GP2015 Biosimilar (Etanercept)

United States Food and Drug Administration
Arthritis Advisory Committee

July 13, 2016

SANDOZ A Novartis Division

GP2015 Etanercept
Introduction and Concept

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Sandoz Biopharmaceuticals

Totality of Evidence Shows GP2015 Is Highly Similar to US-Licensed Enbrel® (etanercept)

FDA and Sandoz reviews both concluded:

- Extensive analytical and PK data
  - Demonstrated high similarly
  - Confirmed relevance of clinical and non-clinical data with EU-approved Enbrel (scientific bridge)
- Clinical development program
  - Demonstrated no clinically meaningful differences in the indication studied
  - Transition did not result in a different safety or immunogenicity profile
- Extensive data package to address scientific considerations for extrapolation

Totality of Evidence Supports Extrapolation Across Indications

- We will demonstrate today that
  - Extensive analytical and PK data show that the active ingredient of GP2015 is essentially the same as Enbrel®
  - Confirmatory clinical study in a sensitive indication further contributes to the totality of evidence
- GP2015 may be used in all approved indications for US-licensed Enbrel

Sandoz Is a Pioneer in the Development and Marketing of Biosimilars

- Sandoz has extensive in-house biologic drug development and manufacturing experience
  - Started recombinant biologics efforts 30 years ago
  - Started biosimilar development activities 20 years ago
- Multiple firsts
  - First biosimilar product (somatropin) in the EU in 2006 followed by epoetin alfa in 2007 and filgrastim in 2009
  - First biosimilar in Australia, Canada, Japan, and the US (Zarxio® in 2015)
- Sandoz biosimilars are sold in more than 60 countries and have generated >250 million patient-days exposure

Unmet Medical Need: Our Passion Is Directed at Improving Access to Biologics

- Etanercept is a biologic therapy that has changed the practice of medicine and has improved patients' lives
  - Many patients in the US remain unable to access this valuable therapy or must negotiate multiple hurdles
- GP2015 is a proposed biosimilar to Enbrel®
  - Potential to expand patient access and reduce burden on US healthcare system

The Proposed Indications of GP2015 Are Identical to Those of the US Label for Enbrel®

- Justified by demonstrating biosimilarity according to FDA's guidance with the totality of evidence supporting extrapolation
  - Rheumatoid arthritis (RA)
  - Polyarticular juvenile idiopathic arthritis (JIA)
  - Psoriatic arthritis (PsA)
  - Ankylosing spondylitis (AS)
  - Plaque psoriasis (PsO)

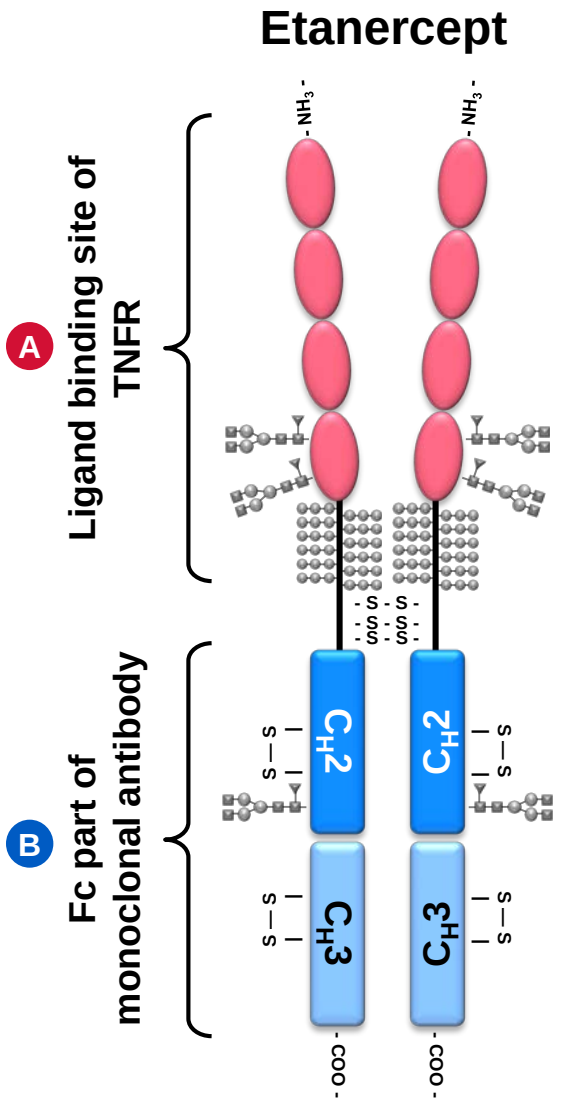
Etanercept Molecule and Mechanism of Action

Etanercept (a dimeric fusion protein)

- Extracellular ligand-binding portion of the human (p75) tumor necrosis factor receptor (TNFR)
- Linked to the Fc portion of a human IgG1 antibody

The Mechanism of Action (MoA)

- Competitive inhibitor of soluble TNF-α binding to its receptor

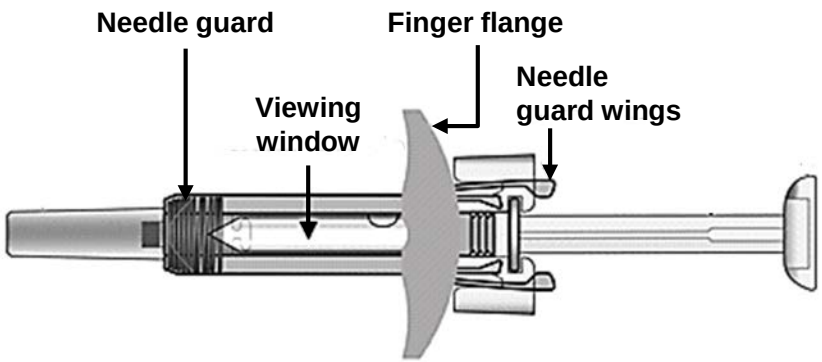


GP2015 Will Have Comparable Dosage Forms

	Enbrel®	GP2015
Dosage forms	• 25 mg/0.5 mL pre-filled syringe (50 mg/mL) • 50 mg/1.0 mL pre-filled syringe (50 mg/mL) • 50 mg/1.0 mL pre-filled autoinjector (50 mg/mL)	• 25 mg/0.5 mL pre-filled syringe (50 mg/mL) • 50 mg/1.0 mL pre-filled syringe (50 mg/mL) • 50 mg/1.0 mL pre-filled autoinjector (50 mg/mL)
Administration	SC application once or twice a week depending on indication	SC application once or twice a week depending on indication

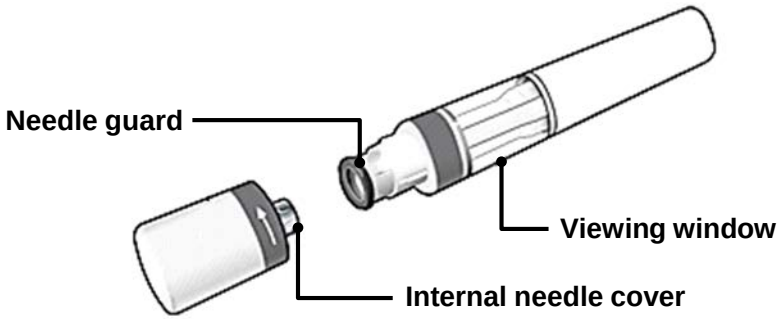
GP2015 Available as Pre-filled Syringe and as Pre-filled Autoinjector

GP2015 pre-filled syringe (PFS)

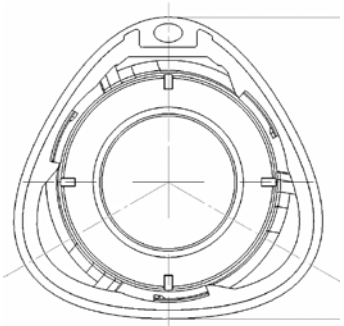


Enlarged finger flange
Needle safety guard

GP2015 pre-filled autoinjector (AI)

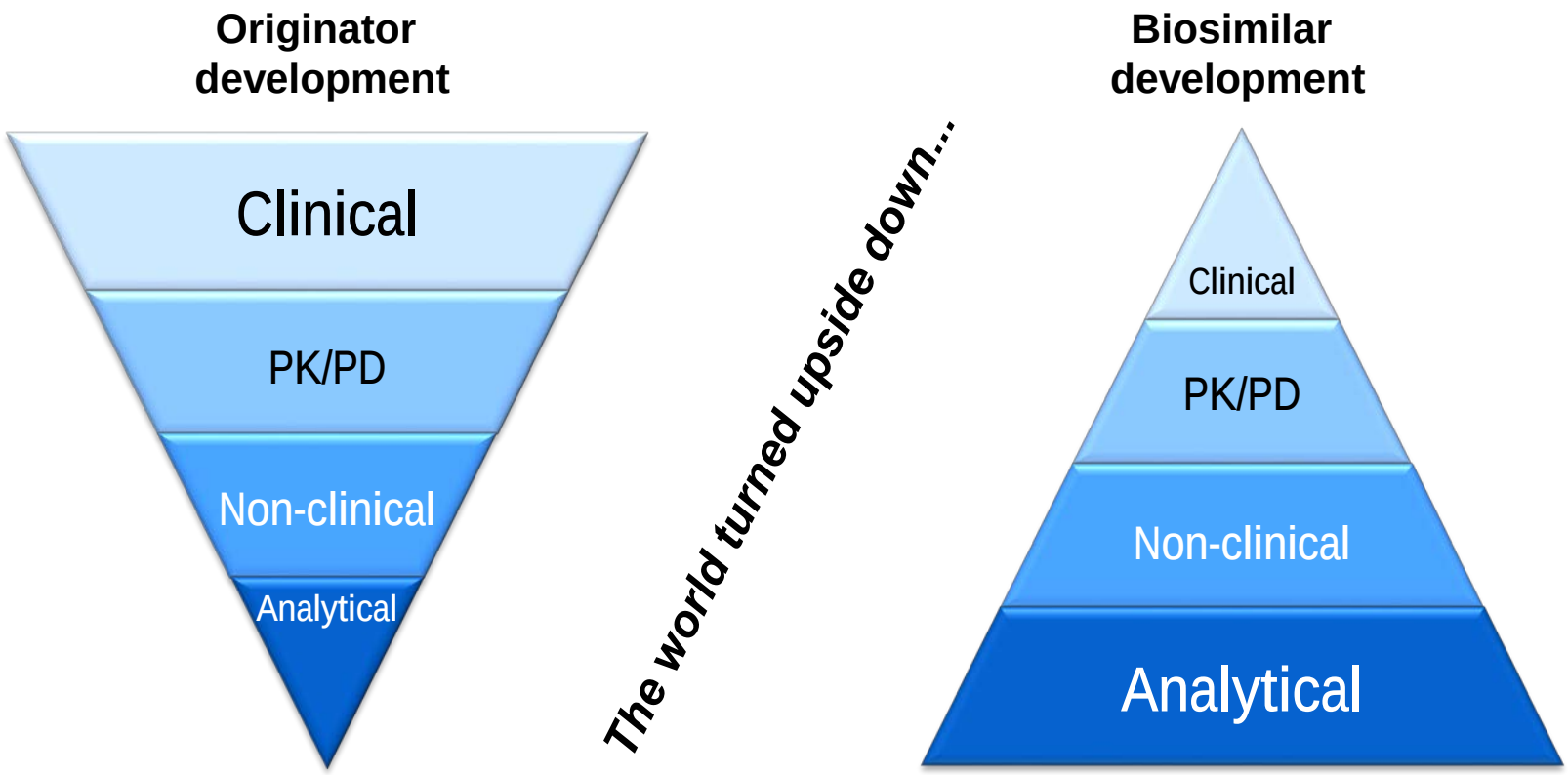


Triangular shape for better grip
2-step injection



Development of a Biosimilar Requires a Paradigm Shift

Comparison with the reference product



Biosimilar Development Approach Pioneered by Sandoz Encompasses 5 Steps

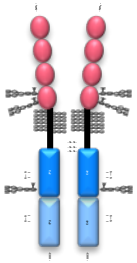
1 **Target definition**	▪ Understand originator **target molecule variability** ▪ Map the significant variability and criticality in quality attributes ▪ Define biosimilar “goal posts”
2 **Target-directed development**	▪ **Systematically engineer** biosimilar to match the reference product across cell line, bioprocess, and drug product development
3 **Characterization of biosimilarity**	▪ Establish similarity based on **physicochemical, biological, and functional characterization**
4 **Regulatory interactions**	▪ Interact with regulatory authorities to reach consensus on the appropriate clinical programs required to confirm biosimilarity (innovative trial designs and unique endpoints)
5 **Clinical confirmation**	▪ Conduct clinical trials to **confirm biosimilarity in the clinical setting**

Extrapolation Concept Is Based on Extrapolation From Molecule to Molecule

Extrapolation is....

...from Reference Product to Biosimilar...

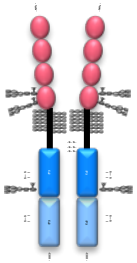
Enbrel®



Reference Product

"Sameness"

GP2015

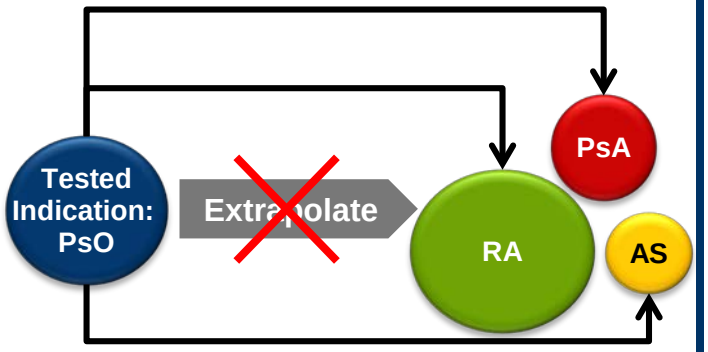


Biosimilar

- Demonstration of "**sameness**" of biosimilar to reference product: **extrapolation scientifically justified**
- **Extrapolating from one molecule to the other:** safe use of the biosimilar in all indications approved for the reference product that share the same MoA

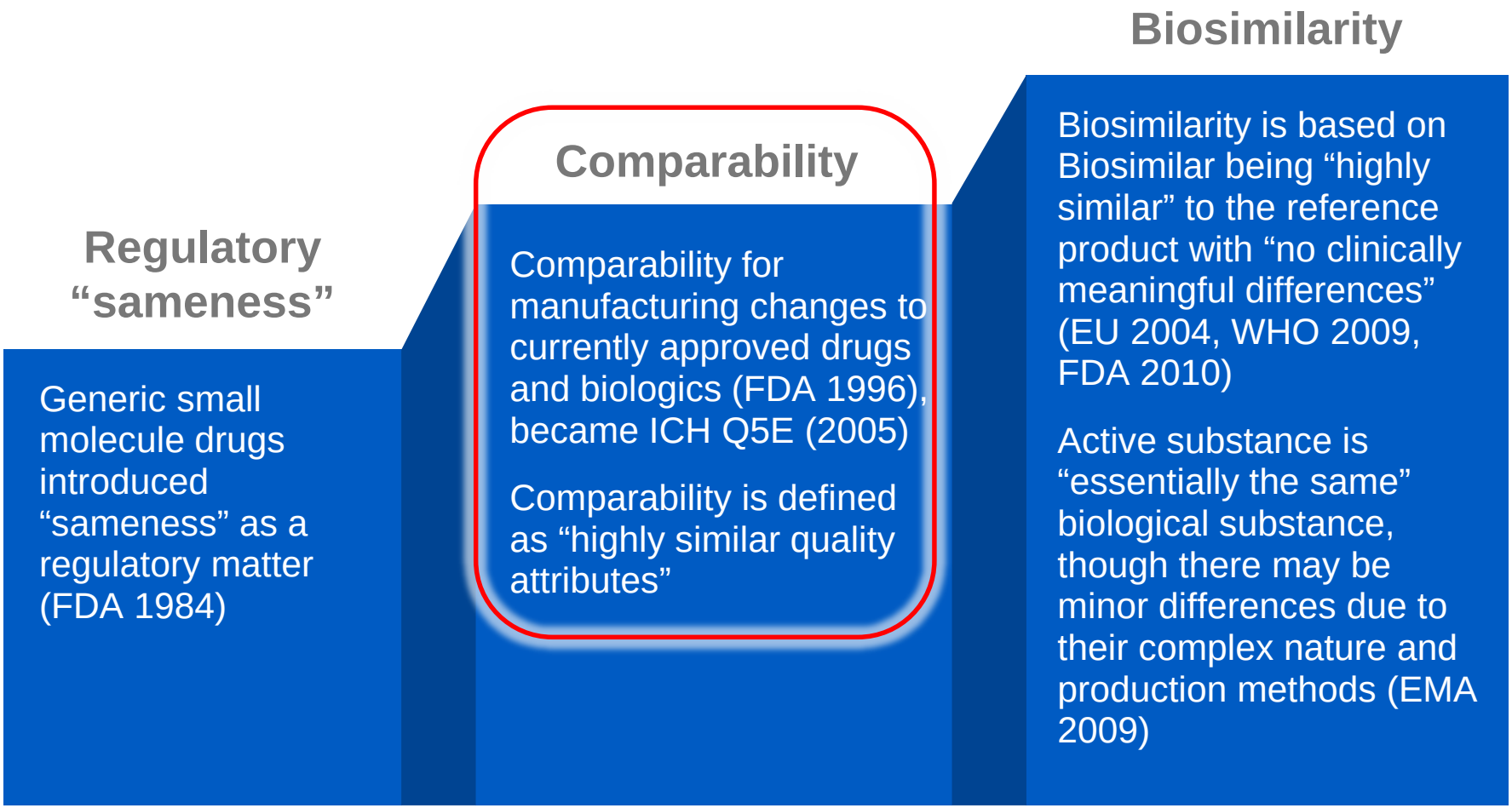
...not from Indication to Indication...

- **Extrapolation is not from one clinical experience to another...**



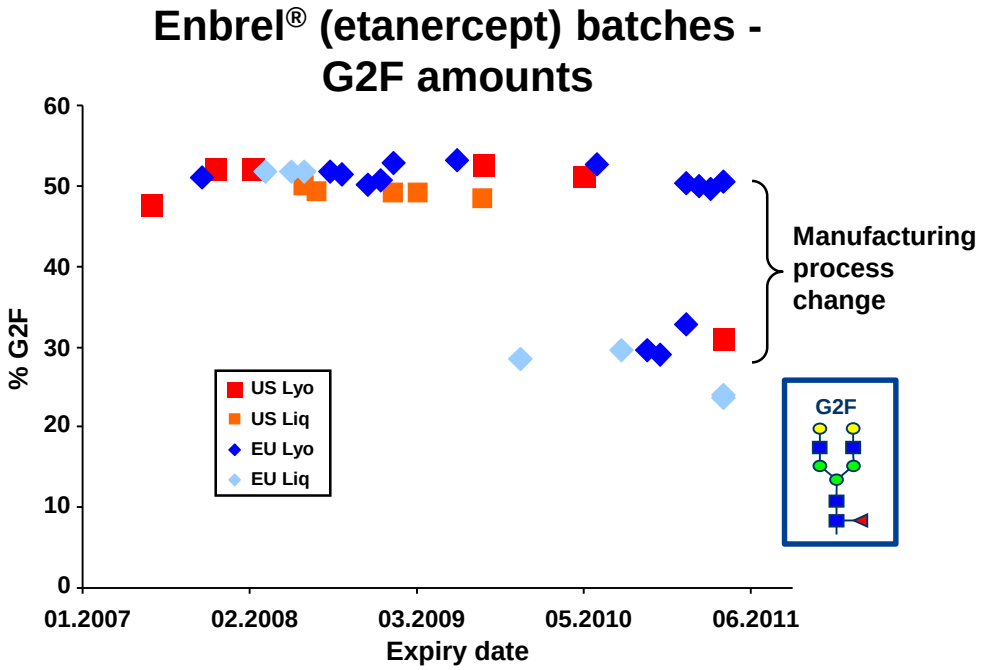
Weise M, et al. *Blood*. 2012;120(26):5111-1117; Kurki P, et al. *J Crohns Colitis*. 2014;8(3):258.
http://www.ema.europa.eu/docs/en_GB/document_library/ Scientific_guideline/2012/06/WC500128686.pdf

Regulatory Concept of "Sameness" Is Key to Establishing Biosimilarity Allowing Extrapolation



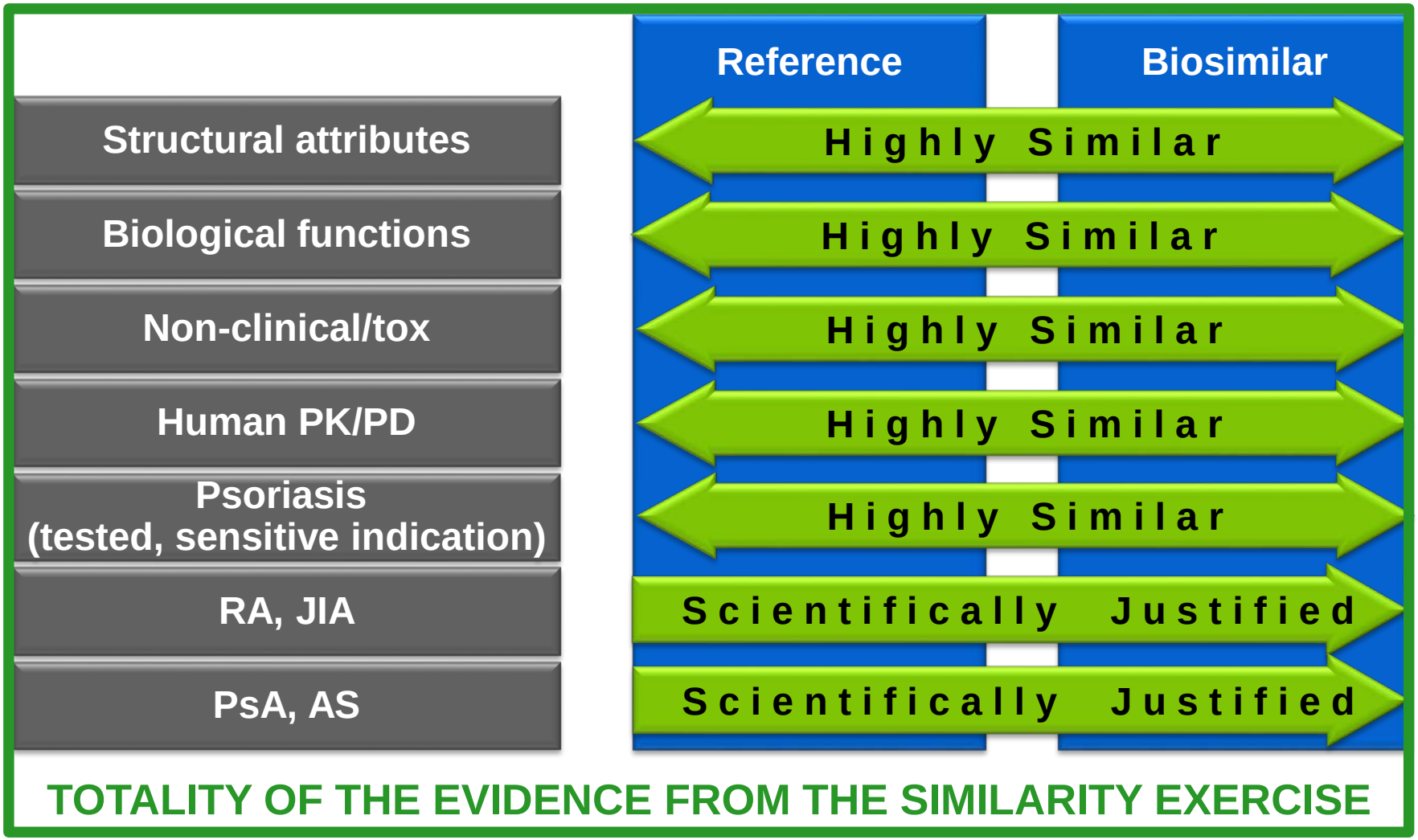
Manufacturing Changes of Enbrel® Approved and Extrapolated to All Indications

- Schiestl documented manufacturing changes not previously reported
- These changes were evaluated and deemed to be highly similar or comparable
- The modified process was approved as producing a highly similar product under the same label
- Its use was extrapolated to all approved indications



Schiestl M, et al. *Nat Biotechnol*. 2011;29(4):310-312.
McCamish M, et al. *Clin Pharmaco Ther*. 2012;91(3):405-417.

Totality of Data Showing That GP2015 Is "Essentially The Same" as Enbrel® Justifies Extrapolation



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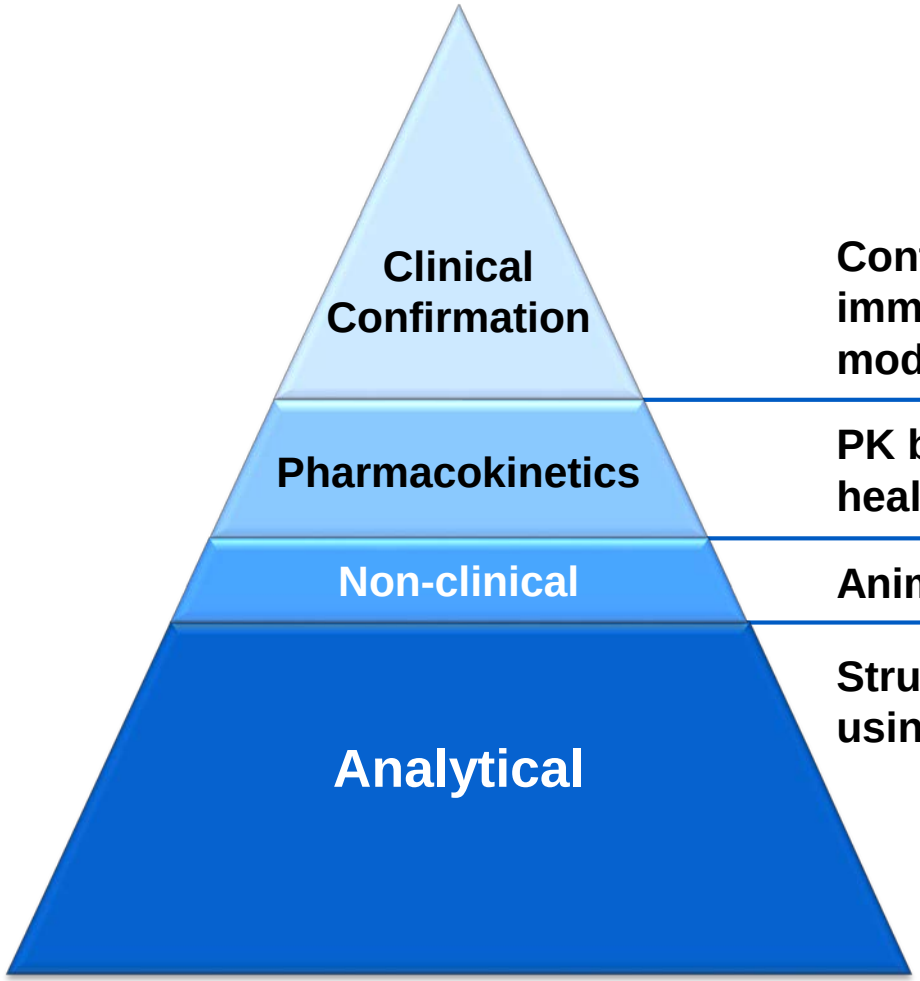
Comparative Evaluation of GP2015 and Enbrel® Justifies Extrapolation



Confirmatory efficacy, safety, and immunogenicity study in patients with moderate-to-severe plaque psoriasis

PK bioequivalence studies in healthy volunteers

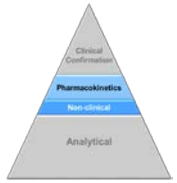
Animal PD, PK, toxicity

Structural and functional comparison using state-of-the-art technology

The totality of the evidence

→ The **totality of data** supports that GP2015 is **essentially the same** as Enbrel
→ This supports **Biosimilarity** and justifies **Extrapolation** to all indications for which Enbrel is approved

Agenda

Analytical Characterization	Martin Schiestl, PhD	
Non-clinical and PK Characterization	Oliver von Richter, PhD, FCP	
Clinical Confirmation	Malte Peters, MD	
Use in Clinical Practice	Jonathan Kay, MD	
Conclusions	Mark McCamish, MD, PhD	

Consultants

- Jonathan Kay, MD
  Timothy S. and Elaine L. Peterson Chair in Rheumatology
  Professor of Medicine
  Director of Clinical Research, Rheumatology
  University of Massachusetts Medical School
  Worcester, MA

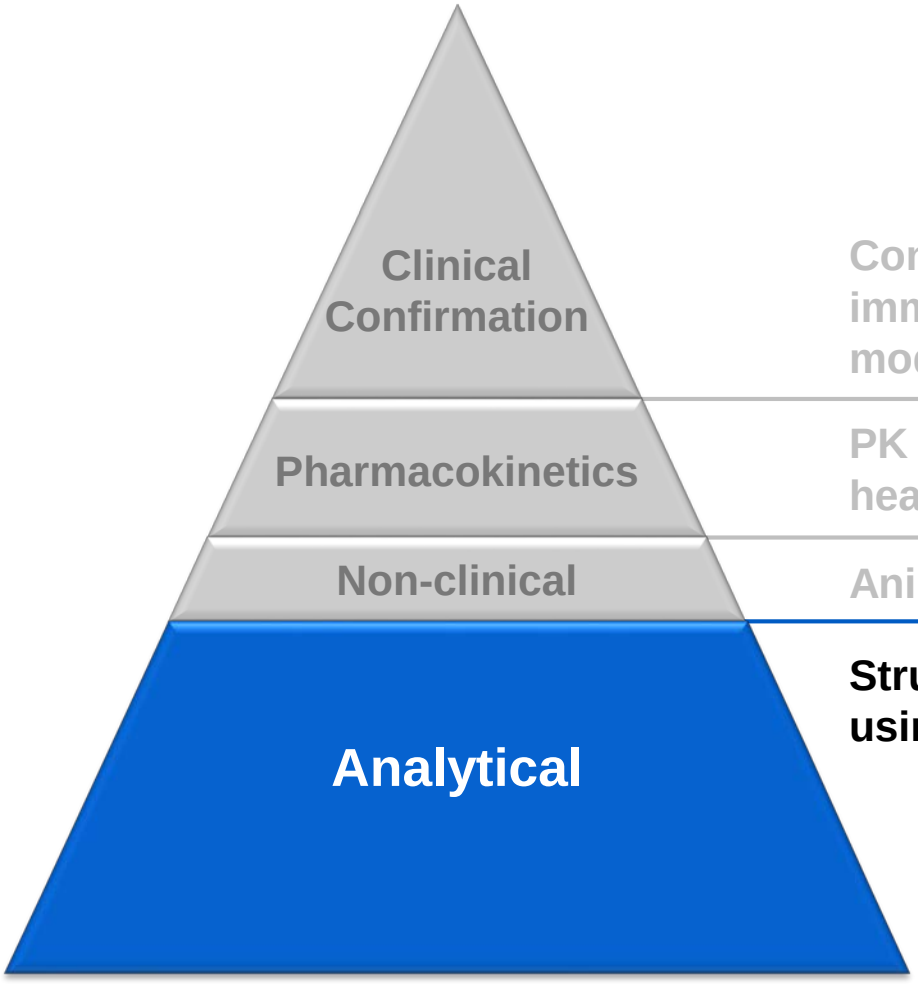
- Craig L. Leonardi, MD
  Adjunct Professor of Dermatology
  Saint Louis University School of Medicine
  St. Louis, MO
  Central Dermatology
  St. Louis, MO

Analytical Demonstration of Similarity

Martin Schiestl, PhD

Chief Science Officer
Sandoz Biopharmaceuticals

Comprehensive Comparative Evaluation of GP2015 and Enbrel®



Confirmatory efficacy, safety, and immunogenicity study in patients with moderate-to-severe plaque psoriasis

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Animal PD, PK, toxicology

Structural and functional comparison using state-of-the-art technology

Targeted Development of GP2015

Target definition
Analyzing numerous batches of Enbrel®

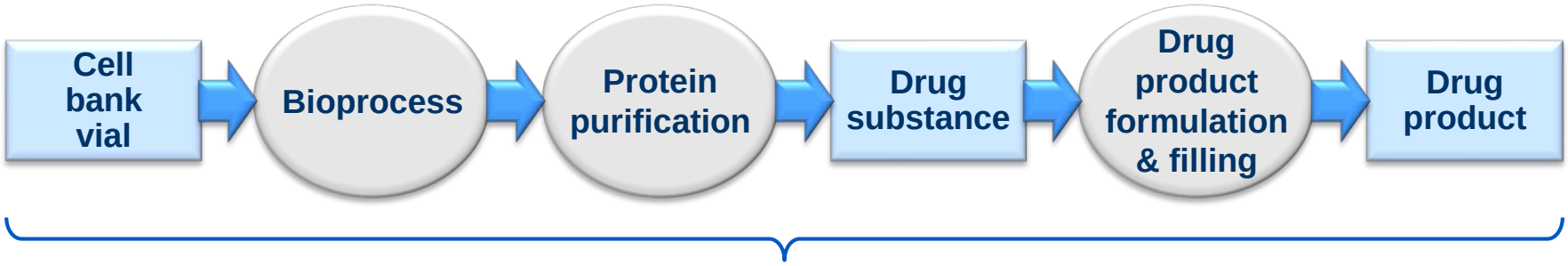
Iterative development of all process steps to match the Enbrel target quality

1. Cell line development
2. Bioprocess development
3. Protein purification
4. Drug product development

Knowledge of relevance of molecular attributes for efficacy and safety

Demonstration of similarity

Manufacturing Process Designed to Deliver a Consistent Biosimilar Product

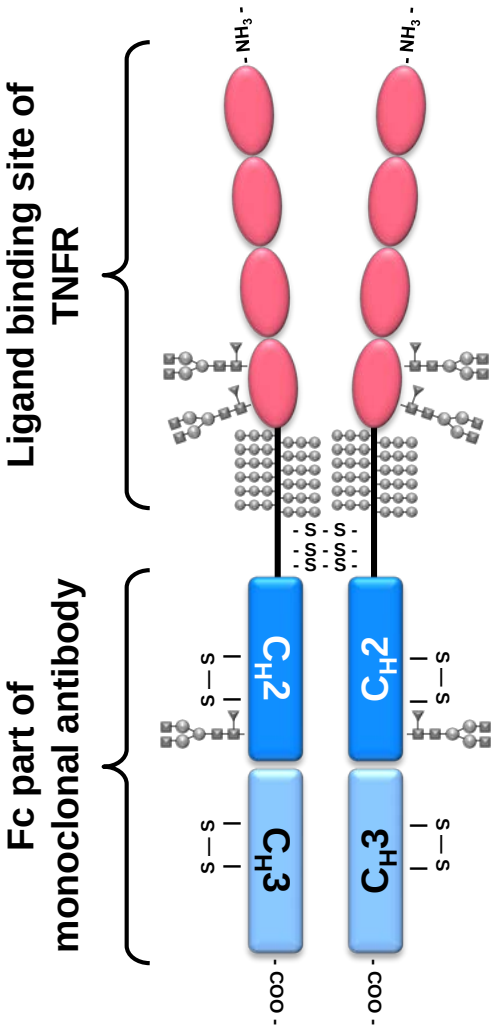


Manufacturing process controlled by

- Raw material controls
- Process design
- In-process testing and control of process parameters
- Release testing of harvest, drug substance, and final dosage form

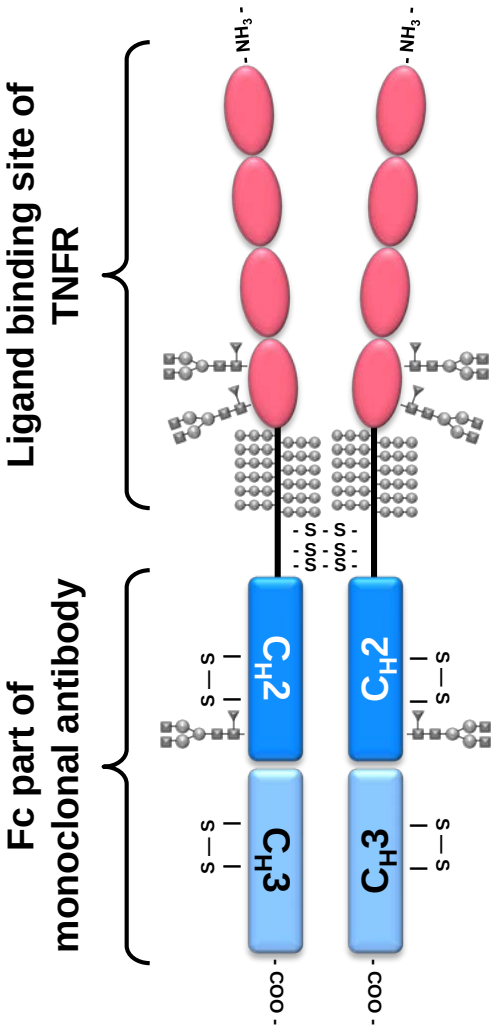
Quality System governed by Quality Assurance functions
Compliance with Good Manufacturing Practices (GMP)

Etanercept—A Well-Characterized Molecule



- Manufactured by a bioprocess using a well-established recombinant Chinese hamster ovary (CHO) cell line
- Etanercept is a dimeric, secreted, soluble protein
- It has multiple glycosylation sites and disulfide bonds

Multiple Quality Attributes Assessed as Part of Molecule Characterization



Primary structure (amino acid sequence)

Higher order structure (protein folding)

- Secondary structure
- Tertiary structure

Protein modifications

- N-Glycosylation
- O-Glycosylation
- Sialic acids
- Oxidation
- Deamidation
- Charge variants
- Glycation
- N- and C-terminal heterogeneity

Impurities

- Aggregates, fragments
- DNA
- Protein A
- HCP

Biological activity

- TNF-α neutralization
- TNF-β neutralization
- TNF binding
- ADCC activity
- CDC activity

Which Quality Attributes Matter Clinically?
Criticality Assessment

Quality attributes related to

- Etanercept molecule
- Process materials
- Excipients

Assessment on clinical relevance

- Immunogenicity
- Safety/Toxicity
- Pharmacokinetics
- Efficacy

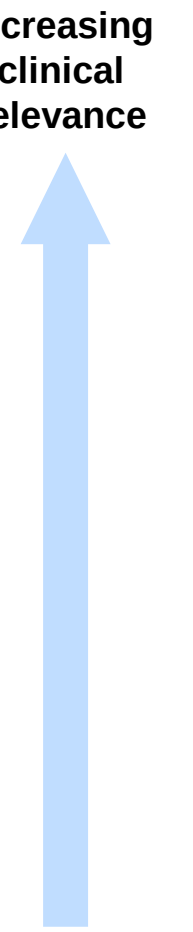
Existing product knowledge

- Literature
- In-house studies
- Related molecules

Criticality	Criticality score
Very high	121 - 140
High	86 - 120
Moderate	56 - 85
Low	31 - 55
Very low	2 - 30

Clinical Importance of Quality Attributes
Excerpt Overview Table

Criticality	Number of attributes	Examples of Critical Quality Attributes (clinical parameter impacted)
Very high	22	TNF-α neutralization (efficacy), TNF-β neutralization (efficacy), TNF-α binding (efficacy), protein content (efficacy)
High	14	Higher order structure (efficacy), alpha-galactosylation (immunogenicity), incorrect disulfide bond variants (efficacy), terminal GlcNAc – variants (PK/PD), FcRn binding (PK), aggregation (efficacy), degradation products (efficacy), purity
Moderate	25	Acidic variants, oxidation, deamidation, non-fucosylated glycans, sialylation, ADCC activity, CDC activity, binding to Fc gamma receptors
Low	10	Basic variants, succinimide, proline amide, N-terminal variant -leucine/ -leucine/proline, free thiols
Very low	13	Lysine variants, quality of sodium hydroxide, quality of nitrogen, quality of sodium chloride



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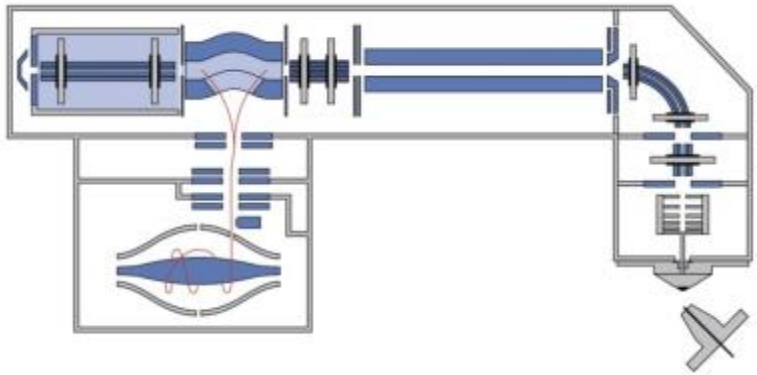
Very low	13	Lysine variants, quality of sodium hydroxide, quality of nitrogen, quality of sodium chloride

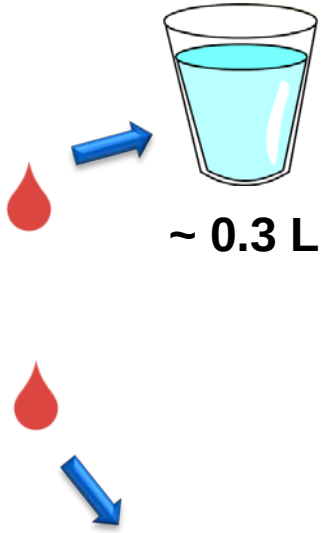
Results for attributes with very high/ high criticality shown on following slides

Powerful Tools Have Evolved to Allow Comprehensive Characterization

Year	MS- Detection limit for peptides (pmol)	Analogue
1990	100	
1993	10	
1997	1	
2000	0.1	
2003	0.01	
2005	0.001	
2008	0.0001	
2011	0.00001	

Mass spectrometry





~ 3,000,000 L

10 million-fold increase

Adapted from presentation by Anthony Mire-Sluis, 9th Symposium on the Practical Applications of Mass Spectrometry in the Biotechnology Industry (Mass Spec 2012); September 11-14, 2012, San Diego, CA, USA.

Analytical Similarity Assessment GP2015 vs Enbrel®

- Demonstrated similarity between GP2015 and Enbrel on physicochemical and in vitro functional biological level based on
  - More than 80 batches of Enbrel
- Extended characterization of GP2015, Enbrel/EU, and Enbrel/US using state-of-the-art analytical methods

Analytical Similarity Assessment GP2015 vs Enbrel®

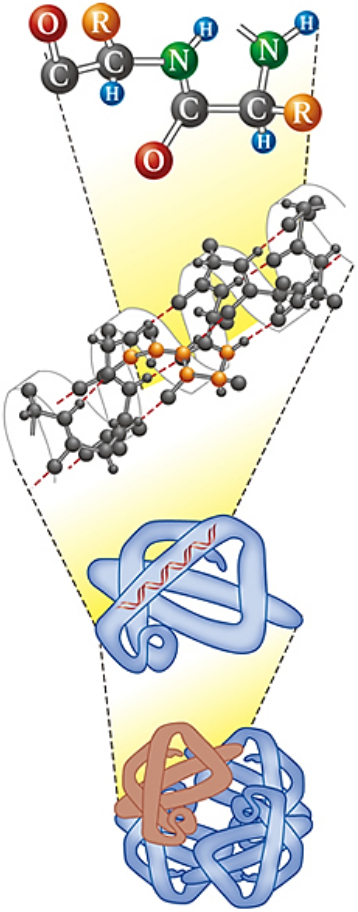
Critical Quality Attributes

- ❑ Primary structure
- ❑ Higher order structure
- ❑ TNF-α neutralization
- ❑ Content
- ❑ FcRn binding
- ❑ Product related impurities[a]

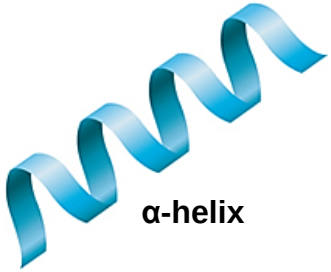
- ❑ Stability behavior

[a] Includes alpha-galactosylation, incorrect disulfide bond variants, aggregation and degradation products.

Primary Structure/Higher Order Structure



Amino acid sequence



α-helix

Total shape

Complex

Primary structure

Higher order structure

Critical Quality Attributes

- ❑ Primary structure
- ❑ Higher order structure
- ❑ TNF-α neutralization
- ❑ Content
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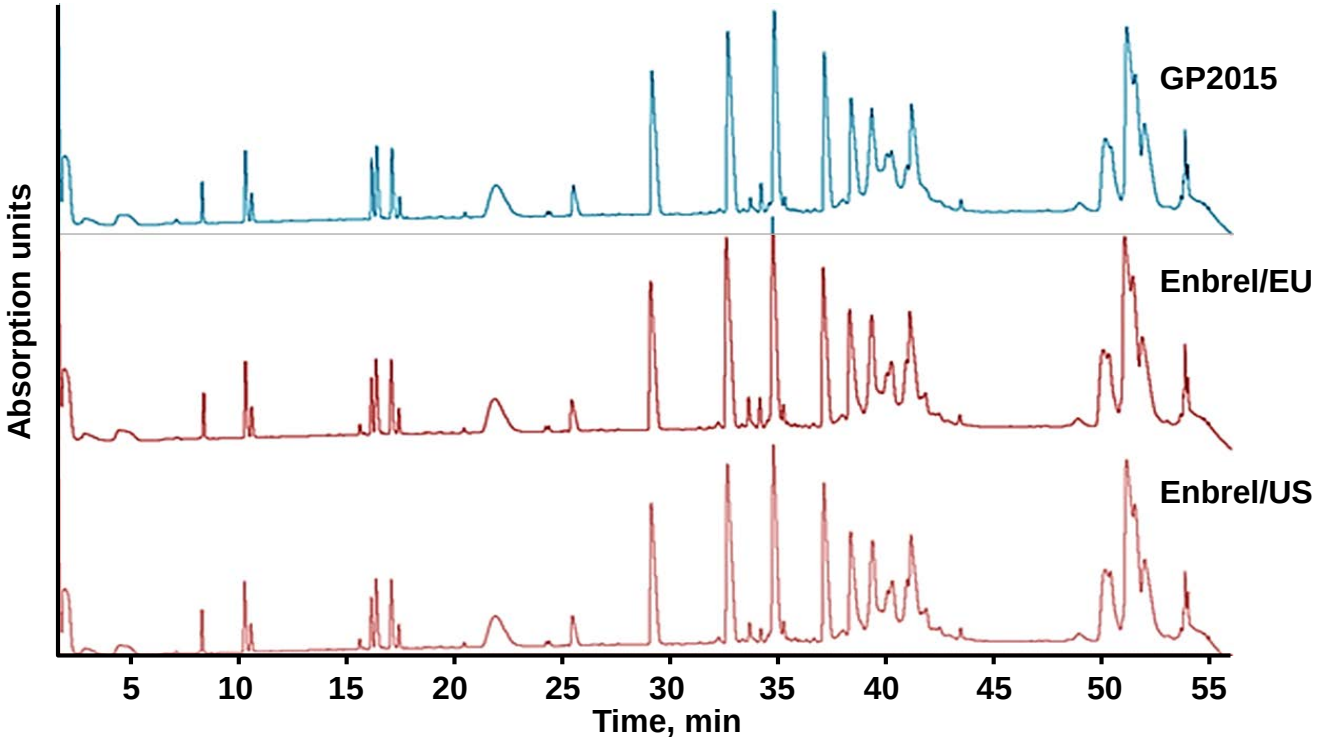
Amino Acid Sequence of GP2015 and Enbrel®

Assessment of primary structure by peptide mapping and mass spectrometry



Data confirm

- **100% identical primary structure of GP2015 and Enbrel**
- **Identity of Enbrel/US and Enbrel/EU**

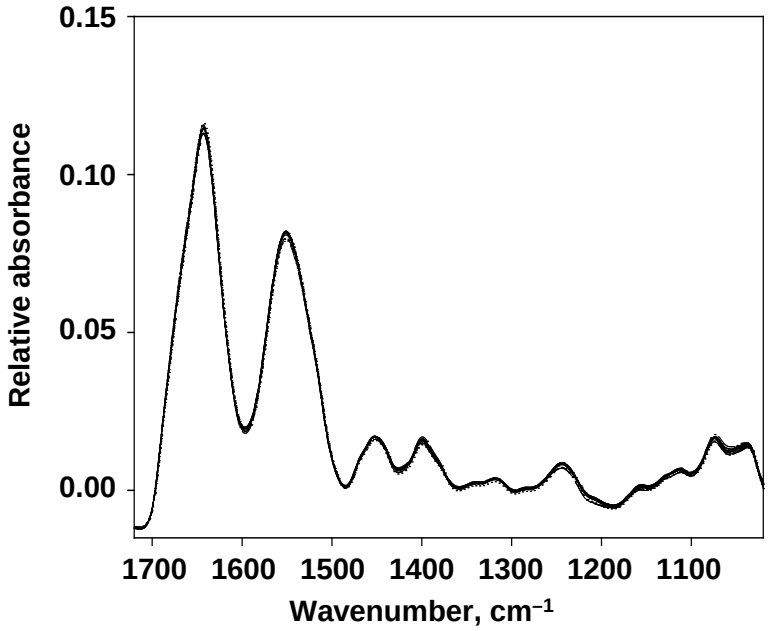
Critical Quality Attributes

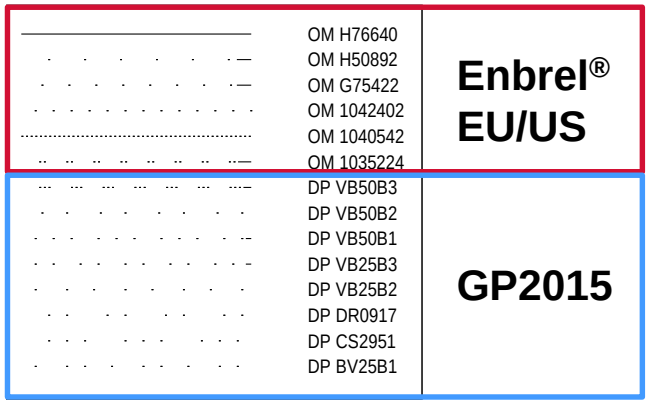
- ✓ Primary structure
- ☐ Higher order structure
- ☐ TNF-α neutralization
- ☐ Content
- ☐ FcRn binding
- ☐ Product related impurities

- ☐ Stability behavior

Indistinguishable Higher Order Structure Demonstrated by FTIR...

Assessment of higher order structure by Fourier-transform infrared spectroscopy (FTIR)





Critical Quality Attributes

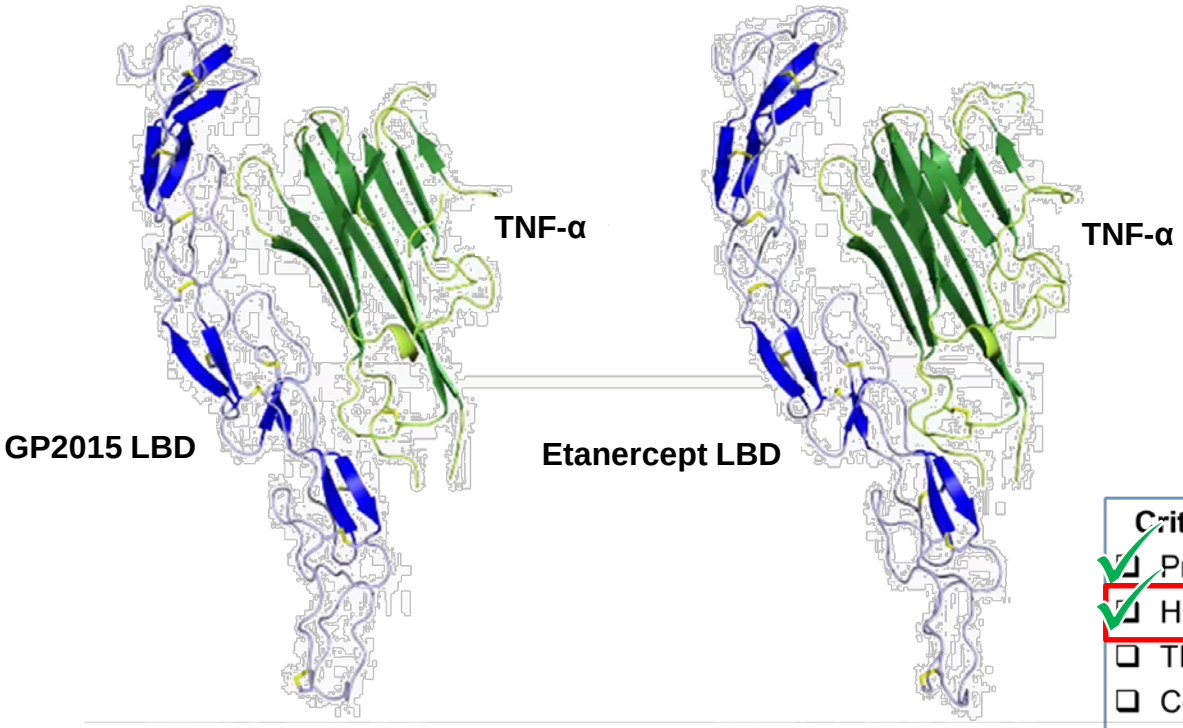
- ☑ Primary structure
- ☑ Higher order structure
- ☐ TNF-α neutralization
- ☐ Content
- ☐ FcRn binding
- ☐ Product related impurities
- ☐ Stability behavior

FTIR confirms indistinguishable higher order structure of

- **GP2015 and Enbrel**
- **Enbrel/US and Enbrel/EU**

Indistinguishable Higher Order Structure Demonstrated by X-ray Crystallography

Assessment of higher order structure by X-ray crystallography



Critical Quality Attributes

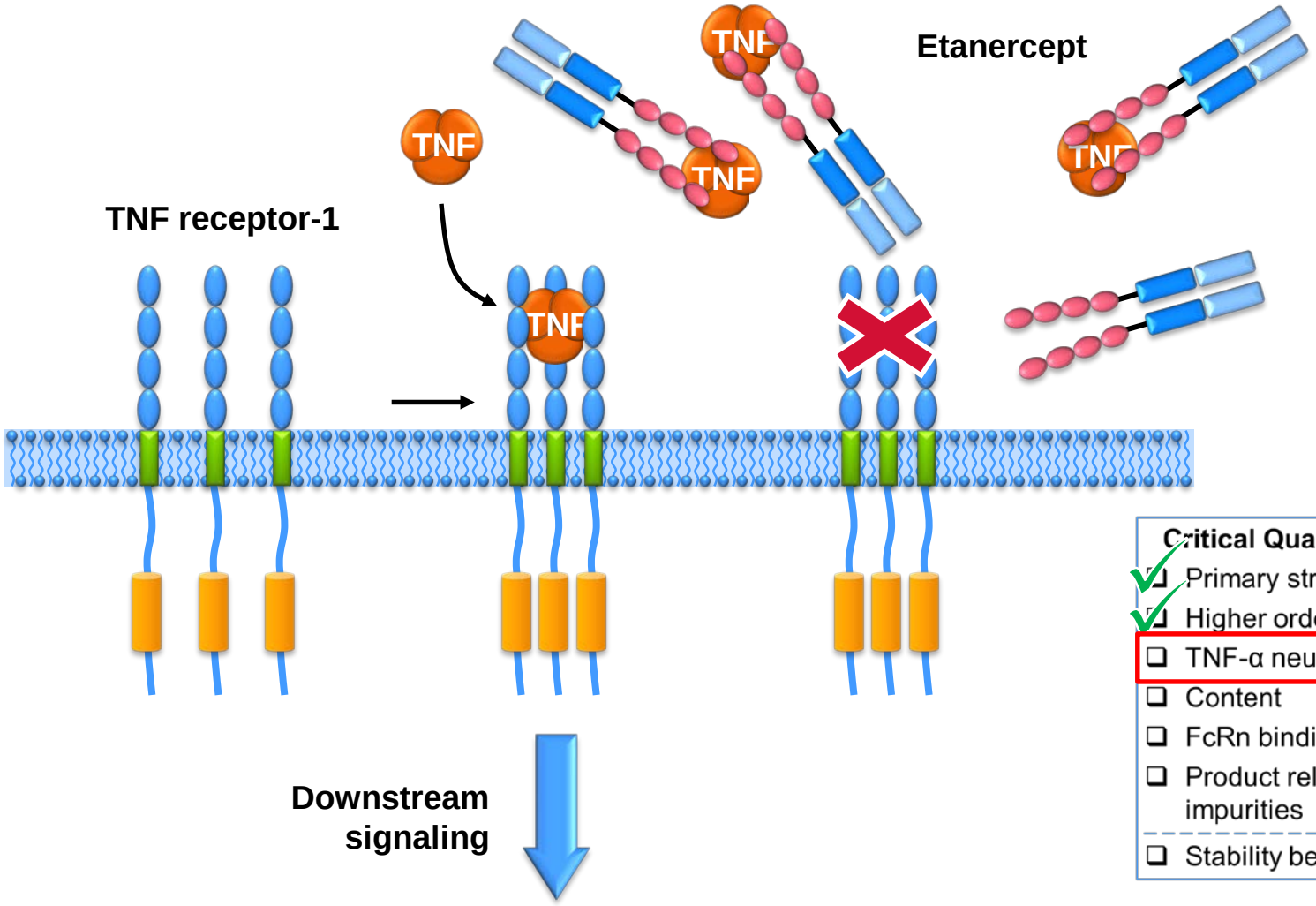
- ☑ Primary structure
- ☑ Higher order structure
- ☐ TNF-α neutralization
- ☐ Content
- ☐ FcRn binding
- ☐ Product related impurities
- ☐ Stability behavior

X-ray confirms indistinguishable higher order structure of

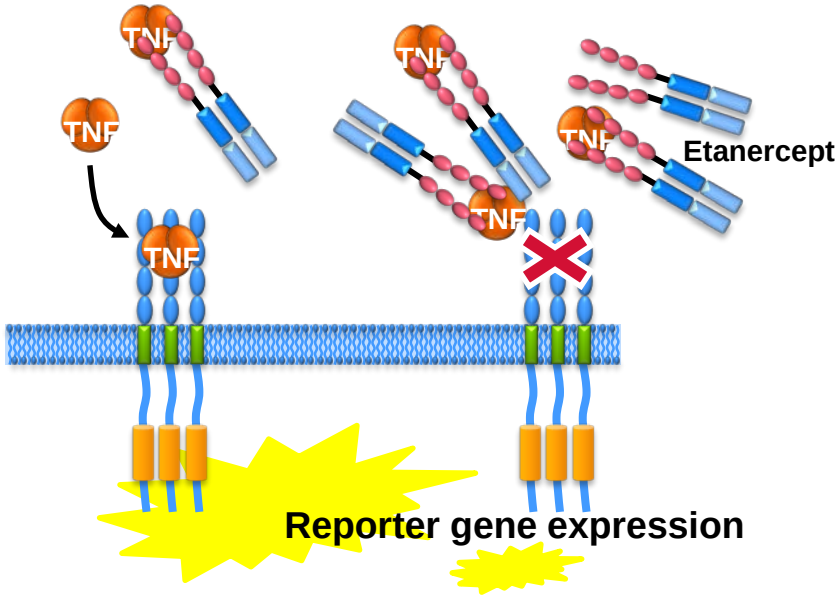
- **GP2015 and Enbrel®**
- **Enbrel/US and Enbrel/EU**

Same higher order structure of GP2015 and Enbrel/US confirmed also by HDX, CD, NMR, DSC. Enbrel/US and Enbrel EU also similar by FT-IR, CD, DSC, X-ray.

Mechanism of Action of Etanercept
TNF-α Neutralization



Assessment of Biological Activity: Neutralization of TNF-α



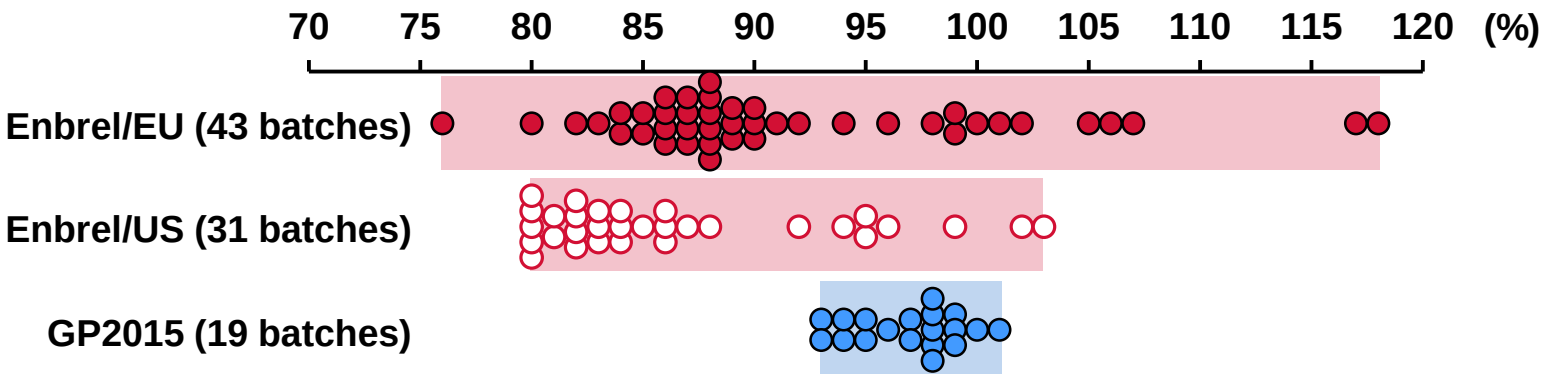
- Cell-based potency assay quantifies the neutralization of soluble TNF-α
- Recombinant luciferase reporter cell line responds to stimulation with TNF-α
- GP2015 or Enbrel® leads to dose-dependent suppression of TNF-α activity

Critical Quality Attributes

- ✓ Primary structure
- ✓ Higher order structure
- TNF-α neutralization
- Content
- FcRn binding
- Product related impurities
- Stability behavior

Data Show Similar Activity for GP2015 and Enbrel® in TNF-α Neutralization

Biological activity by TNF-α reporter gene assay (RGA)



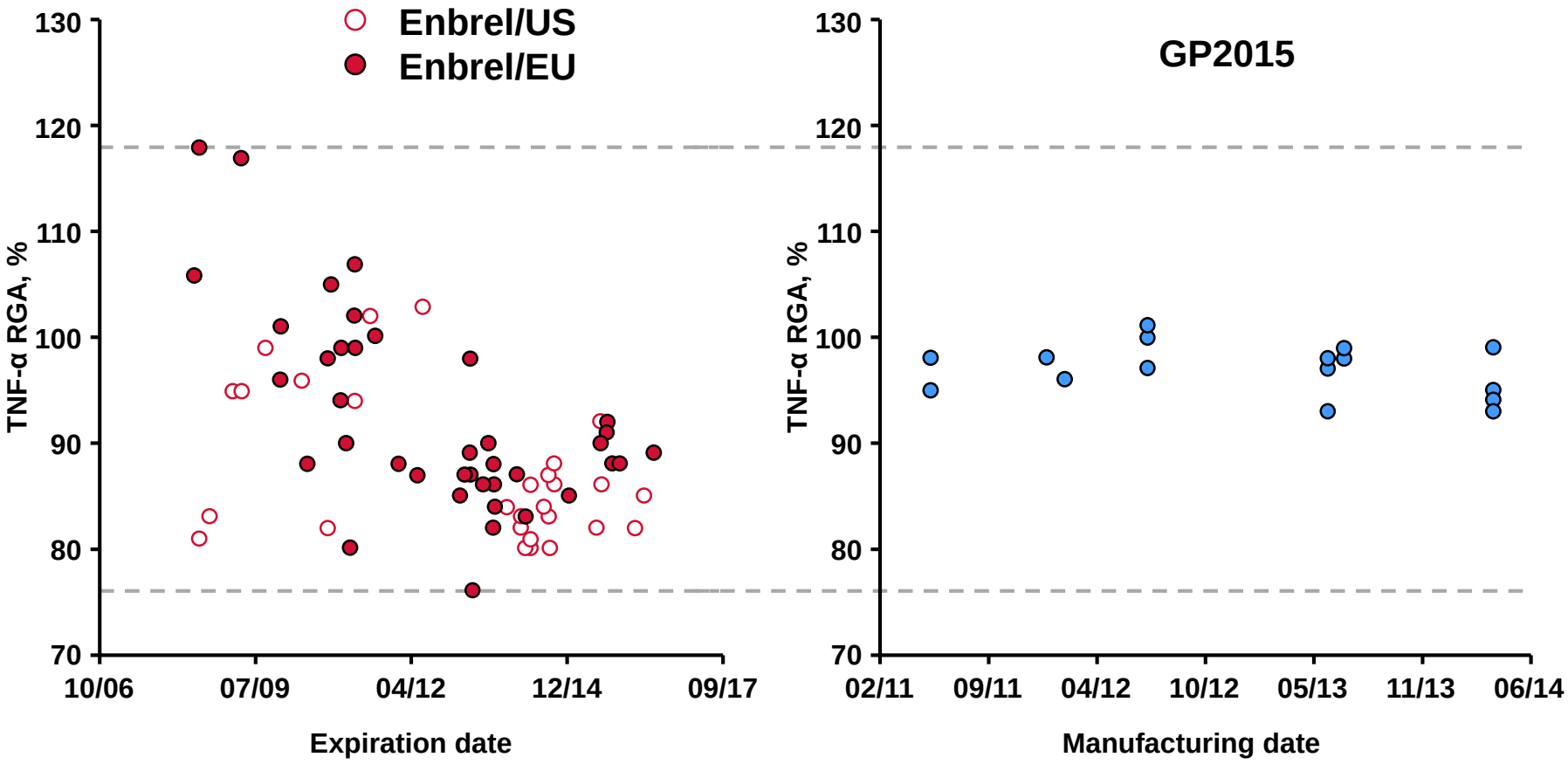
Biological activity of Enbrel/US and Enbrel/EU measured by TNF-α reporter gene assay is similar

Critical Quality Attributes

- ✓ Primary structure
- ✓ Higher order structure
- ✓ TNF-α neutralization
- ☐ Content
- ☐ FcRn binding
- ☐ Product related impurities

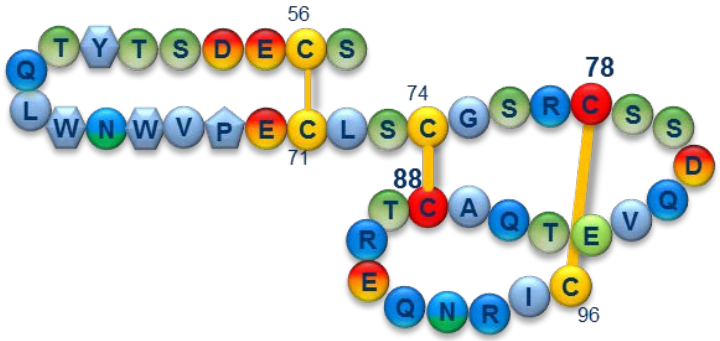
- ☐ Stability behavior

TNF-α Neutralization Activity of GP2015 Is Within Enbrel® Range of Variability



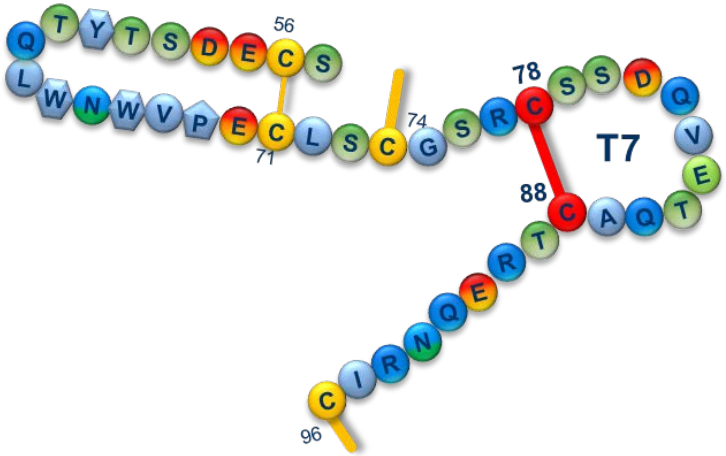
Incorrect Disulfide Bond Variants Present in Etanercept

Correct disulfide bonds



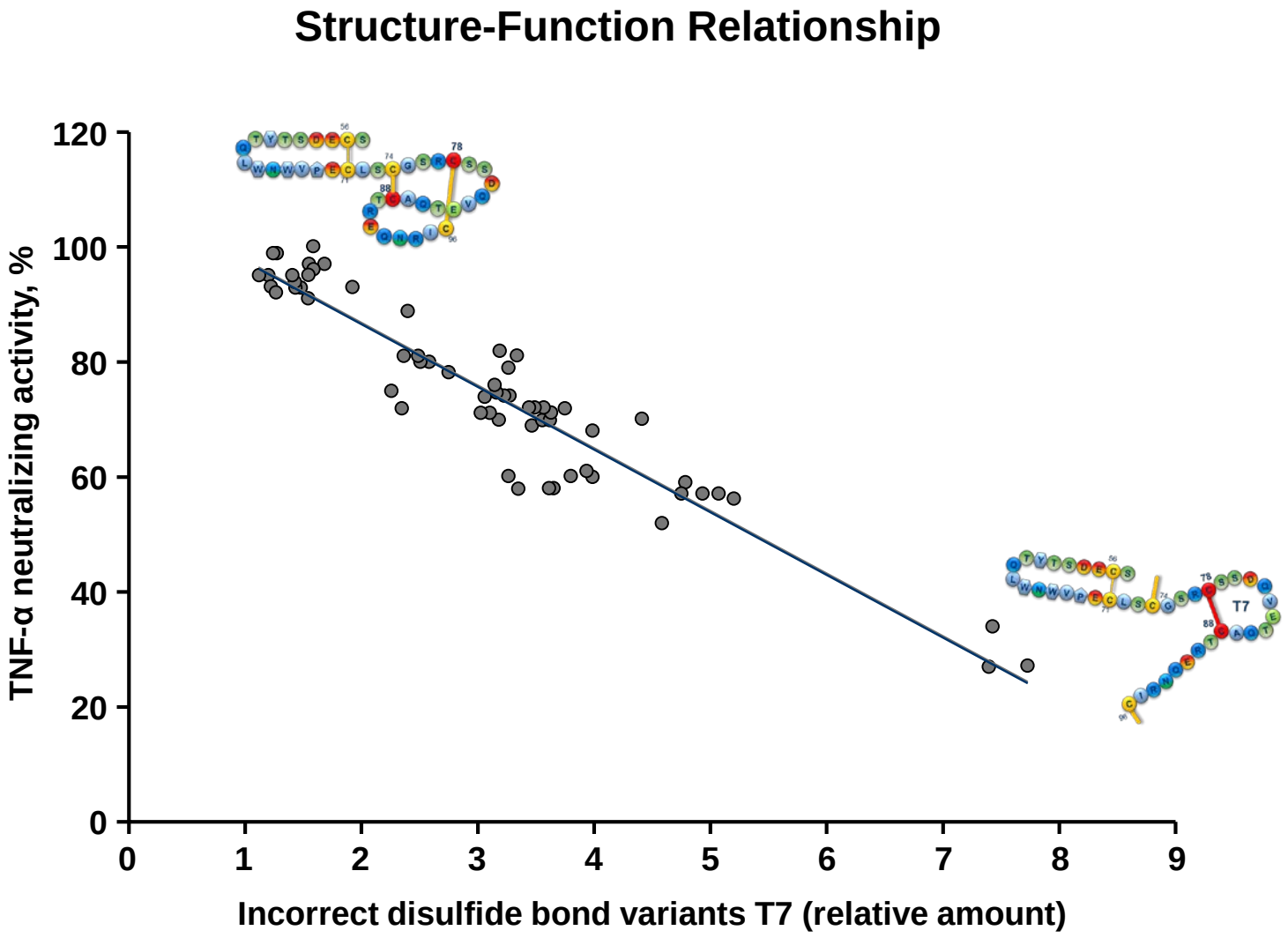
Active

Incorrect disulfide bond variant (T7 example)



Inactive

Incorrect Disulfide Bond Variants Are Inactive

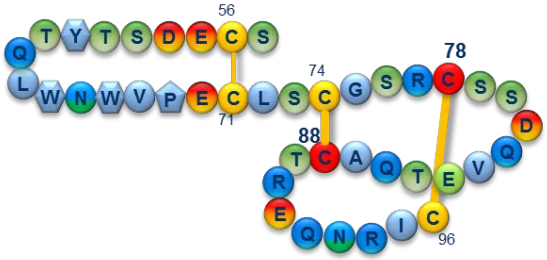


Incorrect Disulfide Bond Variants Are Corrected Under Physiological Conditions

Incorrect disulfide bond variant (T7)

Incubation redox system

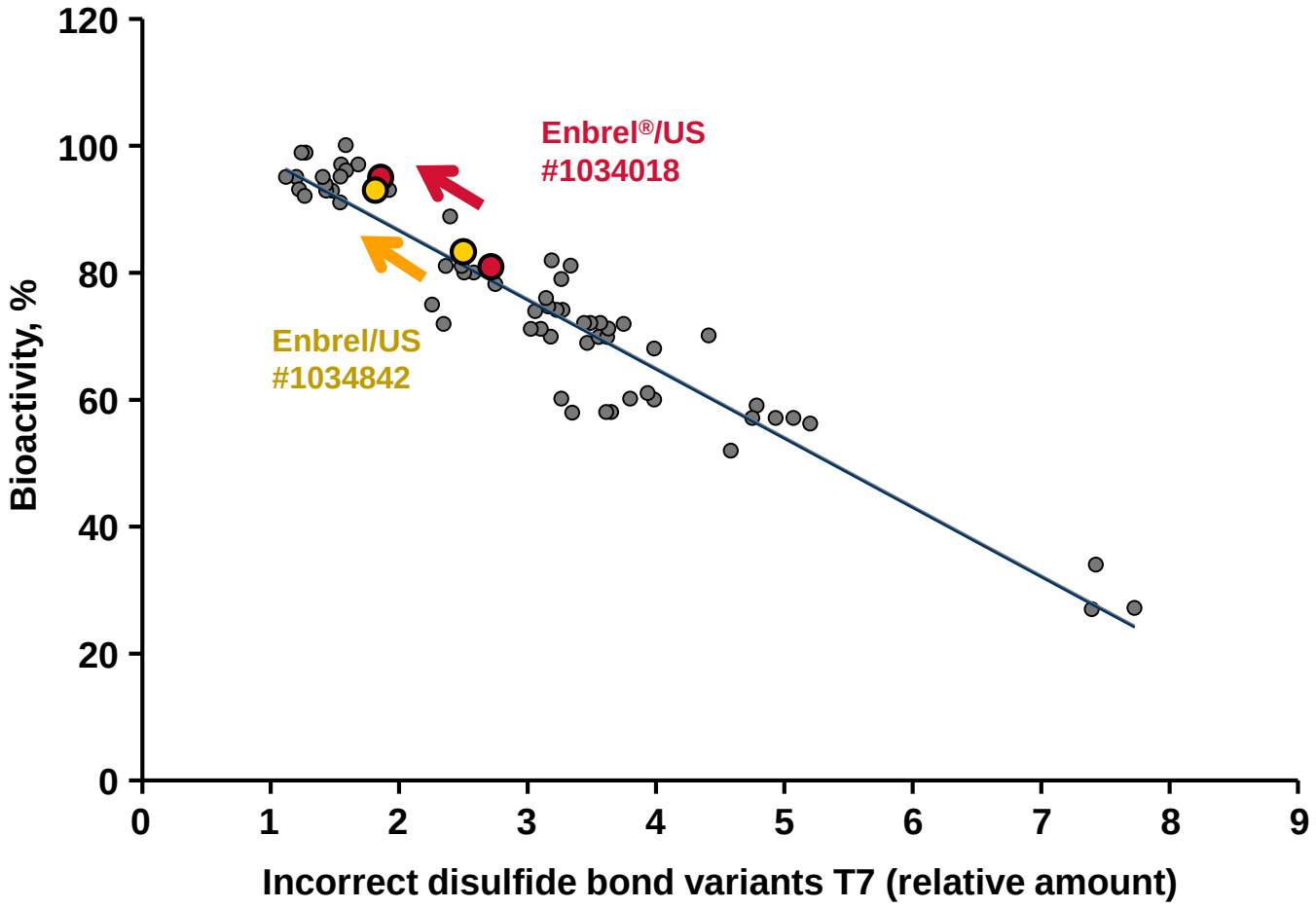
Correct disulfide bond variant



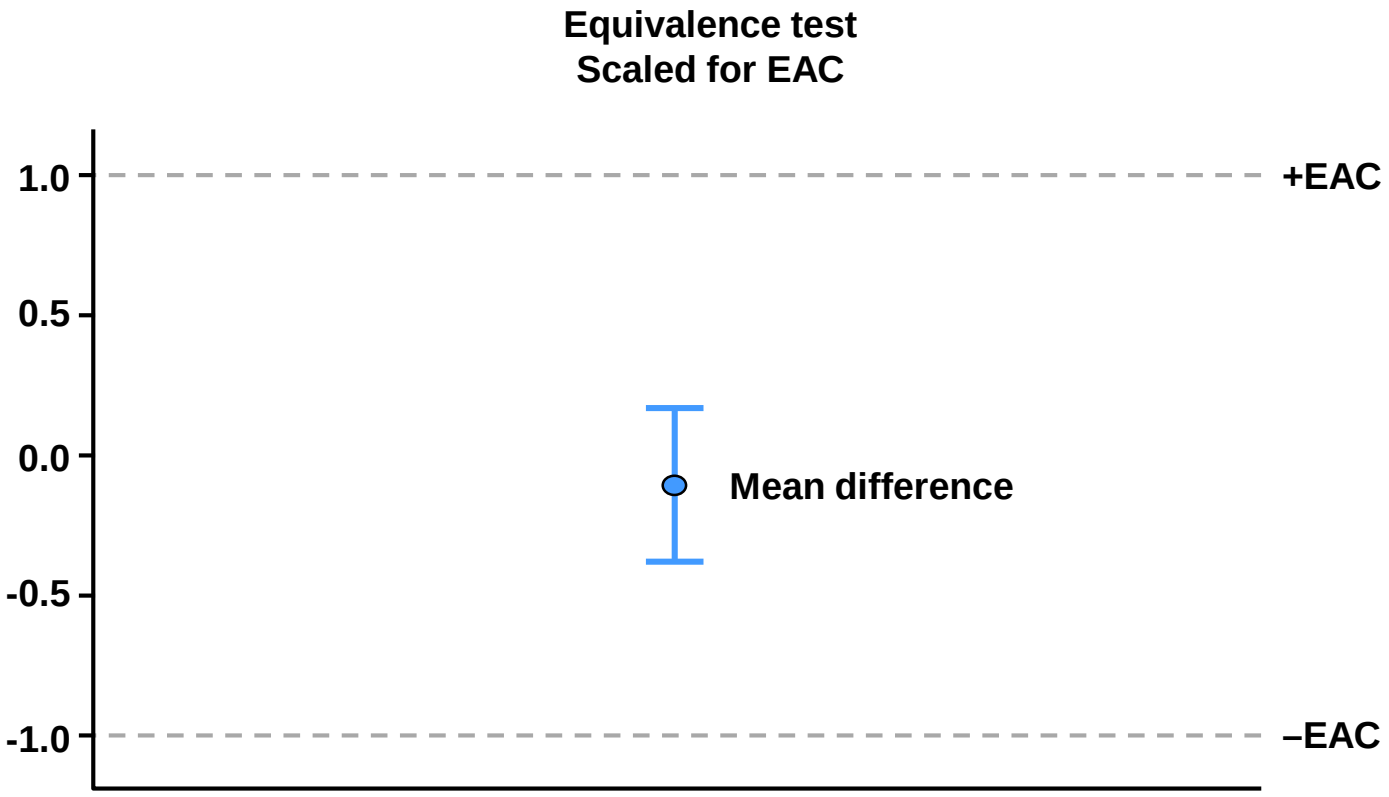
Redox system mimicking *in vivo* physiological redox conditions: Cysteine/Cystamine, Tris/HCl pH 8.0

Anderson 1993, Liu 2013.

TNF-α Neutralization Activity Increases Following Exposure to Redox Conditions



TNF-α Neutralization: GP2015 and Enbrel Bioactivity Is Equivalent

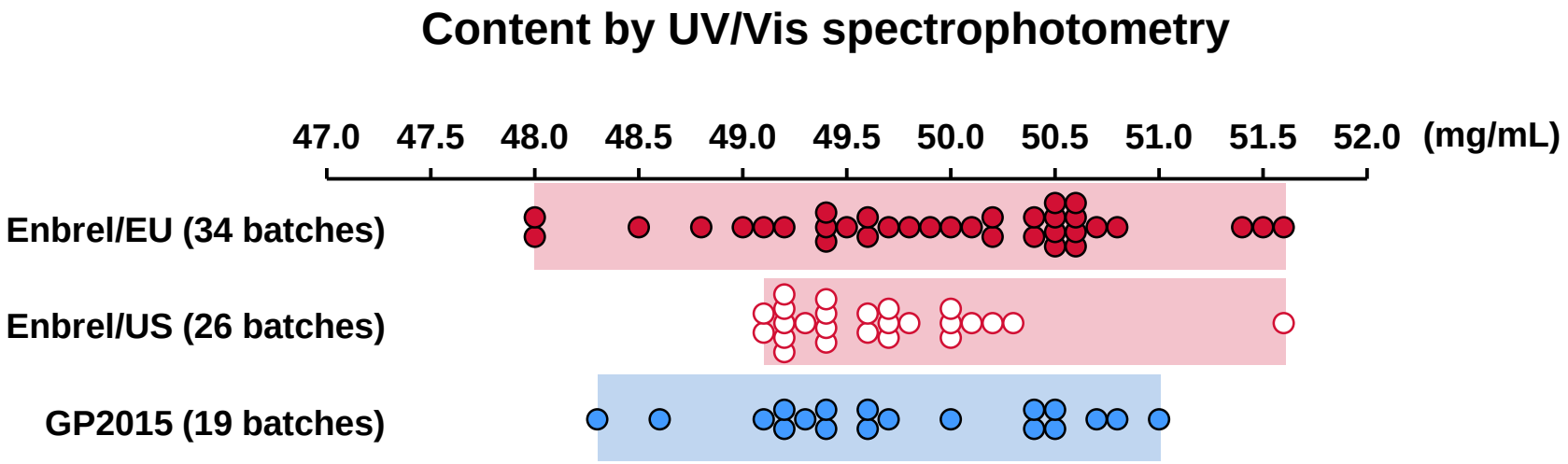


Note: Equivalence acceptance criteria (EAC) are calculated to have at least 80% power if the acceptable difference between the products is 1 sigma, given the current sample size.
EAC = $c_{80\%\ power} \times \sigma_{ref}$

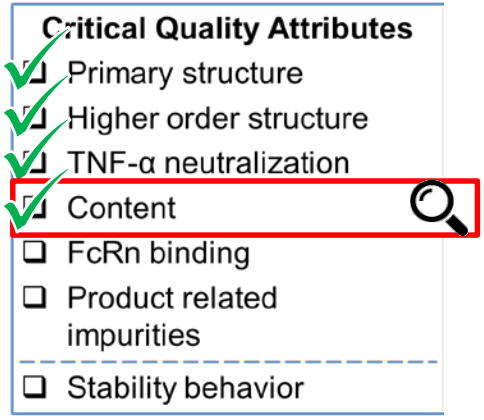
Confirmation of Similar Biological Activity

- ✓ TNF-α neutralization
- ✓ TNF-α binding
- ✓ TNF-β neutralization
- ✓ Inhibition of TNF-α mediated apoptosis

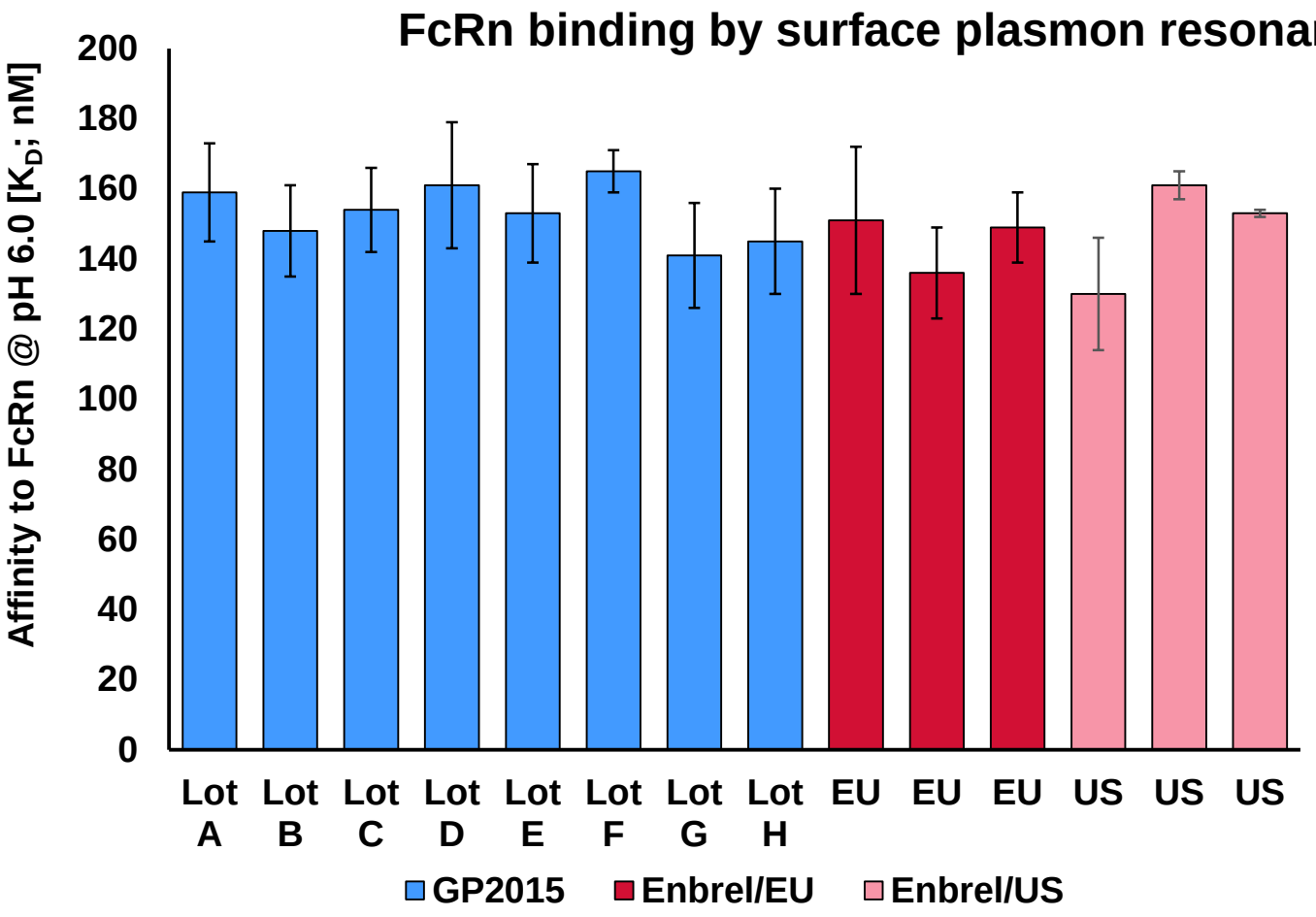
UV/Vis Spectrophotometry Demonstrates That Content Is Similar for GP2015 and Enbrel®



Content of GP2015 is within the combined ranges of Enbrel/US and Enbrel/EU



FcRn Binding Is Similar for GP2015 and Enbrel®

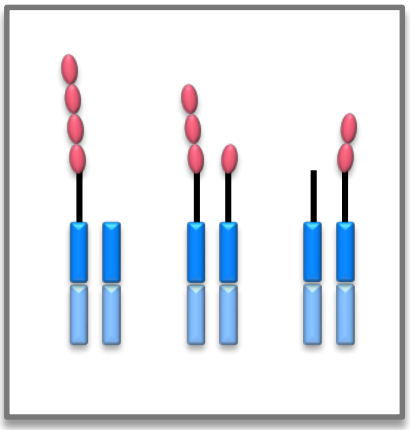


Critical Quality Attributes

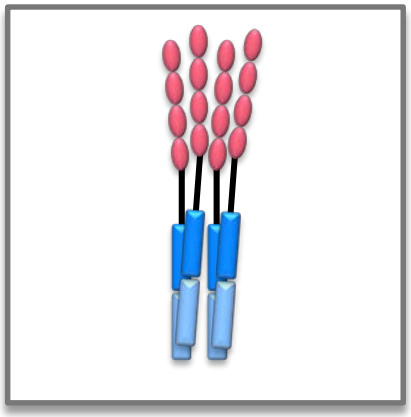
- ☑ Primary structure
- ☑ Higher order structure
- ☑ TNF-α neutralization
- ☑ Content
- ☑ FcRn binding
- ☐ Product related impurities
- ☐ Stability behavior

Binding affinity to FcRn as measured by surface plasmon resonance is similar

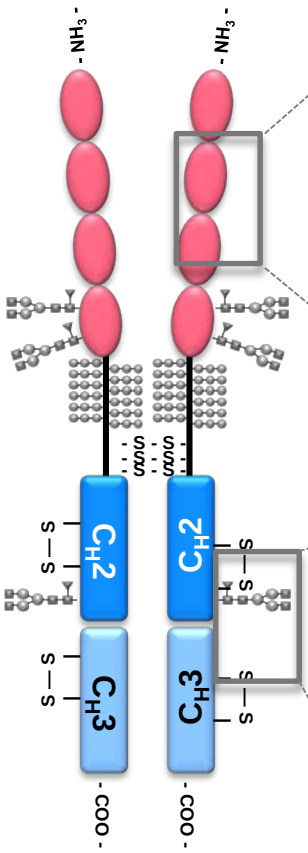
Product Related Impurities



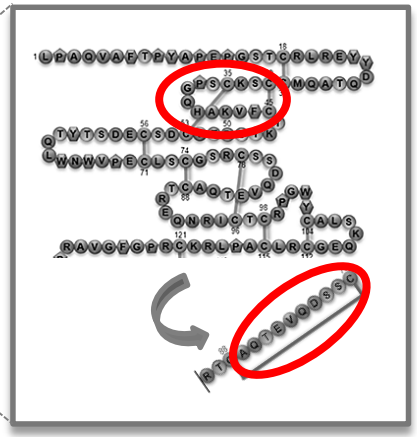
Degradation



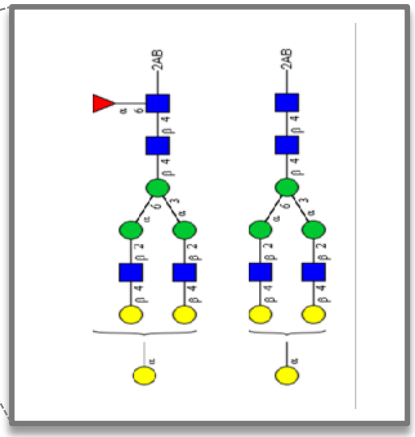
Aggregation



Intact molecule



Incorrect disulfide bond variants



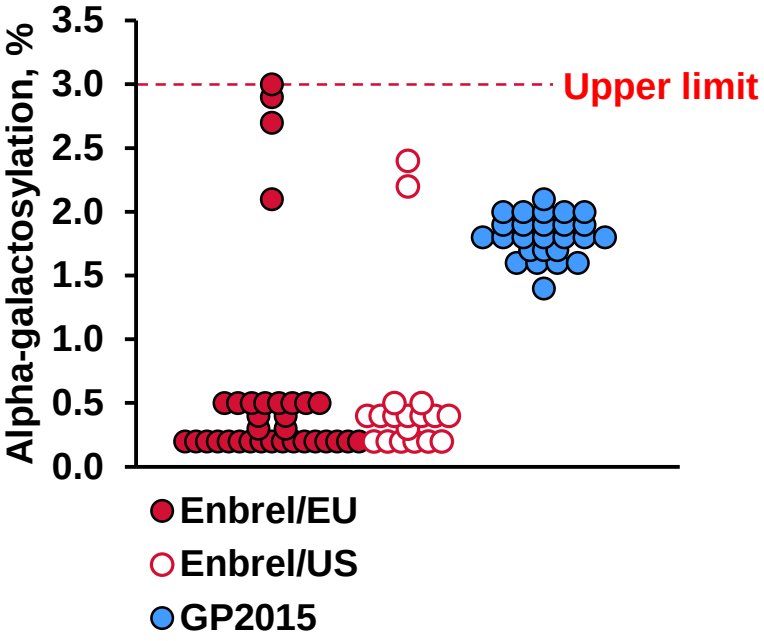
Alpha-galactosylation variants

Critical Quality Attributes

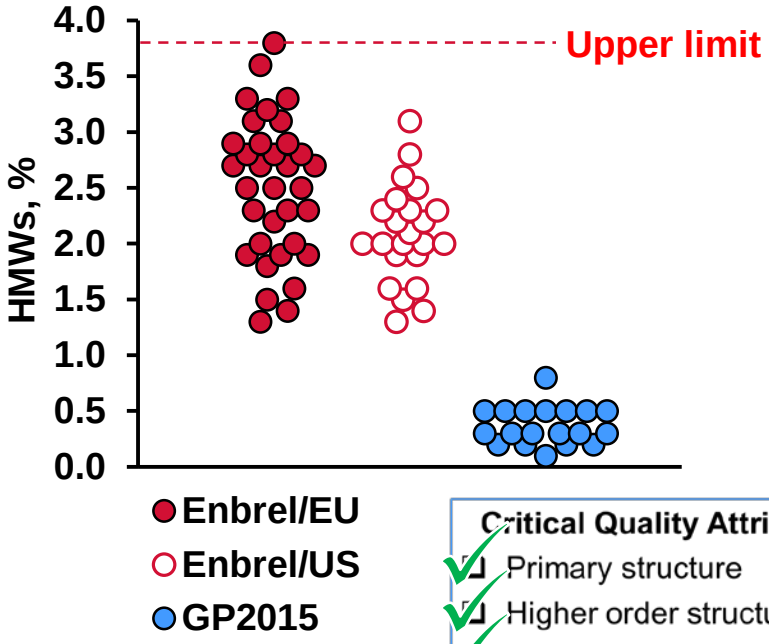
- ☑ Primary structure
- ☑ Higher order structure
- ☑ TNF-α neutralization
- ☑ Content
- ☑ FcRn binding
- ☐ Product related impurities
- ☐ Stability behavior

GP2015 Impurities Are Below the Limit of Enbrel®

Alpha-galactosylation (by NP-HPLC)



Aggregation products (by size exclusion chromatography)

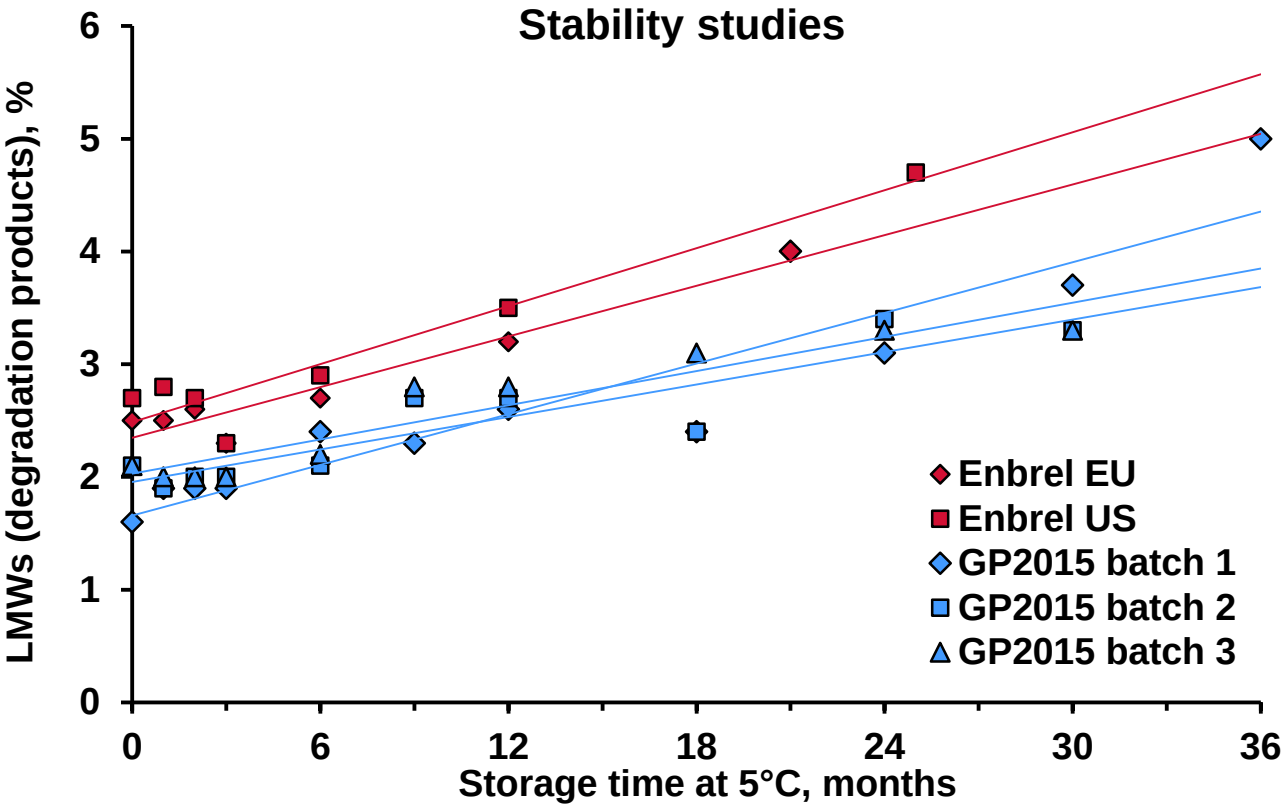


Critical Quality Attributes

- ☑ Primary structure
- ☑ Higher order structure
- ☑ TNF-α neutralization
- ☑ Content
- ☑ FcRn binding
- ☐ Product related impurities
- ☐ Stability behavior

Product related impurity profiles confirm sameness of Enbrel/US and Enbrel/EU

Degradation Rates of GP2015 and Enbrel® Are Similar at Intended Storage (2° to 8°C)



Product related impurity profile similar between

- **GP2015 and Enbrel**
- **Enbrel/US and Enbrel/EU**

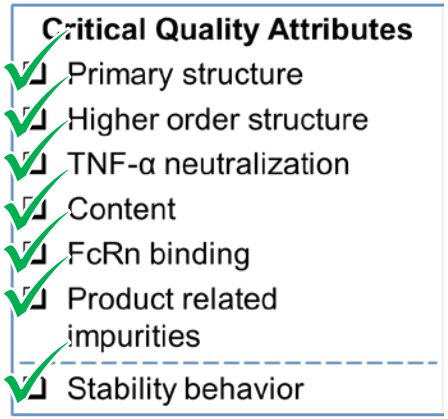
Critical Quality Attributes

- ✓ Primary structure
- ✓ Higher order structure
- ✓ TNF-α neutralization
- ✓ Content
- ✓ FcRn binding
- ✓ Product related impurities
- ✓ Stability behavior

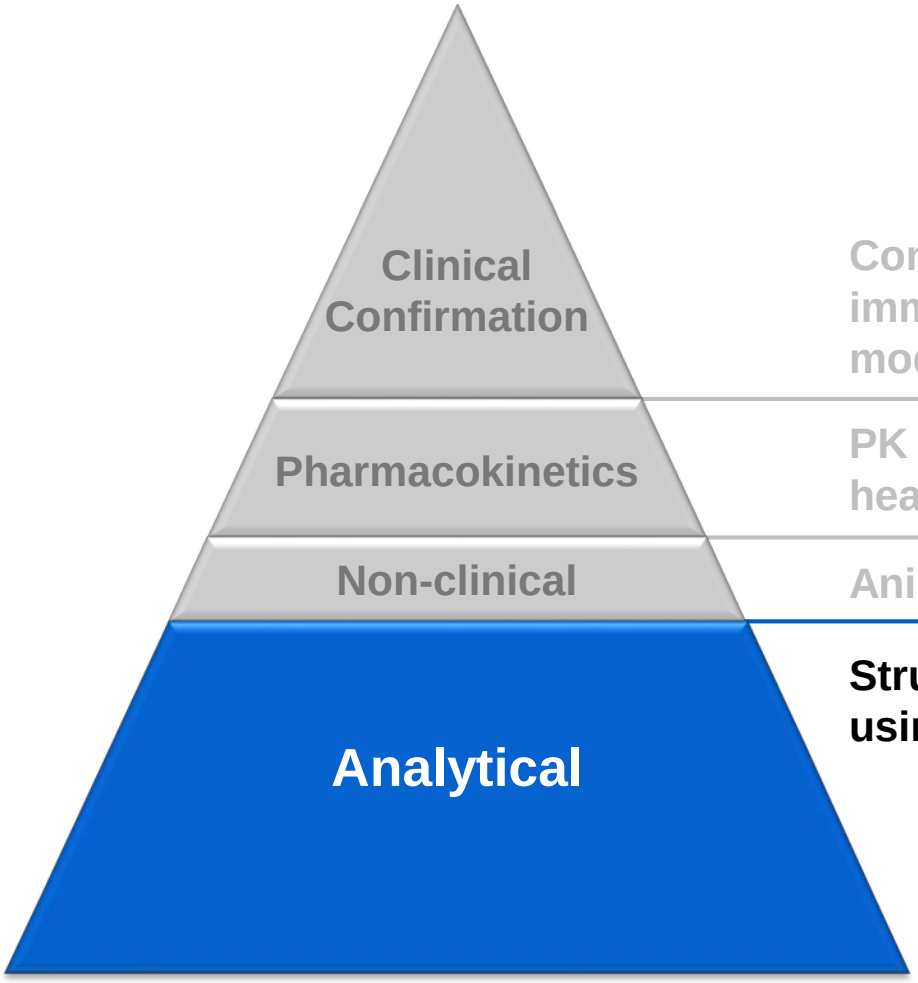
LMWs=low molecular weight species.

GP2015 and Enbrel® Are Highly Similar

- GP2015 was engineered to match Enbrel
- Sandoz has confirmed the high degree of similarity of GP2015 and Enbrel
  - Primary structure—100% identical
  - Higher order structure
  - Bioactivity
  - Product related impurities
  - Stability behavior
- Enbrel/US and Enbrel/EU are analytically indistinguishable



Analytical Similarity Was Established



Confirmatory efficacy, safety, and immunogenicity study in patients with moderate-to-severe plaque psoriasis ☐

PK bioequivalence studies in healthy volunteers ☐

Animal PD, PK, toxicology ☐

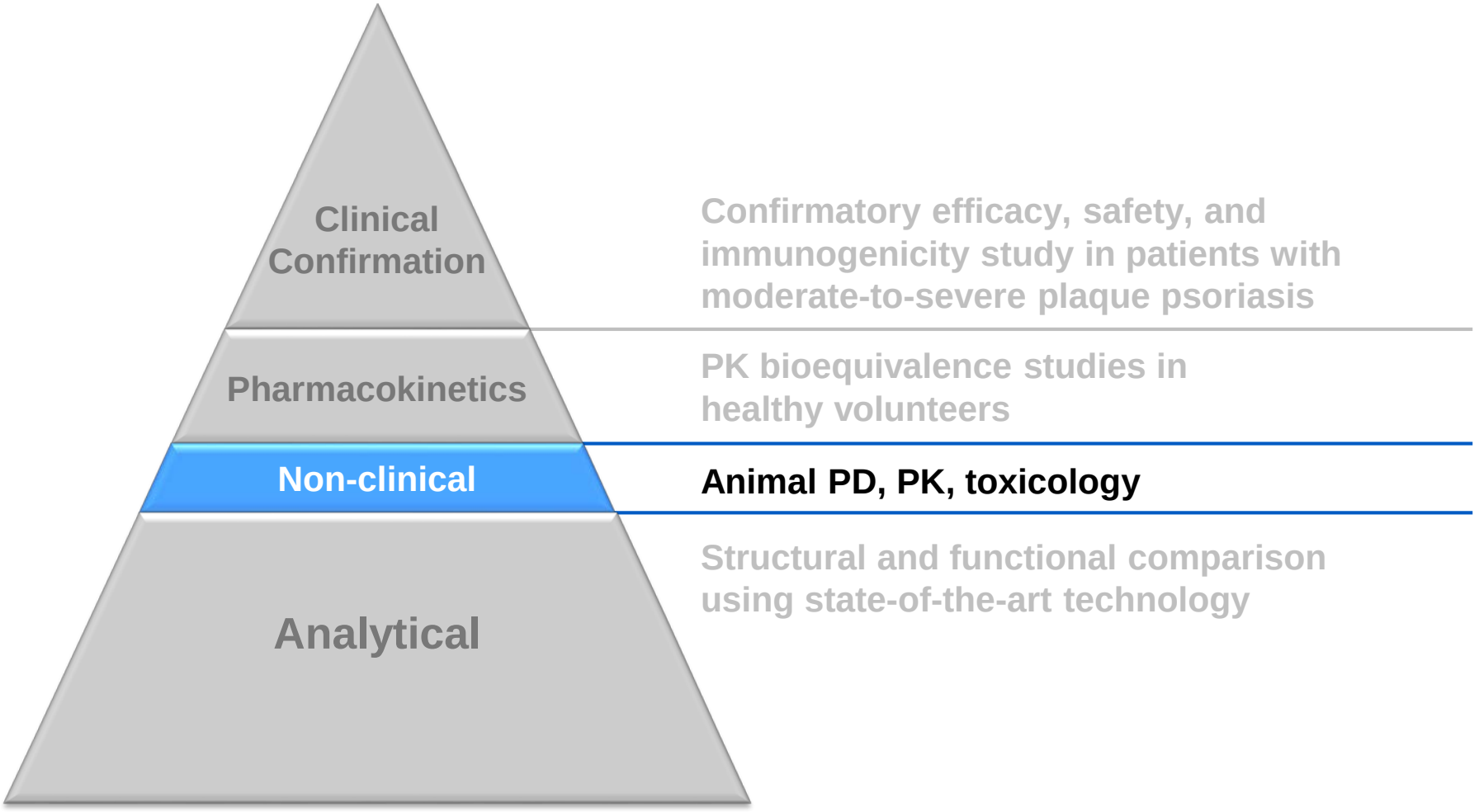
Structural and functional comparison using state-of-the-art technology ☑

Non-clinical and Pharmacokinetic Characterization of GP2015

Oliver von Richter, PhD, FCP

Global Clinical Development
Sandoz Biopharmaceuticals

Evaluation of Similarity Between GP2015 and Enbrel®

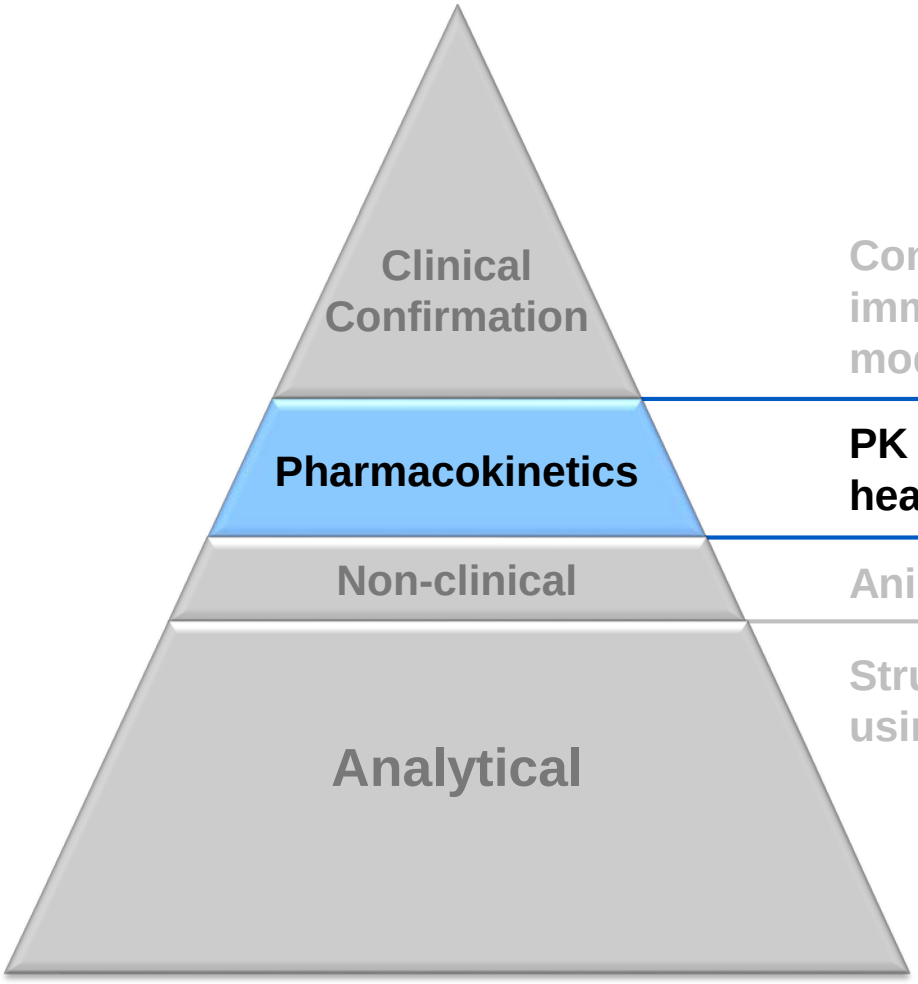


Summary of Non-clinical Studies: GP2015 and Enbrel® Were Highly Similar

Study	Study type	Study summary
Pharmacodynamics: Transgenic human TNF-α arthritic mouse model		
GP15-004	Pilot dose-finding PD study	Disease activity score for Enbrel at different dose levels: 10 mg/kg given ip defined as most sensitive
GP15-007	**Pivotal, comparative efficacy of GP2015 and Enbrel at 10 mg/kg**	**Similar profile observed for GP2015 and Enbrel/EU**
Pharmacokinetics: Rabbits		
GP15-001	Pilot single-dose PK study	GP2015 formulation with lysine/citrate defined to be similar to Enbrel reference formulation
GP15-006	**Pivotal, comparative single-dose PK study**	**Similar PK profile for GP2015 and Enbrel/EU**
Toxicology: Monkeys		
GP15-003	**Pivotal, comparative repeat-dose 4-week toxicology study**	**Similar safety profile and toxicokinetics for GP2015 and Enbrel/EU**

ip=intraperitoneal.

Evaluation of Similarity Between GP2015 and Enbrel®



Confirmatory efficacy, safety, and immunogenicity study in patients with moderate-to-severe plaque psoriasis

PK bioequivalence studies in healthy volunteers

Animal PD, PK, toxicology

Structural and functional comparison using state-of-the-art technology

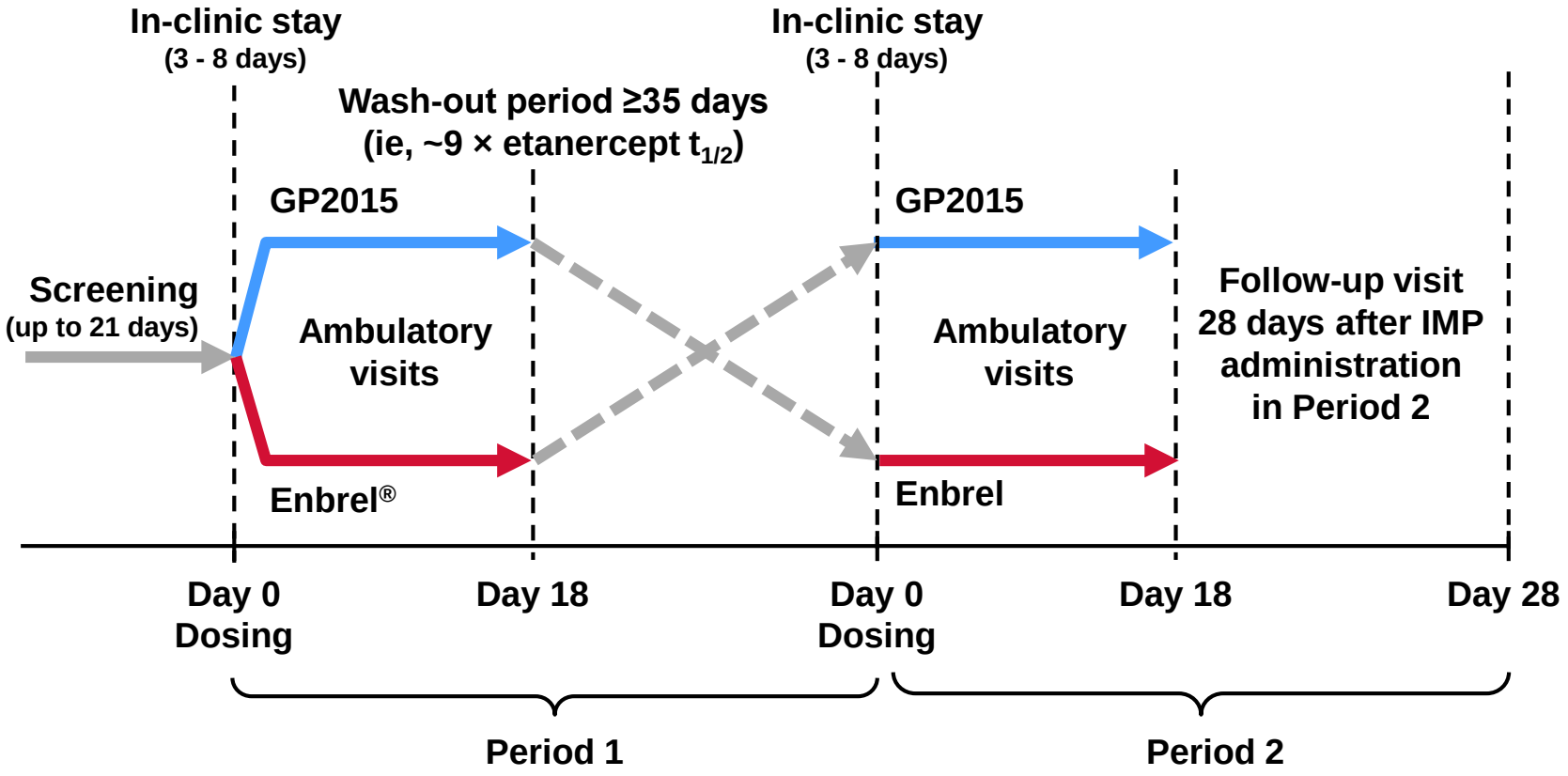
Overview of PK Studies

Study	Study description	Study population	Study duration
Pivotal PK study		**Healthy volunteers**	
GP15-102[a]	Randomized, double-blind, two-way crossover, Enbrel®/US	N=57	Up to 3 months
Supportive PK studies			
GP15-101[a]	Randomized, double-blind, two-way crossover, Enbrel/EU	N=54	Up to 3 months
GP15-104	Randomized, double-blind, two-way crossover, Enbrel/EU	N=54	Up to 3 months
GP15-103	Randomized, open-label, two-way crossover, GP2015 PFS vs AI	N=51	Up to 3 months
PK substudy in the confirmatory efficacy and safety study in psoriasis patients			
GP15-302	Randomized, double-blind, multicenter; PK substudy evaluating trough concentrations over 12 weeks	Patients with moderate to severe chronic plaque-type psoriasis PK set, n=147	12 weeks (C_{trough} PK substudy)

AI=autoinjector; PFS=pre-filled syringe.

[a] GP15-102 and GP15-101 have identical study designs. Additionally, prospectively planned cross-study comparison of the studies GP15-102 and GP15-101 was performed (denoted as report GP15-105).

Crossover Study Design for PK Evaluation in Healthy Volunteers—General Concept



In-clinic stays differed between studies:

- **GP15-101 and -102: D –1 to at least 24 hours post-dose**
- **GP15-103: D –1 to at least 120 hours post-dose**
- **GP15-104: D –1 to at least 48 hours post-dose**

Subject Disposition in GP2015 Healthy Volunteer PK Studies

Study	Comparison	Patients, n (%)		
		Dosed	Completed	Withdrawn
GP15-102	GP2015/ Enbrel®/US	57 (100)	54 (94.7)	3 (5.3)
GP15-103	GP2015 PFS/ GP2015 AI	51 (100)	49[a] (96.1)	2 (3.9)
GP15-101	GP2015/ Enbrel/EU	54 (100)	51 (94.4)	3 (5.6)
GP15-104	GP2015/ Enbrel/EU	54 (100)	54 (100)	0
Overall		**216 (100)**	**208 (96.3)**	**8 (3.7)**

AI=autoinjector; PFS=pre-filled syringe.

[a] 1 patient was exluded from the PK population due to high pre-dose values in Treatment Period 2.

Bioequivalence Assessment Between GP2015 and Enbrel®/US—Study Objectives

Study GP15-102

Primary objective

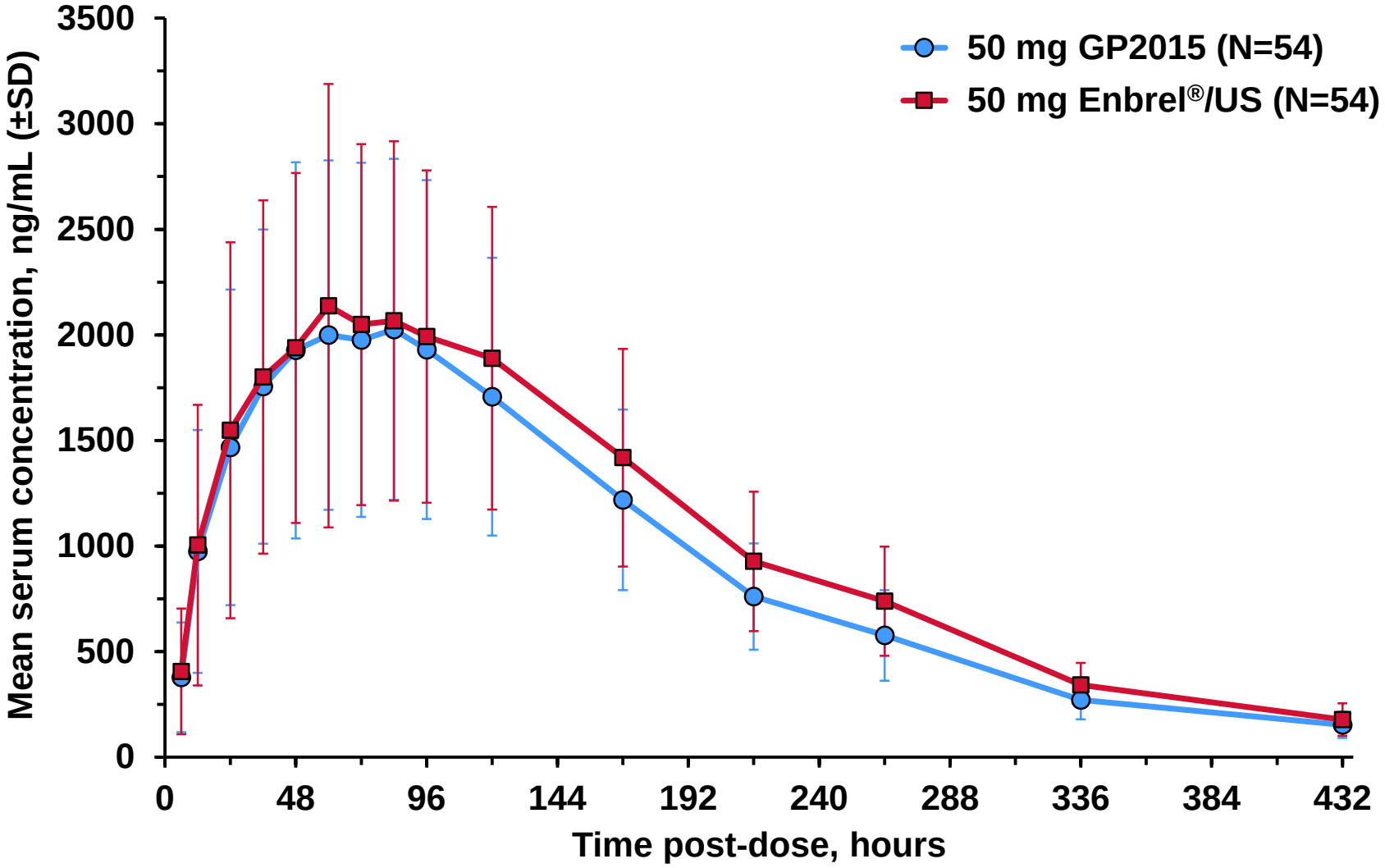
- To determine bioequivalence of GP2015 and Enbrel/US in terms of the PK parameters $AUC_{0\text{-tlast}}$ and C_{max} following a single subcutaneous injection of 50 mg

Secondary objectives

- Remaining PK parameters ($AUC_{0\text{-}\infty}$, t_{max}, k_{el}, $t_{1/2}$)
- Immunogenicity, safety, local tolerance

Time Course of Mean Serum Concentrations

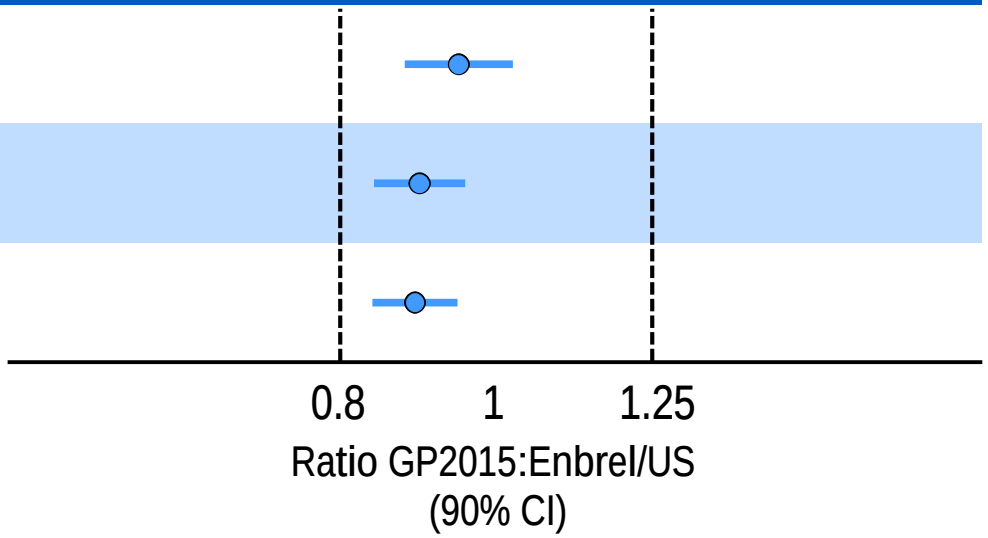
Study GP15-102—Per-Protocol Set



GP2015 and Enbrel®/US Are Bioequivalent

Study GP15-102—Per-Protocol Set

Parameter	Geometric LS means GP2015	Enbrel/US
C_{max}, ng/mL	2055	2163
$AUC_{0\text{-}tlast}$, ng·h/mL	376279	418797
$AUC_{0\text{-}\infty}$, ng·h/mL	397239	445118



Statistical assessment of bioequivalence

90% confidence intervals for geometric mean ratios for $AUC_{0\text{-}tlast}$ and C_{max} to be within conventional bioequivalence limits of 0.8 - 1.25 pre-specified by FDA

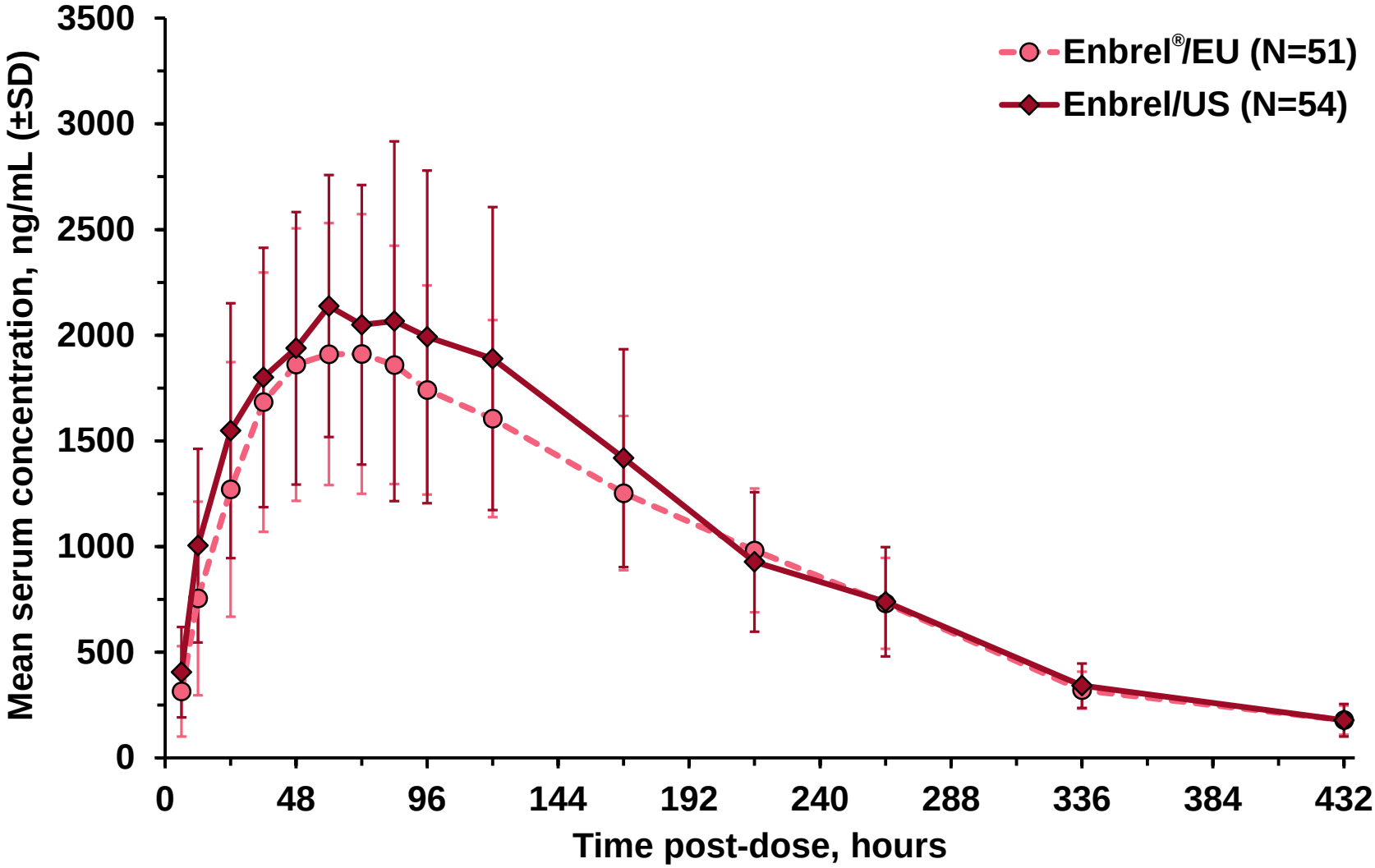
AUC=area under the serum concentration-time curve between the specified time points;
C_{max}=maximum observed serum concentration.

Scientific Bridge Between Enbrel®/US and Enbrel/EU

- Required because Enbrel/EU was used in all non-clinical studies and in Study GP15-302
- Builds on the analytical similarity between Enbrel/US and Enbrel/EU
- Is supported by Studies GP15-101 and GP15-102 (identical in design)
  - Pre-specified comparison of PK parameters of Enbrel/US and Enbrel/EU (presented in report GP15-105)
  - Cross-study comparison between Enbrel/EU (data from GP15-101) and Enbrel/US (data from GP15-102)

Time Course of Mean Serum Concentrations

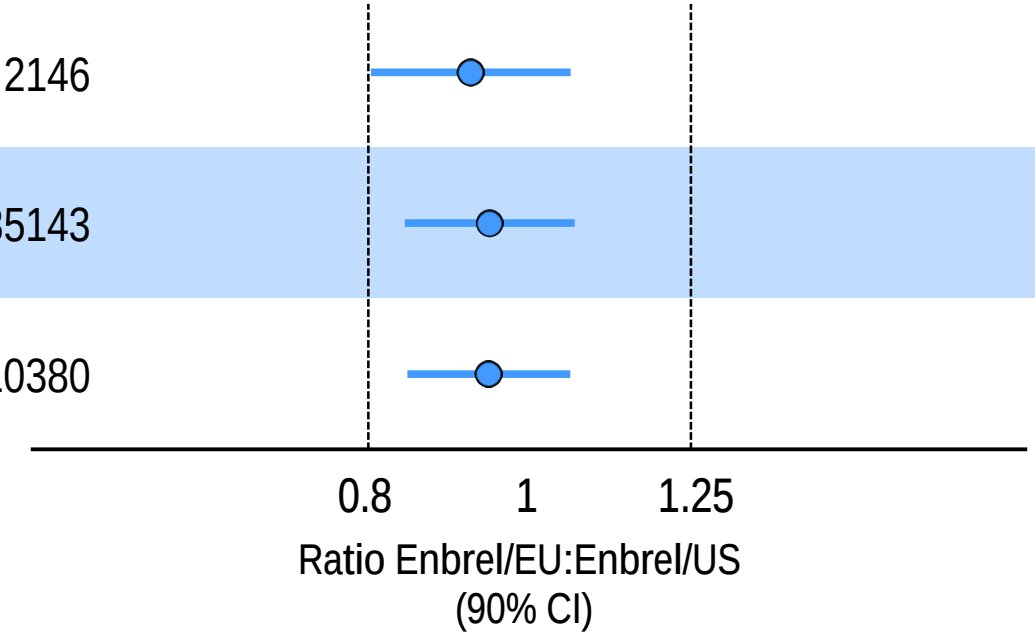
Report GP15-105—Per-Protocol Set



Use of Enbrel®/EU as a Comparator Is Justified

Report GP15-105—Per-Protocol Set

PK parameter	Geometric LS means	
	Enbrel/EU	Enbrel/US
C_{max}, ng/mL	1979	2146
$AUC_{0\text{-tlast}}$, ng·h/mL	411530	435143
$AUC_{0\text{-}\infty}$, ng·h/mL	388578	410380



Statistical assessment of bioequivalence

90% confidence intervals for geometric mean ratios for $AUC_{0\text{-tlast}}$ and C_{max} to be within conventional bioequivalence limits of 0.8 - 1.25 pre-specified by FDA

AUC=area under the serum concentration-time curve between the specified time points;
C_{max}=maximum observed serum concentration.

Comparison of Pre-filled Syringe vs Autoinjector—Study Objectives

Study GP15-103

Primary objective

- To demonstrate bioequivalence of GP2015 applied by an autoinjector (AI) and a pre-filled syringe (PFS) in terms of the PK parameters $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max}

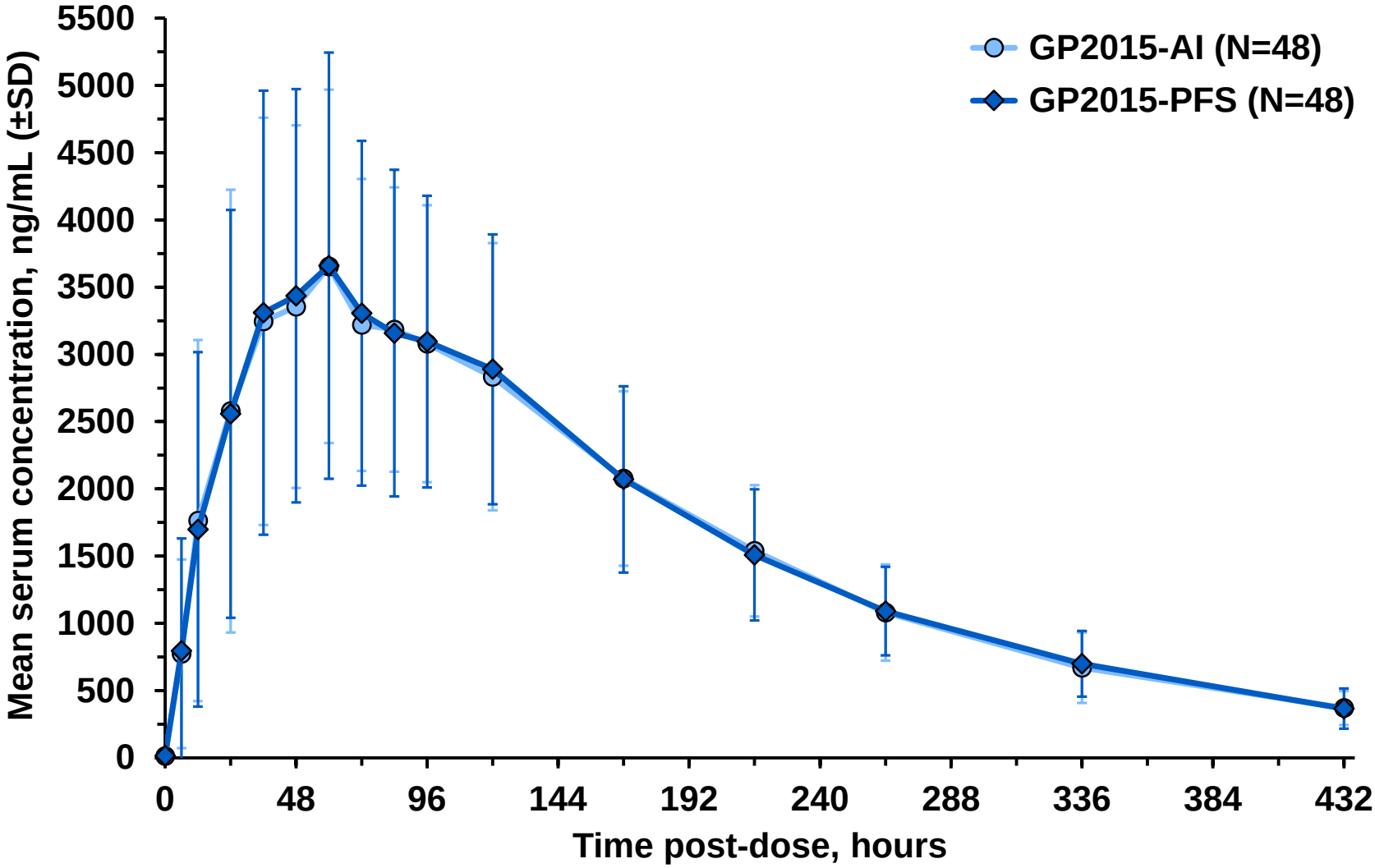
Secondary objectives

- To compare PK parameters $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max}, by weight category (low: 50.0-79.9, medium: 80.0-99.9, and high: 100.0-140.0 kg)
- To compare remaining PK parameters t_{max}, k_{el}, $t_{1/2}$
- Safety, tolerability, and local tolerance

AUC=area under the serum concentration-time curve between the specified time points;
C_{max}=maximum observed serum concentration.

Time Course of Mean Serum Concentrations

Study GP15-103—Per-Protocol Set

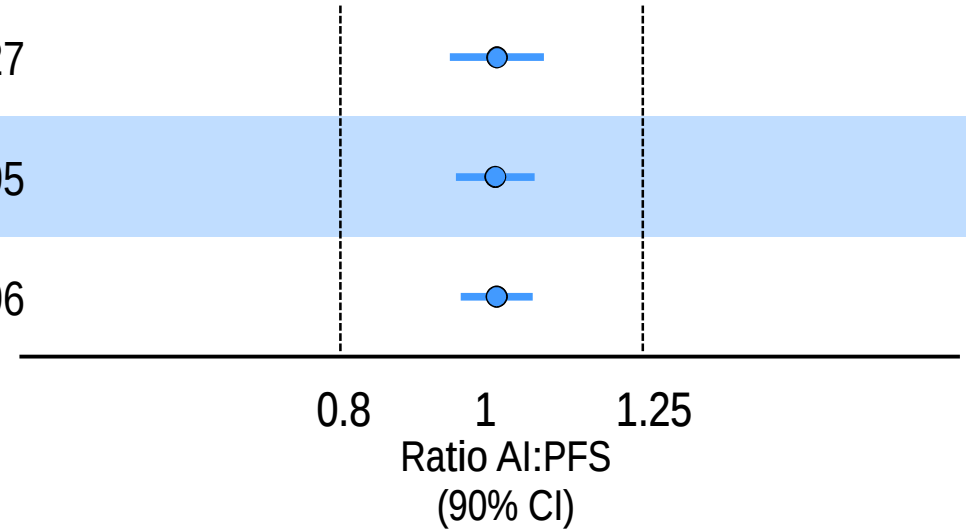


AI=autoinjector; PFS=pre-filled syringe.

Autoinjector and Pre-filled Syringe Provide Equivalent Etanercept Exposure

Study GP15-103—Per-Protocol Set

Parameter	Geometric LS means GP2015-AI	GP2015-PFS
C_{max}, ng/mL	3666	3627
$AUC_{0\text{-}tlast}$, ng·h/mL	684131	678395
$AUC_{0\text{-}\infty}$, ng·h/mL	745169	737396



Statistical assessment of bioequivalence

90% confidence intervals for geometric mean ratios for $AUC_{0\text{-}tlast}$ and C_{max} to be within conventional bioequivalence limits of 0.8 - 1.25 pre-specified by the FDA

AI=autoinjector; AUC=area under the serum concentration-time curve between the specified time points; C_{max}=maximum observed serum concentration; PFS=pre-filled syringe.

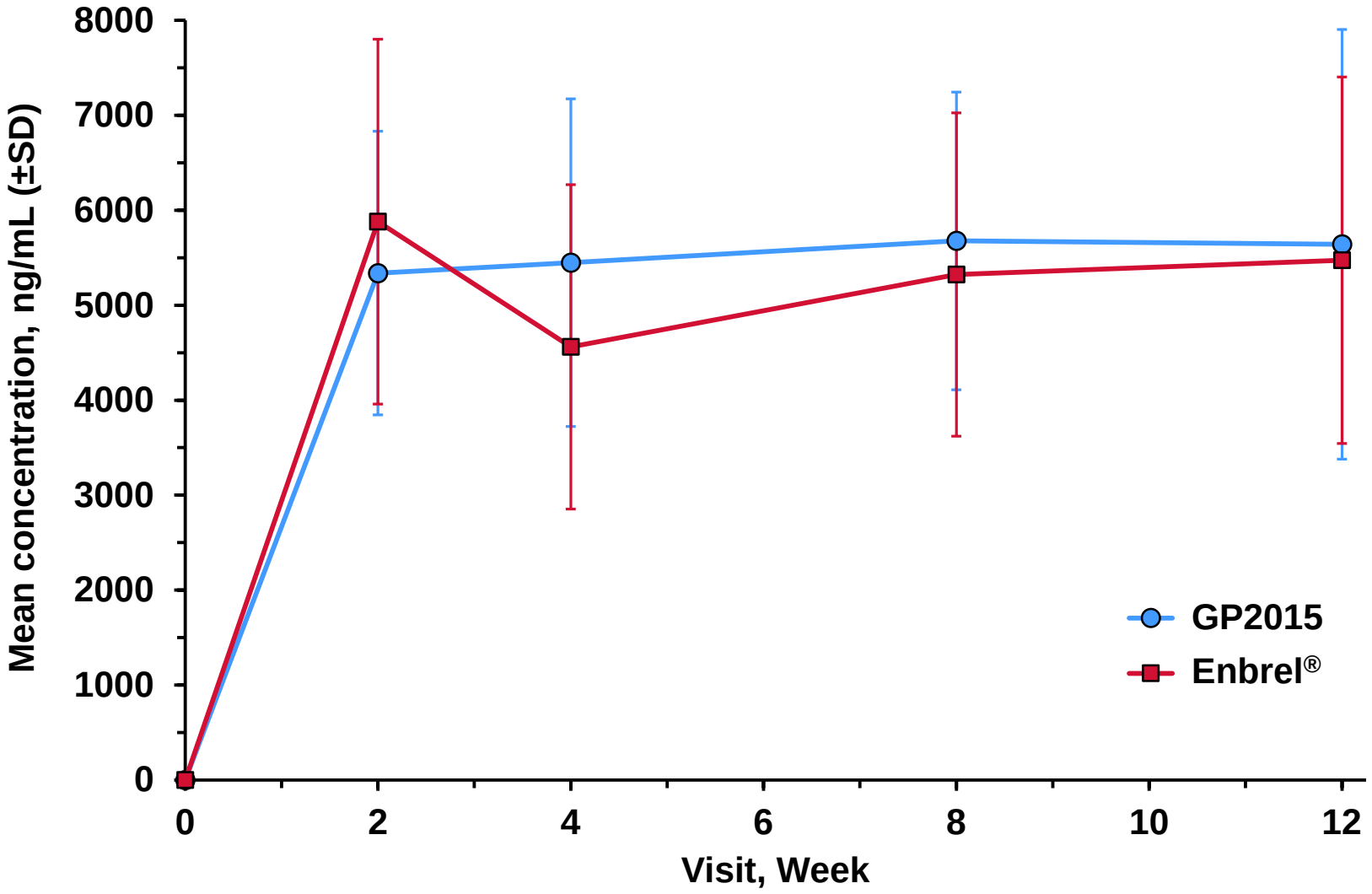
Trough PK Levels in Psoriasis Patients

PK Substudy of Study GP15-302

- Study GP15-302 is the confirmatory comparative efficacy and safety study of GP2015 and Enbrel® in psoriasis patients
- Objective of the PK substudy was to evaluate trough serum concentrations of etanercept in a subset of patients (N=147)
- Samples were collected at baseline (Day 1) and Weeks 2, 4, 8, and 12

Time Course of Mean Trough Concentrations

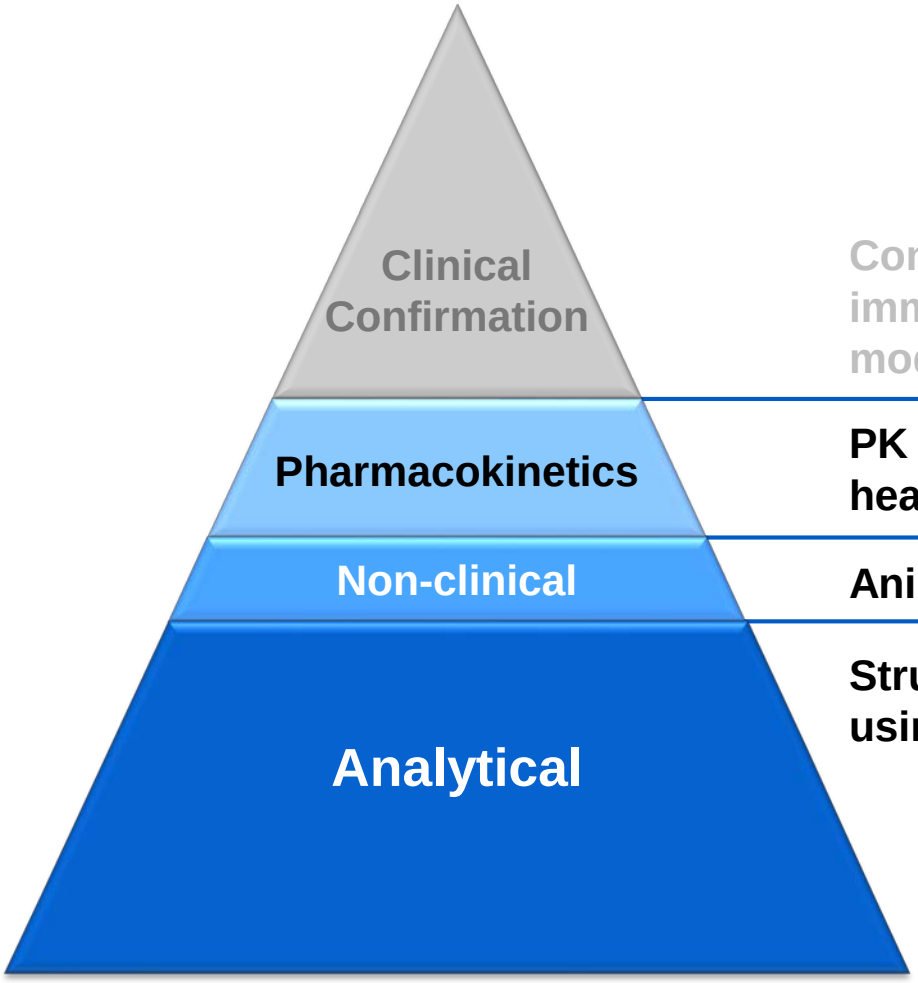
Study GP15-302—PK Analysis Set



Overall PK Conclusions

- GP2015 is bioequivalent to Enbrel® in healthy volunteers
- The pre-filled syringe and the autoinjector are equally suitable for administering GP2015
- Enbrel/US and Enbrel/EU are one Enbrel from an analytical and PK perspective
- The PK substudy in psoriasis patients showed similar PK trough levels
- The PK assessments contribute to the totality of evidence for biosimilarity

Similarity Was Established



Confirmatory efficacy, safety, and immunogenicity study in patients with moderate-to-severe plaque psoriasis ☐

PK bioequivalence studies in healthy volunteers ☑

Animal PD, PK, toxicology ☑

Structural and functional comparison using state-of-the-art technology ☑

Clinical Confirmation of GP2015 Equivalence to Enbrel®

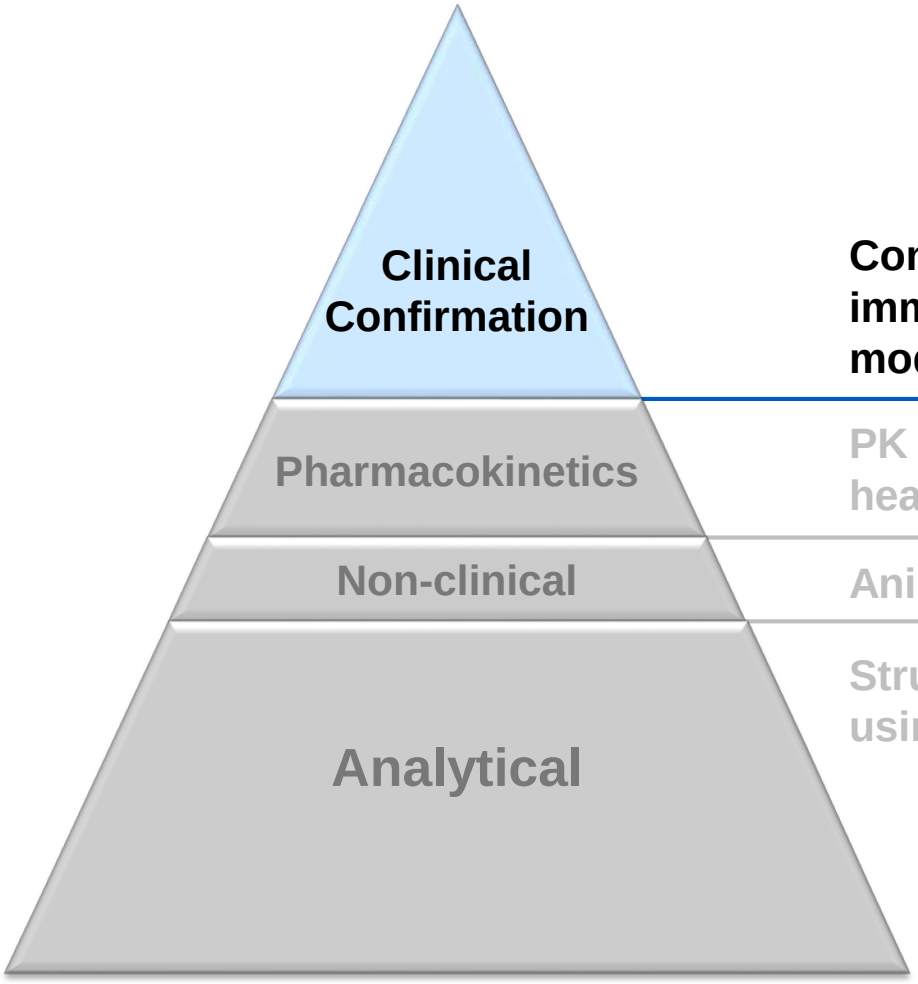
Malte Peters, MD

Global Head Clinical Development, Biopharmaceuticals
Sandoz Biopharmaceuticals

Presentation Overview

- Overview of GP2015 program
- Design of confirmatory safety and efficacy Study GP15-302
- Efficacy, safety, and immunogenicity results
- Summary and conclusions

Comprehensive Comparative Evaluation of GP2015 and Enbrel®



Confirmatory efficacy, safety, and immunogenicity study in patients with moderate-to-severe plaque psoriasis

PK bioequivalence studies in healthy volunteers

Animal PD, PK, toxicology

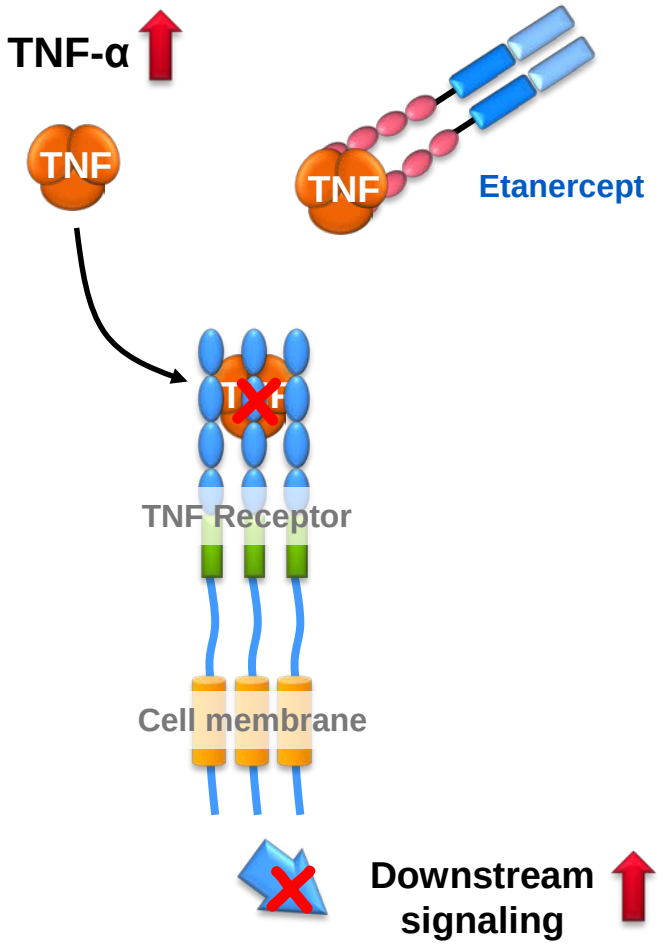
Structural and functional comparison using state-of-the-art technology

Overview of Clinical Evaluation Program

Study	Randomized, n	Duration	Treatment
PK studies	**Healthy volunteers**		
GP15-102 (pivotal) GP2015 vs Enbrel®/US	57	Up to 3 mo	2 single doses, 50 mg SC
GP15-101 (supportive) GP2015 vs Enbrel/EU	54	Up to 3 mo	2 single doses, 50 mg SC
GP15-104[a] (supportive) GP2015 vs Enbrel/EU	54	Up to 3 mo	2 single doses, 50 mg SC
GP15-103 (supportive) GP2015 administration AI vs PFS	51	Up to 3 mo	2 single doses, 50 mg SC
Confirmatory efficacy and safety study	**Patients**		
GP15-302 (pivotal) GP2015 vs Enbrel/EU (patients with plaque-type psoriasis)	531	52 wk	50 mg SC 2x/wk followed by 50 mg SC 1x/wk

[a] **Study GP15-104 study is a repetition of Study GP15-101.**

Pathophysiology of Etanercept Indications



- An increase of TNF-α is the common pathophysiology of all Enbrel® indications
  - Rheumatoid arthritis (RA)
  - Polyarticular juvenile idiopathic arthritis (JIA)
  - Psoriatic arthritis (PsA)
  - Ankylosing spondylitis (AS)
  - Plaque psoriasis (PsO)
- Blocking the binding of soluble TNF-α to its receptor is the common mechanism of action (MoA) for all indications

Study Rationale
Study GP15-302

- Psoriasis represents the most sensitive indication to detect potential differences in efficacy and safety between GP2015 and Enbrel®
  - There is an adequately large effect size
  - Enbrel is used as monotherapy in psoriasis, which reduces
    - Confounding factors
    - Risk of immunosuppression resulting from concomitant medication (eg, methotrexate treatment)
  - 50 mg PsO dose in linear phase of the dose-response curve: increases the likelihood to detect differences between proposed biosimilar and originator, should they exist
- FDA approved Enbrel for adult patients with moderate-to-severe PsO in 2004

Study Objectives

Study GP15-302

- To demonstrate equivalence in efficacy and similarity in the safety profiles of GP2015 and Enbrel® in patients with moderate-to-severe chronic plaque-type psoriasis
- To compare long term efficacy, safety, and immunogenicity data on continued treatment of GP2015 and Enbrel
- To evaluate the effects of repeated switching on efficacy, overall safety, and immunogenicity
- To evaluate trough serum concentrations of GP2015 and Enbrel in a subset of patients

Key Inclusion/Exclusion Criteria

Inclusion Criteria

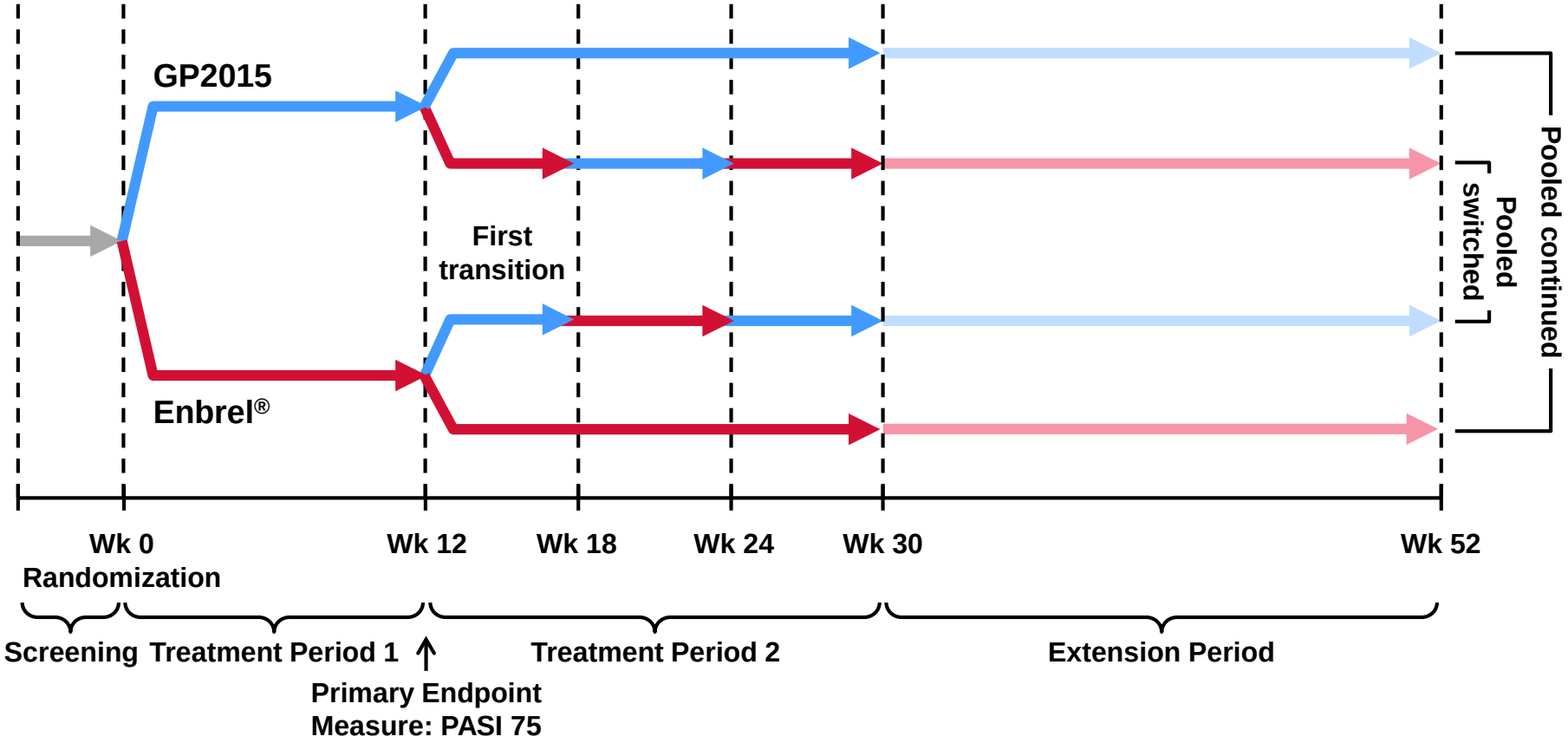
- Adult male and female patients ≥18 years at screening
- Active, but clinically stable chronic plaque-type psoriasis diagnosed ≥6 months prior to baseline with
  - PASI score ≥10 and,
  - IGA score ≥3 and,
  - BSA affected by plaque-type psoriasis ≥10%
- Patients with previous phototherapy or systemic therapy for psoriasis or who are candidates for such therapy in investigator opinion

Exclusion Criteria

- All forms of psoriasis other than chronic plaque-type
- Ongoing use of prohibited psoriasis or non-psoriasis treatment
- Previous exposure to etanercept
- Active ongoing inflammatory diseases other than psoriasis
- History of an ongoing, chronic or recurrent infectious disease, including TB

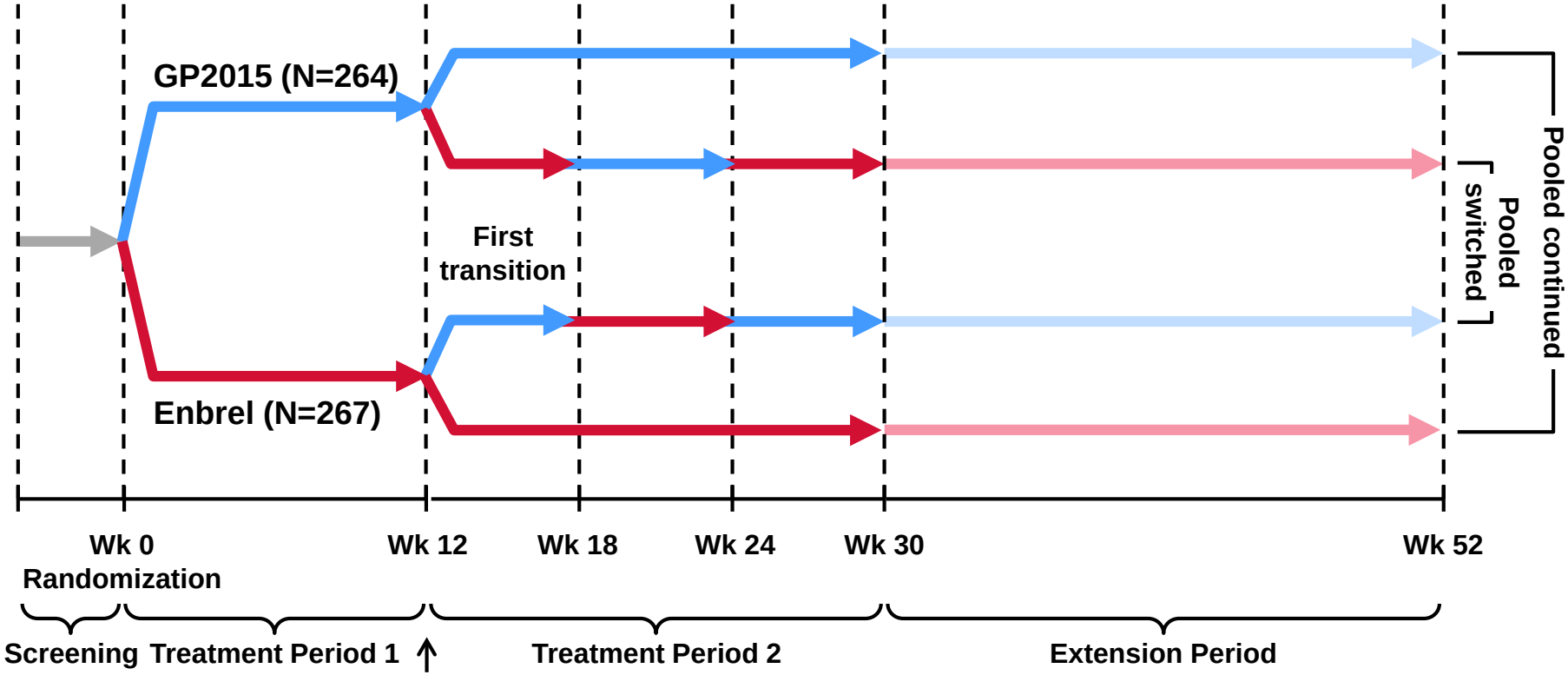
Novel Study Design With Multiple Treatment Periods

Study GP15-302



Treatment Period 1: GP2015 or Enbrel® for 12 Weeks

Study GP15-302

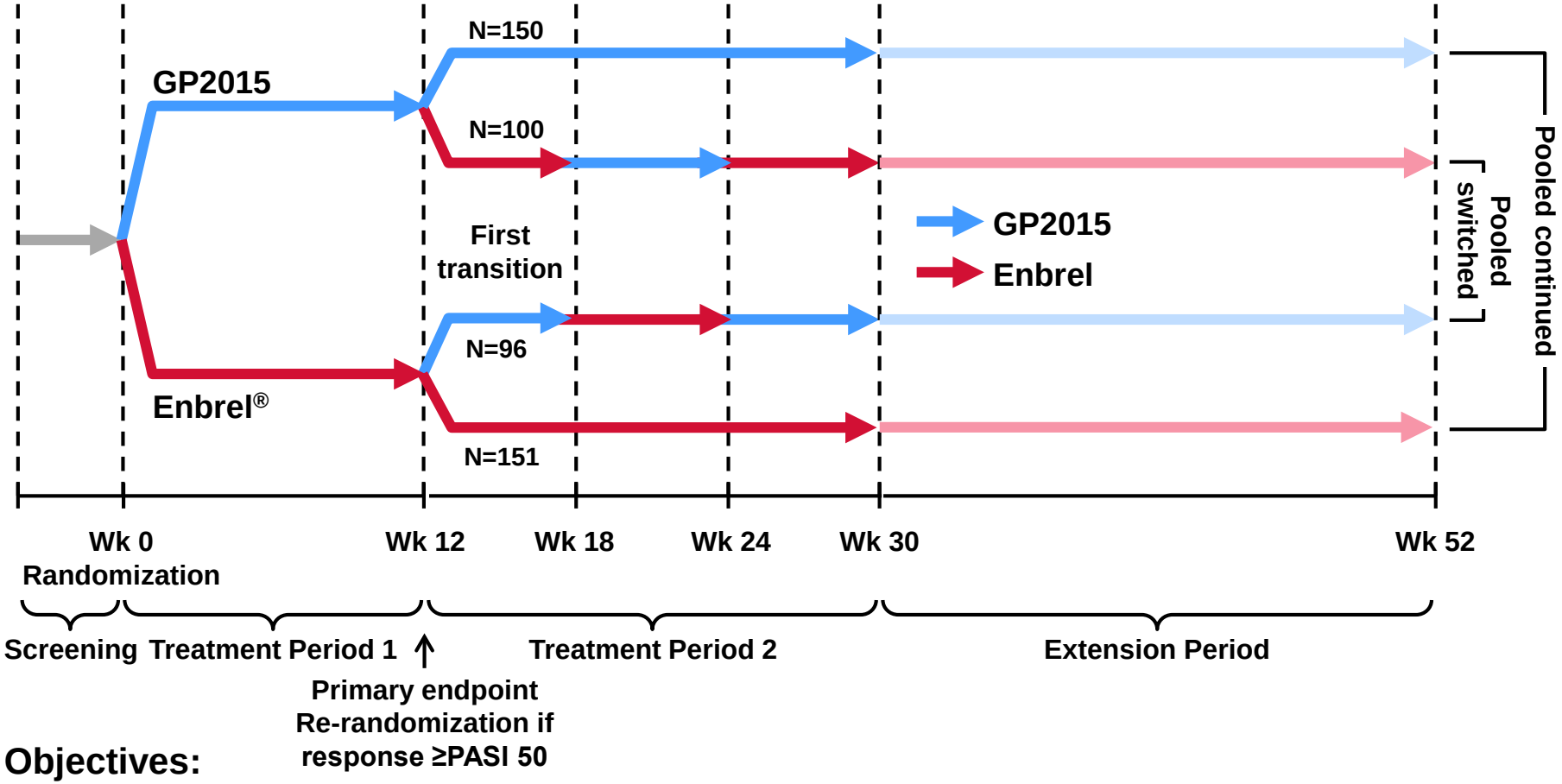


Objective:

- To demonstrate equivalence in efficacy and similarity in the safety and immunogenicity profiles of GP2015 and Enbrel in patients with moderate-to-severe chronic plaque-type psoriasis

Treatment Period 2: Compare Multiple Switches With Continued Treatment

Study GP15-302



Objectives:

- To compare efficacy, safety, and immunogenicity between
  - **Continued** treatment arms
  - **Pooled** (GP2015 and Enbrel) continued treatment arms and **pooled** treatment arms undergoing repeated switches (GP2015 and Enbrel)

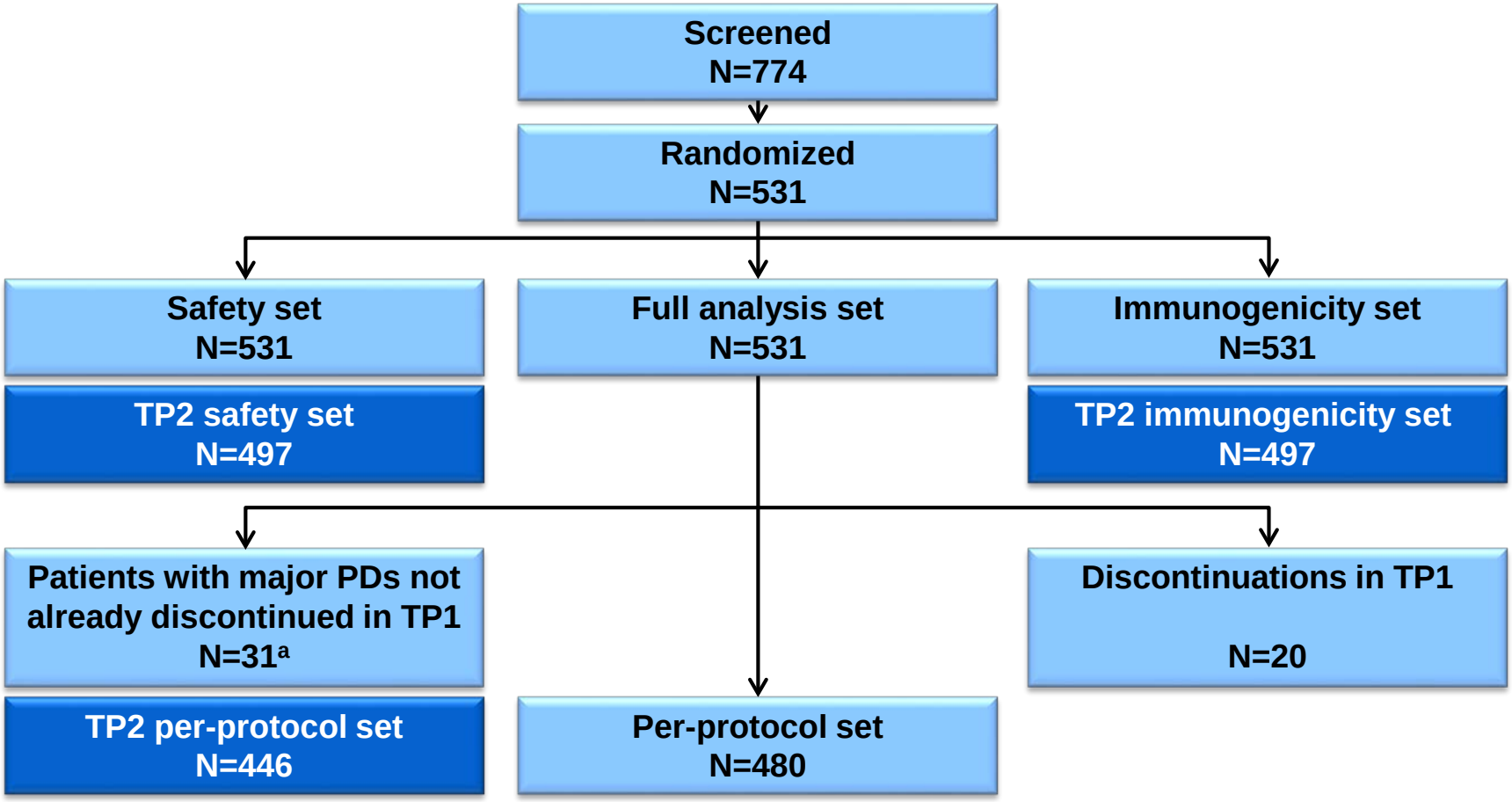
Statistical Requirements

- Primary endpoint
  - 95% confidence interval for **difference between treatment groups in PASI 75 at Week 12**
  - Pre-specified equivalence margin of 18%
  - 90% power used for sample size calculation
- Key (power > 90%) secondary endpoints
  - Longitudinal analyses of **% change of PASI score from baseline to Week 12** using 2 different statistical approaches
  - Pre-specified equivalence margin of 15%

The primary analysis set was the per-protocol set (PPS). Supportive analyses using the full analysis set (FAS) were performed.

Patient Disposition

Study GP15-302



79 sites were initiated in 12 European countries + South Africa, of which 74 sites screened patients and 71 sites randomized patients

N=number of patients; PD=protocol deviation; TP=treatment period.

[a] Of total 34 patients with major PDs, 3 were already discontinued from study during TP1.

Patient Demographics and Baseline Characteristics

Study GP15-302—TP1 Full Analysis Set

Variable		GP2015 N=264	Enbrel N=267
Age, years	Mean (SD)	42.1 (12.3)	42.7 (12.9)
	Median (range)	41 (18-78)	42 (19-75)
Sex, n (%)	Male	157 (59.5)	172 (64.4)
	Female	107 (40.5)	95 (35.6)
Race, n (%)	Caucasian	263 (99.6)	264 (98.9)
	Black	1 (0.4)	0
	Asian	0	1 (0.4)
	Unknown	0	1 (0.4)
Weight, kg	Mean (SD)	86.3 (21.1)	85.9 (18.7)
	Median (range)	84 (47-148.5)	85 (46.5-158)
BMI, kg/m^2	Mean (SD)	28.6 (6.1)	28.5 (5.5)
	Median (range)	27.7 (16.7-48.4)	28.2 (17.4-46.1)

BMI=body mass index.
Percentages based on number of patients within treatment groups in the FAS (N).

Patient Disease History

Study GP15-302—Full Analysis Set

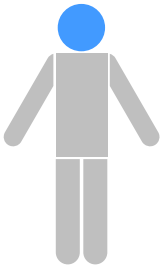
Parameter		GP2015 N=264	Enbrel N=267
Time since initial diagnosis, years	Mean (SD)	17.6 (11.3)	17.8 (11.9)
	Median (range)	16.0 (0.6-55.0)	15.9 (0.7-51.7)
Psoriatic arthritis, n (%)	Present	54 (20.5)	53 (19.9)
Prior systemic therapy, n (%)[a]	None	182 (68.9)	184 (68.9)
	Any (except TNF antagonist)	79 (29.9)	81 (30.3)
	TNF antagonist	3 (1.1)	2 (0.7)
IGA of psoriasis, n (%)	2=Mild	0	1 (0.4)
	3=Moderate	191 (72.3)	186 (69.7)
	4=Severe	73 (27.7)	80 (30.0)
PASI score	Mean (SD)	22.5 (8.9)	22.5 (9.5)
	Median (range)	20.6 (9.4-55.2)	20.0 (10.1-55.2)
BSA affected, %	Mean (SD)	30.5 (13.8)	30.9 (14.8)
	Median (range)	28 (9.5-77.0)	28.8 (8.7-76.0)

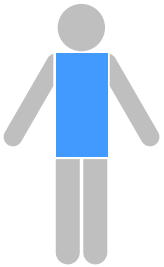
BSA=body surface area; IGA=investigator's global assessment;
PASI=Psoriasis Area and Severity Index; SD=standard deviation; TNF=tumor necrosis factor.
Percentages based on number of patients within treatment groups.

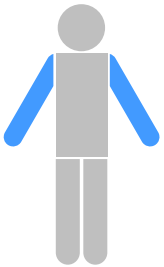
Efficacy Results—TP1

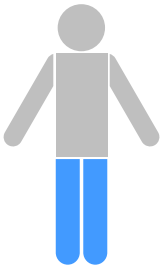
Study GP15-302

PASI Scoring System Is a Well-Established Assessment for Psoriasis

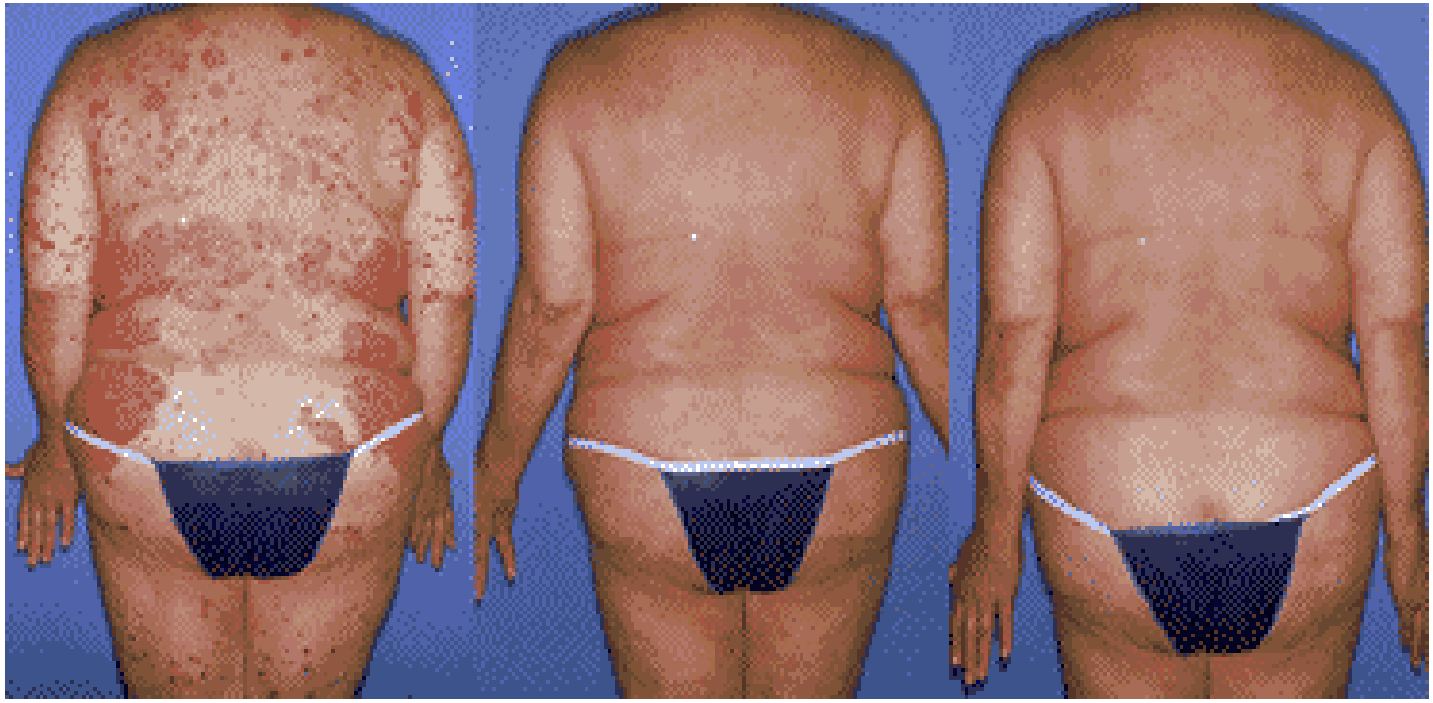
Head		
	Area, %	❍ 0 ❍ <10 ❍ 10-29 ❍ 30-49 ❍ 50-69 ❍ 70-89 ❍ 90-100
	Erythema (redness)	❍ 0 ❍ 1 ❍ 2 ❍ 3 ❍ 4
	Induration (thickness)	❍ 0 ❍ 1 ❍ 2 ❍ 3 ❍ 4
	Desquamation (scaling)	❍ 0 ❍ 1 ❍ 2 ❍ 3 ❍ 4

Trunk		
	Area, %	❍ 0 ❍ <10 ❍ 10-29 ❍ 30-49 ❍ 50-69 ❍ 70-89 ❍ 90-100
	Erythema (redness)	❍ 0 ❍ 1 ❍ 2 ❍ 3 ❍ 4
	Induration (thickness)	❍ 0 ❍ 1 ❍ 2 ❍ 3 ❍ 4
	Desquamation (scaling)	❍ 0 ❍ 1 ❍ 2 ❍ 3 ❍ 4

Upper limbs		
	Area, %	❍ 0 ❍ <10 ❍ 10-29 ❍ 30-49 ❍ 50-69 ❍ 70-89 ❍ 90-100
	Erythema (redness)	❍ 0 ❍ 1 ❍ 2 ❍ 3 ❍ 4
	Induration (thickness)	❍ 0 ❍ 1 ❍ 2 ❍ 3 ❍ 4
	Desquamation (scaling)	❍ 0 ❍ 1 ❍ 2 ❍ 3 ❍ 4

Lower limbs		
	Area, %	❍ 0 ❍ <10 ❍ 10-29 ❍ 30-49 ❍ 50-69 ❍ 70-89 ❍ 90-100
	Erythema (redness)	❍ 0 ❍ 1 ❍ 2 ❍ 3 ❍ 4
	Induration (thickness)	❍ 0 ❍ 1 ❍ 2 ❍ 3 ❍ 4
	Desquamation (scaling)	❍ 0 ❍ 1 ❍ 2 ❍ 3 ❍ 4

Example of PASI Scores in a Patient Treated with Enbrel®

	Week 0	Week 12	Week 24
			
PASI	22.7	6.3 (72%)[a]	3.8 (83%)[a]

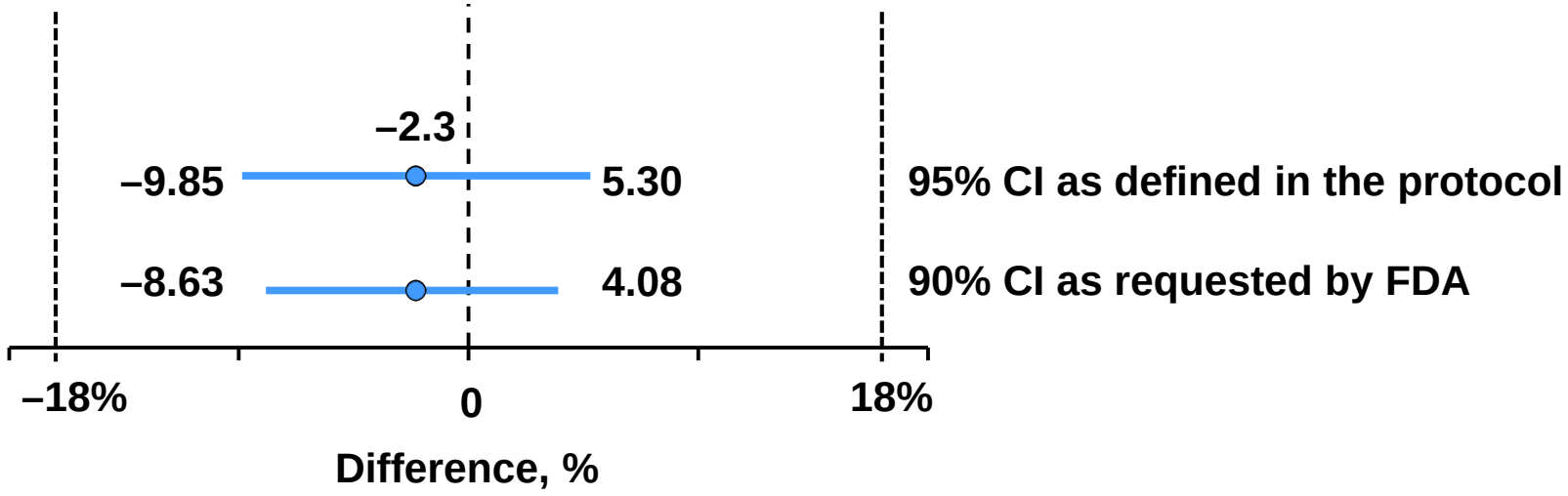
PASI 50/75/90 describe a 50%/75%/90% improvement in PASI score

[a] Percent improvement (decrease) in PASI score vs baseline.
Photo courtesy of Leonardi C, et al. IID 2003. Poster 409.

Primary Endpoint Met—GP2015 and Enbrel® Are Equivalent

Study GP15-302—TP1 Per-Protocol Set

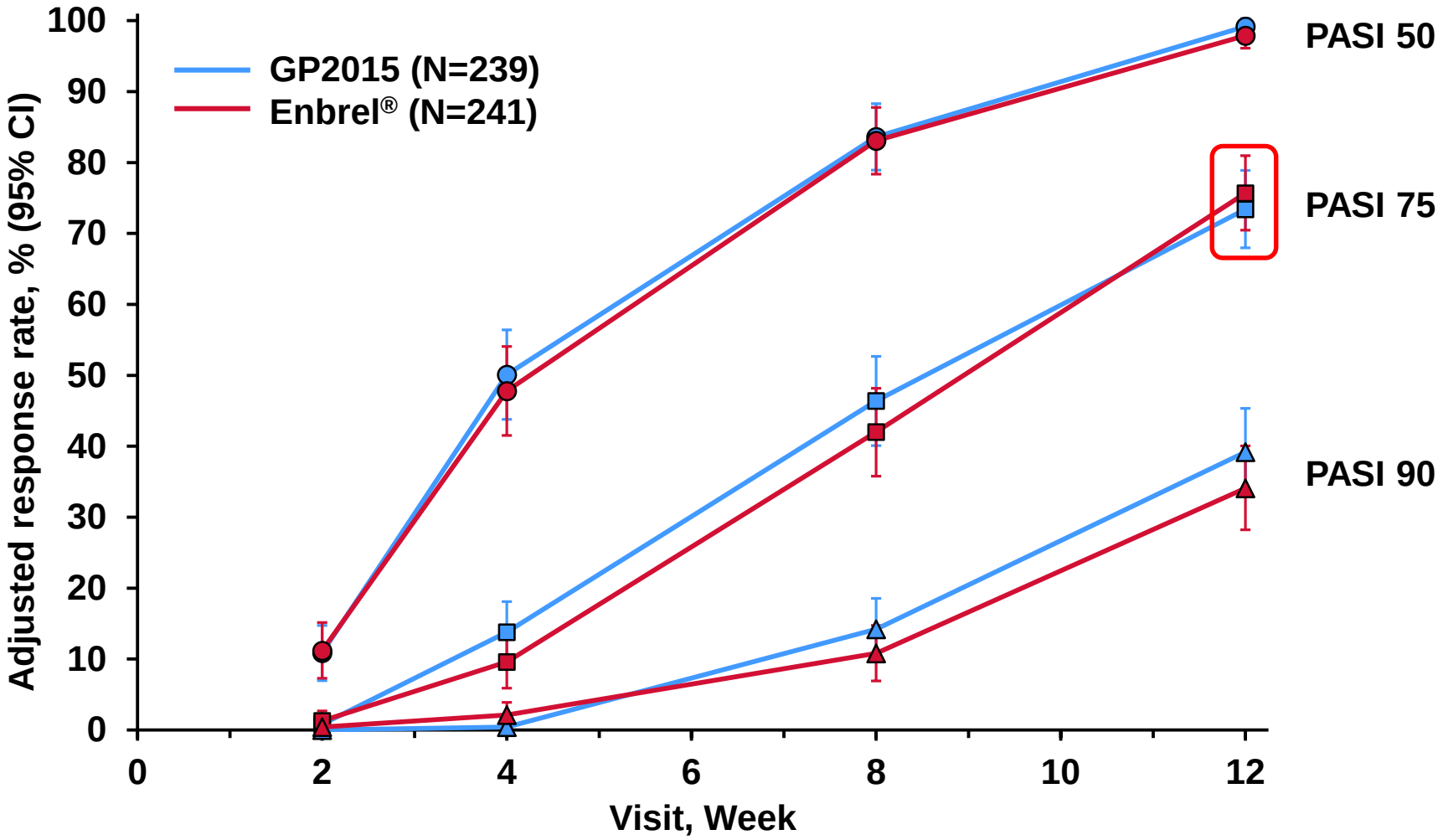
Adjusted[a] PASI 75 response rates at Week 12		
GP2015 N=239	Enbrel N=241	Difference, %
73.4%	75.7%	–2.3



[a] Logistic regression adjusted for stratification factors.

Response Rates for PASI 50, 75, and 90 Were Similar

Study GP15-302—TP1 Per-Protocol Set

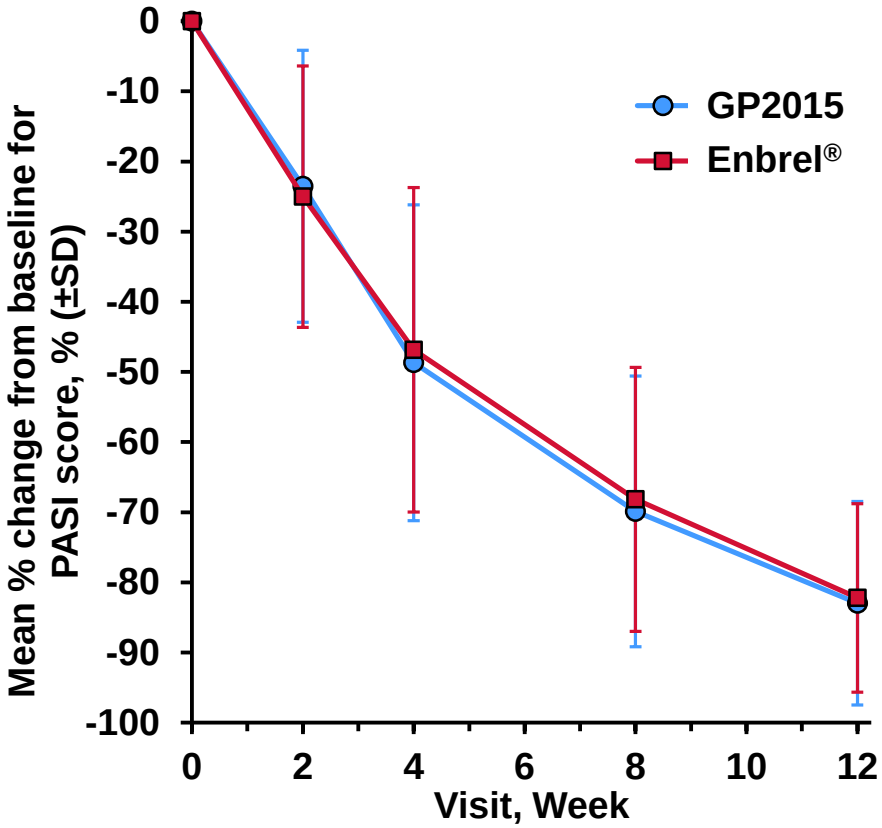


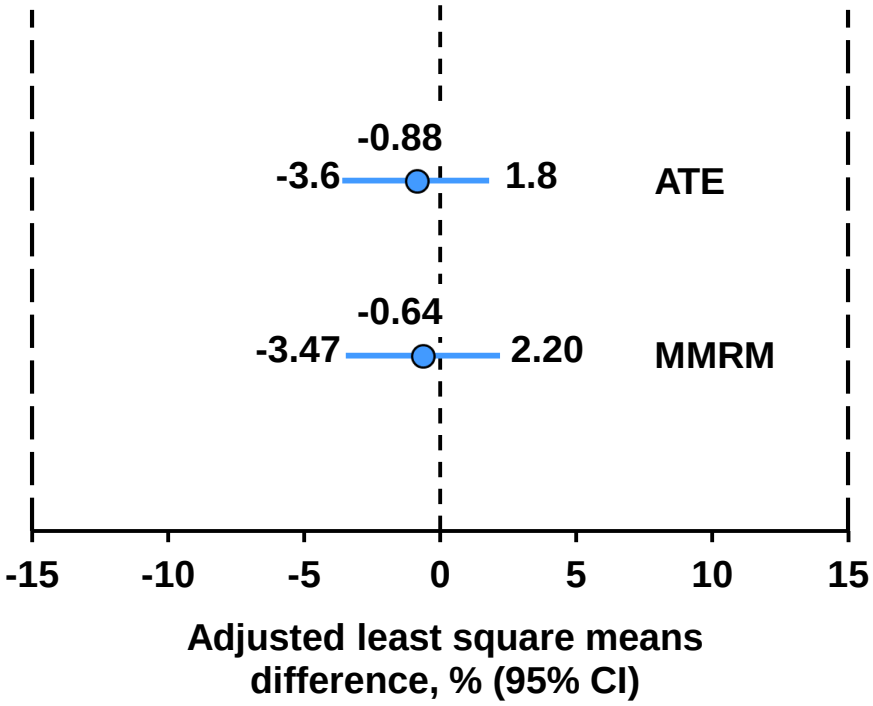
PASI=Psoriasis Area and Severity Index.
Note: adjusted response rates resulted from the statistical model.

Key Secondary Endpoints Were Met

Study GP15-302—TP1 Per-Protocol Set

Difference in percent change from baseline in PASI score up to Week 12





ATE=averaged treatment effect; MMRM=mixed-model repeated measures; PASI=Psoriasis Area and Severity Index; SD=standard deviation.

Investigator's Global Assessment (IGA) Rating Scale

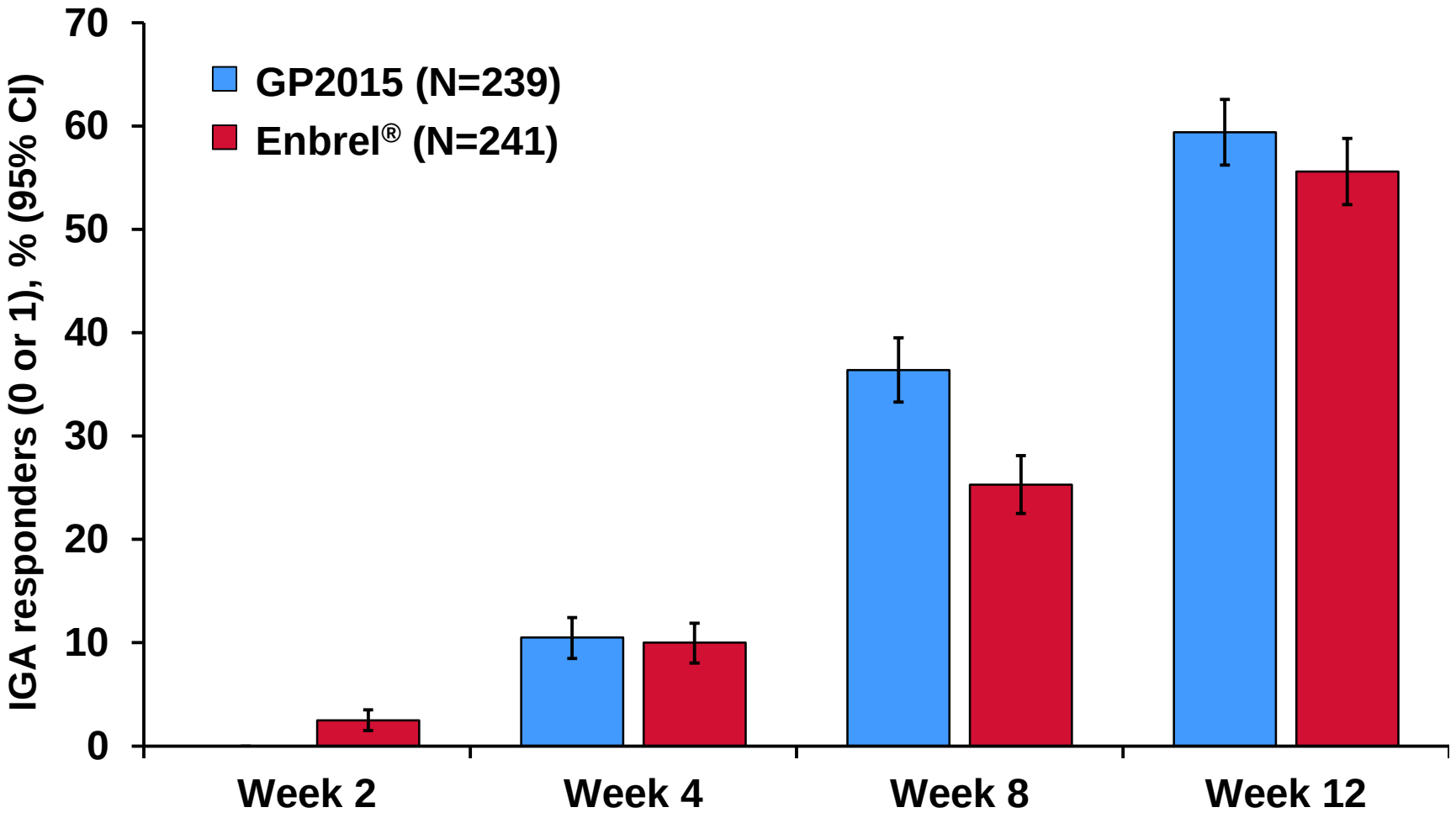
Study GP15-302

Score	Brief description	Detailed description
0	Clear	• No signs of psoriasis • Post-inflammatory hyperpigmentation could be present
1	Almost clear	• Normal to pink coloration of lesions • No thickening • No to minimal (focal) scaling
2	Mild	• Pink to light red coloration • Just detectable to mild thickening • Predominantly fine scaling
3	Moderate	• Dull bright red, clearly distinguishable erythema • Clearly distinguishable to moderate thickening • Moderate scaling
4	Severe	• Bright to deep dark red coloration • Severe thickening with hard edges • Severe/coarse scaling covering almost all or all lesions

Patients were required to have IGA score of 3 or 4 to be eligible for enrollment

Marked and Similar Improvements of IGA Scores Achieved in Both Treatment Arms

Study GP15-302—TP1 Per-Protocol Set



IGA=investigator's global assessment; N=number of patients showing IGA decrease to 0 or 1. Percentages are based on the total number of patients with evaluable data in each treatment group in that visit.

Safety Results—TP1

Study GP15-302

Exposure to Study Drug

Study GP15-302—TP1 Safety Set

Drug administration details	GP2015 N=264	Enbrel® N=267
Duration of exposure, days		
Mean (SD)	80.6 (9.7)	79.2 (11.6)
Median (range)	81.0 (4.0-149.0)	81.0 (1.0-89.0)
Patient exposure, yr	58.3	57.9
Missed doses, n (%)		
0	229 (86.7)	231 (86.5)
1	17 (6.4)	14 (5.2)
2	4 (1.5)	8 (3.0)
3	4 (1.5)	1 (0.4)
4	3 (1.1)	1 (0.4)
>4[a]	7 (2.7)	12 (4.5)

[a] **Patients considered incompliant to study drug during Blinded Data Review Meeting.**

TEAEs
Study GP15-302—TP1 Safety Set

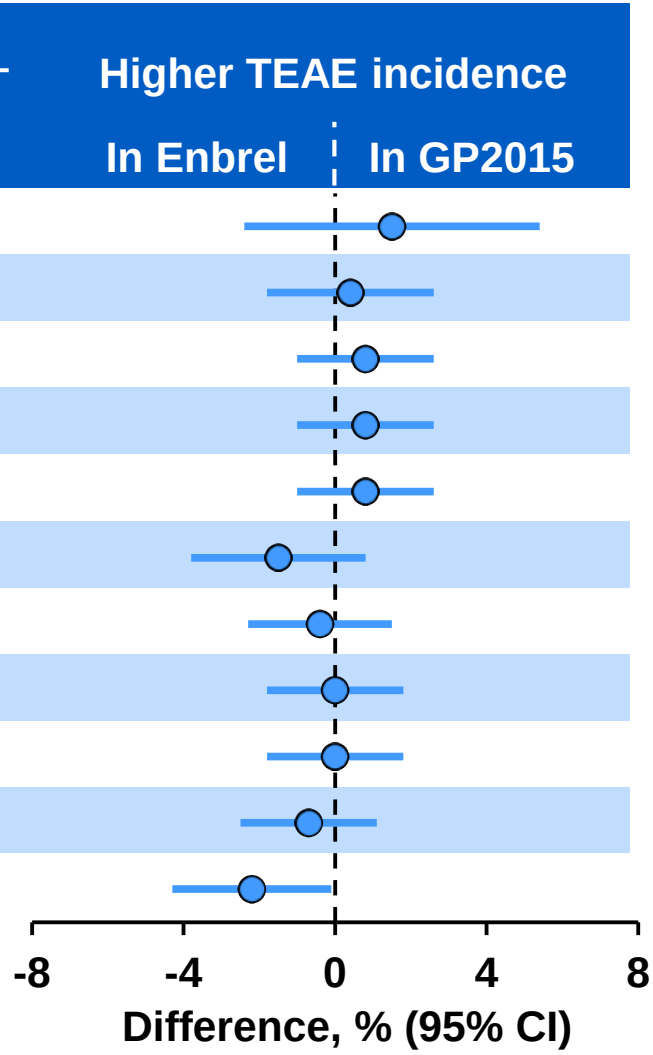
	Patients, n (%)	
	GP2015 N=264	Enbrel® N=267
≥1 TEAE	99 (37.5)	96 (36.0)
≥1 SAE	4 (1.5)	3 (1.1)
≥1 treatment-related TEAE	35 (13.3)	37 (13.9)
≥1 severe TEAE	4 (1.5)	4 (1.5)
≥1 treatment-related SAE	0	1 (0.4)
Discontinuation due to TEAE	5 (1.9)	4 (1.5)
Study drug interrupted due to TEAE	3 (1.1)	6 (2.2)
≥1 AE of special interest	9 (3.4)	5 (1.9)
Deaths	0	1 (0.4)

AE=adverse event; N=Number of total patients; n=number of patients in sub-category; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

TEAEs (Incidence >1%) Regardless of Study Drug Relationship Are Balanced

Study GP15-302—TP1 Safety Set

Preferred term	Patients, n (%) GP2015 N=264	Patients, n (%) Enbrel® N=267
Nasopharyngitis	17 (6.4)	13 (4.9)
Upper respiratory tract infection	5 (1.9)	4 (1.5)
Alanine aminotransferase increased	4 (1.5)	2 (0.7)
Headache	4 (1.5)	2 (0.7)
Respiratory tract infection viral	4 (1.5)	2 (0.7)
Pharyngitis	3 (1.1)	7 (2.6)
Viral upper respiratory tract infection	3 (1.1)	4 (1.5)
Back pain	3 (1.1)	3 (1.1)
Weight increased	3 (1.1)	3 (1.1)
Hypertension	2 (0.8)	4 (1.5)
Arthralgia	1 (0.4)	7 (2.6)



N=Number of total patients; n=number of patients.

TEAEs of Special Interest by System Organ Class and Preferred Term

Study GP15-302—TP1 Safety Set

531 total patients in Treatment Period 1

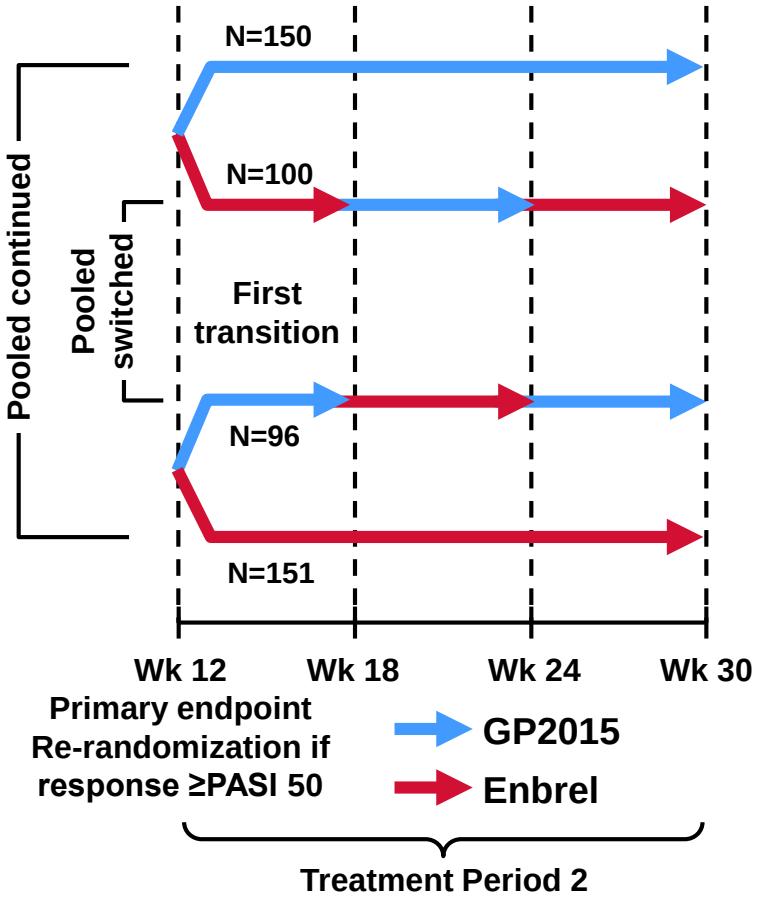
System organ class Preferred term	Patients, n (%) GP2015 N=264	 Enbrel® N=267
≥1 TEAE	**9 (3.4)**	**5 (1.9)**
Infections and infestations	3 (1.1)	3 (1.1)
Oral herpes	1 (0.4)	2 (0.7)
Herpes simplex	1 (0.4)	1 (0.4)
Tinea infection	1 (0.4)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (1.9)	1 (0.4)
Skin papilloma	1 (0.4)	1 (0.4)
Colon neoplasm	1 (0.4)	0
Lipoma	1 (0.4)	0
Malignant melanoma in situ	1 (0.4)	0
Melanocytic nevus	1 (0.4)	0
Immune system disorders	1 (0.4)	0
Hypersensitivity	1 (0.4)	0
Investigations	1 (0.4)	0
White blood cell count decreased	1 (0.4)	0
Skin and subcutaneous tissue disorders	0	1 (0.4)
Swelling face	0	1 (0.4)

Efficacy Results—TP2

Study GP15-302

Treatment Period 2: Compare Multiple Switches With Continued Treatment

Study GP15-302

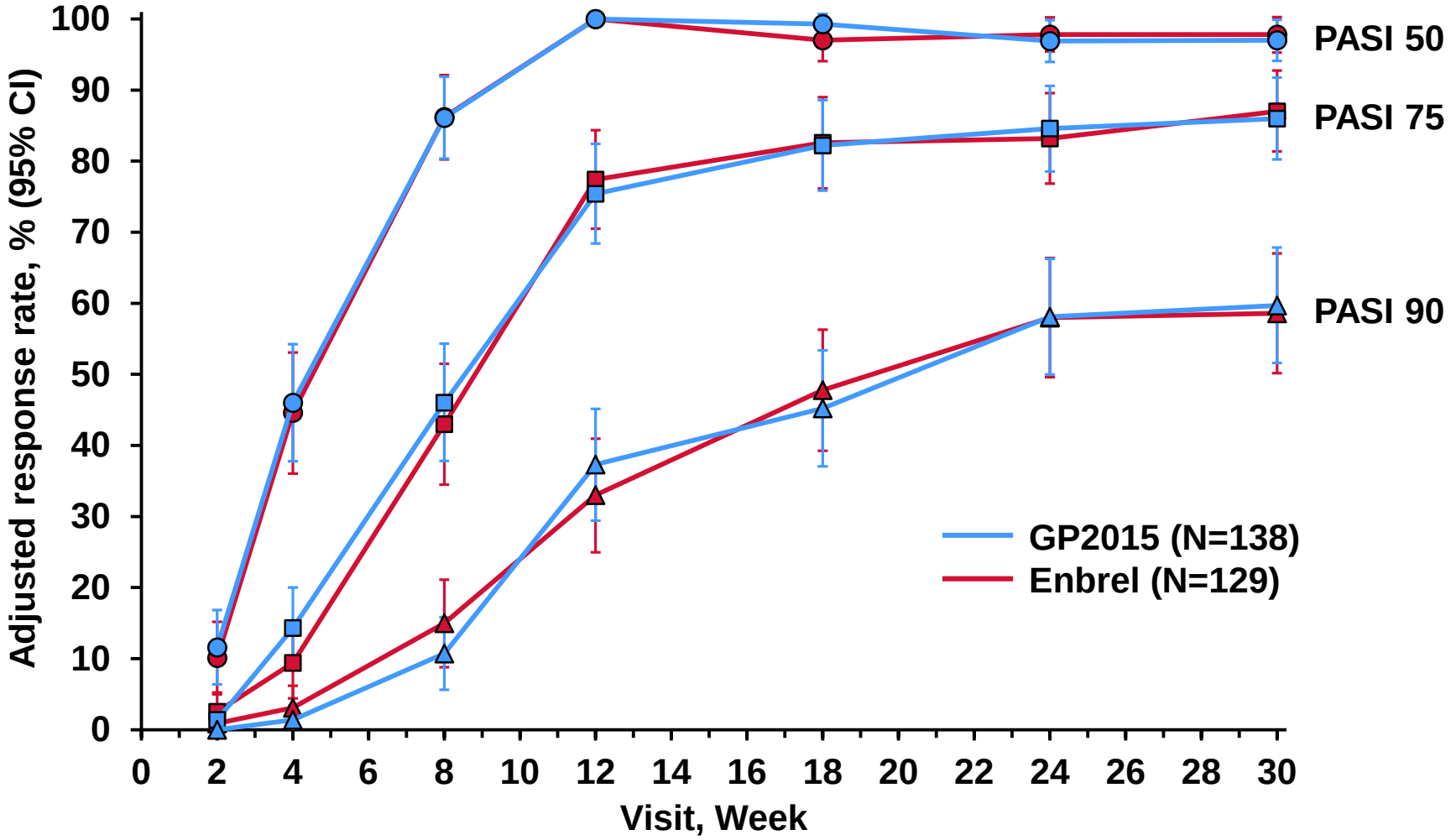


Objectives:

- To compare efficacy, safety, and immunogenicity between
  - The **continued** treatment arms
  - The **pooled** (GP2015 and Enbrel®) continued treatment arms and the **pooled** treatment arms undergoing repeated switches (GP2015 and Enbrel)

Comparable PASI Response Between Continued GP2015 and Enbrel®

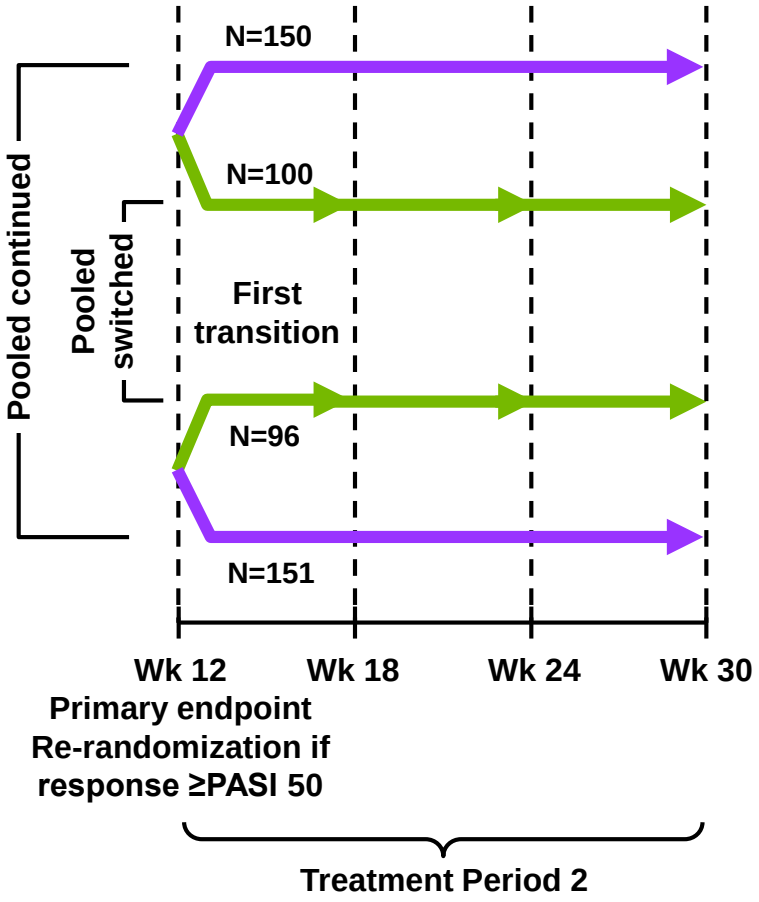
Study GP15-302—TP2 Per-Protocol Set



PASI=Psoriasis Area and Severity Index; TP=treatment period.

Treatment Period 2: Compare Multiple Switches With Continued Treatment

Study GP15-302



Objectives:

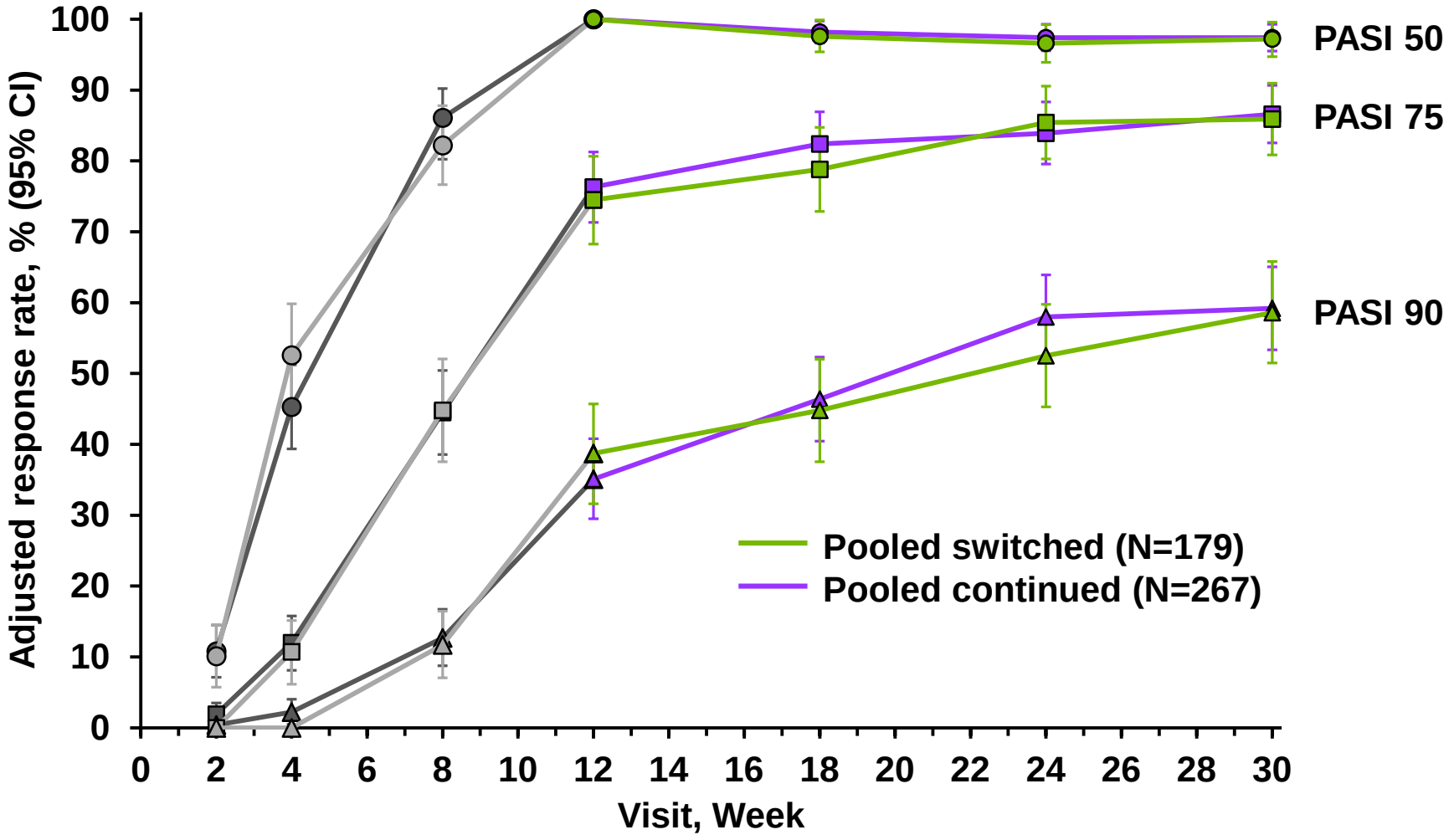
- To compare efficacy, safety, and immunogenicity between
  - The continued treatment arms
  - The **pooled** (GP2015 and Enbrel®) continued treatment arms and the **pooled** treatment arms undergoing repeated switches (GP2015 and Enbrel)

Pooled switched

Pooled continued

No Impact of Switching on PASI Response

Study GP15-302—TP2 Per-Protocol Set



PASI=Psoriasis Area and Severity Index; TP=treatment period.

TEAEs
Study GP15-302—TP2 Safety Set

	Patients, n (%)	
	Continued GP2015 N=150	Continued Enbrel® N=151
≥1 TEAE	47 (31.3)	52 (34.4)
≥1 SAE	1 (0.7)	2 (1.3)
≥1 treatment-related TEAE	13 (8.7)	16 (10.6)
≥1 severe TEAE	1 (0.7)	4 (2.6)
≥1 treatment-related SAE	0	0
Discontinued due to TEAE	1 (0.7)	2 (1.3)
Study drug interrupted due to TEAE	6 (4.0)	6 (4.0)
AEs of special interest	7 (4.7)	3 (2.0)
Deaths	0	0

AE=adverse event; N=Number of total patients; n=number of patients in sub-category; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TP=treatment period.

Overall TEAEs by Pooled Treatment Groups

Study GP15-302—TP2 Safety Set

	Patients, n (%)	
	Pooled continued N=301	Pooled switched N=196
≥1 TEAE	99 (32.9)	67 (34.2)
≥1 SAE	3 (1.0)	6 (3.1)
≥1 treatment-related TEAE	29 (9.6)	18 (9.2)
≥1 severe TEAE	5 (1.7)	5 (2.6)
≥1 treatment-related SAE	0	0
Discontinued due to TEAE	3 (1.0)	6 (3.1)
Study drug interrupted due to TEAE	12 (4.0)	4 (2.0)
AEs of special interest	10 (3.3)	5 (2.6)
Deaths	0	0

AE=adverse event; N=Number of total patients; n=number of patients in sub-category; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TP=treatment period.

Immunogenicity Assessment: Bioanalytical Strategy and Methodology

Bioanalytical strategy for immunogenicity assessment

- 3-step procedure; validated screening, confirmatory and neutralization antibody assay
- Conservative 1-assay approach for the detection of ADA using GP2015 as capture and detection reagent

Immunogenicity testing

- Electrochemiluminescence (ECL) bridging immunogenicity assay for screening and confirmatory step
  - High assay sensitivity (<500 ng/mL[a]): 116.5 ng/mL (psoriasis indication)
  - High drug tolerance level: ≥20,000 ng/mL (trough levels in study GP15-302 were all <15,000 ng/mL)
  - Suitability of method to detect ADA against innovator and biosimilar drug was demonstrated in method validation
- Determination of neutralizing capacity of confirmed ADA-positive samples

ADA=anti-drug antibodies.
[a] Recommended by FDA Guidance for Industry, Assay Development for Immunogenicity Testing of Therapeutic Proteins, 2009.

Immunogenicity

Study GP15-302—TP1

	Patients, n (%)	
	GP2015 N=264	Enbrel N=267
ADA-positive	0	5 (1.9)

- Only 5 patients, all in the Enbrel® group, showed confirmed ADA-positive samples up to Week 12
- This corresponds to a rate of 1.9% of ADAs for Enbrel, in line with published data
- All ADAs were non-neutralizing, transient (in initial 4 weeks of treatment), and low in titer
- No additional ADA-positive results observed up to Week 30

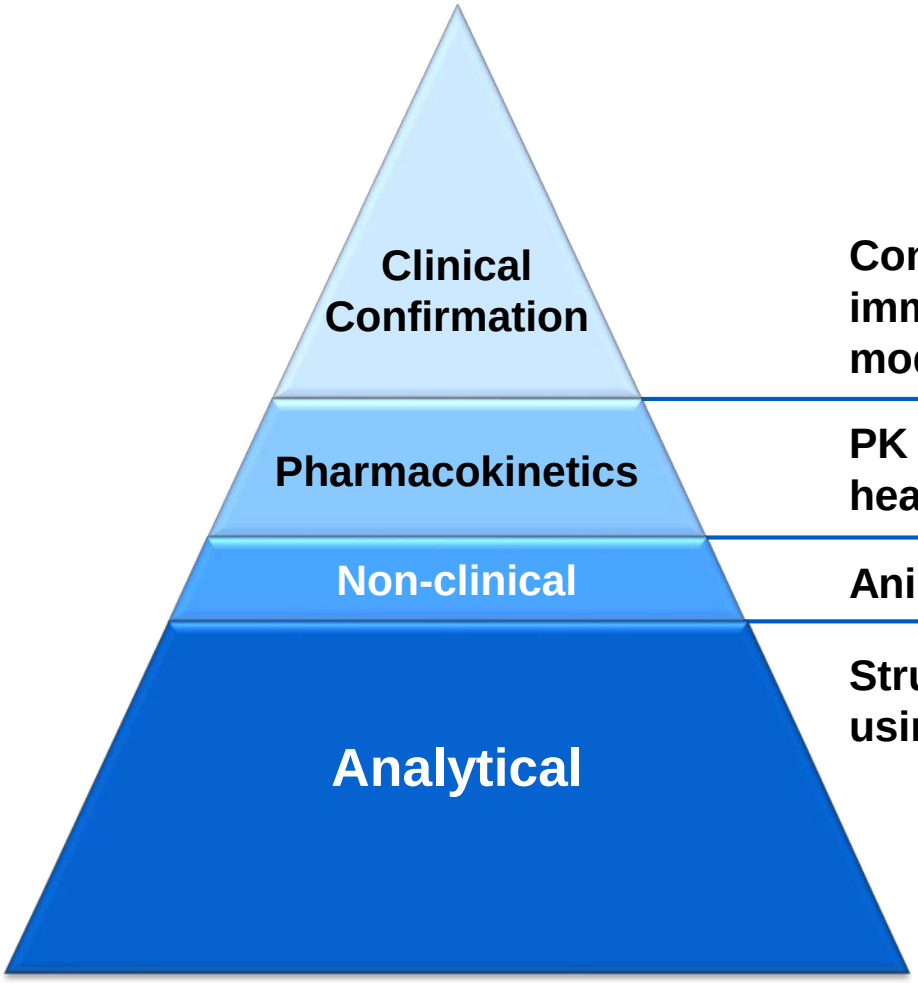
Conclusions

Study GP15-302

Conclusions
Study GP15-302

- The efficacy of GP2015 is equivalent to the efficacy of Enbrel®
- GP2015 is comparable to Enbrel in PK and safety
- No immunogenicity concerns for GP2015 vs Enbrel
- Switching has no effect on efficacy, safety, and immunogenicity

Similarity Was Established at All Levels



Confirmatory efficacy, safety, and immunogenicity study in patients with moderate-to-severe plaque psoriasis

PK bioequivalence studies in healthy volunteers

Animal PD, PK, toxicology

Structural and functional comparison using state-of-the-art technology

Use In Clinical Practice

Jonathan Kay, MD
Timothy S. and Elaine L. Peterson Chair in Rheumatology
Professor of Medicine
Director of Clinical Research, Rheumatology
University of Massachusetts Medical School
Worcester, MA

TNF Inhibition in Clinical Practice

- Introduction of TNF inhibitors has dramatically improved treatment of RA, JIA, AS, PsA, PsO, and other inflammatory diseases
- Over ~20 years, TNF inhibitors have proven to be safe and effective
- High cost limits access for some patients

Potential Benefits of Biosimilars

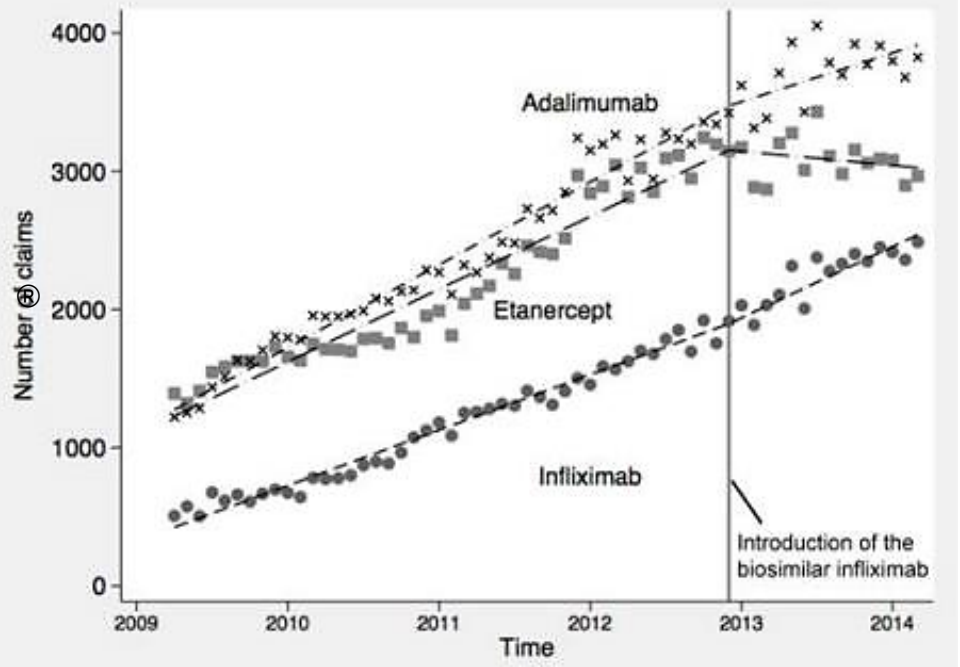
- Availability of lower-priced biosimilars should decrease cost of treating patients
- Biosimilars should be more readily available to patients for whom the bio-originator has been inaccessible
- Greater global access to effective biosimilars should reduce disability, morbidity, and mortality associated with inflammatory diseases

Kay J. *Arthritis Rheum*. 2016;68(5):1049-1052.

Effect of CT-P13 Introduction on TNF Inhibitor Use in South Korea

By March 2014 (15 months after CT-P13 introduction)

- 19% of insurance claims for infliximab were for CT-P13
- Additional increase in use of both branded and biosimilar infliximab
  (9 claims/month, 95% CI: 2, 17)
- Decrease in use of etanercept
  (–52 claims/month, 95% CI: –66, –38)
- Decrease in use of adalimumab
  (–21 claims/month, 95% CI: –35, –6)



Reprinted from Kim SC, et al. *Arthritis Rheum*. 2016;68(5):1076-1079.

GP2015 in Rheumatology

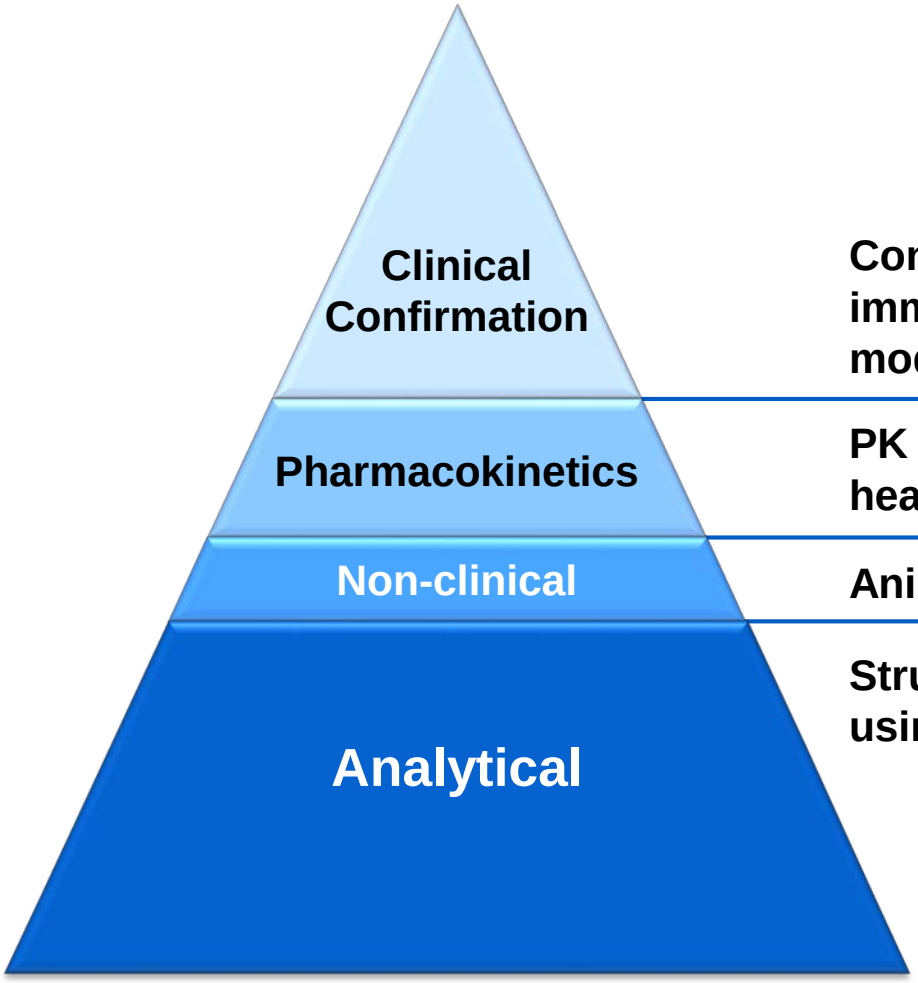
- RA, PsO, PsA, AS, and JIA all respond to TNF inhibition
- PsO is a prototypic inflammatory disease (no concomitant MTX)
- PASI is a direct assessment of disease activity
  - Measures extent of target organ involvement
  - Does not include subjective patient assessment
  - Sensitive to detecting change over time
  - Should detect subtle differences in response
- Extrapolation to other indications is justified based on totality of the evidence demonstrating sameness of GP2015 to Enbrel®
  - Analytical data demonstrating high similarity of GP2015 to Enbrel®
  - Equivalent efficacy and comparable safety of GP2015 to Enbrel® in psoriasis
  - Accumulated clinical experience with Enbrel® in multiple indications

How I Would Use GP2015 in Clinical Practice

- Initiate patients naïve to TNF inhibition on a lower-cost biosimilar
- Strongly consider transitioning patients on the bio-originator to a lower-cost biosimilar to conserve resources
- Use the biosimilar to treat patients with any of the indications for which the bio-originator is approved

GP2015 Is a Biosimilar to Enbrel®

GP2015 Is “Essentially the Same” as Enbrel®



- **Confirmatory efficacy, safety, and immunogenicity study in patients with moderate-to-severe plaque psoriasis**
- **PK bioequivalence studies in healthy volunteers**
- **Animal PD, PK, toxicology**
- **Structural and functional comparison using state-of-the-art technology**

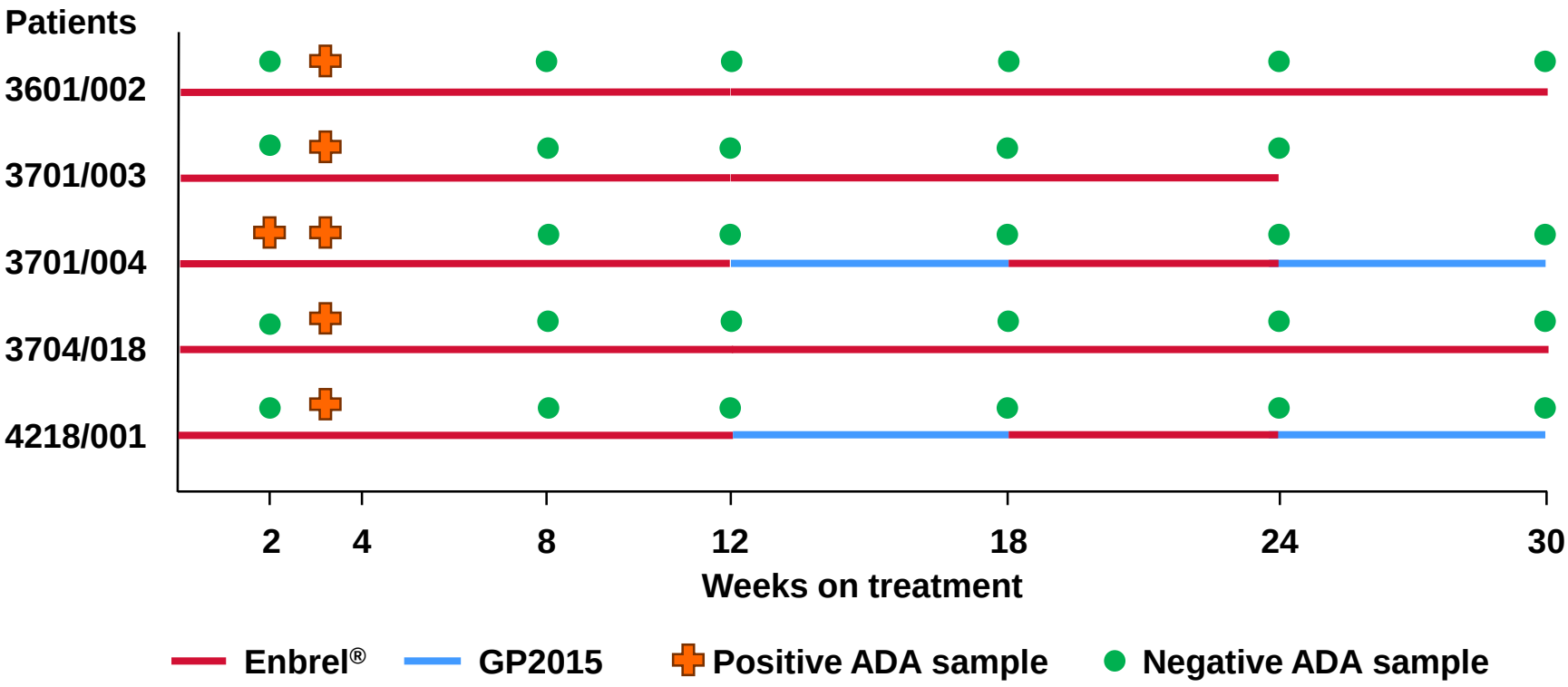
Conclusions

- Modern technology and analytics allow for creation and full characterization of biosimilars
- GP2015 has been demonstrated both analytically and clinically to be highly similar to the reference product, Enbrel®
- This high similarity supports extrapolation to all indications for the reference product
- Biologic drugs are important therapeutic agents, and a biosimilar will provide competition and increased access
- Approval of GP2015 will expand options available to healthcare providers and patients

Backup Slides Shown

Immunogenicity

Study GP15-302 Up to Week 30

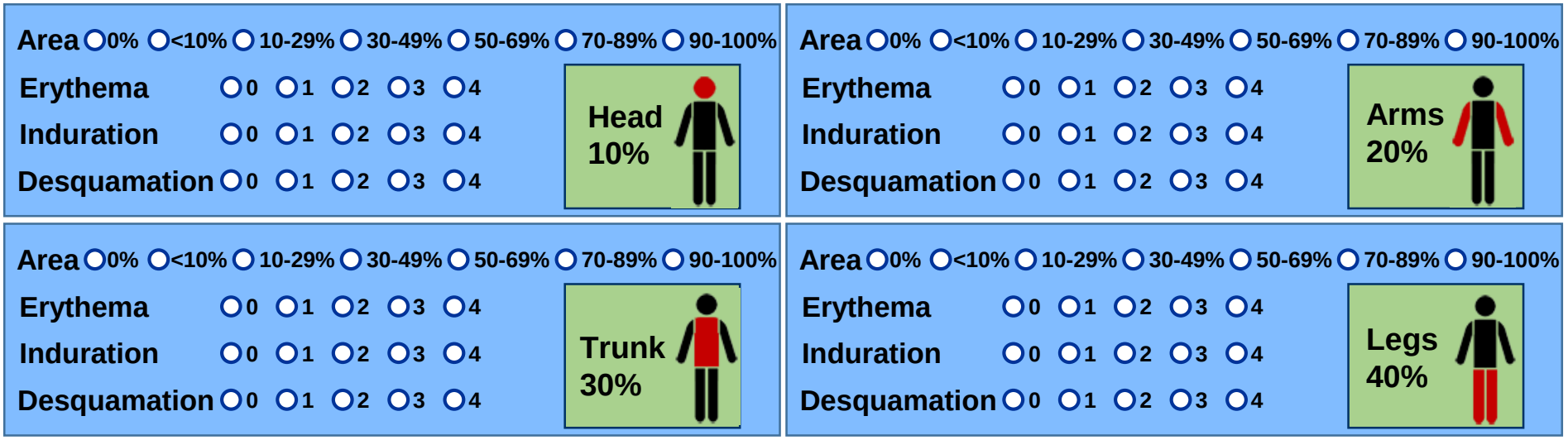


- **5 patients, all in the Enbrel group, showed confirmed ADA positive samples**,
- All were non-neutralizing, transient, and low titer (*corresponds to a rate of 1.9% for Enbrel → in line with published data)*
- **No additional ADA-positive results** up to Week 30

→ **No increased risks of development of ADAs for GP2015 compared to Enbrel**

PASI 75 Is a Sensitive Endpoint in Psoriasis

- Psoriasis lesions are visible and relatively easy to quantify
- PASI is a measure of the average redness, thickness and scaliness of the lesions, weighted by area of involvement
  - Final scores range from 0–72; higher scores indicate more severe disease
  - A 75% reduction from the PASI baseline score (PASI 75) is considered a clinically meaningful improvement and is used as a benchmark in most clinical trials, making comparisons possible

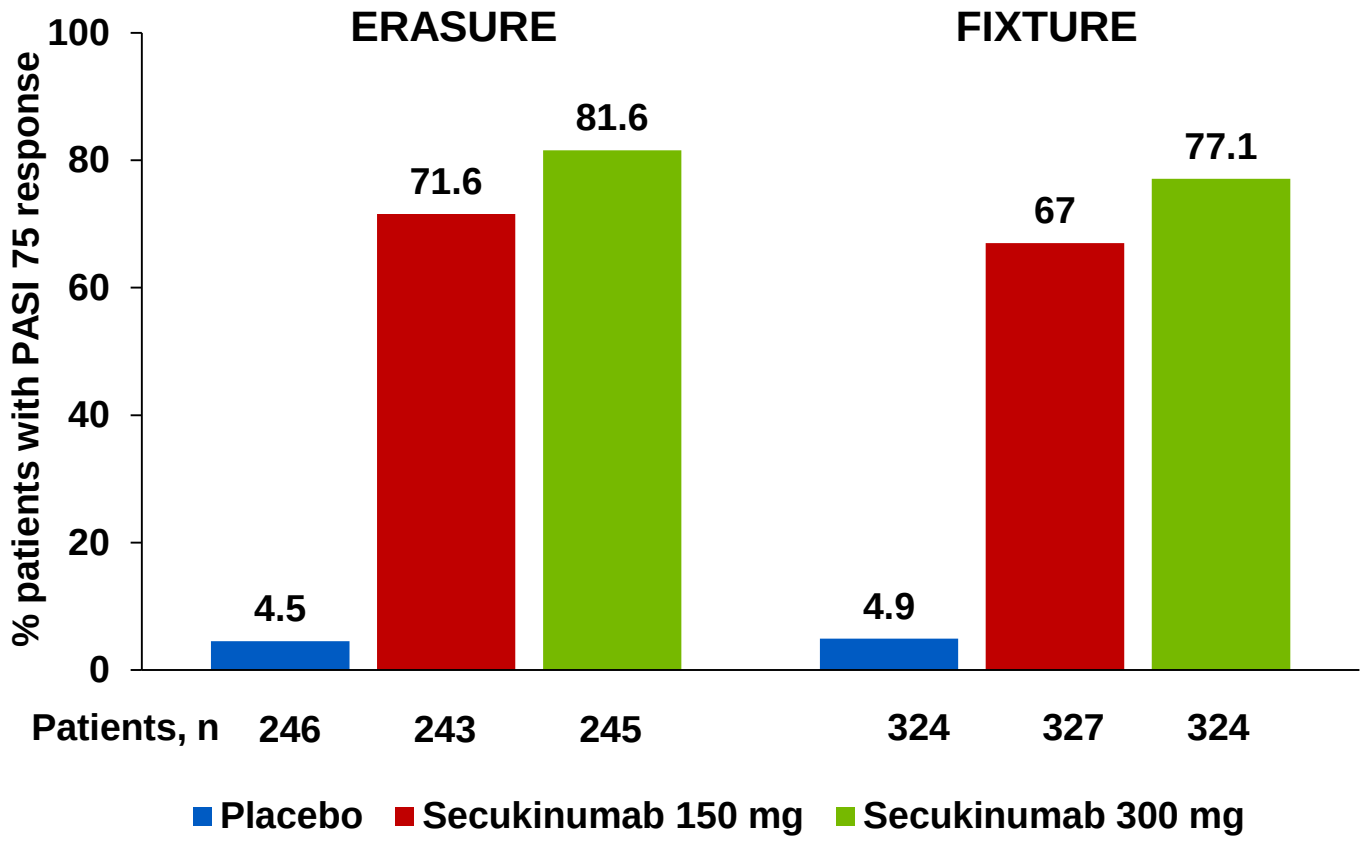


PASI=Psoriasis Area Severity Index

Feldman SR, Krueger GG. *Ann Rheum Dis*. 2005;64 Suppl 2:ii65–8; Fredriksson T, Pettersson U. *Dermatologica*. 1978;157.

Well Conducted Psoriasis Trials Have Consistent PASI Responses

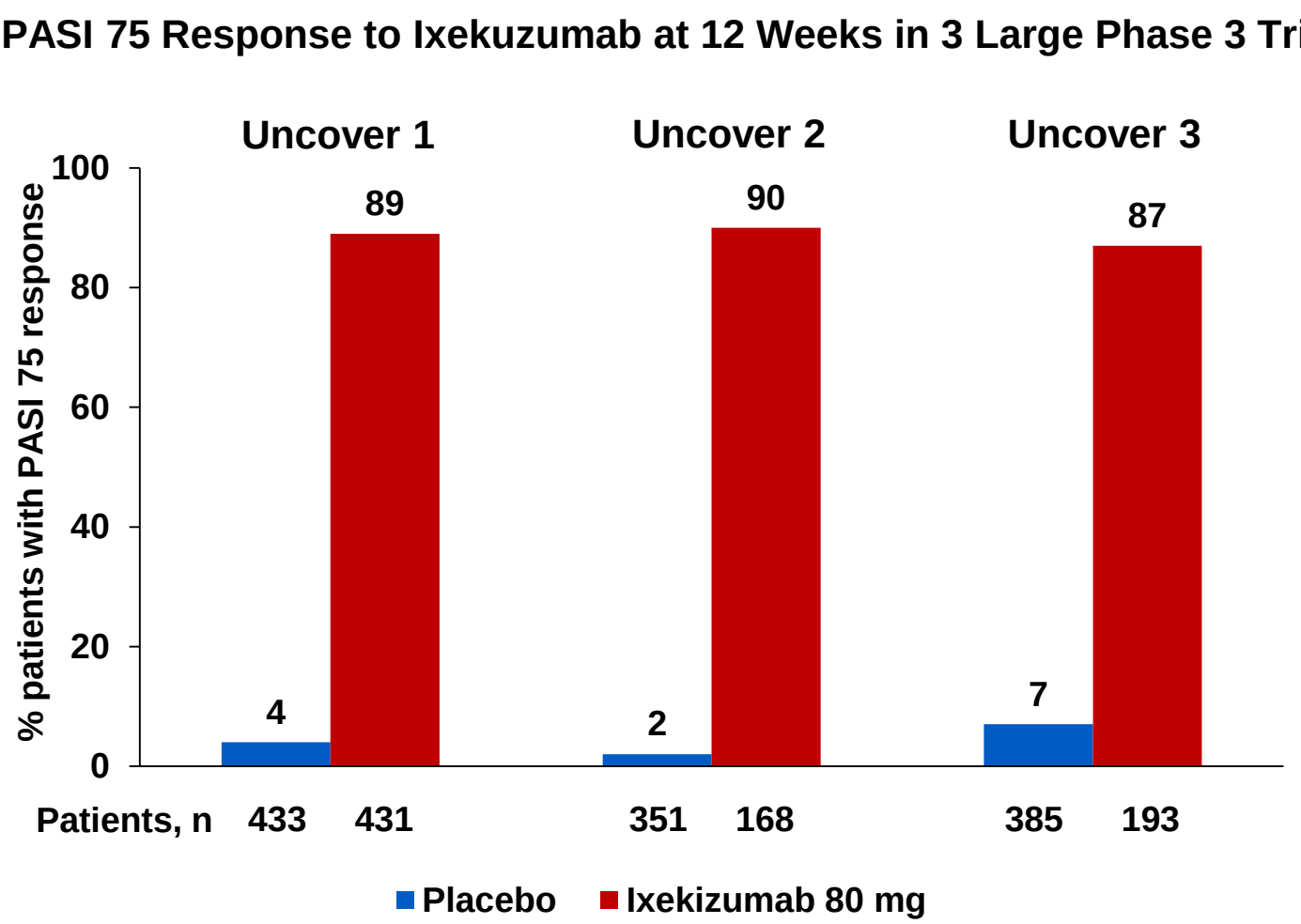
% patients in trials of secukinumab with PASI 75 response at Week 12



PASI=Psoriasis Area Severity Index.

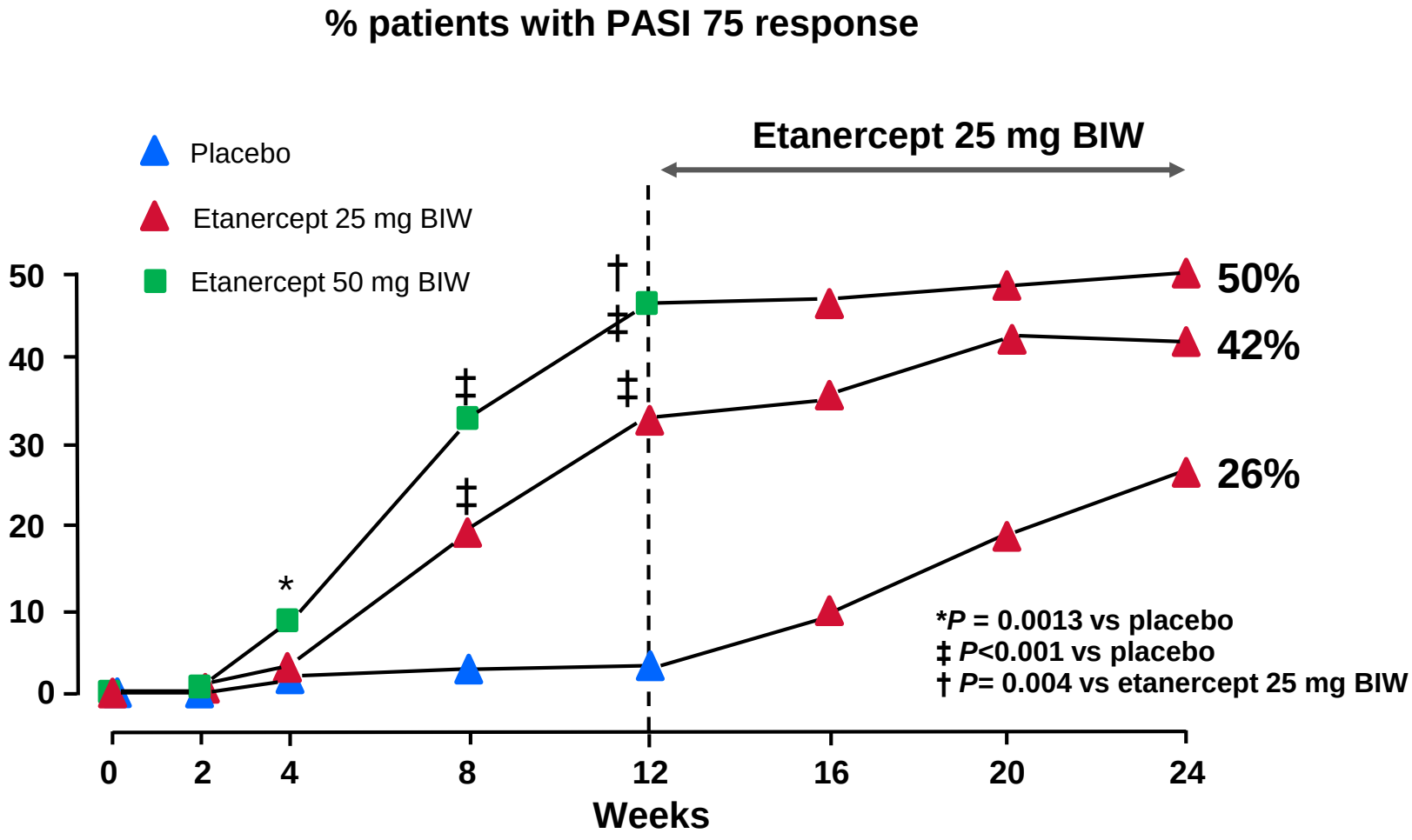
Langley R, et al. *N Engl J Med*. 2014;371:326-338.

Well Conducted Psoriasis Trials Have Consistent PASI Responses



Source: US FDA Prescribing Information Accessed 7/11/2016

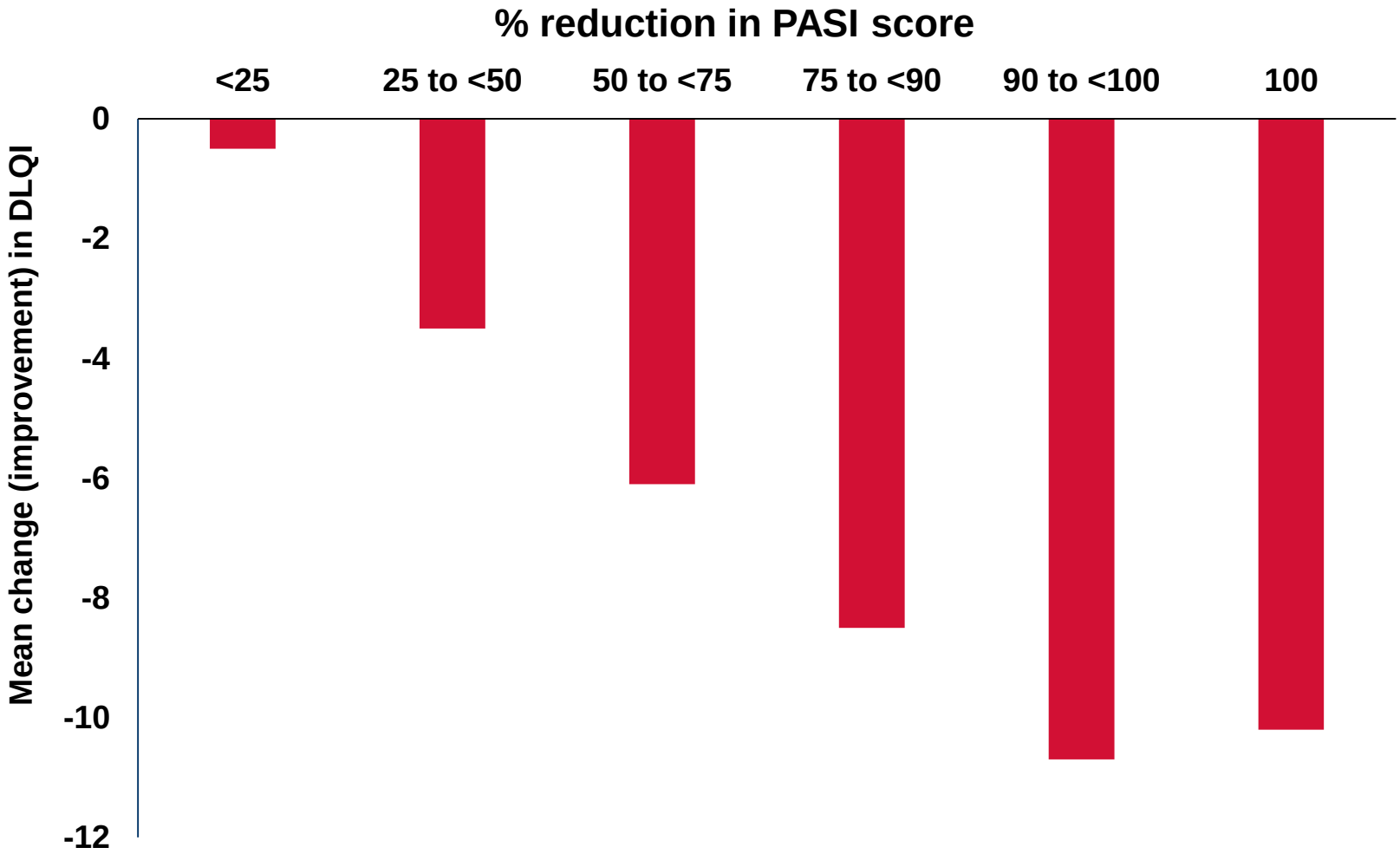
PASI 75 Is Sensitive to Dose-response Changes



BIW=twice weekly

Papp KA, et al. *Br J Derm.* 2005;152:1304-1312.

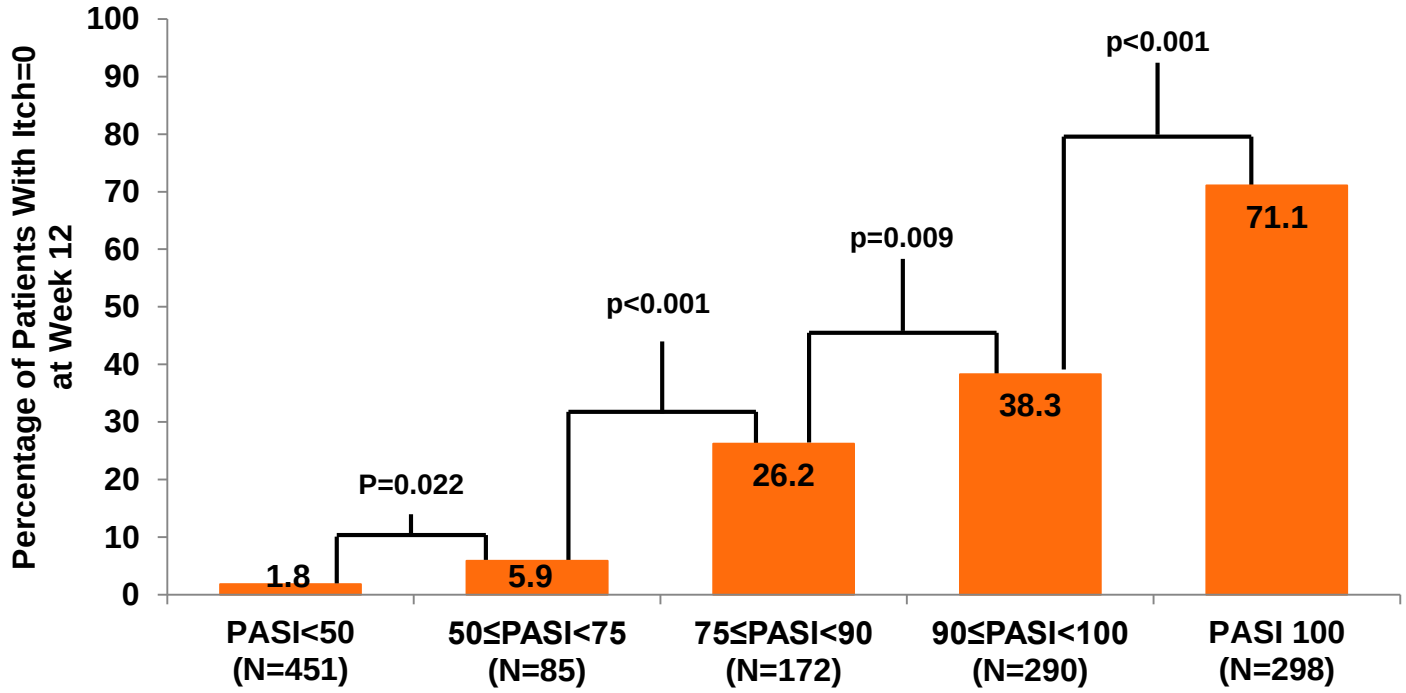
Secukinumab: Changes in the PASI Correspond With Improvement in Dermatology Life Quality Index (DLQI) in Psoriasis Patients



PASI=Psoriasis Area Severity Index.

Revicki DA, et al. *Dermatology*. 2008;216(3):260-270.

Ixekizumab: Itch NRS=0 Correlates With Level of Treatment Response at Week 12



What Makes Psoriasis a Preferred Indication for the Assessment of Biosimilarity?

- Well understood and shared MOA with RA, AS, JIA, and PsA
- Psoriasis patients are typically younger and healthier
- Fewer comorbid diseases and concomitant medications
- Disease is on display and easy to assess; no invasive testing
- In dermatology, biologics are accepted as monotherapy
  - MTX and other DMARDS might interfere with PK/PD effects, immunogenicity and safety issues
- Well established primary endpoints (PASI, PGA)
- Large treatment effect size
  - Allows for detection of small differences in efficacy
- Skin responses are rapid (12 – 16 weeks)

MTX=methotrexate; PASI=Psoriasis Area Severity Index; PGA=Physician's Global Assessment

El-Gabalawy H, et al. *J Rheumatol*. Suppl 2010;85:2-10;
Feldman SR, Krueger GG. *Ann Rheum Dis*. 2005;64 Suppl 2:ii65-8; Lee H. *AAPS J.* 2014;16:22–6;
Nast A, et al. *J Eur Acad Dermatol Venereol*. 2015;29(12):2277-2294.

HRQoL Instruments

Study GP15-302

DLQI

- 10-item general dermatology disability index questionnaire

EQ-5D™

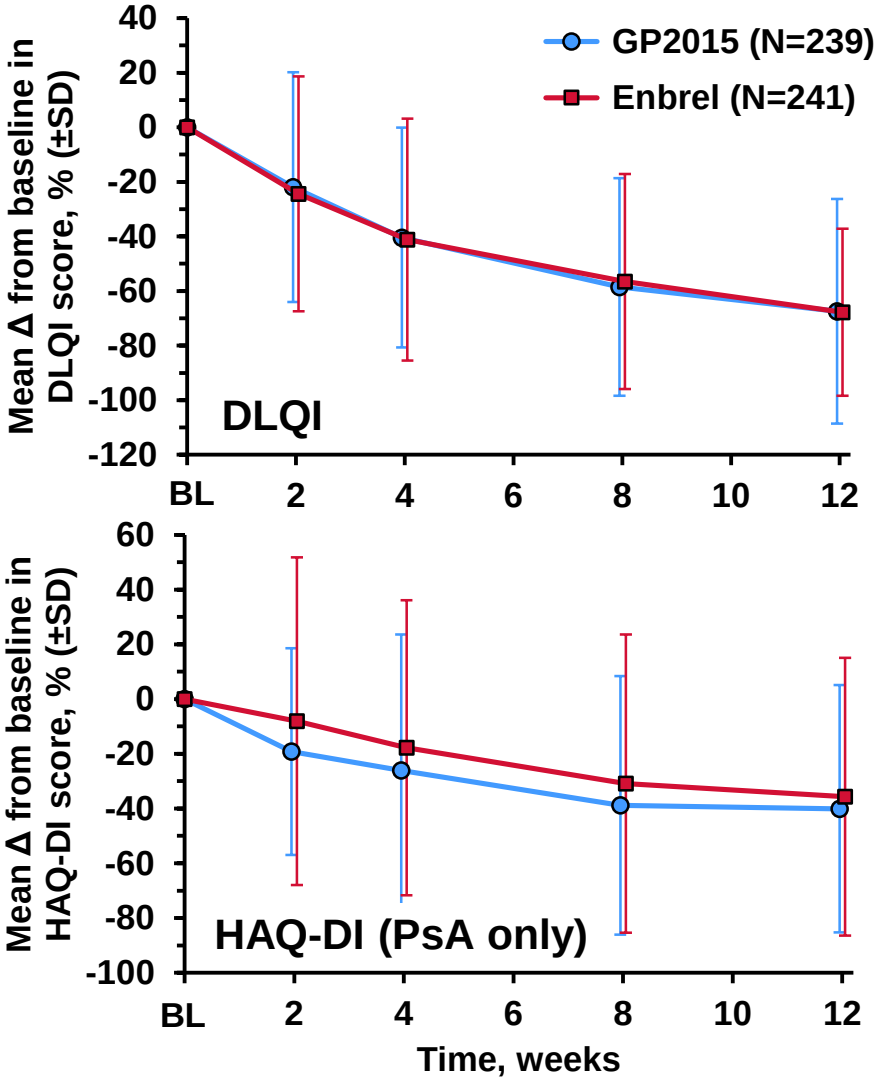
- Generic instrument to assess a patient's health status

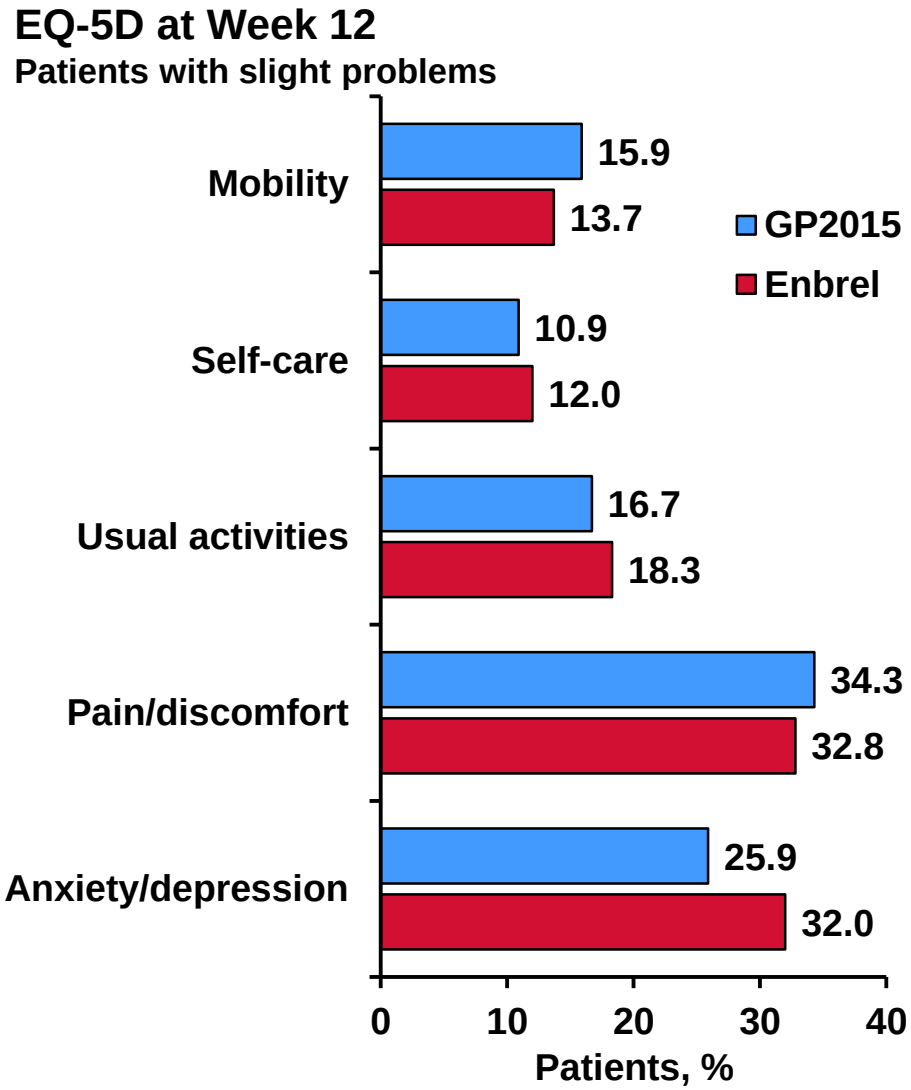
HAQ-DI©

- Administered only to study patients with a medical history of psoriatic arthritis
- Assesses physical function and activity limitation

GP2015 and Enbrel® Were Similar in All HRQoL Measurements

Study GP15-302—TP1 PPS



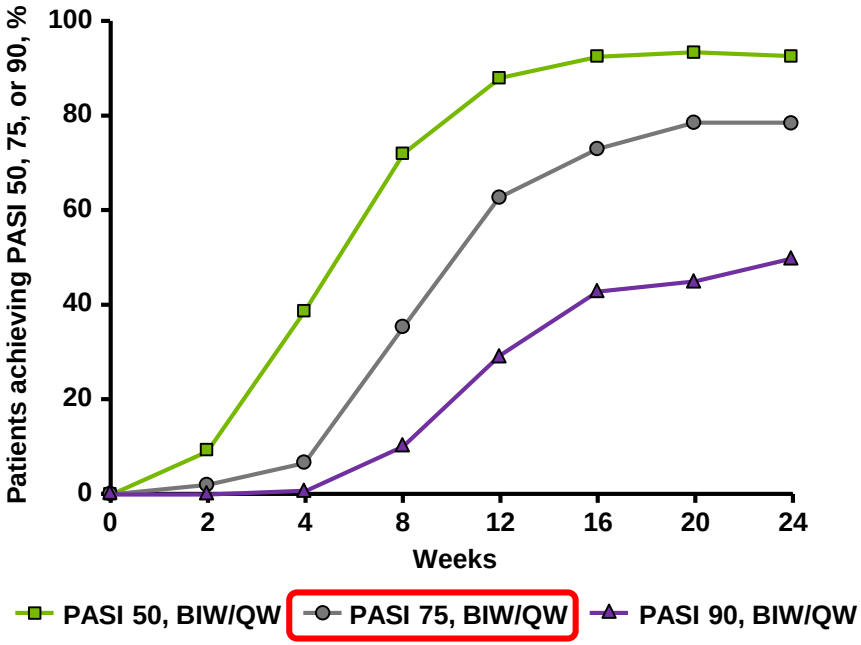


DLQI=Dermatology Life Quality Index; HAQ-DI=Health Assessment Questionnaire-Disability Index; EQ-5D=EuroQol 5-Dimension Health Status Questionnaire.

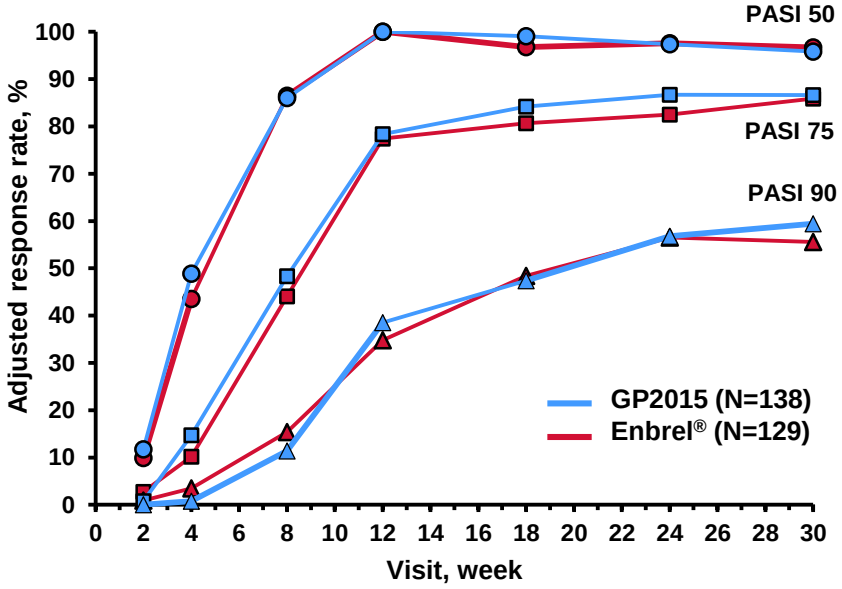
Plateau of PASI 75 Response Rate Comparable to Other Published Data Beyond Week 12

Evolution of PASI response in a comparable psoriasis study (Strohal 2013) vs EGALITY

PRISTINE



EGALITY



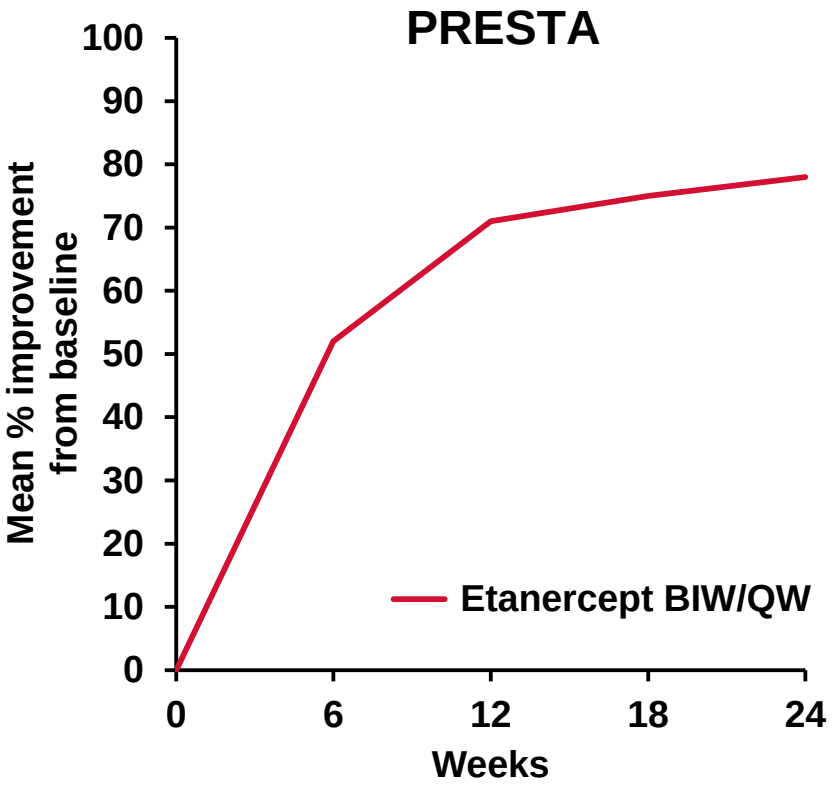
→ Longer term response rates (Week 20 to Week 24) are comparable between both studies: approx. 80% PASI 75 response rate for both

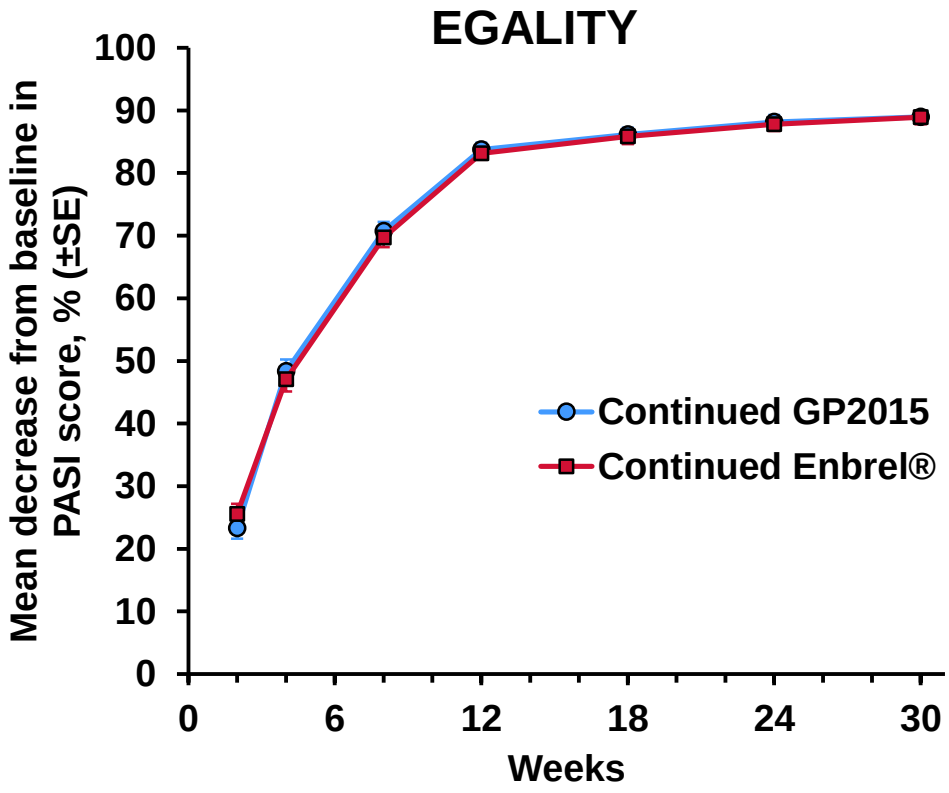
BIW=twice weekly; QW=once weekly.

Strohal R, et al. *J Dermatolog Treat*. 2013;24(3):169-178.

Plateau of % PASI Change From Baseline Comparable to Published Data Beyond Week 12

Evolution of % PASI change from baseline in a comparable study (Sterry et al 2010 in a psoriatic arthritis population) vs EGALITY





→ long-term response rates (24-30 weeks) are comparable between EGALITY (just over 80%) and the literature (just under 80%)

BIW=twice weekly; QW=once weekly.

Sterry W, et al. *BMJ*. 2010;340:c147.

Observations Regarding High PASI 75 Response Rates at Week 12

Study GP15-302

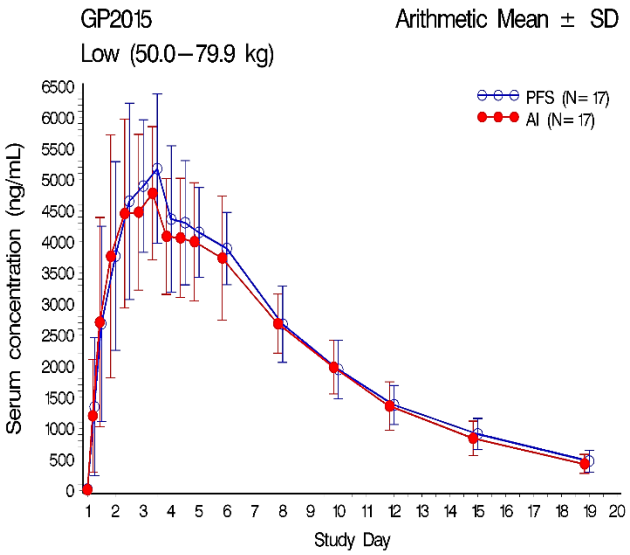
1. Only active substance, no placebo control
2. Lower body weight in GP15-302 vs published Enbrel® studies
3. PPS instead of FAS (following the intent-to-treat principle)
4. Response beyond 12-16 weeks of treatment comparable to published studies
5. Higher response rates in more recent Enbrel psoriasis studies

PPS=per-protocol set; FAS=full analysis set; LOCF=last observation carried forward.

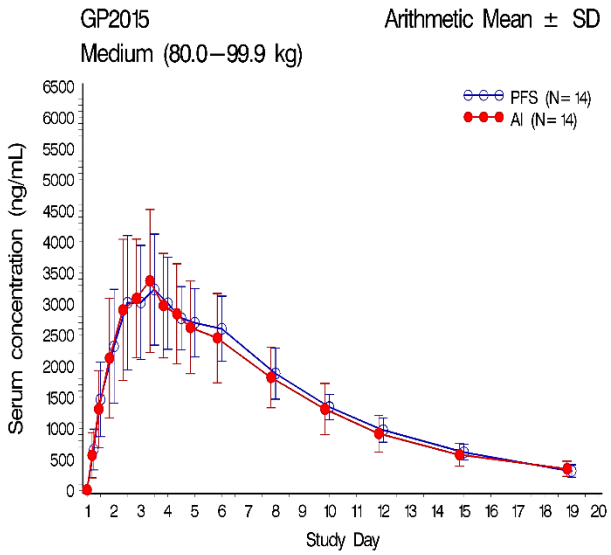
Mean Serum Concentration Curves By Weight Category

Study GP15-103

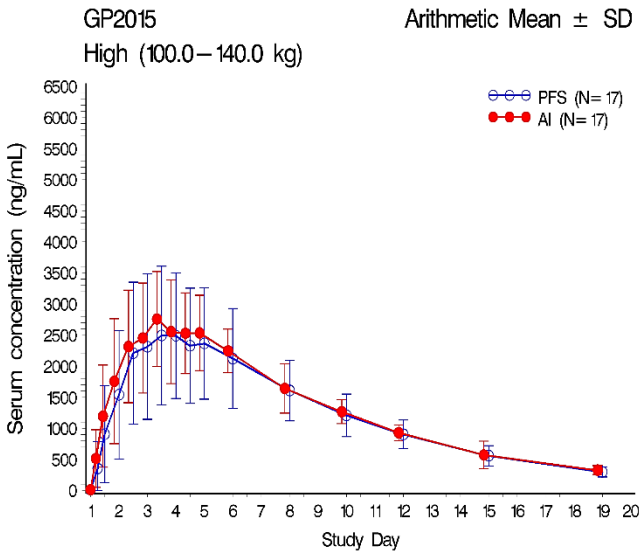
Low



Medium



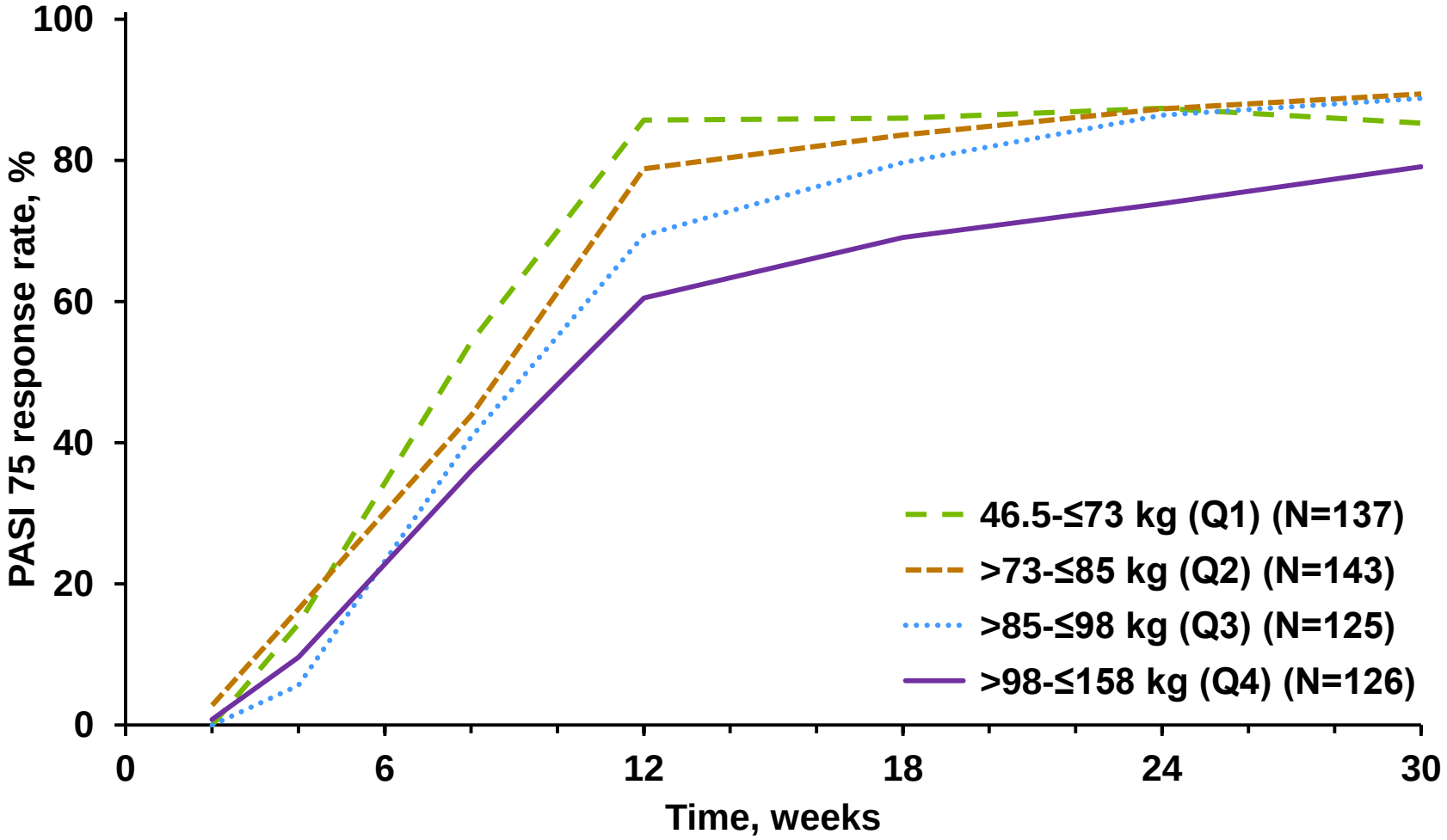
High



AI=Autoinjector. PFS=pre-filled syringe. SD=standard deviation.

PASI 75 Response Rate Correlates With Body Weight

Study GP15-302—TP2 FAS (Pooled Data)



All Main Efficacy Endpoints Demonstrated Equivalence

Study GP15-302—TP1, PPS and FAS

Endpoint	Main analysis in PPS: difference % (95%CI)	Supportive analysis in FAS: difference % (95%CI)	Pre-specified equivalence limits, %	Outcome
Primary[a]: PASI 75 response at Week 12	−2.3 (−9.85, 5.30)	−1.2 (−8.77, 6.45)	(−18, 18)	GP2015 is equivalent to Enbrel®
Secondary: Percentage change from baseline in PASI score up to 12 weeks (MMRM)	−0.64 (−3.47, 2.20)	−1.59 (−4.37, 1.18)	(−15, 15)	GP2015 is equivalent to Enbrel
Secondary: Analysis of averaged treatment effect (ATE) of percent PASI change (ANCOVA)	−0.88 (−3.61, 1.85)	−2.14 (−4.97, 0.69)	(−15, 15)	GP2015 is equivalent to Enbrel

[a] logistic regression model used for primary endpoint analysis
ANCOVA=analysis of covariance; CI=confidence intervals; FAS=full analysis set (missing data imputed as non-responders);
MMRM=mixed-model repeated measures; PASI=psoriasis area and severity index;
PPS=per-protocol set.

SAEs Regardless of Study Drug Relationship by SOC and Preferred Term

Study GP15-302—TP2 Safety Set (N=497)

System organ class Preferred term	Patients, n (%) Pooled continued N=301	Pooled switched N=196
≥1 SAE	3 (1.0)	6 (3.1)
Infections and infestations		
Diverticulitis	0	1 (0.5)
Pneumonia	1 (0.3)	0
Tonsillitis	0	1 (0.5)
Injury, poisoning and procedural complications		
Meniscus injury	1 (0.3)	0
Upper limb fracture	1 (0.3)	0
Gastrointestinal disorders		
Umbilical hernia	0	1 (0.5)
Hepatobiliary disorders		
Cholelithiasis	0	1 (0.5)
Musculoskeletal and connective tissue disorders		
Psoriatic arthropathy	0	1 (0.5)
Respiratory, thoracic, and mediastinal disorders		
Pulmonary sarcoidosis	0	1 (0.5)
Skin and subcutaneous tissue disorders		
Psoriasis	0	1 (0.5)