Biosimilars in Rheumatology
Learning Objectives

Upon completion of this program, the participant will be able to:

• Differentiate biosimilars from “biomimics”
• Recognize consequences of process changes in manufacture of biopharmaceuticals
• Identify requirements for regulatory approval of biosimilars
• Distinguish between switching and interchangeability of biosimilars with reference products
## Overview

- Definition of biosimilars
- Biomimics
- Biosimilars for rheumatologic diseases
- Biopharmaceuticals
  - Structure
  - Changes in manufacture
- Regulatory Aspects
- Comparative effectiveness trials
  - CT-P13
  - BOW015
- Immunogenicity
- Extrapolation of indications
- Interchangeability
What Are Biosimilars?

- Also called
  - Subsequent entry biopharmaceuticals (SEBs) – Canada¹
  - Biocomparables – Mexico²
- Regulatory definitions

A biosimilar is a biologic medicinal product that contains a version of the active substance of an already authorized original biologic medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biologic activity, safety, and efficacy based on a comprehensive comparability exercise.

Biosimilarity means “that the biologic product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biologic product and the reference product in terms of the safety, purity, and potency of the product”

Biosimilars Are Not “Second-Generation” Biopharmaceuticals

- “Second-Generation” Biopharmaceuticals
  - Structurally different from originally licensed biopharmaceutical
  - Intended to improve performance while preserving mechanism of action
  - Example:
    - Infliximab
    - Adalimumab
    - Golimumab
  - Not considered to be biosimilar

Biosimilars Are Not Generics

- Biosimilars are more complex than small-molecule drugs:
  - Manufacturing process is several orders of magnitude more complex
  - Regulated through different statutes

Small molecule
- Proof of quality (identical chemical structure)
- Pharmacokinetic bioequivalence
- Relies on clinical data from reference product

Biopharmaceutical
- Proof of quality & similarity
- Pharmacokinetic bioequivalence
- Clinical data showing comparable safety and efficacy

Generics

Biosimilars

Biosimilars Are Not “Biomimics” (AKA “Intended Copies”)

- Copy not developed, assessed, or approved according to regulatory guidelines for biosimilars
- Similarity not demonstrated by a stepwise and comprehensive comparability exercise
- May have differences in primary structure
- May differ from reference product in formulation, doses/dosing regimen, efficacy, safety, and immunogenicity; which may result in clinically significant differences

Biosimilars Are Biopharmaceuticals

- Highly similar to originator (reference) products\(^2\)
  - Biosimilars are developed to match the reference product
  - Biosimilars exhibit a range of structural similarities to reference product
    - Generally similar (eg, some natural products)
    - Highly similar (eg, some recombinant proteins)
    - Identical (eg, some peptides)

Marketed “Biomimics” Based On Biologic Agents Used To Treat Rheumatologic Diseases

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Manufacturer (location)</th>
<th>Marketed in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab biomimic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reditux™</td>
<td>Dr. Reddy’s Laboratories (India)</td>
<td>Bolivia, Chile, Ecuador, India, and Peru</td>
</tr>
<tr>
<td>Kikuzubam™</td>
<td>Probiomed (Mexico)</td>
<td>Withdrawn in March 2014 Bolivia, Chile, Mexico, and Peru</td>
</tr>
<tr>
<td>Etanercept biomimic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yisaipu</td>
<td>Shanghai CP Goujian Pharmaceutical Co. (China)</td>
<td>China</td>
</tr>
<tr>
<td>Etanar™</td>
<td>Shanghai CP Goujian Pharmaceutical Co. (China)</td>
<td>Colombia</td>
</tr>
<tr>
<td>Etacept™</td>
<td>Shanghai CP Goujian Pharmaceutical Co. (China)</td>
<td>India</td>
</tr>
<tr>
<td>Etart™</td>
<td>Shanghai CP Goujian Pharmaceutical Co. (China)</td>
<td>Mexico</td>
</tr>
<tr>
<td>Infinitam™</td>
<td>Probiomed (Mexico)</td>
<td>Mexico</td>
</tr>
</tbody>
</table>

http://www.latinlink.com/tag/latin-america-pharma/
CT-P13: First Approved Biosimilar mAb

- July 23, 2012: South Korean Ministry of Food & Drug Safety (MOFDS) granted approval
- June 27, 2013: CHMP recommended EMA approval
  - Remsima™ (Celltrion)
  - Inflectra™ (Hospira)
- September 10, 2013: European Commission granted approval
- Remsima™ has been launched in: Azerbaijan, Belarus, Bulgaria, Czech Republic, Finland, Georgia, Iceland, Kazakhstan, Latvia, Lithuania, Malta, Norway, Poland, Portugal, & Slovakia
- December 16, 2013: Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA) granted approval in Colombia
- January 15, 2014: Health Canada granted approval
- July 4, 2014: Pharmaceuticals Medical Devices Agency granted approval in Japan
- July 16, 2014: Ministry of Health granted approval in Turkey

http://www.gabionline.net/Biosimilars/News/Biosimilar-monoclonal-antibody-approved-in-Korea;
http://www.gabionline.net/Biosimilars/News/Remsima-approved-in-Colombia;
http://www.gabionline.net/Biosimilars/News/Biosimilar-infliximab-receives-approval-in-Japan-and-Turkey
CT-P13: Biosimilar Infliximab
Approved Indications

<table>
<thead>
<tr>
<th></th>
<th>Rheumatoid Arthritis</th>
<th>Ankylosing Spondylitis</th>
<th>Psoriatic Arthritis</th>
<th>Psoriasis</th>
<th>Crohn's Disease</th>
<th>Ulcerative Colitis</th>
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<tbody>
<tr>
<td>South Korea</td>
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<tr>
<td>European Union</td>
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<tr>
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<td>X</td>
<td></td>
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<td>X</td>
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<td>X</td>
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<tr>
<td>Japan</td>
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<tr>
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<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
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http://www.gabionline.net/Biosimilars/News/Biosimilar-monoclonal-antibody-approved-in-Korea;
http://www.gabionline.net/Biosimilars/News/Remsima-approved-in-Colombia;
http://www.gabionline.net/Biosimilars/News/Biosimilar-infliximab-receives-approval-in-Japan-and-Turkey
BOW015: Approved Biosimilar Infliximab

- Developed by EPIRUS Biopharmaceuticals, Inc.
- September 15, 2014: Drug Controller General of India (DCGI) granted approval
- Manufactured by Reliance Life Sciences at a facility in Mumbai, India
- December 1, 2014: Marketed in India as Infimab™ by Ranbaxy Laboratories Ltd.

http://www.gabionline.net/Biosimilars/News/Infliximab-similar-biologic-receives-Indian-approval
HD203: First Approved Biosimilar Etanercept

- Developed by Hanwha Chemical Corp. of South Korea

- November 11, 2014: South Korean Ministry of Food & Drug Safety (MOFDS) granted approval

http://www.hcplive.com/conferences/acr-2014/HD203-Biosimilar-is-Clinically-Equivalent-to-Etanercept
# Biosimilar TNF Inhibitors in Development To Treat Rheumatic Diseases

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Manufacturer (location)</th>
<th>Current status‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adalimumab biosimilar</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABP 501</td>
<td>Amgen (US)</td>
<td>Clinical trials (Phase III)</td>
</tr>
<tr>
<td>BI695501</td>
<td>Boehringer Ingelheim Pharmaceuticals (Germany)</td>
<td>Clinical trials (Phase III)</td>
</tr>
<tr>
<td>SB5</td>
<td>Samsung Bioepis (South Korea)</td>
<td>Clinical trials (Phase III)</td>
</tr>
<tr>
<td>PF-06410293</td>
<td>Pfizer (US)</td>
<td>Clinical trials (Phase I in Belgium &amp; US)</td>
</tr>
<tr>
<td>BOW050</td>
<td>EPIRUS Biopharmaceuticals (US)</td>
<td>Preclinical studies</td>
</tr>
<tr>
<td><strong>Etanercept biosimilar</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SB4</td>
<td>Samsung Bioepis (South Korea)</td>
<td>Clinical trials (Phase III)</td>
</tr>
<tr>
<td>TuNEX® (ENIA11)</td>
<td>TSH Biopharm Co., Ltd. (Taiwan)</td>
<td>Clinical trials (Phase III in Taiwan)</td>
</tr>
<tr>
<td>CHS-0214</td>
<td>Coherus Biosciences (US)/Baxter /Daiichi Sankyo</td>
<td>Clinical trials (Phase III)</td>
</tr>
<tr>
<td>LBEC0101</td>
<td>LG Life Sciences Ltd. (South Korea)</td>
<td>Clinical trials (Phase I in South Korea)</td>
</tr>
<tr>
<td>DWP422</td>
<td>Daewoong Pharmaceutical Co. Ltd. (South Korea)</td>
<td>Clinical trials (Phase I in South Korea)</td>
</tr>
<tr>
<td>Avent™</td>
<td>Avesthagen (India)</td>
<td>Preclinical studies</td>
</tr>
<tr>
<td>PRX-106 (plant cells)</td>
<td>Protalix Biotherapeutics (Israel)</td>
<td>Preclinical studies</td>
</tr>
<tr>
<td><strong>Infliximab biosimilar</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SB2</td>
<td>Samsung Bioepis (South Korea)</td>
<td>Clinical trials (Phase III)</td>
</tr>
<tr>
<td>PF-06438179</td>
<td>Pfizer (US)</td>
<td>Clinical trials (Phase III)</td>
</tr>
<tr>
<td>GS-071</td>
<td>Aprogen (South Korea)</td>
<td>Clinical trials (Phase I)</td>
</tr>
</tbody>
</table>

*BioXpress Therapeutics SA (Switzerland) is currently developing biosimilars for abatacept, adalimumab, etanercept, golimumab, infliximab, rituximab & tocilizumab.

‡As of December 2014.
# Rituximab Biosimilars in Development To Treat Rheumatic Diseases

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Manufacturer (location)</th>
<th>Current status‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCD-020</td>
<td>Biocad (Russian Federation)</td>
<td>Clinical trials (Phase III in Belarus, Colombia, India, Russian Federation, Ukraine)</td>
</tr>
<tr>
<td>BI695500</td>
<td>Boehringer Ingelheim Pharmaceuticals (Germany)</td>
<td>Clinical trials (Phase III in Belgium, Canada, Chile, Estonia, France, Germany, Hungary, Mexico, Poland, Portugal, Spain, US)</td>
</tr>
<tr>
<td>CT-P10</td>
<td>Celltrion (South Korea)</td>
<td>Clinical trials (Phase III)</td>
</tr>
<tr>
<td>SAIT101</td>
<td>Samsung (South Korea)</td>
<td>Clinical trials (Phase I/III in Argentina, Belgium, Brazil, Canada, Czech Republic, Korea, Chile, Mexico, Romania, Russian Federation, South Africa, Spain, Switzerland, Taiwan, Turkey, UK) – prematurely ended</td>
</tr>
<tr>
<td>TL011</td>
<td>Teva Pharmaceutical Industries (Israel)</td>
<td>Clinical trials (Phase III in Bulgaria, Czech Republic, Georgia, Germany, Hungary, Macedonia, Poland, Romania, Russian Federation, Serbia, Spain, Ukraine) – prematurely ended</td>
</tr>
<tr>
<td>PF-05280586</td>
<td>Pfizer (US)</td>
<td>Clinical trials (Phase I/II in US, Australia, Canada, Colombia, Germany, Israel, Mexico, Russian Federation, South Africa, UK)</td>
</tr>
<tr>
<td>GP2013</td>
<td>Sandoz Biopharmaceuticals (Switzerland)</td>
<td>Clinical trials (Phase I/II in Argentina, Austria, Brazil, France, Germany, India, Italy, Spain and Turkey)</td>
</tr>
<tr>
<td>MK-8808</td>
<td>Merck (US)</td>
<td>Clinical trials (Phase I in US, Belarus, Bulgaria, Colombia, Hungary, Poland, Russian Federation, Spain, UK)</td>
</tr>
<tr>
<td>MAb (plant cells)</td>
<td>iBio (US)</td>
<td>Preclinical studies</td>
</tr>
</tbody>
</table>

*BioXpress Therapeutics SA (Switzerland) is currently developing biosimilars for abatacept, adalimumab, etanercept, golimumab, infliximab, rituximab & tocilizumab.
‡As of December 2014.
Biopharmaceuticals (Originators and Biosimilars) Are Complex Proteins

Four Levels of Protein Structure

Primary

Secondary

Tertiary

Quaternary

All Biopharmaceuticals (Originators and Biosimilars) Are Subject to Variability

Variability Can Be Due to Changes In

- Protein-folding variants
- Misfolding
- Aggregation
- Enzymatic cleavage
- Glycosylation
- Disulfide bond formation
- Phosphorylation
- Deamidation
- Oxidation
- Amino acid substitution
- Degradation
- Other

Range of Structural Relationships Between Biosimilars & Reference Product

• Most biosimilars are not identical to their reference product

• Proteins produced by recombinant DNA exhibit a range of structural similarities
  – Share primary amino acid sequence
    • May have N- and C-terminal modifications
  – Different post-translational modifications
Originator Manufacturing Process Changes

- Small modifications may result in gradual changes
- Chemical characterization of different commercial lots of rituximab and etanercept produced between 2007 and 2011 revealed variations in both C-terminal lysine content and glycosylation

Despite these differences, when the products are within a prespecified acceptable range, the products are marketed with no change in label

If large alterations occur, analytical (and possibly additional clinical studies) are required to compare post-change product with existing pre-change product

Biosimilar Development Goal: Develop Product Highly Similar to Reference Product

- Approximately 3-fold increase in unfucosylated G0 glycans in later batches of rituximab resulted in more potent ADCC

Biosimilar Development Goal: Develop Product Highly Similar to Reference Product

Exercise to Claim Biosimilarity Must Demonstrate Equivalence Within Prespecified Margins (“Goalposts”)

Development of Biosimilars – Time Axis

Initial reference product quality range

Current reference product quality range

Pre-change

Post-change

Range for control of biosimilar product

Biosimilar Development Goal:
Develop Product Highly Similar to Reference Product

Exercise to Claim Biosimilarity Must Demonstrate Equivalence Within Prespecified Margins (“Goalposts”)

Development of Biosimilars – Time Axis

Initial reference product quality range

Current reference product quality range

Pre-change

Post-change

Range for control of biosimilar product

Figure adapted from McCamish M, Woollett G. mAbs. 2011;3(2):209-217. Worldwide experience with biosimilar development, Landes Bioscience, 2011.
Biopharmaceuticals: Changes in Manufacture

- Changes in production have resulted in decreased immunogenicity
  - Avonex® (interferon β1a produced by Biogen Idec in a new cell line) had decreased immunogenicity compared to the interferon β1a that had been produced in the original Chinese hamster ovary cell line by Bioferon Biochemische Substanzen GmbH & Co.

- Changes in formulation or packaging have resulted in increased immunogenicity with clinical consequences
  - Eprex® (rhEPO, Ortho Biotech)
    - Formulation change (switching protein stabilizer from human serum albumin to polysorbate 80) and
    - New packaging system (pre-filled syringe with rubber plunger for s.c. administration)
    - Resulted in formation of anti-EPO Ab that cross-reacted with endogenous EPO → 175 cases of pure red cell aplasia between 1998 and 2004

Worldwide Status of Regulations for the Approval of Biosimilar Agents*

The Objective of a Biosimilar Development Program is to **Establish Biosimilarity Based Upon Totality of Evidence, Not to Re-Establish Benefit**\(^1,2\)

**Biosimilar Pathway Represents a Paradigm Shift From Standard Originator Registration Pathway**

Originator Pathway [§ 351(a)]\(^3,4\)

- Clinical Studies
- Clinical pharmacology
- Preclinical
- Analytical

Biosimilar Pathway [§ 351(k)]\(^3,4\)

- Clinical Studies
- Clinical pharmacology
- PK/PD
- Preclinical
- Analytical
- Confirm safety and efficacy in a disease population (dose ranging not necessary)

PD = pharmacodynamics; PK = pharmacokinetics.

<table>
<thead>
<tr>
<th></th>
<th>WHO¹</th>
<th>EMA²</th>
<th>FDA³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference product</strong></td>
<td>Approved in country or licensed/marketed in jurisdiction with well-established regulatory framework</td>
<td>Authorized in EU based on complete dossier</td>
<td>Licensed by FDA</td>
</tr>
<tr>
<td><strong>Amino acid sequence</strong></td>
<td>If heterogeneity exists, must demonstrate no effect on efficacy/safety</td>
<td>Active substance must be similar in <em>molecular</em> and <em>biologic</em> terms</td>
<td>Same except for minor modifications such as N- or C-terminal truncations with no effect on safety, purity, potency</td>
</tr>
<tr>
<td><strong>Requirement for demonstration of PK bioequivalence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phase III endpoints: prespecified equivalence/noninferiority margins</strong></td>
<td>Must be justified based on clinical relevance</td>
<td>Must be clinically justified</td>
<td>Must be scientifically based</td>
</tr>
</tbody>
</table>

FDA = Food and Drug Administration; EMA = European Medicines Agency; EU = European union; WHO = World Health Organization.
## Synopsis and Comparison of Biosimilar Regulatory Guidance: WHO, EMA, and FDA (cont’d)

<table>
<thead>
<tr>
<th>Duration of immunogenicity study and comparative vs noncomparative phase</th>
<th>WHO¹</th>
<th>EMA²</th>
<th>FDA³,⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dependent on duration of therapy and expected antibody development time</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product-dependent; 1-year follow-up data required pre-license for chronic administration</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Extent and timing of program will vary</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Interchangeability</th>
<th>WHO¹</th>
<th>EMA²</th>
<th>FDA³,⁴</th>
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</thead>
<tbody>
<tr>
<td>Not under EMA jurisdiction</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>“…the risk in terms of safety or diminished efficacy of alternating or switching between the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.”</td>
<td></td>
<td></td>
<td>✓</td>
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</table>

<table>
<thead>
<tr>
<th>Postmarketing pharmacovigilance</th>
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<th>EMA²</th>
<th>FDA³,⁴</th>
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<tbody>
<tr>
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<td>✓</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extrapolation of indication (Extrapolation possible if sensitive clinical test model, similar MOA, and similar safety and immunogenicity issues in different population)</th>
<th>WHO¹</th>
<th>EMA²</th>
<th>FDA³,⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

MOA = mechanism of action.
May 2014: FDA Draft Guidance on Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product

- Defines “assessments within a development-phase continuum” based upon comparative analytical characterization.
  - Not similar
  - Similar
  - Highly similar
  - Highly similar with fingerprint-like similarity

- Specifies requirements for clinical trial
  - Comparison to US-licensed reference product
  - Parallel group design to assess similarity of biopharmaceuticals with long $t_{1/2}$ or potential for immunogenicity
  - “Most sensitive” route of administration “for detecting clinically meaningful differences”
  - “Frequent sampling at early time points following product administration with decreased frequency later” for PK measures

Biosimilars: Clinical Trial Design Issues

• Biosimilar must be studied at the same dose that is licensed for the reference biopharmaceutical
  – Dose-ranging studies (phase 2) are not needed for biosimilars

• Since the biosimilar must be almost identical to the reference biopharmaceutical, an active comparator clinical trial must demonstrate similarity within a prespecified margin ("goalposts")
  – If the ‘biosimilar’ is superior to the reference biopharmaceutical (‘bio-better’), it is not biosimilar
  – Thus, non-inferiority trial design is not adequate to assess biosimilarity
Phase 1 Double-Blind RCT of CT-P13 vs. Remicade® in Ankylosing Spondylitis

- 250 patients with active AS randomized 1:1 to receive either CT-P13 or Remicade® (5 mg/kg 2-hour IV infusion per dose)
  - Dose-loading phase: Weeks 0, 2, & 6
  - Maintenance phase: Weeks 14, 22, 30, 38, & 46
- Assessments
  - Ratios of geometric means of primary PK parameters between Weeks 22-30 were subjected to ANCOVA analysis at 90% CIs
  - ASAS20 & ASAS40 at Week 30
  - Safety (incidence of AEs)
- Primary endpoint: Ratio of geometric means of PK parameters in CT-P13 & Remicade® arms (Weeks 22-30)
  - AUCₜ: 1.05 (90% CI 0.94 to 1.16)
  - Cₘₐₓ,ss : 1.02 (90% CI 0.95 to 1.09)

<table>
<thead>
<tr>
<th>Related AEs (to Week 54)</th>
<th>CT-P13 (n=128)</th>
<th>Remicade® (n=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>62 (48.4%)</td>
<td>63 (51.6%)</td>
</tr>
<tr>
<td>Infections</td>
<td>30 (23.4%)</td>
<td>24 (19.7%)</td>
</tr>
<tr>
<td>Infusion reactions</td>
<td>4 (3.1%)</td>
<td>11 (9.0%)</td>
</tr>
<tr>
<td>TB</td>
<td>2 (1.6%)</td>
<td>1 (0.8%)</td>
</tr>
</tbody>
</table>

Phase 3 Double-Blind RCT of CT-P13 vs. Remicade® in Rheumatoid Arthritis

- 606 patients with active RA despite previous DMARDs randomized 1:1 to receive either CT-P13 or Remicade® (3 mg/kg 2-hour IV infusion per dose) + MTX & folic acid
  - Dose-loading phase: Wks 0, 2, & 6
  - Maintenance phase: Wks 14, 22, 30, 38, & 46
- Primary endpoint: Proportion of patients achieving ACR20 at week 30
  - Equivalence between treatments defined using exact binomial test with 95% CIs within margin of ±15%
- Secondary endpoints
  - ACR50/70
  - Frequency of AEs

![ACR Responses up to Week 54 ITT population graph]

<table>
<thead>
<tr>
<th>Related AEs (to Week 54)</th>
<th>CT-P13 (n=302)</th>
<th>Remicade® (n=300)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>131 (43.4%)</td>
<td>134 (44.7%)</td>
</tr>
<tr>
<td>Infections</td>
<td>69 (22.2%)</td>
<td>69 (23.0%)</td>
</tr>
<tr>
<td>Infusion reactions</td>
<td>23 (7.6%)</td>
<td>31 (10.3%)</td>
</tr>
<tr>
<td>TB</td>
<td>3 (1.0%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Patterns of Pharmacodynamic Response Over Time

- At primary endpoint of 30 weeks, each drug produces a similar response
- However, kinetics of response differ—most evident during initial 12 weeks
- To detect differences between biosimilars and originator biopharmaceuticals with greatest sensitivity, study multiple time points during steep phase of the time-response curve

Phase 3 Double-Blind RCT of BOW015 vs Remicade® in RA

Double-blind Phase

- BOW015 (infliximab biosimilar)
  - BOW015 (n=127)
- Reference Infliximab (INX)
  - INX (n=62)

Response assessment

Responders: BOW015 (n=161)

Non-responders: Followed to Week 26 (n=20)

Open-label Phase

Weeks

- 0
- 2
- 6
- 14
- 16
- 18
- 22
- 30
- 38
- 46
- 54
- 58

Infusions

- ↑↑
- ↑

1° endpoint

Phase 3 RCT of BOW015 vs Remicade® in RA: ACR20 Responders Over 54 Weeks

Kay J et al., ACR 2014, Poster LB21
Phase 3 Double-Blind RCT of BOW015 vs Remicade® in RA

- First clinical trial of a biosimilar infliximab to demonstrate & report kinetics of response to treatment at multiple time points prior to plateau phase
  - Greatest sensitivity to detect differences between biosimilar & reference biopharmaceutical is during steep phase of time-response curve.
  - Convincing evidence of therapeutic equivalence demonstrated by comparable % responders at each early time point through Week 16 primary endpoint & through Week 54
  - Comparable immunogenicity through Week 54
- New paradigm for comparative effectiveness testing of biosimilars

Kay J et al., ACR 2014, Poster LB21
Immunogenicity

- Anti-drug antibodies (ADA) develop in patients treated with reference biologic alone or with biosimilar alone
  - Most are not neutralizing
- Small differences between biosimilar & reference biologic might result in increased immunogenicity with interchange
- Development of ADA may depend more upon underlying disease process than upon concomitant methotrexate use
## CT-P13: Immunogenicity

### PLANETAS

<table>
<thead>
<tr>
<th>Week</th>
<th>CT-P13 5 mg/kg (N=128)</th>
<th>INX 5 mg/kg (N=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>9.1% (n=11)</td>
<td>11.0% (n=13)</td>
</tr>
<tr>
<td>30</td>
<td>27.4% (n=32)</td>
<td>22.5% (n=25)</td>
</tr>
</tbody>
</table>

### PLANETRA

<table>
<thead>
<tr>
<th>Week</th>
<th>MTX + CT-P13 3 mg/kg (N=302)</th>
<th>MTX + INX 3 mg/kg (N=304)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>25.4% (n=69)</td>
<td>25.8% (n=70)</td>
</tr>
<tr>
<td>30</td>
<td>48.4% (n=122)</td>
<td>48.2% (n=122)</td>
</tr>
<tr>
<td>54</td>
<td>52.3% (n=158)</td>
<td>49.5% (n=150)</td>
</tr>
</tbody>
</table>

Antibodies to infliximab were detected using INX tag

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Biosimilars: Extrapolation of Indications

- **2006**: Extrapolation of efficacy data for biosimilar to another indication, if reference product acts by same mechanism in each disease state
- **2011**: Extrapolation of efficacy & safety data from one indication to other indications
- **2012**: Extrapolation of data from a clinical trial of biosimilar conducted in one disease to support approval for additional indications, for which reference product is already licensed

Biosimilars: Extrapolation of Indications

• In which inflammatory disease(s) should a biosimilar be studied to provide adequate information for extrapolation of indications?
  – Rheumatoid arthritis
  – Juvenile inflammatory arthritis
  – Ankylosing spondylitis
  – Psoriatic arthritis
  – Psoriasis
  – Inflammatory bowel disease
    • Crohn’s disease
    • Ulcerative colitis
Biologics Price Competition and Innovation Act of 2009: Interchangeability

• If a biosimilar is determined to be ‘interchangeable,’ a pharmacist would be allowed to substitute the biosimilar for a prescribed biological therapy without involving the prescribing physician.

• Unlike small-molecule drugs, a biopharmaceutical that is repeatedly interchanged with a similar biological agent may exhibit immunogenicity that could compromise efficacy & safety of both medications.

• There should not be frequent switching between original protein product & biosimilar because even subtle differences, such as impurities introduced during manufacturing, may trigger an immune response to the biosimilar.
Switching versus Substitution

• **Switch = transition**
  – Patient transitioned to biosimilar, after initial treatment with innovator
  – Single switch study

• **Substitution = interchange**
  – Biologics Price Competition Act of 2009 affords 1 year of exclusive marketing rights to first biosimilar approved as being ‘interchangeable’ with reference product
  – Interchange could be initiated without prescriber input
  – Repeated switching study

• **Specific nomenclature would distinguish biosimilar from reference biopharmaceutical**
Summary and Conclusions

• Biosimilars are highly similar to their reference products
• Objective of biosimilar development program is to establish biosimilarity, not to re-establish benefit
• Stepwise and comprehensive comparative approach to claim biosimilarity must demonstrate a “totality of evidence,” with respect to physiochemical characteristics, biologic activity, pharmacokinetics, and clinical safety and efficacy
• Biosimilars undergo a rigorous regulatory approval process, with abbreviated clinical package
• With many biopharmaceuticals going off-patent in near future, opportunity exists to expand patient access through availability of biosimilars