphylaxis (Sampson criteria)	0	0	1 (0.6)	0	0	0	0
Events leading to discontinuation	2 (0.8)	0	1 (0.6)	1 (0.6)	0	0	0

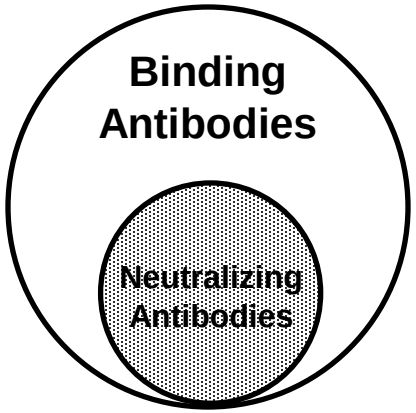
Psoriasis and RA Studies: Malignancy

Malignancy Adverse Event, n (%)	RA		Psoriasis				
			Through Week 16		Weeks 16 – 52		
	ABP 501 N=264	Adalimumab N=262	ABP 501 N=174	Adalimumab N=173	ABP 501/ ABP 501 N=152	Adalimumab/ Adalimumab N=79	Adalimumab/ ABP 501 N=77
Any malignancy AE	1 (0.4)	1 (0.4)	1 (0.6)	1 (0.6)	1 (0.7)	0	0
NMSC (non-melanoma skin cancer)	1 (0.4)	1 (0.4)	0	1 (0.6)	1 (0.7)	0	0
Melanoma	0	0	1 (0.6)	0	0	0	0
Lymphoma	0	0	0	0	0	0	0
Serious events of malignancy	0	0	1 (0.6)	0	0	0	0
Events leading to discontinuation	0	0	1 (0.6)	0	0	0	0

Immunogenicity

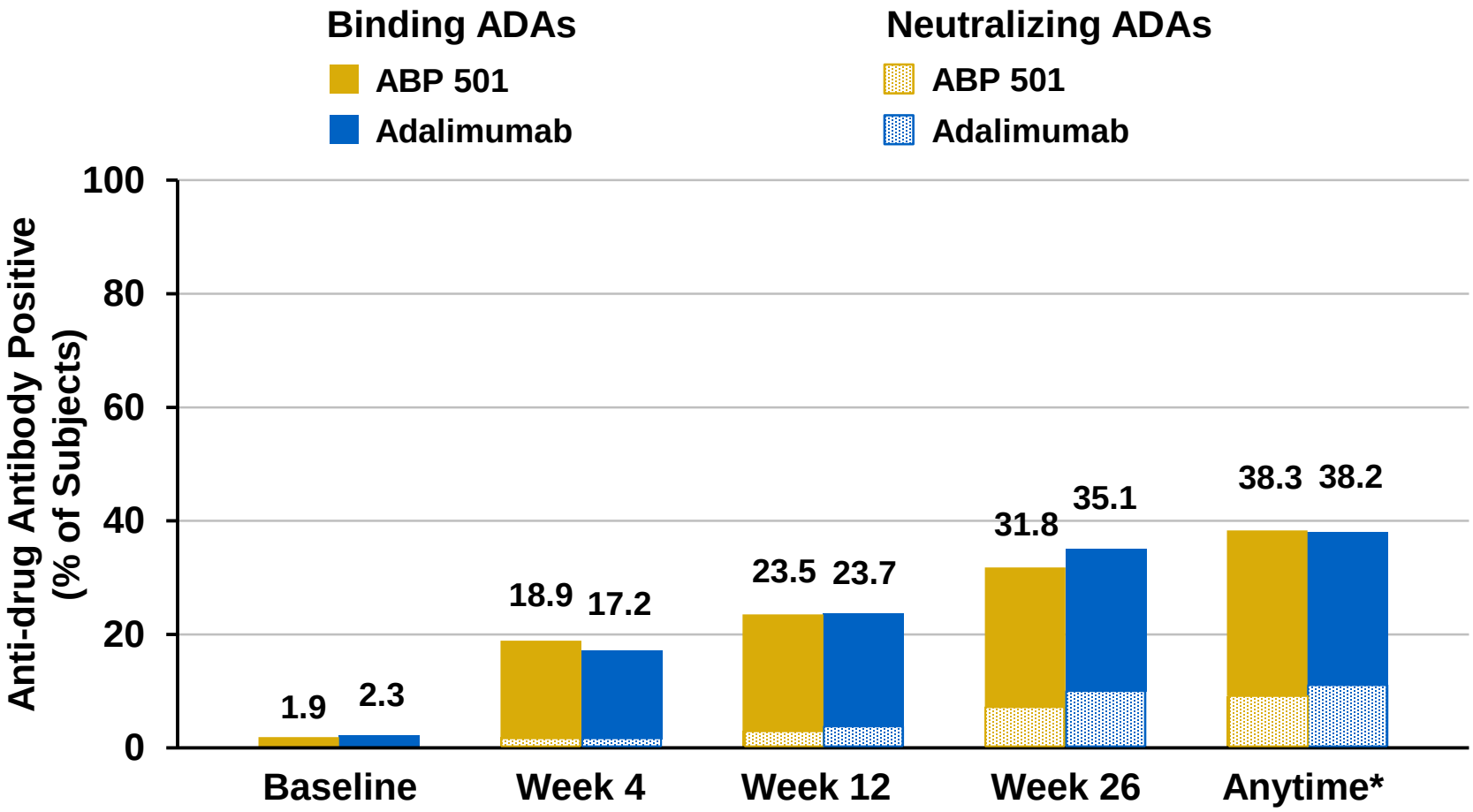
Types of Anti-Drug Antibodies (ADA)

- **Binding Antibodies**
  - All antibody types capable of binding drug
  - May impact PK
  - Do not preclude functional activity



- **Neutralizing Antibodies**
  - A subpopulation of binding antibodies
    - » Binding positive samples are tested for neutralizing activity
  - Inhibits the functional activity of the drug

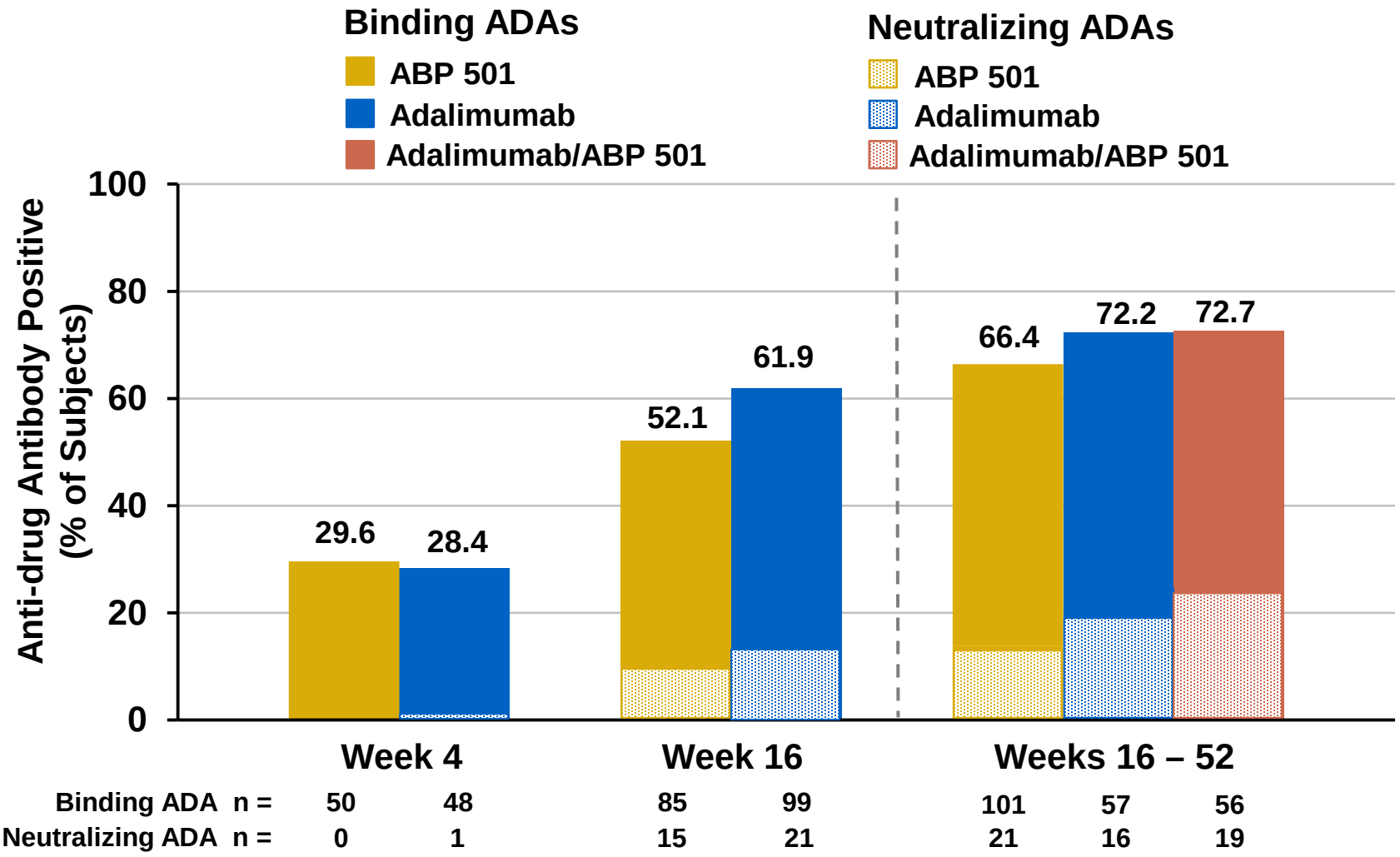
RA Study: Anti-Drug Antibodies



Binding ADA n =	5	6	50	45	62	62	84	92	101	100
Neutralizing ADA n =	0	0	5	4	8	10	19	26	24	29

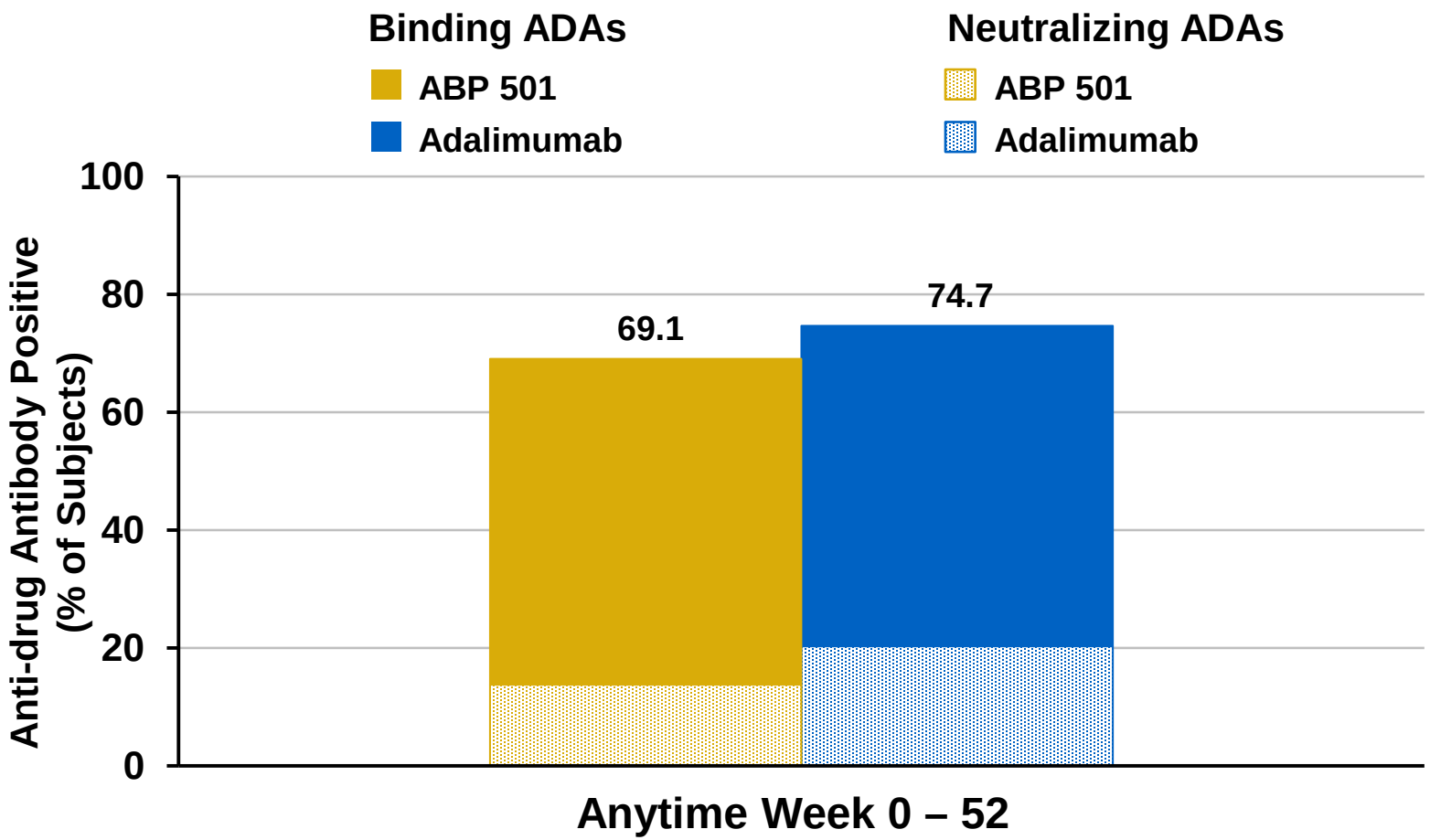
Randomized ABP 501 = 264 and adalimumab = 262.
*post-baseline.

Psoriasis Study: Anti-Drug Antibodies



Randomized N: ABP 501 = 174, adalimumab = 173. Re-randomized N: ABP 501/ABP 501 = 152, Adalimumab/adalimumab = 79, Adalimumab/ABP 501 = 77.

Psoriasis Study: Anti-Drug Antibodies Anytime From Week 0 – 52

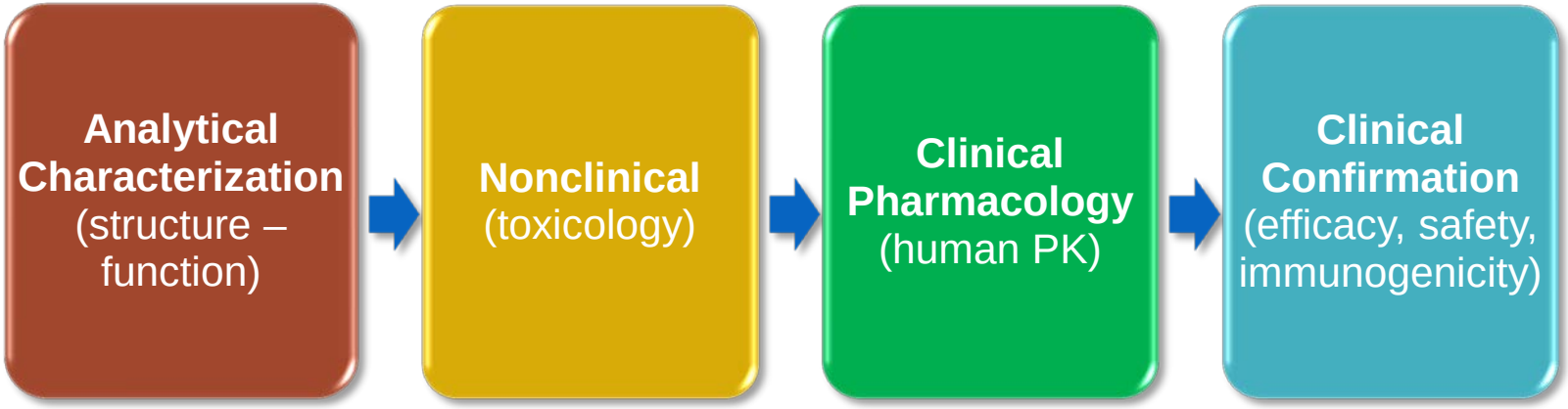


Subjects re-randomized to continue ABP 501 or adalimumab throughout study.

ABP 501 Clinical Summary

- **Similar Efficacy**
  - Met equivalence criteria in two indications
- **Similar Safety**
  - Similar type, frequency, and severity of adverse events and no new safety risks
- **Similar Immunogenicity**
  - Similar rates of binding and neutralizing anti-drug antibodies

Totality of Evidence Demonstrates Biosimilarity of ABP 501



- Same amino acid sequence
- Same strength
- Highly similar structure and function

- Similar kinetics
- Similar toxicology

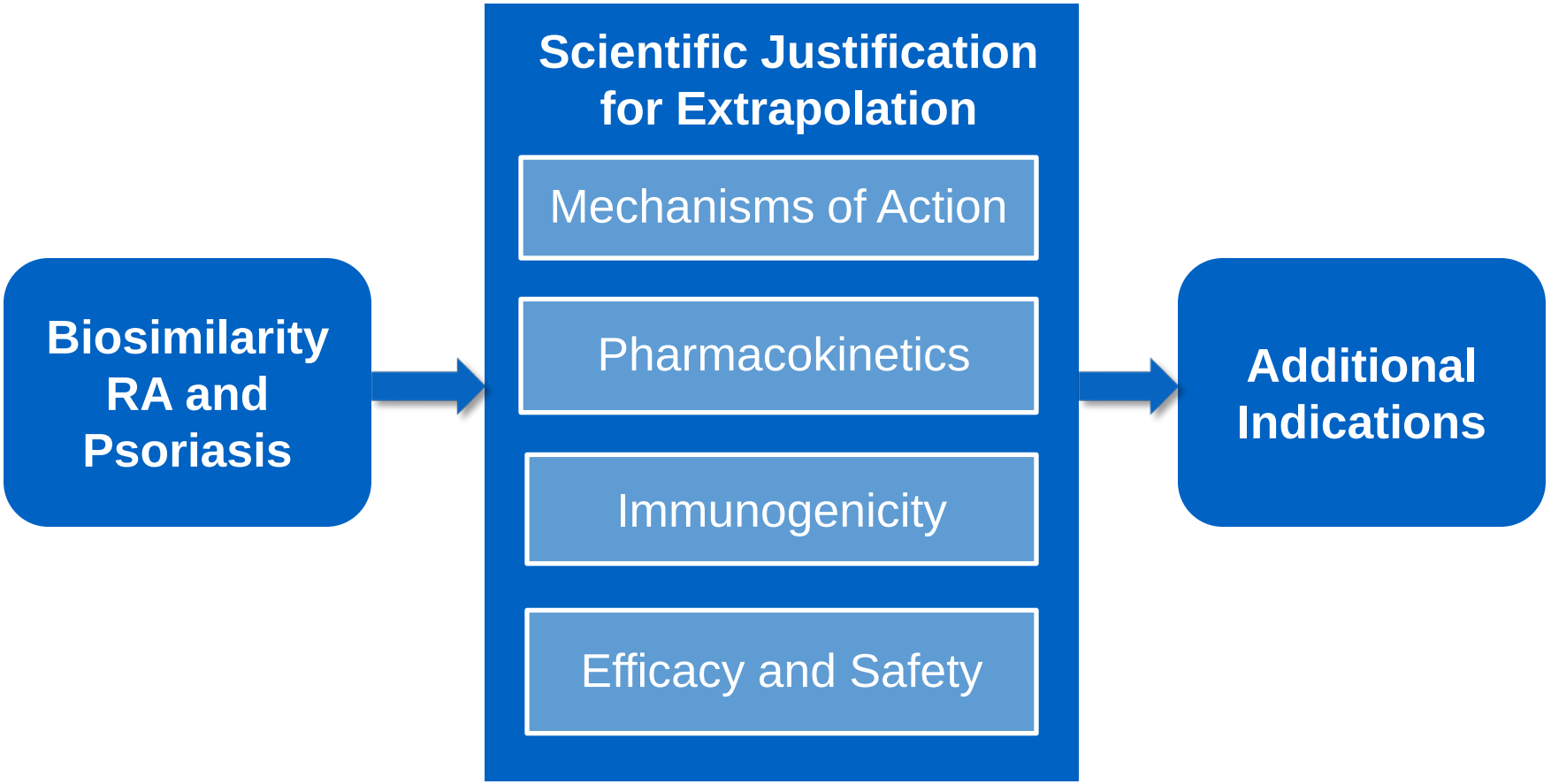
- PK similarity shown in 3-way study

- Similar efficacy
- Similar safety
- Similar immunogenicity

ABP 501 is highly similar to adalimumab with no clinically meaningful differences

Extrapolation

FDA Guidance Describes the Requirements for Extrapolation



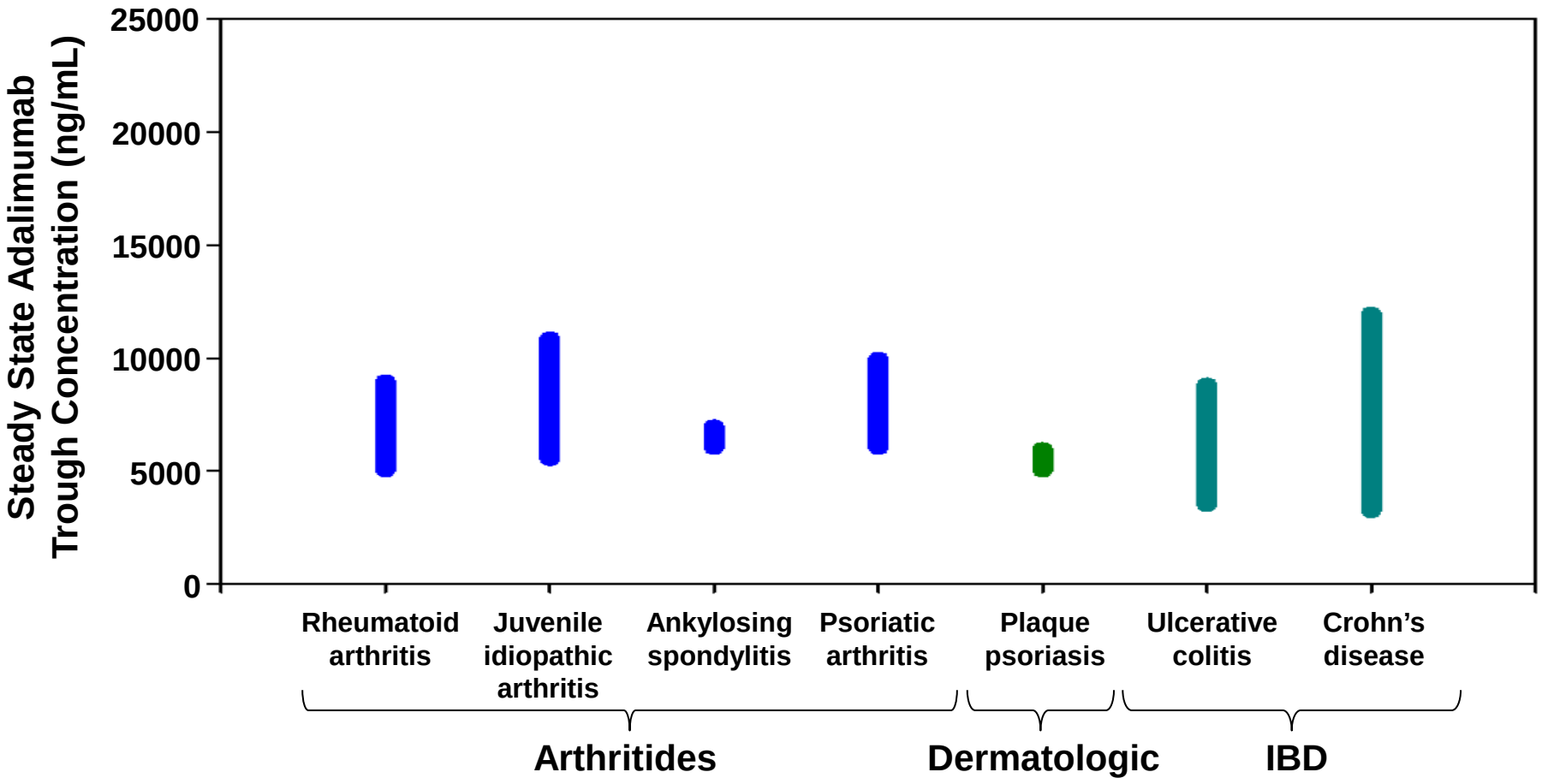
ABP 501 Functional Similarity is Demonstrated in All Mechanisms of Action

	Arthritides	Dermatologic	IBD
sTNF binding	✓	✓	✓
sTNF neutralization	✓	✓	✓
mbTNF binding	NA	NA	✓
Effector functions	NA	NA	✓
Modulation of Immune cells expressing mbTNF	NA	NA	✓

Similarity in common mechanisms, as well as in mechanisms possibly relevant to GI indications, has been demonstrated

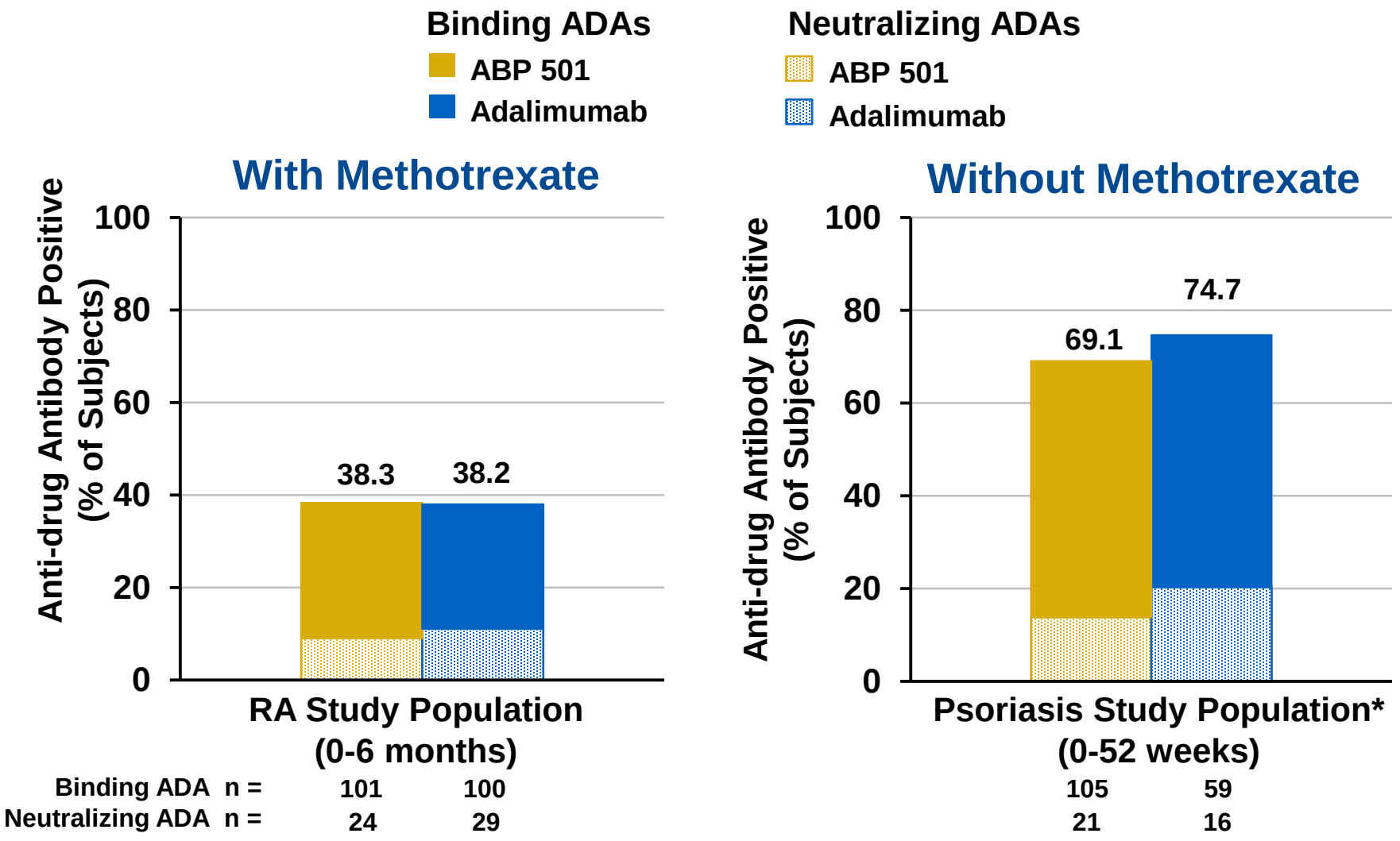
NA = not applicable in indication.

Steady-state Trough Adalimumab Concentration is Consistent Across Different Patient Populations



The presented data represent the ranges of data located in: Humira Summary of Product Characteristics, 2016; Humira United States Prescribing Information; Baert et al, 2014; Karmiris et al, 2009. The dosing regimens were the same as found in the approved Humira United States Prescribing Information 2016.

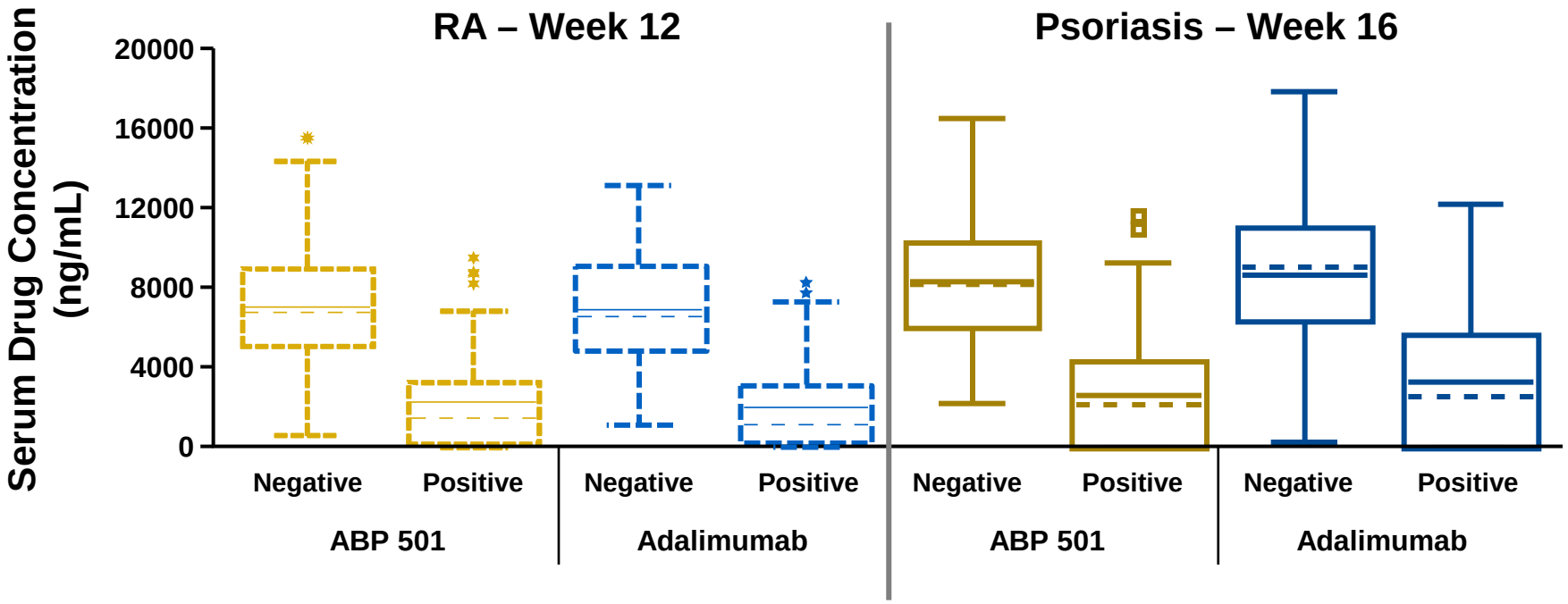
Immunogenicity With and Without Methotrexate



*Subjects re-randomized to continue ABP 501 or adalimumab throughout study.

Effect of Anti-drug Antibodies on PK is Similar for ABP 501 and Adalimumab

Serum Trough Concentrations in Subjects in RA and Psoriasis Studies (Negative and Positive for Binding Anti-drug Antibody)



Confidence in Extrapolation of Similarity to All Patient Populations

- Mechanisms of Action
- Pharmacokinetics
- Immunogenicity
- Efficacy & Safety

- **ABP 501 is highly similar to adalimumab in sTNFα and mbTNFα binding, neutralization, effector functions, and immune cell function**
- **PK is similar between ABP 501 and adalimumab in 3 populations; no expected difference in other indications**
- **Immunogenicity is similar in RA (with methotrexate) and psoriasis (without methotrexate)**
- **Efficacy and safety of ABP 501 are similar to adalimumab in 2 sensitive patient populations**

Agenda

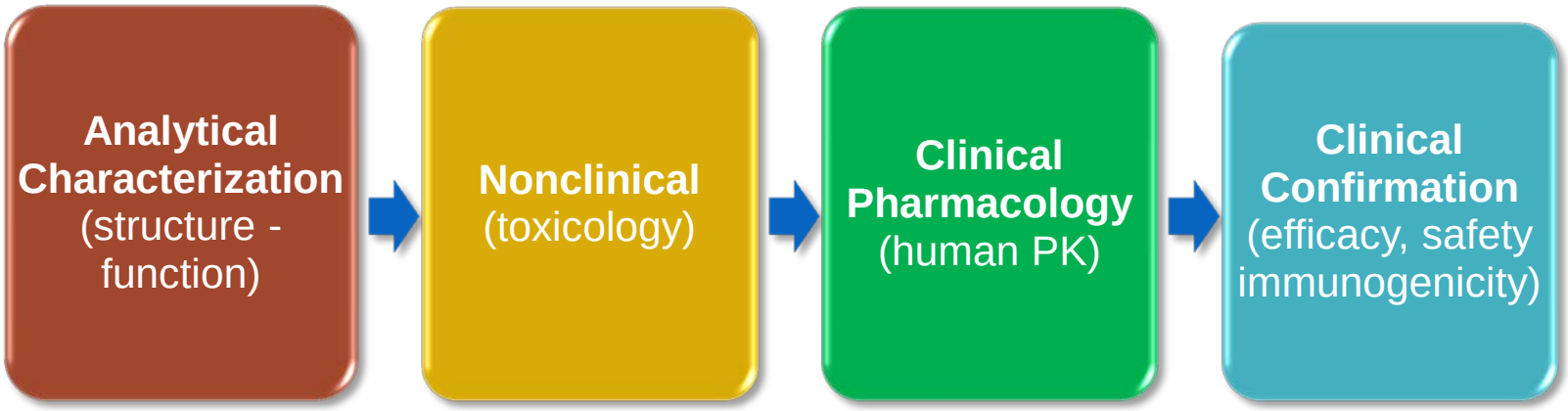
Introduction	**Richard Markus, MD, PhD** Global Development, Amgen
Analytical and Nonclinical Similarity	**Simon Hotchin** Regulatory Affairs, Amgen
Clinical Similarity and Extrapolation to All Indications	**Richard Markus, MD, PhD** Global Development, Amgen
Conclusion	**Steven Galson, MD, MPH** Regulatory Affairs and Safety, Amgen

Conclusions

Steven Galson, MD, MPH

Global Regulatory Affairs & Safety

Totality of Evidence



Totality of the data demonstrates high degree of structural, functional, and clinical similarity, and supports approval of ABP 501 for all indications

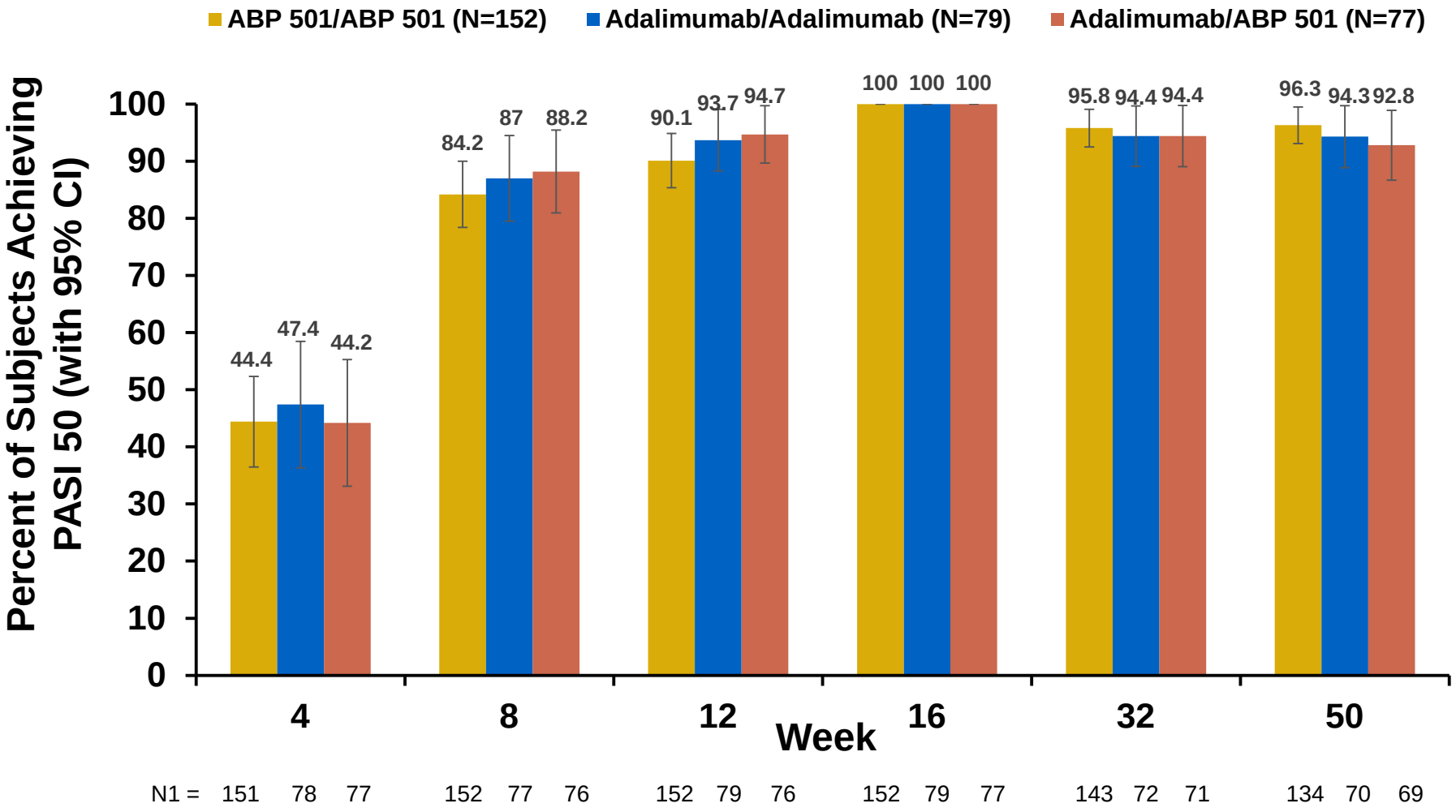
Amgen Biosimilars Commitment To Patients

- **Transparency, safety and availability are critical to long term confidence**
  - Distinguishable nonproprietary name to support traceability
  - Product-specific pharmacovigilance system
  - High quality product, reliably supplied

- **Increased access for patients is our goal**

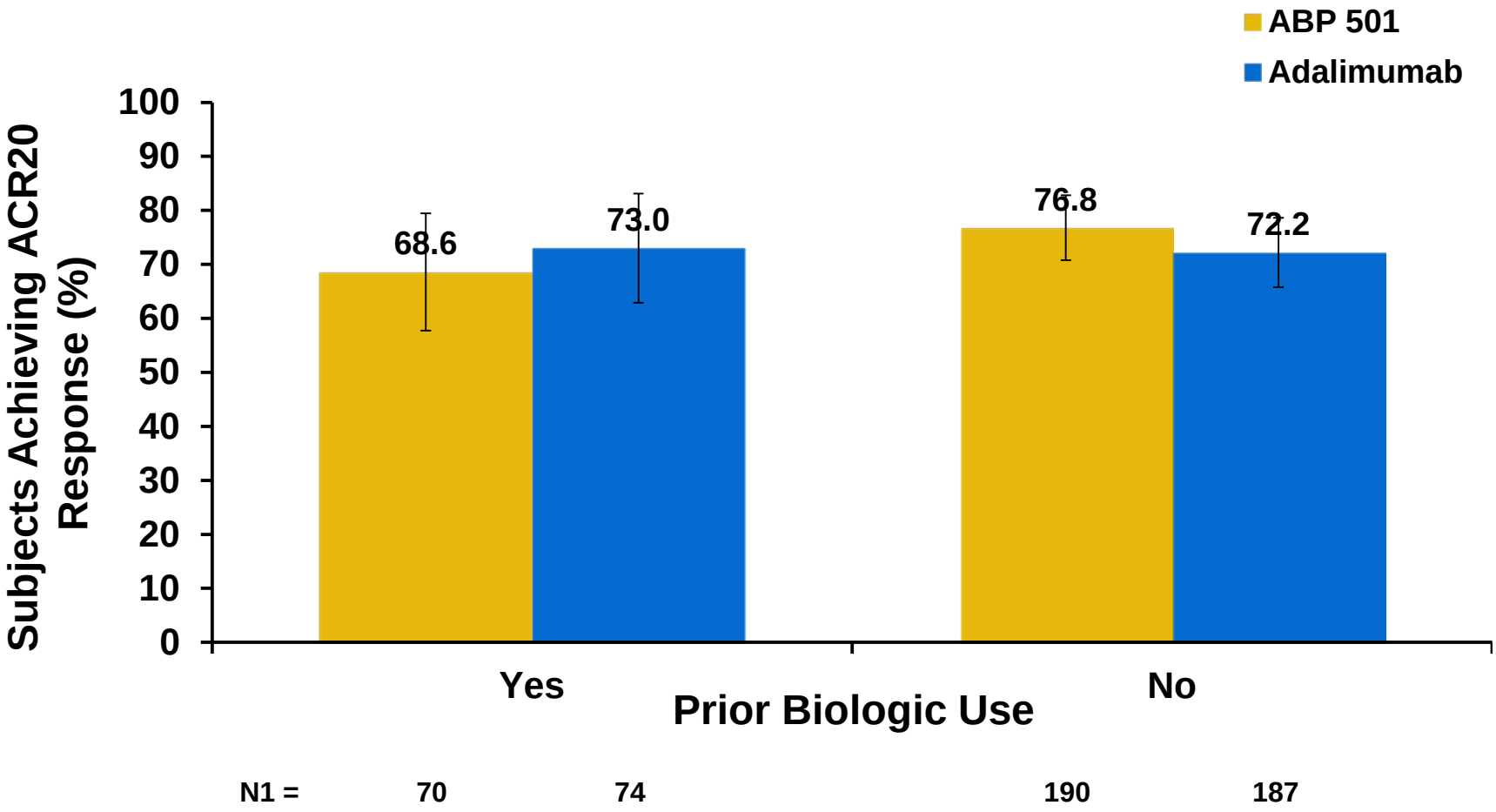
Backups

Psoriasis Study: PASI 50 Response through Week 50



Re-randomized analysis set, as observed.
Data on file, Amgen.

RA Study: Percent of Subjects Achieving ACR20 by Prior Biologic Use at Week 24



Full Analysis Set with LOCF.
Data on File, Amgen

T5. pg 49. Summary of all Functional Similarity Assays

Assay	Tier - Similarity Assessment Approach	Demonstrated Similarity
Apoptosis inhibition bioassay	1 – Equivalence acceptance criterion	√
Soluble TNFα binding	1 – Equivalence acceptance criterion	√
Binding kinetics to soluble TNFα	3 - Qualitative comparison	√
Binding to transmembrane TNFα	3 - Qualitative comparison	√
Inhibition of soluble TNFα-induced IL-8 in HUVEC	3 - Qualitative comparison	√
Inhibition of soluble TNFα-induced cell death in L929 cells	3 - Qualitative comparison	√
Inhibition of soluble TNFα induced chemokines ex vivo	3 - Qualitative comparison	√
Specificity against LTα in a HUVEC assay	3 - Qualitative comparison	√
FcγRIIIa (158V) binding	2 - Quality range	√
FcγRIIIa (158V) + TNFα binding	3 - Qualitative comparison	√
FcγRIa binding	3 - Qualitative comparison	√
FcγRIIa (131H) binding	3 - Qualitative comparison	√
FcγRIIIa (158F) binding	3 - Qualitative comparison	√
C1q binding	3 - Qualitative comparison	√
FcRn binding	2 - Quality range	√
Induction of ADCC	2 - Quality range	√
Induction of CDC	2 - Quality range	√
Inhibition of proliferation in an MLR	3 - Qualitative comparison	√

ADCC = antibody-dependent cell-mediated cytotoxicity; C1q = complement component 1,q; CDC = complement-dependent cytotoxicity; F = phenylalanine; Fab = fragment antigen binding; Fc = fragment crystallizable; FcγRIa = Fc gamma receptor type Ia; FcγRIIa = Fc gamma receptor type IIa; FcγRIIIa = Fc gamma receptor type IIIa; FcRn = neonatal Fc receptor; H = histidine; HUVEC =human umbilical vein endothelial cells; IL-8 = interleukin-8; LTα = lymphotoxin alpha; MLR = mixed lymphocyte reaction; soluble TNFα = soluble tumor necrosis factor alpha; V = valine.