Biosimilars: Clinical Study Design, Extrapolation, and Interchangeability

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DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

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Advisory Board – AbbVie, Amgen, Dermira, Janssen, Eli Lilly, Pfizer, Novartis, UCB Pharma, Medac, Stiefel/GlaxoSmithKline, UCB

Consultant – AbbVie, Amgen, Dermira, Janssen, Pfizer, Celgene, Eli Lilly, Merck, Novartis, Maruho, Medac, UCB, Xenoport

Honoraria – Abbvie

Biosimilar Clinical Trials

Biosimilar Clinical Trials

- Studies are smaller than registrational phase 3 clinical trials
  - Yet, quite rigorous
- Performed in a limited number of indications; less broad than the approved indications for the reference product
  - eg, biosimilar adalimumab tested in only psoriasis or rheumatoid arthritis in an effort to gain approval for all indications for Humira®

Equivalence Studies Are Necessary to Demonstrate Biosimilarity

Superiority study	Non-inferiority study	Equivalence study
Intended to demonstrate: – Proposed product provides superior efficacy	Intended to demonstrate: – Proposed product provides superior efficacy or – Proposed product is not inferior	Intended to demonstrate (based on a prespecified margin): – Proposed product is not inferior – Proposed product is not superior
Usually used for: new agents vs standard of care		

1. US Food and Drug Administration. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291128.pdf. Accessed May 2015. 2. Peter C. *Curr Control Trials Cardiovasc Med.* 2004;5:8.

Considerations for Demonstrating Clinical Equivalence

Objective: To demonstrate that the biosimilar has neither decreased nor increased efficacy compared with the reference product and has similar immunogenicity

Study Design

- Two-sided test to demonstrate equivalence; with an appropriate equivalence margin
- A one-sided non-inferiority design is more appropriate in certain circumstances

Endpoints and Study Population

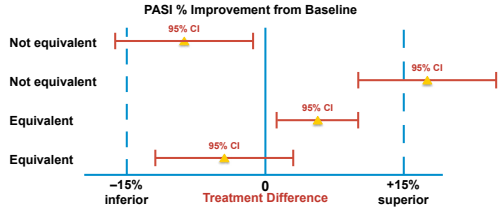
- Clinically relevant and sensitive in detecting clinically meaningful differences
- Selected by considering comorbidities and effect on disease state (eg, immunosuppressed)

Important Considerations

- Clinical trial should allow:
  - Sufficient exposure
  - Detection of relevant safety signals
  - Detection of clinically meaningful differences in effectiveness and safety

US Food and Drug Administration. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM405113.pdf. Accessed February 7, 2015.

Clinical Equivalence Margin

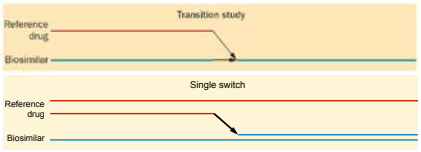


- **Margin:** The degree of inferiority/superiority of the biosimilar to the reference that the trial will exclude statistically
- **Margin Choice:** Defined prior to the start of the trial, taking historical data and relevant clinical and statistical considerations into account
- **Equivalence:** Requires that the difference between the means of the test and the control agent (95% CI) falls *entirely* within the equivalence margin

Peter C. *Curr Control Trials Cardiovasc Med.* 2004;5:8.

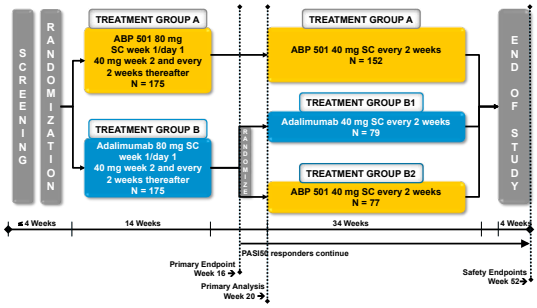
Biosimilar Switch Study Designs

- Biosimilar studies may be designed to include switching between the reference biologic and the biosimilar



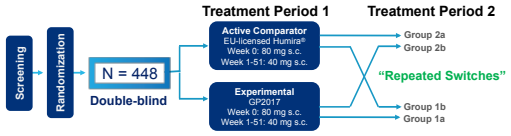
1. Dörner T, Kay J. *Nat Rev Rheumatol* [published online ahead of print August 18, 2015] doi:10.1038/nrrheum.2015.110. 2. Papp, et al. Poster presented at: European Academy of Dermatology and Venereology Congress; October 7–11, 2015; Copenhagen, Denmark. Poster: P1736.

In the Phase 3 Study of ABP 501 at Week 16, Patients With Moderate to Severe Plaque Psoriasis Receiving Adalimumab Are Re-randomized to Receive ABP 501 or Continue on Adalimumab



Papp, et al. Poster presented at: European Academy of Dermatology and Venereology Congress; October 7–11, 2015; Copenhagen, Denmark. Poster: P1736.

ADACCESS Study: Phase 3 Study to Demonstrate Equivalent Efficacy and to Compare Safety of GP2017 (Biosimilar to Adalimumab) and Humira® in Patients with Plaque Psoriasis



s.c. subcutaneous
ClinicalTrials.gov: http://clinicaltrials.gov/ct2/show/NCT02167555. Accessed September 2015; EU Clinical Trials Register: https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-000747-11/BG. Accessed September 2015.

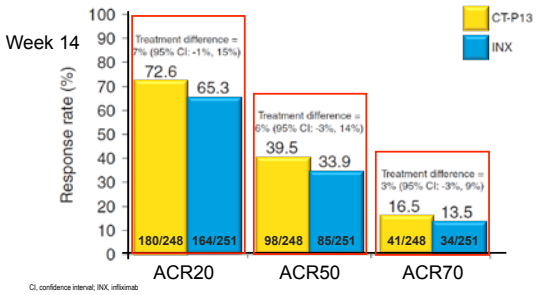
What do the completed biosimilar clinical trials demonstrate?

Biosimilar Clinical Trial: Infliximab

- Infliximab → chimeric monoclonal antibody against TNF-α
  - Reference product: Remicade® (Janssen Biotech, Inc.)
    - Approved by the FDA for the treatment of rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and psoriasis
  - Biosimilar product: CT-P13, or Inflectra™/Remsima™ (Hospira and Celltrion Healthcare)
    - Recommended by the EMA for authorization in the same indications as Remicade, including rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and psoriasis[1]
    - Health Canada approved Remsima™ for all indications of Remicade ® except adult and pediatric Crohn's disease and ulcerative colitis[2,3]
      - Differences were observed in *in vitro* ADCC assays
      - "Because ADCC cannot be ruled out as a mechanism of drug action in inflammatory bowel disease, extrapolation to these indications was not supported by the data provided"

EMA, European Medicines Agency; FDA, US Food and Drug Administration
1. European Medicines Agency. News release; June 28, 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002578/WC500144892.pdf. Accessed September 2015. 2.Feldman SR. *Semin Arthritis Rheum.* 2015;44:S16-S21. 3. Health Canada. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smb/drug-medsbd_smd_2014_remsima_180195-eng.php#bkd. Accessed March 2015.

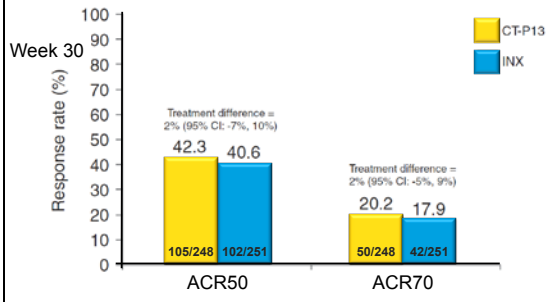
Biosimilar Clinical Trial: Infliximab



CI, confidence interval; INX, infliximab

Yoo HD, et al. *Ann Rheum Dis.* 2013; 72:1613-1620.

Biosimilar Clinical Trial: Infliximab



Yoo HD, et al. *Ann Rheum Dis.* 2013; 72:1613-1620.

Biosimilar Clinical Trial: Infliximab

Treatment-emergent adverse events

Related TEAEs reported in at least 1% of patients in either treatment group, number (%)	CT-P13: 3 mg/kg (n=301)*	INX: 3 mg/kg (n=301)*	Total (N=602)
Alanine aminotransferase increased	12 (4.0)	11 (3.7)	23 (3.8)
Aspartate aminotransferase increased	8 (2.7)	8 (2.7)	16 (2.7)
γ-Glutamyltransferase increased	2 (0.7)	3 (1.0)	5 (0.8)
Latent tuberculosis	13 (4.3)	14 (4.7)	27 (4.5)
Upper respiratory tract infection	4 (1.3)	4 (1.3)	8 (1.3)
Urinary tract infection	4 (1.3)	7 (2.3)	11 (1.8)
Bronchitis	4 (1.3)	4 (1.3)	8 (1.3)
Nasopharyngitis	6 (2.0)	4 (1.3)	10 (1.7)
Gastroenteritis	2 (0.7)	3 (1.0)	5 (0.8)
Herpes zoster	1 (0.3)	3 (1.0)	4 (0.7)
Rhinitis	0	3 (1.0)	3 (0.5)
Tuberculosis	3 (1.0)	0	3 (0.5)
Infusion-related reaction	20 (6.6)	25 (8.3)	45 (7.5)
Anemia	2 (0.7)	3 (1.0)	5 (0.8)
Neutropenia	3 (1.0)	2 (0.7)	5 (0.8)
Leukopenia	1 (0.3)	3 (1.0)	4 (0.7)
Headache	4 (1.3)	6 (2.0)	10 (1.7)
Pyrexia	0	3 (1.0)	4 (0.7)
Rash	1 (0.3)	4 (1.3)	5 (0.8)
Nausea	1 (0.3)	3 (1.0)	4 (0.7)
Flare in rheumatoid arthritis activity	7 (2.3)	4 (1.3)	11 (1.8)
Bone pain	3 (1.0)	0	6 (1.0)
Hypertension	5 (1.7)	3 (1.0)	8 (1.3)

*Patients who received at least one (full or partial) dose of CT-P13 were included in the CT-P13 group for safety analyses, irrespective of their randomization

TEAE, treatment-emergent adverse event

Yoo HD, et al. *Ann Rheum Dis.* 2013; 72:1613-1620.

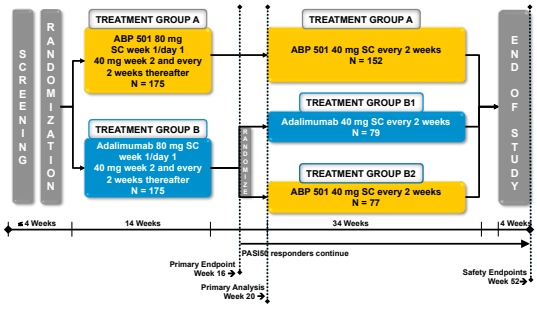
Biosimilar Clinical Trial: Infliximab and Immunogenicity

- Antibodies to infliximab (immunogenicity)
  - 25.4% (n = 69) and 25.8% (n = 70) of patients for CT-P13 and INX at week 14
  - 48.4% (n = 122) and 48.2% (n = 122) of patients for CT-P13 and INX, respectively, at week 30
- Pharmacokinetics (C_{max})
  - CT-P13, range 83.9–111.9 µg/mL
  - INX, range 83.8–105.1 µg/mL)

C_{max}, maximum concentration

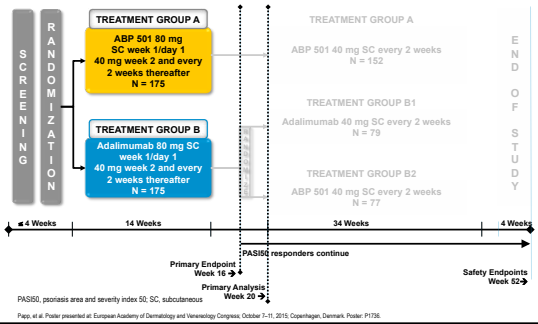
Yoo HD, et al. *Ann Rheum Dis.* 2013; 72:1613-1620.

Biosimilar Clinical Trial: Adalimumab



Papp, et al. Poster presented at: European Academy of Dermatology and Venereology Congress; October 7–11, 2015; Copenhagen, Denmark. Poster: P1736.

Biosimilar Clinical Trial: Adalimumab



PASI50, psoriasis area and severity index 50; SC, subcutaneous

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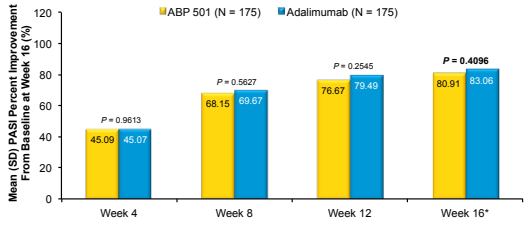
Adalimumab: PASI Percent Improvement



- **At week 16, the mean treatment difference* was –2.18 (95% CI, –7.39, 3.02); *P* = 0.4096**
- **The 95% CI was within the predefined equivalence margin of (–15, 15)**

*Primary endpoint; †estimated using ANCOVA model adjusted for prior biologic use for psoriasis, region, and baseline PASI score
Full analysis set; LOCF
ANCOVA, analysis of covariance; LOCF, last observation carried forward

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Adalimumab: Treatment-Emergent Adverse Events Reported in >2% of Subjects in Any Treatment Group by Preferred Term Through Week 16

Preferred Term	ABP 501 (N = 174) Number of Subjects n (%)	Adalimumab (N = 173) Number of Subjects n (%)
Any adverse event	117 (67.2)	110 (63.6)
Nasopharyngitis	25 (14.4)	27 (15.6)
Headache	13 (7.5)	18 (10.4)
Upper respiratory tract infection	9 (5.2)	9 (5.2)
Arthralgia	5 (2.9)	7 (4.0)
Back pain	7 (4.0)	1 (0.6)
Pruritus	3 (1.7)	6 (3.5)
Rhinitis	3 (1.7)	6 (3.5)

Adverse events are coded using MedDRA version 17.0. Only treatment-emergent adverse events are summarized. For each preferred term, a subject is included only once, even if he/she experienced multiple events in that preferred term

- No imbalances ≥ 5% observed between ABP 501 and adalimumab at the preferred term level

MedDRA, Medical Dictionary for Regulatory Activities

Papp, et al. Poster presented at: European Academy of Dermatology and Venereology Congress; October 7–11, 2015; Copenhagen, Denmark. Poster: P1736.

Adalimumab: Immunogencity

Variable	ABP 501 (N = 174)	Adalimumab (N = 173)
Binding-antibody-positive post-baseline, n (%)	96 (55.2)	110 (63.6)
95% CI for treatment difference*	(–18.2, 2.0)	
Neutralizing-antibody-positive post-baseline, n (%)	17 (9.8)	24 (13.9)

Baseline is defined as the last non-missing assessment taken prior to the first dose of study investigational product
Estimated using a generalized linear model adjusted for the following factors: prior biologic use for psoriasis and region

Papp, et al. Poster presented at: European Academy of Dermatology and Venereology Congress; October 7–11, 2015; Copenhagen, Denmark. Poster: P1736.

Extrapolation: Approval in one indication confers approval in all indications of the reference product

Extrapolation: Timeline of Select Regulatory Agency Guidance

Extrapolation:

A proposed biosimilar product may be licensed in one or more additional indications for which the reference product is licensed, if appropriate scientific justification is provided

2006
EMA CHMP: Efficacy data for a biosimilar could be generalized from one indication to another

2011
EMA CHMP: extended extrapolation to include safety data in addition to efficacy data

2012
FDA: Data from a clinical trial of a biosimilar conducted in one disease could be used to support extrapolation

CHMP, Committee for Medicinal Products for Human Use
European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf. Accessed September 2015.
US Food and Drug Administration. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm444861.pdf. Accessed September 2015.

In Addition to Totality of Evidence, Extrapolation of Indications Requires Scientific Justification

Scientific Justification Should Establish:

- PK, PD, and immunogenicity in different patient populations
- Differences in expected toxicities in each indication
- MoA in each indication[a]
- Any other factor that may affect safety or effectiveness in each indication

Health authorities may have differing perspectives on what evidence is sufficient to support extrapolation

[a]MoA in each indication may include target/receptors for each relevant activity/function; binding, dose/concentration of response, and pattern of molecular signaling upon engagement of target; relationship between product structure and target/receptor interactions; and location and expression of target/receptors
MoA, mechanism of action

US Food and Drug Administration. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM405138.pdf. Accessed April 30, 2015.

FDA Recommendations Address Considerations Related to Extrapolation

Considerations[1]

Potential for distinct MoA in each therapeutic indication

- Extrapolation considered on case by-case basis
- When MoA is not fully understood, need separate clinical trials in each indication
- Biological data covering all functional aspects of agent, demonstrating high similarity to reference, is required

1. Dörner T, et al. *Ann Rheum Dis.* 2013;72:322-328. 2. US Food and Drug Administration. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed February 7, 2015. 3. Feagan BG, et al. *Biologicals.* 2014;42:177-183.

FDA Recommendations Address Considerations Related to Extrapolation

Considerations[1]

Variable optimal doses for efficacy or safety profiles in different patient groups

- Data are produced using patient population and clinical endpoint most sensitive to detect clinically meaningful differences in efficacy and safety

1. Dörner T, et al. *Ann Rheum Dis.* 2013;72:322-328. 2. US Food and Drug Administration. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed February 7, 2015. 3. Feagan BG, et al. *Biologicals.* 2014;42:177-183.

FDA Recommendations Address Considerations Related to Extrapolation

Considerations[1]

Influence of individual patient characteristics on treatment response

- Careful consideration must be given to comorbidities/ concomitant medications and intersubject variability

1. Dörner T, et al. *Ann Rheum Dis.* 2013;72:322-328. 2. US Food and Drug Administration. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed February 7, 2015. 3. Feagan BG, et al. *Biologicals.* 2014;42:177-183.

Extrapolation Is Not Always Granted

EU

Remsima™ (**Infliximab**)

Investigated In:

- Rheumatoid Arthritis
- Ankylosing Spondylitis

Extrapolated to:

- Psoriasis
- Psoriatic Arthritis
- Pediatric Crohn's Disease/ Ulcerative Colitis
- Crohn's Disease/ Ulcerative Colitis

Health Canada. http://www.hc-sc.gc.ca/dhp-mps/prodpharm/sbd-smb/drug-med/sbd_smd_2014_remsima_160195-eng.php. Accessed September 2015.

Interchangeability: FDA Draft Guidance*

- Designation of a biosimilar based on additional evidence demonstrating that the biosimilar can be expected to produce the same clinical result as the reference product in any given patient[1]
- If the biosimilar is administered more than once to an individual, the risks in terms of safety or diminished efficacy of switching between the biosimilar and the reference product are not greater than using the reference product alone[1]

*The FDA has not yet issued final guidance on interchangeability[1,2]

1. US Food and Drug Administration. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf. Accessed August 2015. 2. US Food and Drug Administration. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291128.pdf. Accessed August 2015.

Thank you