GP2015 Biosimilar (Etanercept)

United States Food and Drug Administration
Arthritis Advisory Committee

July 13, 2016
GP2015 Etanercept
Introduction and Concept

Mark McCamish, MD, PhD

Global Head Biopharmaceuticals Development
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

<table>
<thead>
<tr>
<th>Dosage forms</th>
<th>Enbrel®</th>
<th>GP2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• 25 mg/0.5 mL pre-filled syringe (50 mg/mL)</td>
<td>• 25 mg/0.5 mL pre-filled syringe (50 mg/mL)</td>
</tr>
<tr>
<td></td>
<td>• 50 mg/1.0 mL pre-filled syringe (50 mg/mL)</td>
<td>• 50 mg/1.0 mL pre-filled syringe (50 mg/mL)</td>
</tr>
<tr>
<td></td>
<td>• 50 mg/1.0 mL pre-filled autoinjector (50 mg/mL)</td>
<td>• 50 mg/1.0 mL pre-filled autoinjector (50 mg/mL)</td>
</tr>
</tbody>
</table>

| 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)  GP2015 pre-filled autoinjector (AI)

- Enlarged finger flange
- Needle safety guard

- Needle guard
- Finger flange
- Needle guard wings
- Viewing window

- Triangular shape for better grip
- 2-step injection

- Needle guard
- Viewing window
- Internal needle cover
Development of a Biosimilar Requires a Paradigm Shift

Comparison with the reference product

Originator development

Clinical
PK/PD
Non-clinical
Analytical

Biosimilar development

Analytical
Non-clinical
PK/PD
Clinical

The world turned upside down...
# Biosimilar Development Approach

Pioneered by Sandoz, the approach 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...

- 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...

Regulatory Concept of “Sameness” Is Key to Establishing Biosimilarity Allowing Extrapolation

Comparability

Comparability for manufacturing changes to currently approved drugs and biologics (FDA 1996), became ICH Q5E (2005)

Comparability is defined as “highly similar quality attributes”

Biosimilarity

Biosimilarity is based on Biosimilar being “highly similar” to the reference product with “no clinically meaningful differences” (EU 2004, WHO 2009, FDA 2010)

Active substance is “essentially the same” biological substance, though there may be minor differences due to their complex nature and production methods (EMA 2009)

Generic small molecule drugs introduced “sameness” as a regulatory matter (FDA 1984)
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

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

TOTALITY OF THE EVIDENCE FROM THE SIMILARITY EXERCISE

Reference

Biosimilar

Structural attributes

Biological functions

Non-clinical/tox

Human PK/PD

Psoriasis (tested, sensitive indication)

RA, JIA

PsA, AS

Highly Similar

Highly Similar

Highly Similar

Highly Similar

Highly Similar

Highly Similar

Scientifically Justified

Scientifically Justified

Comparative Evaluation of GP2015 and Enbrel® Justifies Extrapolation

Analytical

Non-clinical

Pharmacokinetics

Clinical Confirmation

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 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®

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

- **Non-clinical**
  - Animal PD, PK, toxicology

- **Pharmacokinetics**
  - PK bioequivalence studies in healthy volunteers

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

- 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

Fc part of monoclonal antibody
Ligand binding site of TNFR
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

Criticality Criticality score

<table>
<thead>
<tr>
<th>Criticality</th>
<th>Criticality score</th>
</tr>
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<tbody>
<tr>
<td>Very high</td>
<td>121 - 140</td>
</tr>
<tr>
<td>High</td>
<td>86 - 120</td>
</tr>
<tr>
<td>Moderate</td>
<td>56 - 85</td>
</tr>
<tr>
<td>Low</td>
<td>31 - 55</td>
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<tr>
<td>Very low</td>
<td>2 - 30</td>
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Existing product knowledge
• Literature
• In-house studies
• Related molecules
## Clinical Importance of Quality Attributes

### Excerpt Overview Table

<table>
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<th>Number of attributes</th>
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<tr>
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<td>22</td>
<td>TNF-α neutralization (efficacy), TNF-β neutralization (efficacy), TNF-α binding (efficacy), protein content (efficacy)</td>
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<tr>
<td>High</td>
<td>14</td>
<td>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</td>
</tr>
<tr>
<td>Moderate</td>
<td>25</td>
<td>Acidic variants, oxidation, deamidation, non-fucosylated glycans, sialylation, ADCC activity, CDC activity, binding to Fc gamma receptors</td>
</tr>
<tr>
<td>Low</td>
<td>10</td>
<td>Basic variants, succinimide, proline amide, N-terminal variant -leucine/-leucine/proline, free thiols</td>
</tr>
<tr>
<td>Very low</td>
<td>13</td>
<td>Lysine variants, quality of sodium hydroxide, quality of nitrogen, quality of sodium chloride</td>
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# Clinical Importance of Quality Attributes

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Results for attributes with very high/ high criticality shown on following slides
Powerful Tools Have Evolved to Allow Comprehensive Characterization

<table>
<thead>
<tr>
<th>Year</th>
<th>MS- Detection limit for peptides (pmol)</th>
<th>Analogue</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>1993</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>0.00001</td>
<td></td>
</tr>
</tbody>
</table>

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
- FcRn binding
- Product related impurities
- Stability behavior
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
Indistinguishable Higher Order Structure Demonstrated by FTIR...

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

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

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.

Critical Quality Attributes
- Primary structure
- Higher order structure
- TNF-α neutralization
- Content
- FcRn binding
- Product related impurities
- Stability behavior
Mechanism of Action of Etanercept TNF-α Neutralization

Etanercept

TNF receptor-1

TNF

Downstream signaling

Critical Quality Attributes

- Primary structure
- Higher order structure
- TNF-α neutralization
- Content
- FcRn binding
- Product related impurities
- Stability behavior
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
Data Show Similar Activity for GP2015 and Enbrel® in TNF-α Neutralization

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

- Enbrel/EU (43 batches)
- Enbrel/US (31 batches)
- GP2015 (19 batches)

Biological activity of Enbrel/US and Enbrel/EU measured by TNF-α reporter gene assay is similar
TNF-α Neutralization Activity of GP2015 Is Within Enbrel® Range of Variability
Incorrect Disulfide Bond Variants Present in Etanercept

Correct disulfide bonds

Incorrect disulfide bond variant (T7 example)

Active

Inactive
Incorrect Disulfide Bond Variants Are Inactive

Structure-Function Relationship

- Incorrect disulfide bond variants T7 (relative amount)
- TNF-α neutralizing activity, %
Incorrect Disulfide Bond Variants Are Corrected Under Physiological Conditions

Incorrect disulfide bond variant (T7)

Correct disulfide bond variant

Incubation redox system

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

TNF-α Neutralization Activity Increases Following Exposure to Redox Conditions

Bioactivity, %

Incorrect disulfide bond variants T7 (relative amount)

Enbrel®/US #1034018

Enbrel/US #1034842
TNF-α Neutralization: GP2015 and Enbrel Bioactivity Is Equivalent

Equivalence test
Scaled for EAC

Mean difference

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\% \text{ power}} \times \sigma_{\text{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 by UV/Vis spectrophotometry

Content of GP2015 is within the combined ranges of Enbrel/US and Enbrel/EU
FcRn Binding Is Similar for GP2015 and Enbrel®

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

Degradation

Incorrect disulfide bond variants

Intact molecule

Alpha-galactosylation variants

Aggregation

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)**

- **Upper limit**
- **Enbrel/EU**
- **Enbrel/US**
- **GP2015**

**Aggregation products (by size exclusion chromatography)**

- **Upper limit**
- **Enbrel/EU**
- **Enbrel/US**
- **GP2015**

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)

Stability studies

Product related impurity profile similar between
- GP2015 and Enbrel
- Enbrel/US and Enbrel/EU

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

Critical Quality Attributes
- Primary structure
- Higher order structure
- TNF-α neutralization
- Content
- FcRn binding
- Product related impurities
- Stability behavior
Analytical Similarity Was Established

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

- **Non-clinical**
  - Animal PD, PK, toxicology

- **Pharmacokinetics**
  - PK bioequivalence studies in healthy volunteers

- **Clinical Confirmation**
  - Confirmatory efficacy, safety, and immunogenicity study in patients with moderate-to-severe plaque psoriasis
Non-clinical and Pharmacokinetic Characterization of GP2015

Oliver von Richter, PhD, FCP
Global Clinical Development
Sandoz Biopharmaceuticals
Evaluation of Similarity Between GP2015 and Enbrel®

- Clinical Confirmation: Confirmatory efficacy, safety, and immunogenicity study in patients with moderate-to-severe plaque psoriasis
- Pharmacokinetics: PK bioequivalence studies in healthy volunteers
- Non-clinical: Animal PD, PK, toxicology
- Analytical: Structural and functional comparison using state-of-the-art technology
## Summary of Non-clinical Studies: GP2015 and Enbrel® Were Highly Similar

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

*ip=intraperitoneal.*
Evaluation of Similarity Between GP2015 and Enbrel®

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

- **Non-clinical**
  - Animal PD, PK, toxicology

- **Pharmacokinetics**
  - PK bioequivalence studies in healthy volunteers

- **Clinical Confirmation**
  - Confirmatory efficacy, safety, and immunogenicity study in patients with moderate-to-severe plaque psoriasis
## Overview of PK Studies

<table>
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<tr>
<th>Study</th>
<th>Study description</th>
<th>Study population</th>
<th>Study duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pivotal PK study</strong></td>
<td></td>
<td>Healthy volunteers</td>
<td></td>
</tr>
<tr>
<td>GP15-102a</td>
<td>Randomized, double-blind, two-way crossover, Enbrel®/US</td>
<td>N=57</td>
<td>Up to 3 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supportive PK studies</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>GP15-101a</td>
<td>Randomized, double-blind, two-way crossover, Enbrel/EU</td>
<td>N=54</td>
<td>Up to 3 months</td>
</tr>
<tr>
<td>GP15-104</td>
<td>Randomized, double-blind, two-way crossover, Enbrel/EU</td>
<td>N=54</td>
<td>Up to 3 months</td>
</tr>
<tr>
<td>GP15-103</td>
<td>Randomized, open-label, two-way crossover, GP2015 PFS vs Al</td>
<td>N=51</td>
<td>Up to 3 months</td>
</tr>
</tbody>
</table>

| 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\text{\_trough} PK substudy) |

Al=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 stay (3 - 8 days)

Wash-out period ≥35 days (ie, ~9 × etanercept t₁/₂)

Period 1

Day 0
Dosing

Ambulatory
visits

Day 18

Enbrel®

Day 0
Dosing

Ambulatory
visits

Enbrel

In-clinic stay (3 - 8 days)

Follow-up visit
28 days after IMP administration in Period 2

Day 28

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Patients, n (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Dosed</td>
<td>Completed</td>
<td>Withdrawn</td>
<td></td>
</tr>
<tr>
<td>GP15-102</td>
<td>GP2015/Enbrel®/US</td>
<td>57 (100)</td>
<td>54 (94.7)</td>
<td>3 (5.3)</td>
<td></td>
</tr>
<tr>
<td>GP15-103</td>
<td>GP2015 PFS/GP2015 AI</td>
<td>51 (100)</td>
<td>49&lt;sup&gt;a&lt;/sup&gt; (96.1)</td>
<td>2 (3.9)</td>
<td></td>
</tr>
<tr>
<td>GP15-101</td>
<td>GP2015/Enbrel/EU</td>
<td>54 (100)</td>
<td>51 (94.4)</td>
<td>3 (5.6)</td>
<td></td>
</tr>
<tr>
<td>GP15-104</td>
<td>GP2015/Enbrel/EU</td>
<td>54 (100)</td>
<td>54 (100)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>216 (100)</td>
<td>208 (96.3)</td>
<td>8 (3.7)</td>
<td></td>
</tr>
</tbody>
</table>

AI=autoinjector; PFS=pre-filled syringe.

<sup>a</sup> 1 patient was excluded from the PK population due to high pre-dose values in Treatment Period 2.
Primary objective

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

Secondary objectives

- Remaining PK parameters ($\text{AUC}_{0-\infty}$, $t_{\text{max}}$, $k_{\text{el}}$, $t_{1/2}$)
- Immunogenicity, safety, local tolerance
Time Course of Mean Serum Concentrations
Study GP15-102—Per-Protocol Set

Mean serum concentration, ng/mL (±SD)

Time post-dose, hours

- 50 mg GP2015 (N=54)
- 50 mg Enbrel®/US (N=54)
### GP2015 and Enbrel®/US Are Bioequivalent

Study GP15-102—Per-Protocol Set

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric LS means</th>
<th>Ratio GP2015:Enbrel/US (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$, ng/mL</td>
<td>2055</td>
<td>0.8 - 1.25</td>
</tr>
<tr>
<td>$AUC_{0-\text{tlast}}$, ng·h/mL</td>
<td>376279</td>
<td></td>
</tr>
<tr>
<td>$AUC_{0-\infty}$, ng·h/mL</td>
<td>397239</td>
<td></td>
</tr>
<tr>
<td>Enbrel/US</td>
<td>2163</td>
<td></td>
</tr>
<tr>
<td>418797</td>
<td>445118</td>
<td></td>
</tr>
</tbody>
</table>

#### Statistical assessment of bioequivalence

90% confidence intervals for geometric mean ratios for $AUC_{0-\text{tlast}}$ and $C_{\text{max}}$ 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;  
$C_{\text{max}}$ = 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

Mean serum concentration, ng/mL (±SD)

Time post-dose, hours

- Enbrel®/EU (N=51)
- Enbrel/US (N=54)
Use of Enbrel®/EU as a Comparator Is Justified
Report GP15-105—Per-Protocol Set

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Geometric LS means</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>0.8</th>
<th>1</th>
<th>1.25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enbrel/EU</td>
<td>Enbrel/US</td>
<td>Ratio Enbrel/EU:Enbrel/US</td>
<td>(90% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$, ng/mL</td>
<td>1979</td>
<td>2146</td>
<td>0.8 1.251</td>
<td>1.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$AUC_{0-\text{tlast}}, \text{ng} \cdot \text{h/mL}$</td>
<td>411530</td>
<td>435143</td>
<td>1.25</td>
<td>1.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$AUC_{0-\infty}, \text{ng} \cdot \text{h/mL}$</td>
<td>388578</td>
<td>410380</td>
<td>0.8 1.251</td>
<td>1.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Statistical assessment of bioequivalence**

90% confidence intervals for geometric mean ratios for $AUC_{0-\text{tlast}}$ and $C_{\text{max}}$ 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; $C_{\text{max}}$ = maximum observed serum concentration.
Primary objective

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

Secondary objectives

- To compare PK parameters $\text{AUC}_{0-\text{t}_{\text{last}}}$, $\text{AUC}_{0-\infty}$, and $C_{\text{max}}$, 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 $t_{\text{max}}$, $k_{\text{el}}$, $t_{1/2}$
- Safety, tolerability, and local tolerance

AUC = area under the serum concentration-time curve between the specified time points; $C_{\text{max}}$ = maximum observed serum concentration.
Time Course of Mean Serum Concentrations
Study GP15-103—Per-Protocol Set

Mean serum concentration, ng/mL (±SD)

Time post-dose, hours

GP2015-AI (N=48)
GP2015-PFS (N=48)

Al=autoinjector; PFS=pre-filled syringe.
**Statistical assessment of bioequivalence**

90% confidence intervals for geometric mean ratios for \( \text{AUC}_{0-t_{\text{last}}} \) and \( C_{\text{max}} \) to be within conventional bioequivalence limits of 0.8 - 1.25 pre-specified by the FDA

---

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric LS means</th>
<th>Ratio AI:PFS (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{max}}, , \text{ng/mL} )</td>
<td>3666, 3627</td>
<td>0.8, 1, 1.25</td>
</tr>
<tr>
<td>( \text{AUC}<em>{0-t</em>{\text{last}}}, , \text{ng·h/mL} )</td>
<td>684131, 678395</td>
<td></td>
</tr>
<tr>
<td>( \text{AUC}_{0-\infty}, , \text{ng·h/mL} )</td>
<td>745169, 737396</td>
<td></td>
</tr>
</tbody>
</table>

**Autoinjector and Pre-filled Syringe Provide Equivalent Etanercept Exposure**

Study GP15-103—Per-Protocol Set

Using PROC MIXED (ANCOVA) with body weight as covariate.

\( \text{AI} = \text{autoinjector}; \  \text{AUC} = \text{area under the serum concentration-time curve between the specified time points}; \  \text{C}_{\text{max}} = \text{maximum observed serum concentration}; \  \text{PFS} = \text{pre-filled syringe}. \)
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

Mean concentration, ng/mL (±SD)

Visit, Week

GP2015
Enbrel®
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

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

Clinical Confirmation

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

Pharmacokinetics

PK bioequivalence studies in healthy volunteers

Non-clinical

Animal PD, PK, toxicology

Analytical

Structural and functional comparison using state-of-the-art technology
## Overview of Clinical Evaluation Program

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomized, n</th>
<th>Duration</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK studies</td>
<td>Healthy volunteers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP15-102 (pivotal)</td>
<td>57</td>
<td>Up to 3 mo</td>
<td>2 single doses, 50 mg SC</td>
</tr>
<tr>
<td>GP2015 vs Enbrel®/US</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP15-101 (supportive)</td>
<td>54</td>
<td>Up to 3 mo</td>
<td>2 single doses, 50 mg SC</td>
</tr>
<tr>
<td>GP2015 vs Enbrel/EU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP15-104(^a) (supportive)</td>
<td>54</td>
<td>Up to 3 mo</td>
<td>2 single doses, 50 mg SC</td>
</tr>
<tr>
<td>GP2015 vs Enbrel/EU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP15-103 (supportive)</td>
<td>51</td>
<td>Up to 3 mo</td>
<td>2 single doses, 50 mg SC</td>
</tr>
<tr>
<td>GP2015 administration AI vs PFS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Confirmatory efficacy and safety study**  
**Patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomized, n</th>
<th>Duration</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP15-302 (pivotal)</td>
<td>531</td>
<td>52 wk</td>
<td>50 mg SC 2x/wk followed by 50 mg SC 1x/wk</td>
</tr>
<tr>
<td>GP2015 vs Enbrel/EU (patients with plaque-type psoriasis)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) 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

Wk 0
Randomization

Wk 12
Wk 18
Wk 24
Wk 30
Wk 52

Screening
Treatment Period 1
Primary Endpoint
Measure: PASI 75

Treatment Period 2

Extension Period

First transition
Pooled
switched
Pooled continued

GP2015
Enbrel®
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
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

Screened
N=774

Randomized
N=531

Safety set
N=531

Full analysis set
N=531

Immunogenicity set
N=531

TP2 safety set
N=497

Patients with major PDs not already discontinued in TP1
N=31a

TP2 per-protocol set
N=446

Per-protocol set
N=480

Discontinuations in TP1
N=20

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>GP2015 N=264</th>
<th>Enbrel N=267</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>42.1 (12.3)</td>
<td>42.7 (12.9)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>41 (18-78)</td>
<td>42 (19-75)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>157 (59.5)</td>
<td>172 (64.4)</td>
</tr>
<tr>
<td>Female</td>
<td>107 (40.5)</td>
<td>95 (35.6)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>263 (99.6)</td>
<td>264 (98.9)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>86.3 (21.1)</td>
<td>85.9 (18.7)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>84 (47-148.5)</td>
<td>85 (46.5-158)</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>28.6 (6.1)</td>
<td>28.5 (5.5)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>27.7 (16.7-48.4)</td>
<td>28.2 (17.4-46.1)</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GP2015</th>
<th>Enbrel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=264</strong></td>
<td></td>
<td>N=267</td>
</tr>
<tr>
<td><strong>Time since initial diagnosis, years</strong></td>
<td>Mean (SD)</td>
<td>17.6 (11.3)</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>16.0 (0.6-55.0)</td>
</tr>
<tr>
<td><strong>Psoriatic arthritis, n (%)</strong></td>
<td>Present</td>
<td>54 (20.5)</td>
</tr>
<tr>
<td><strong>Prior systemic therapy, n (%)&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td>None</td>
<td>182 (68.9)</td>
</tr>
<tr>
<td></td>
<td>Any (except TNF antagonist)</td>
<td>79 (29.9)</td>
</tr>
<tr>
<td></td>
<td>TNF antagonist</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td><strong>IGA of psoriasis, n (%)</strong></td>
<td>2=Mild</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3=Moderate</td>
<td>191 (72.3)</td>
</tr>
<tr>
<td></td>
<td>4=Severe</td>
<td>73 (27.7)</td>
</tr>
<tr>
<td><strong>PASI score</strong></td>
<td>Mean (SD)</td>
<td>22.5 (8.9)</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>20.6 (9.4-55.2)</td>
</tr>
<tr>
<td><strong>BSA affected, %</strong></td>
<td>Mean (SD)</td>
<td>30.5 (13.8)</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>28 (9.5-77.0)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Area, %</th>
<th>0</th>
<th>&lt;10</th>
<th>10-29</th>
<th>30-49</th>
<th>50-69</th>
<th>70-89</th>
<th>90-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema (redness)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induration (thickness)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desquamation (scaling)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
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</tbody>
</table>

## Trunk

<table>
<thead>
<tr>
<th></th>
<th>Area, %</th>
<th>0</th>
<th>&lt;10</th>
<th>10-29</th>
<th>30-49</th>
<th>50-69</th>
<th>70-89</th>
<th>90-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema (redness)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Induration (thickness)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desquamation (scaling)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
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</tbody>
</table>

## Upper limbs

<table>
<thead>
<tr>
<th></th>
<th>Area, %</th>
<th>0</th>
<th>&lt;10</th>
<th>10-29</th>
<th>30-49</th>
<th>50-69</th>
<th>70-89</th>
<th>90-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema (redness)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induration (thickness)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Desquamation (scaling)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

## Lower limbs

<table>
<thead>
<tr>
<th></th>
<th>Area, %</th>
<th>0</th>
<th>&lt;10</th>
<th>10-29</th>
<th>30-49</th>
<th>50-69</th>
<th>70-89</th>
<th>90-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema (redness)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induration (thickness)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desquamation (scaling)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example of PASI Scores in a Patient Treated with Enbrel®

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

<table>
<thead>
<tr>
<th>Week</th>
<th>PASI</th>
<th>Percent Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 0</td>
<td>22.7</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>6.3 (72%)a</td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>3.8 (83%)a</td>
<td></td>
</tr>
</tbody>
</table>

*a Percent improvement (decrease) in PASI score vs baseline.

**Primary Endpoint Met—GP2015 and Enbrel<sup>®</sup> Are Equivalent**

*Study GP15-302—TP1 Per-Protocol Set*

### Adjusted<sup>a</sup> PASI 75 response rates at Week 12

<table>
<thead>
<tr>
<th></th>
<th>GP2015 N=239</th>
<th>Enbrel N=241</th>
<th>Difference, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>73.4%</td>
<td>75.7%</td>
<td>−2.3</td>
</tr>
</tbody>
</table>

---

A Logistic regression adjusted for stratification factors.

---

95% CI as defined in the protocol

90% CI as requested by FDA
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.
<table>
<thead>
<tr>
<th>Score</th>
<th>Brief description</th>
<th>Detailed description</th>
</tr>
</thead>
</table>
| 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 responders (0 or 1), % (95% CI)

GP2015 (N=239)
Enbrel® (N=241)

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**

<table>
<thead>
<tr>
<th>Drug administration details</th>
<th>GP2015 N=264</th>
<th>Enbrel® N=267</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of exposure, days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>80.6 (9.7)</td>
<td>79.2 (11.6)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>81.0 (4.0-149.0)</td>
<td>81.0 (1.0-89.0)</td>
</tr>
<tr>
<td><strong>Patient exposure, yr</strong></td>
<td>58.3</td>
<td>57.9</td>
</tr>
<tr>
<td><strong>Missed doses, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>229 (86.7)</td>
<td>231 (86.5)</td>
</tr>
<tr>
<td>1</td>
<td>17 (6.4)</td>
<td>14 (5.2)</td>
</tr>
<tr>
<td>2</td>
<td>4 (1.5)</td>
<td>8 (3.0)</td>
</tr>
<tr>
<td>3</td>
<td>4 (1.5)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>4</td>
<td>3 (1.1)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>&gt;4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7 (2.7)</td>
<td>12 (4.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Patients considered incompliant to study drug during Blinded Data Review Meeting.
### TEAEs

**Study GP15-302—TP1 Safety Set**

<table>
<thead>
<tr>
<th></th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GP2015 N=264</td>
</tr>
<tr>
<td><strong>≥1 TEAE</strong></td>
<td>99 (37.5)</td>
</tr>
<tr>
<td><strong>≥1 SAE</strong></td>
<td>4 (1.5)</td>
</tr>
<tr>
<td><strong>≥1 treatment-related TEAE</strong></td>
<td>35 (13.3)</td>
</tr>
<tr>
<td><strong>≥1 severe TEAE</strong></td>
<td>4 (1.5)</td>
</tr>
<tr>
<td><strong>≥1 treatment-related SAE</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Discontinuation due to TEAE</strong></td>
<td>5 (1.9)</td>
</tr>
<tr>
<td><strong>Study drug interrupted due to TEAE</strong></td>
<td>3 (1.1)</td>
</tr>
<tr>
<td><strong>≥1 AE of special interest</strong></td>
<td>9 (3.4)</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td>0</td>
</tr>
</tbody>
</table>

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

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

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**

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

Primary endpoint:
Re-randomization if response $\geq$ PASI 50

<table>
<thead>
<tr>
<th>Week</th>
<th>GP2015</th>
<th>Enbrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 12</td>
<td>N=150</td>
<td></td>
</tr>
<tr>
<td>Wk 18</td>
<td>N=100</td>
<td></td>
</tr>
<tr>
<td>Wk 24</td>
<td>N=96</td>
<td></td>
</tr>
<tr>
<td>Wk 30</td>
<td>N=151</td>
<td></td>
</tr>
</tbody>
</table>
Comparable PASI Response Between Continued GP2015 and Enbrel®
Study GP15-302—TP2 Per-Protocol Set

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

Adjusted response rate, % (95% CI)

Visit, Week
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)

Primary endpoint
Re-randomization if response ≥PASI 50

Treatment Period 2

N=150
N=100
N=96
N=151
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

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Continued GP2015 N=150</td>
</tr>
<tr>
<td>≥1 TEAE</td>
<td>47 (31.3)</td>
</tr>
<tr>
<td>≥1 SAE</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>≥1 treatment-related TEAE</td>
<td>13 (8.7)</td>
</tr>
<tr>
<td>≥1 severe TEAE</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>≥1 treatment-related SAE</td>
<td>0</td>
</tr>
<tr>
<td>Discontinued due to TEAE</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Study drug interrupted due to TEAE</td>
<td>6 (4.0)</td>
</tr>
<tr>
<td>AEs of special interest</td>
<td>7 (4.7)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
</tr>
</tbody>
</table>

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**

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

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: \(\geq 20,000\) 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.
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

- **Clinical Confirmation**: Confirmatory efficacy, safety, and immunogenicity study in patients with moderate-to-severe plaque psoriasis
- **Pharmacokinetics**: PK bioequivalence studies in healthy volunteers
- **Non-clinical**: Animal PD, PK, toxicology
- **Analytical**: 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

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)

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®

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

Pharmacokinetics
- PK bioequivalence studies in healthy volunteers

Non-clinical
- Animal PD, PK, toxicology

Analytical
- 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
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
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.
Well Conducted Psoriasis Trials Have Consistent PASI Responses

PASI 75 Response to Ixekuzumab at 12 Weeks in 3 Large Phase 3 Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients, n</th>
<th>Placebo</th>
<th>Ixekizumab 80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncover 1</td>
<td>433</td>
<td>4</td>
<td>89</td>
</tr>
<tr>
<td>Uncover 2</td>
<td>351</td>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>Uncover 3</td>
<td>385</td>
<td>7</td>
<td>87</td>
</tr>
</tbody>
</table>

PASI, Psoriasis Area Severity Index

PASI 75 Is Sensitive to Dose-response Changes

% patients with PASI 75 response

- Placebo
- Etanercept 25 mg BIW
- Etanercept 50 mg BIW

* $P = 0.0013$ vs placebo
‡ $P < 0.001$ vs placebo
† $P = 0.004$ vs etanercept 25 mg BIW

BIW = twice weekly

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

PASI=Psoriasis Area Severity Index.
Ixekizumab: Itch NRS=0 Correlates With Level of Treatment Response at Week 12

Percentage of Patients With Itch=0 at Week 12

- PASI<50 (N=451): 1.8% (P=0.022)
- 50≤PASI<75 (N=85): 5.9% (p<0.001)
- 75≤PASI<90 (N=172): 26.2% (p=0.009)
- 90≤PASI<100 (N=290): 38.3% (p<0.001)
- PASI 100 (N=298): 71.1%
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
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

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**Mean Δ from baseline in DLQI score, % (±SD)**

- **GP2015 (N=239)**
- **Enbrel (N=241)**

**Time, weeks**

- **BL**
- **2**
- **4**
- **6**
- **8**
- **10**
- **12**

**Mean Δ from baseline in HAQ-DI score, % (±SD)**

- **GP2015 (PsA only)**
- **Enbrel (PsA only)**

**Time, weeks**

- **BL**
- **2**
- **4**
- **6**
- **8**
- **10**
- **12**

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**EQ-5D at Week 12**

Patients with slight problems

- **Mobility**
  - **GP2015**: 15.9
  - **Enbrel**: 13.7

- **Self-care**
  - **GP2015**: 10.9
  - **Enbrel**: 12.0

- **Usual activities**
  - **GP2015**: 16.7
  - **Enbrel**: 18.3

- **Pain/discomfort**
  - **GP2015**: 34.3
  - **Enbrel**: 32.8

- **Anxiety/depression**
  - **GP2015**: 25.9
  - **Enbrel**: 32.0

**Patients, %**

- **0**
- **10**
- **20**
- **30**
- **40**

---

**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.
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.
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 (50.0–79.9 kg)
Arithmetic Mean ± SD

Medium (80.0–99.9 kg)
Arithmetic Mean ± SD

High (100.0–140.0 kg)
Arithmetic Mean ± SD

Al=Autoinjector. PFS=pre-filled syringe. SD=standard deviation.
PASI 75 Response Rate Correlates With Body Weight

Study GP15-302—TP2 FAS (Pooled Data)
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Main analysis in PPS: difference % (95%CI)</th>
<th>Supportive analysis in FAS: difference % (95%CI)</th>
<th>Pre-specified equivalence limits, %</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong>:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASI 75 response at Week 12</td>
<td>-2.3 (-9.85, 5.30)</td>
<td>-1.2 (-8.77, 6.45)</td>
<td>(-18, 18)</td>
<td>GP2015 is equivalent to Enbrel®</td>
</tr>
<tr>
<td><strong>Secondary</strong>:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage change from baseline in PASI score up to 12 weeks (MMRM)</td>
<td>-0.64 (-3.47, 2.20)</td>
<td>-1.59 (-4.37, 1.18)</td>
<td>(-15, 15)</td>
<td>GP2015 is equivalent to Enbrel</td>
</tr>
<tr>
<td><strong>Secondary</strong>: Analysis of averaged treatment effect (ATE) of percent PASI change (ANCOVA)</td>
<td>-0.88 (-3.61, 1.85)</td>
<td>-2.14 (-4.97, 0.69)</td>
<td>(-15, 15)</td>
<td>GP2015 is equivalent to Enbrel</td>
</tr>
</tbody>
</table>

* 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)**

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