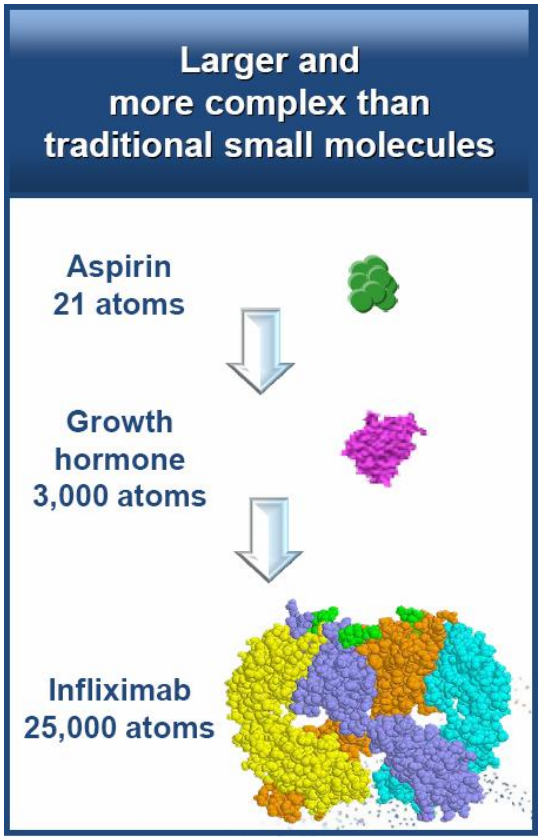
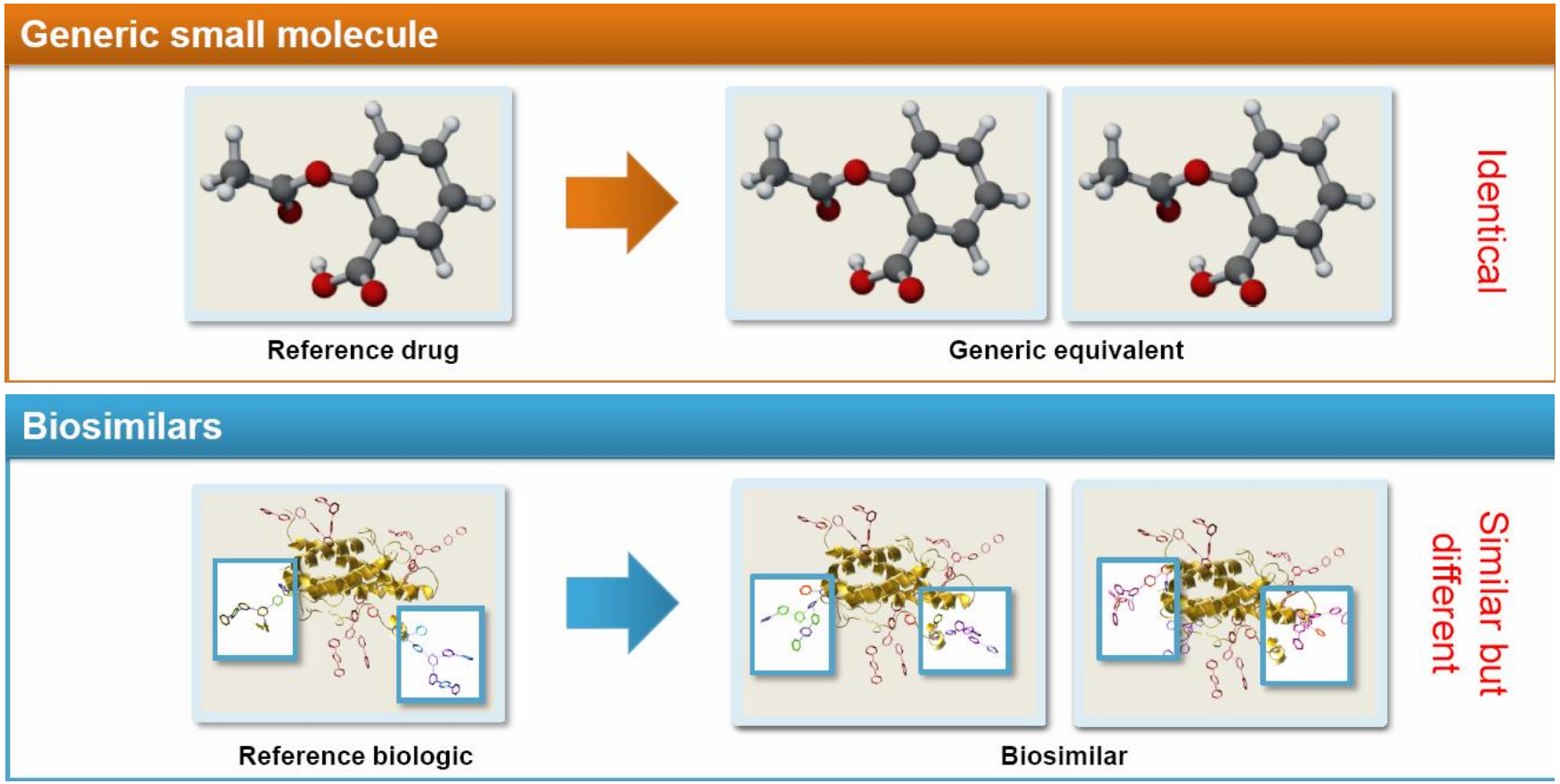
- Biosimilars in Rheumatology:From evidence to experience.
- Morton Scheinberg
- APLAR 2015
- Chennai India.

- There is now considerable interest in biosimilars among rheumatologists,although there is a perception that most rheumatologists in practice are still not familiar with the differences bewteen a true biosimilar and a biomimic (or intended copy).

Larger and more complex than traditional small molecules



Generic drugs versus biosimilars



- Many countries have changed their regulatory requirements to accommodate this new class of medicinal products and to distinguish them from generics.[1,2] Currently, only one biosimilar is approved by the European Medicines Agency (EMA) for the treatment of rheumatologic diseases: an infliximab biosimilar that is commercialized as Remsima®/Inflectra®. Following the lead of the EMA, regulatory agencies inother countries, including South Korea, Canada, Japan, Turkey and Colombia [3], have approved this infliximab biosimilar.

- .....the approved indications differ among these countries. For example, EMA allowed the results of clinical trials conducted in rheumatologic diseases trials to be extrapolated to inflammatory bowel diseases, while HealthCanada did not.[4] Recently, BOW015, an infliximab biosimilar with the commercial name Infimab® [5], and ZRC-3197, an adalimumab biosimilar with the commercial name Exemptia® [6], were approved in India while HD203, an etanercept biosimilar, was approved in South Korea [7]. Whether other countries will approve these products?

Principles of biosimilarity

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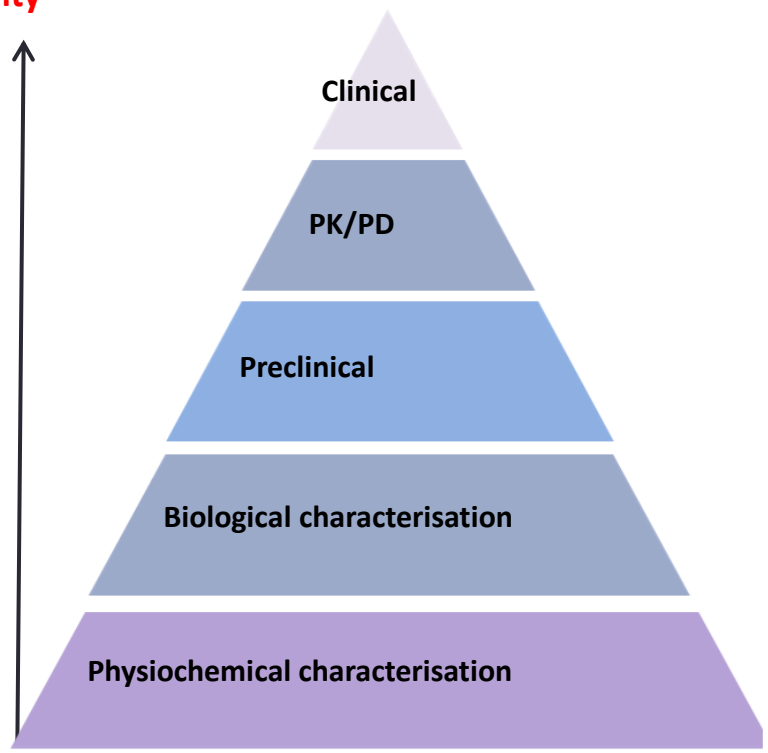
Stepwise approach

Demonstration of Biosimilarity[1,2]



Entire biosimilar process is built on a solid foundation of **extensive** analytical characterization which is **robustly assessed**

Principles of biosimilar comparability exercise are based on the evaluation of the impact of changes in the manufacturing process (ICH Q5E)[2]

1. EMA website. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp Accessed 01 July 2013.
2. ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. Available at: http://www.fda.gov/OHRMS/DOCKETS/98fr/2004d-0118-gdl0001.pdf. Accessed 01 July 2013.

- Understanding the principles by which these trials are designed and analyzed will help the clinician to evaluate and use these drugs in practice.

BIOSIMILARS IN RHEUMATOLOGY: WHAT CLINICIANS SHOULD KNOW

GILBERTO CASTAÑEDA-HERNÁNDEZ[1,2], RODRIGO GONZÁLEZ-RAMÍREZ[1], JONATHAN KAY[3] AND MORTON A. SCHEINBERG[4,5]

RMD APRIL 2015

Gilberto Castañeda-Hernández[1,2], Rodrigo González-Ramírez[1], Jonathan Kay[3] and Morton A. Scheinberg[4,5]

RMD April 2015

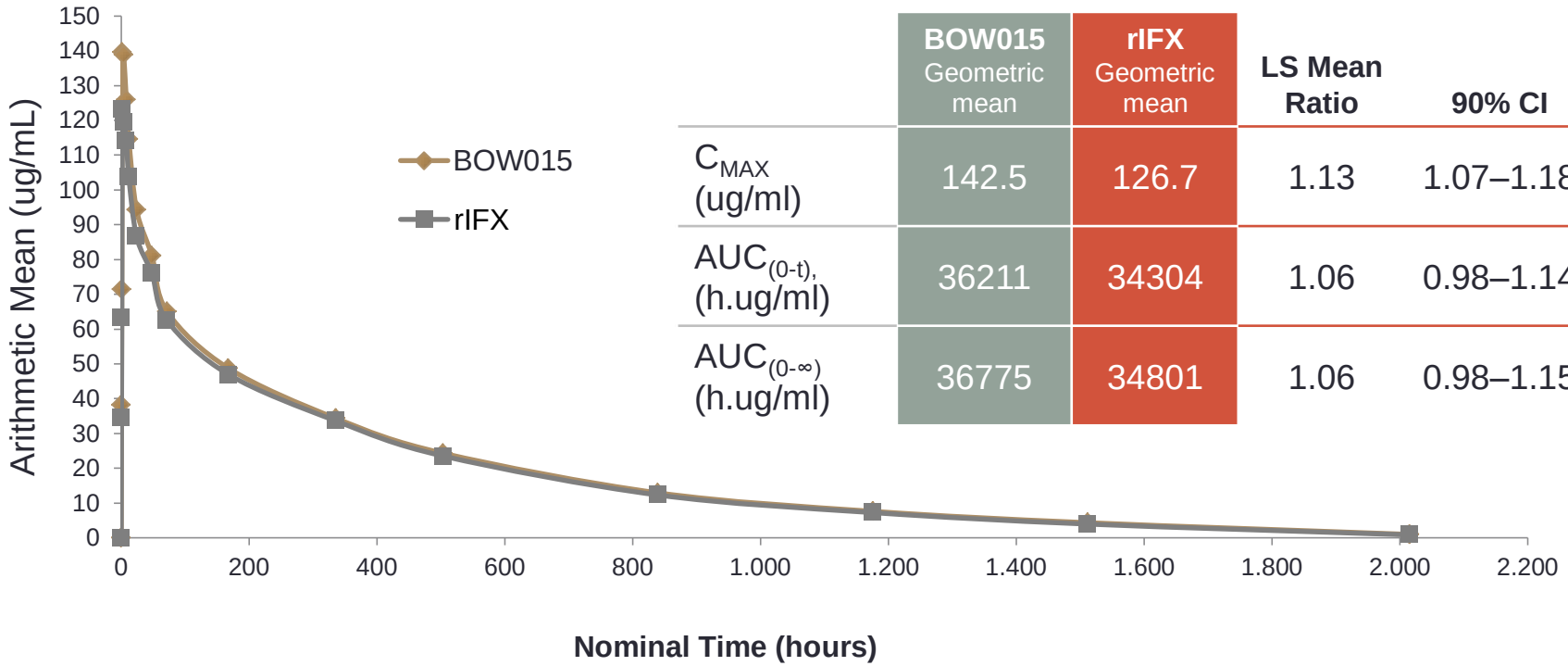
- **Pharmacokinetic studies**

- Pharmacokinetic comparisons demonstrating equivalence of certain biosimilars with their corresponding innovators have been conducted both in healthy volunteers and in patients with rheumatologic diseases.[9-11] Pharmacokinetic equivalence is necessary, but not sufficient, to demonstrate biosimilarity.

- Biosimilars are not identical to innovators. Certain molecular differences, albeit minimal, can modify affinity for the target ligand without modifying pharmacokinetics.[2,8] Hence, innovator and non-innovator products may exhibit differences in clinical efficacy and safety despite comparable pharmacokinetics. This is why, unlike generic small molecule drugs, bioequivalence of a biosimilar with its reference product cannot be established solely on pharmacokinetic grounds.[8,11]

Completed BOW015 Phase 1- *Pharmacokinetics*

Arithmetic Mean Infliximab Serum Concentration versus Nominal Time
Overlaid by Treatment: Linear Scale (PP Population)

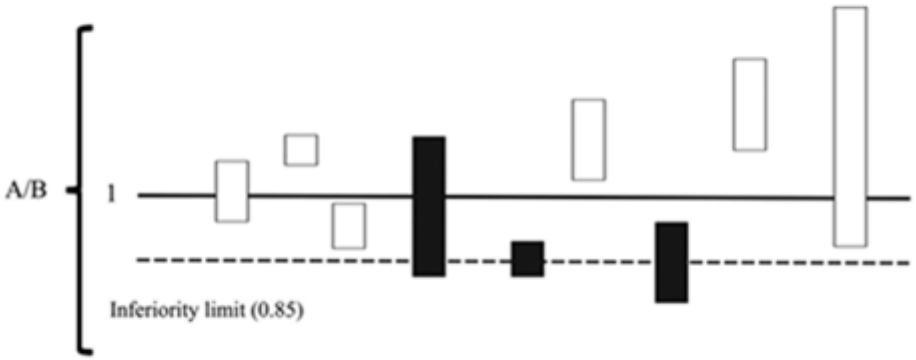


	BOW015 Geometric mean	rIFX Geometric mean	LS Mean Ratio	90% CI
C_{MAX} (ug/ml)	142.5	126.7	1.13	1.07–1.18
$AUC_{(0-t)}$, (h.ug/ml)	36211	34304	1.06	0.98–1.14
$AUC_{(0-\infty)}$ (h.ug/ml)	36775	34801	1.06	0.98–1.15

- Study powered to 90% to detect bioequivalence at 90% confidence interval of BOW015 to rIFX
  - Range 0.8 to 1.25 C_{MAX}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$

Lambert J, et al. Pharmacokinetic Results from a Phase 1, Single-centre, Double-blind, Randomised, Single-dose, Parallel-Group Study Comparing 5 mg/kg IV Infusion of BOW015 and Reference Infliximab in Healthy Male Volunteers [Abstract]. Presented at EULAR 2015.

Graphical representation of non-inferiority analyses.



Gilberto Castañeda-Hernández et al. RMD Open 2015;1:e000010

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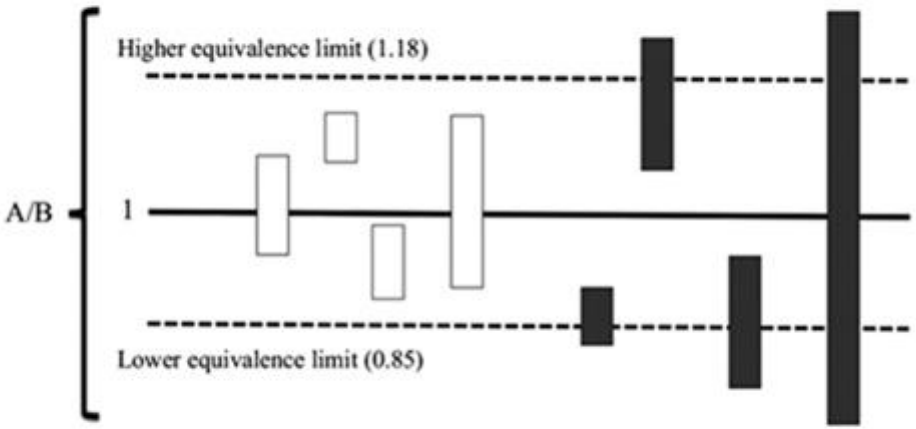
Graphical representation of equivalence analyses.



Gilberto Castañeda-Hernández et al. RMD Open 2015;1:e000010

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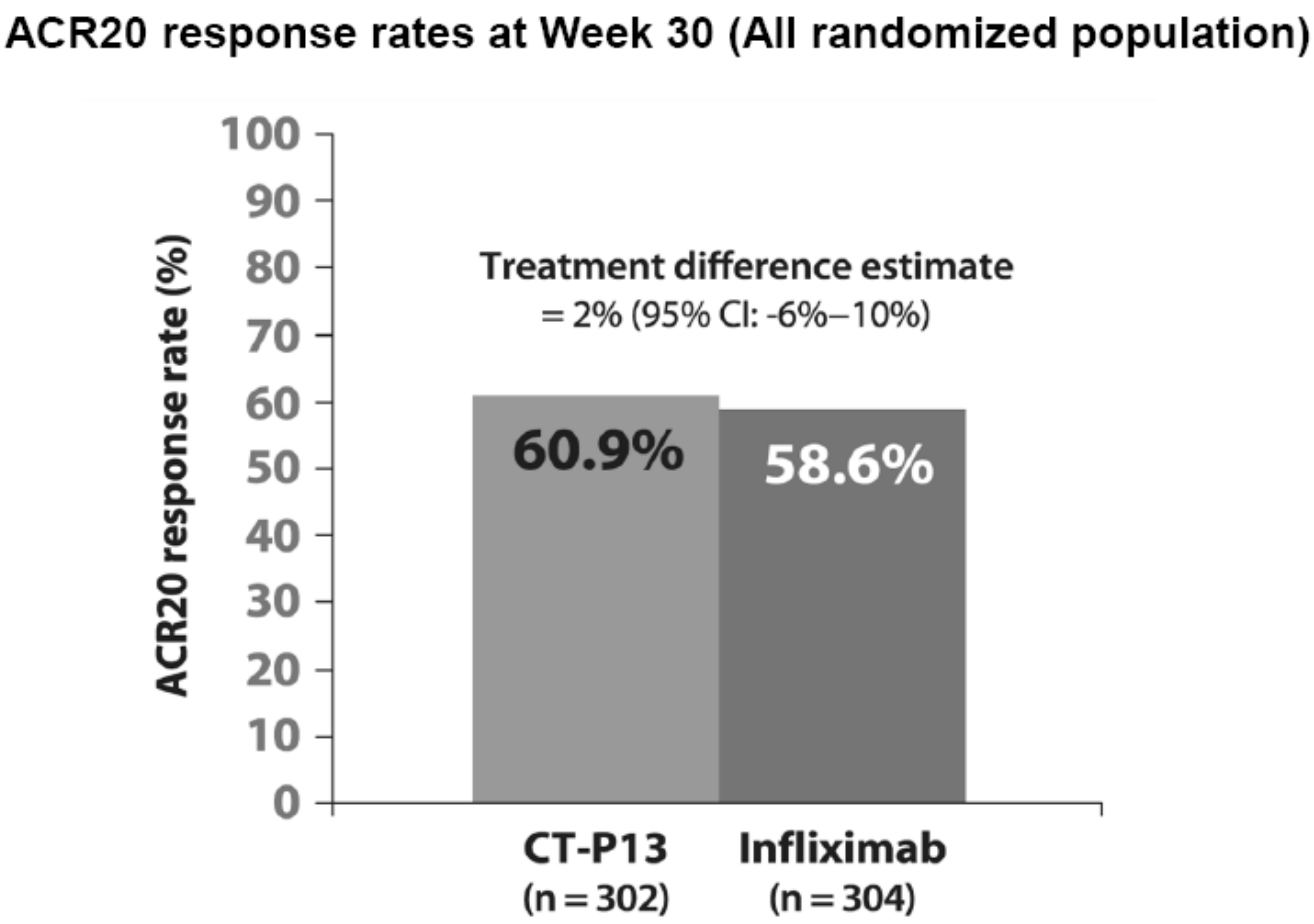
- The infliximab biosimilar CT-P13 showed efficacy equivalent to that of innovator infliximab (Remicade®) in the PLANETRA study.[18] In this study,606 patients with rheumatoid arthritis, inadequately responsive to with methotrexate, were randomized 1:1 to receive either CT-P13 or innovatorinfliximab. The primary efficacy outcome was the proportion of subjectsachieving an ACR20 response at 30 weeks.

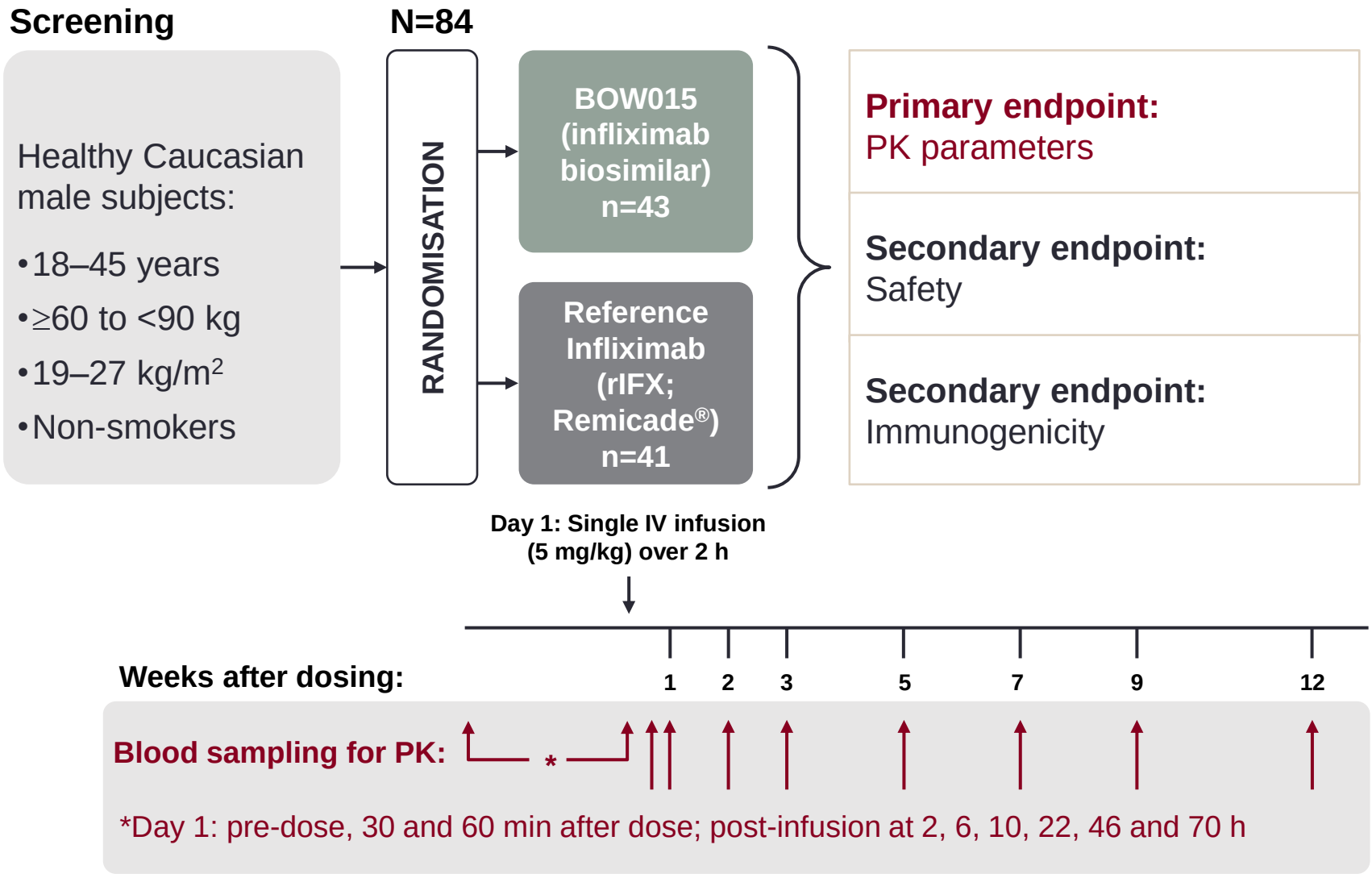
- At this time point, the response rates for the biosimilar and the innovator were 60.9% (184/302) and 58.9% (178/304), respectively, in the intention-to-treat population. The difference between treatments was 2% with a 95% confidence limit of -6% to 10%.

- Since the entirety of this confidence interval lies within the preestablished range of ±15% (0.85 – 1.18 after logarithmic transformation), the efficacy of CT-P13 was considered to be equivalent to that of innovator infliximab. Asimilar finding was observed in the per protocol analysis, where theresponse rates for the biosimilar and the innovator were 73.4% (182/248) and 69.7% (175/251), respectively.
- The difference between treatments in this analysis was 4%, with a 95% confidence interval of -4% to – 12%. Sincethis 95% confidence interval also lies entirely within the preestablished range of ±15%, the two treatments again were considered to be equivalent.

Phase III PLANETRA Efficacy: ACR20 Response rates



Completed BOW015 Phase 1 - *Study Design*



Lambert J, et al. Pharmacokinetic Results from a Phase 1, Single-centre, Double-blind, Randomised, Single-dose, Parallel-Group Study Comparing 5 mg/kg IV Infusion of BOW015 and Reference Infliximab in Healthy Male Volunteers [Abstract]. Presented at EULAR 2015.

Completed BOW015 Phase 1 *Safety*

Adverse Event	BOW015 (n=43) E (%)	rIFX (n=41) E (%)
Nasopharyngitis	6 (13.95)	4 (9.76)
Mycobacterium Tuberculosis Complex Test Positive	0	2 (4.88)
Headache	1 (2.33)	4 (9.76)
Cough	2 (4.65)	0
Oropharyngeal Pain	2 (4.65)	1 (2.44)

E = number of events

- 26 (60%) subjects in the BOW015 group reported 50 treatment-emergent adverse events (TEAE) vs 27 (66%) in the rIFX group who reported 54 TEAE
  - Most considered to be mild intensity
- No withdrawals from either group
- Majority of abnormal clinical laboratory values not significant
  - Clinically significant increase in transminases in 1 patient from each group at week 12
- No difference in immunogenicity between the two groups

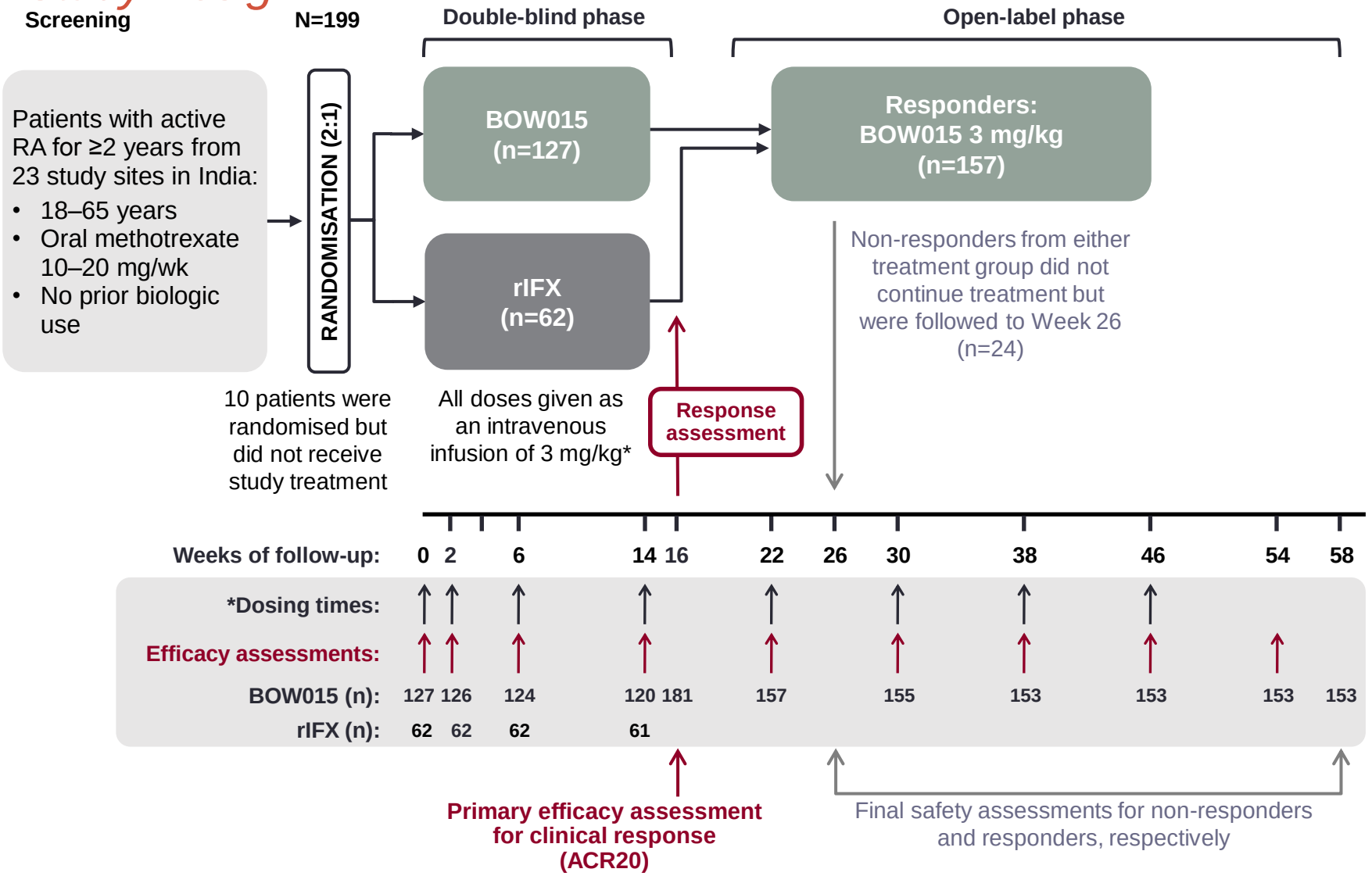
Lambert J, et al. Pharmacokinetic Results from a Phase 1, Single-centre, Double-blind, Randomised, Single-dose, Parallel-Group Study Comparing 5 mg/kg IV Infusion of BOW015 and Reference Infliximab in Healthy Male Volunteers [Abstract]. Presented at EULAR 2015.

COMPLETED BOW015 PHASE 3 STUDY RESULTS

Efficacy, Safety, Immunogenicity

Completed BOW015 Phase 3

Study Design



Kay J, et al. BOW015, a biosimilar infliximab, in patients with active rheumatoid arthritis on stable methotrexate doses: 54-week results of a randomized, double-blind, active comparator study [Abstract]. Arthritis Rheumatol. 2014; 66:3538.

Completed BOW015 Phase 3
Key Inclusion/Exclusion Criteria

Inclusion Criteria

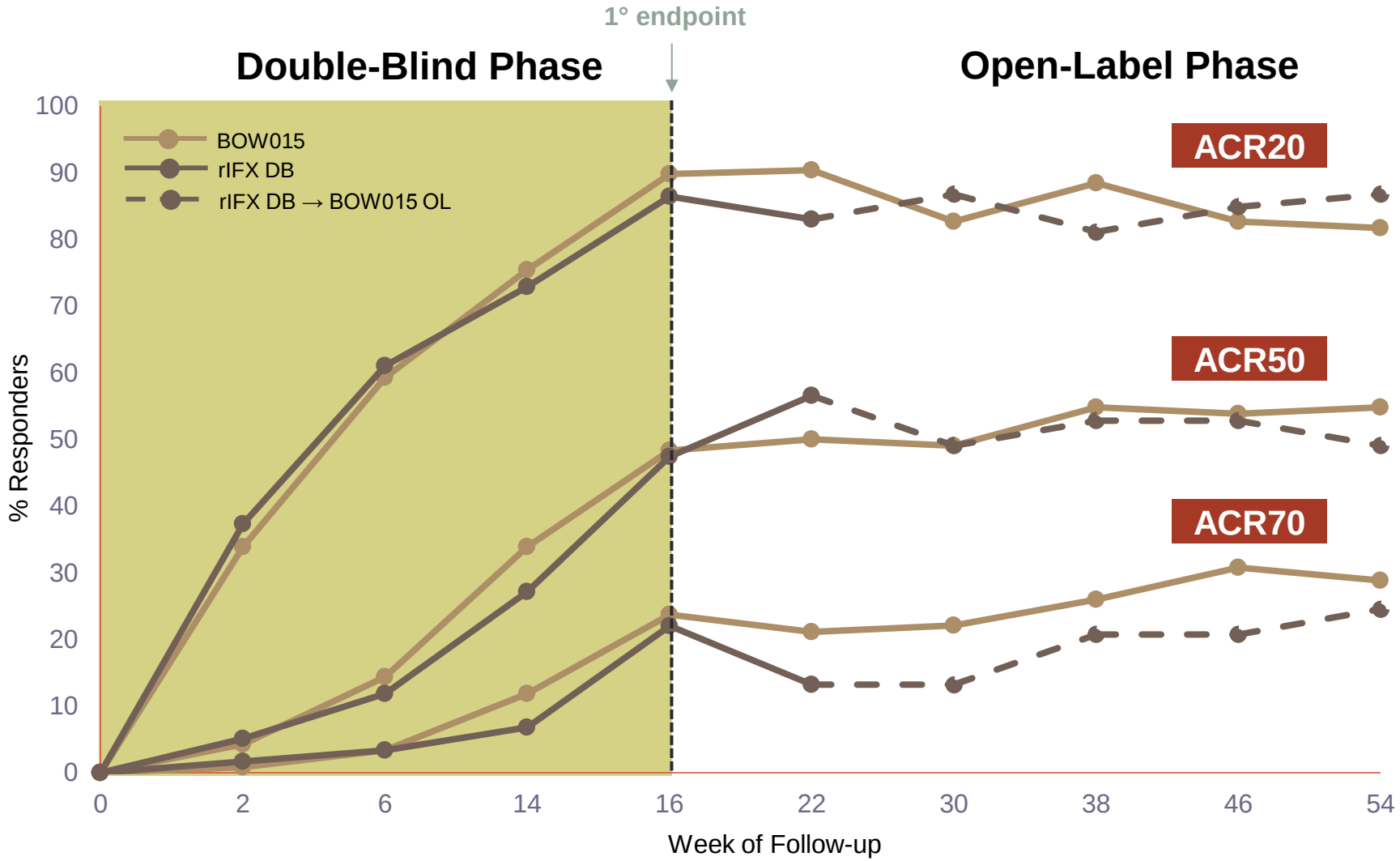
- Age 18–65 years
- RA ≥2 yrs (2010 ACR/EULAR criteria - score ≥6)
  - ≥6 SJC & ≥6 TJC
  - CRP ≥10 mg/L
- Stable medication doses
  - Oral MTX (10-20 mg/week)
  - Oral corticosteroids (≤5 mg/d)
  - NSAIDs

Exclusion Criteria

- Prior biological use
- Active TB
- Evidence of latent TB
  - Chest radiographs
  - PPD
  - QuantiFERON®-TB Gold
  - High resolution chest CT (optional)

Kay J, et al. BOW015, a biosimilar infliximab, in patients with active rheumatoid arthritis on stable methotrexate doses: 54-week results of a randomized, double-blind, active comparator study [Abstract]. Arthritis Rheumatol. 2014; 66:3538.

Completed BOW015 Phase 3 - *ACR Response Rates*



BOW015 – patients who were initiated on BOW015 in the double-blind phase and from among whom responders were maintained on BOW015 in the open-label phase; rIFX DB – patients who were initiated on rIFX in the double-blind phase; rIFX DB → BOW015 OL – responders who switched from rIFX to BOW015 in the open-label phase.

Kay J, et al. BOW015, a biosimilar infliximab, in patients with active rheumatoid arthritis on stable methotrexate doses: 54-week results of a randomized, double-blind, active comparator study [Abstract]. Arthritis Rheumatol. 2014; 66:3538.

Completed BOW015 Phase 3
Serious adverse events (Double Blind Phase)

BOW015		rIFX
• Paranasal sinusitis* • Urinary tract infection* • Right middle lobe infection syndrome* • Enteric infection* • Urinary tract infection*	• Pulmonary tuberculosis† • Left lower limb cellulitis† • Abscess over left thigh‡ • Abscess over right foot around little toe§	• Gastroenteritis* • Supra pubic abscess† • Displaced intramedular nail • Abnormal prolonged uterine bleeding*

N=1 for all serious adverse events listed; *No change in treatment; †Treatment withdrawn; ‡Treatment interrupted; §Subject was in safety follow-up and no change in treatment was planned

Kay J, et al. Safety Profile of BOW015, a Biosimilar Infliximab, in Healthy Subjects and Patients with Active Rheumatoid Arthritis [Abstract]. Presented at EULAR 2015.

Completed BOW015 Phase 3
Efficacy Conclusions

- **Similar % ACR20 response** at each early time point and at week 16 primary endpoint
  - Consistent results for all **secondary efficacy endpoints**
- Long-term efficacy data support the **durability of response** to BOW015, both for patients **initiated** on BOW015 and those **switched** from rIFX to BOW015 in the OL phase

Completed BOW015 Phase 3
Safety Conclusions

- BOW015 was **safe and well-tolerated**, with a safety profile **similar to rIFX** in the DB phase with respect to TEAEs, discontinuations due to TEAEs, infusion reactions, and immunogenicity
  - Three cases of TB were reported during the double-blind comparator portion of the study
  - Given the high incidence of TB in India and the 2:1 randomization of the study, the number of cases is considered within the expected range for anti-TNF treatment
- Long-term safety data demonstrate **no observable difference** in safety for patients **initiated** on BOW015 and those who **switched** from rIFX to BOW015 in the OL phase

Completed BOW015 Phase 3
Overall Conclusions

The “totality of evidence” supports equivalence of BOW015 to rIFX

- ✓ Pharmacokinetics
- ✓ Efficacy
- ✓ Safety
- ✓ Immunogenicity

- **Non-inferiority approach**

- In some circumstances, a non-inferiority approach can be suitable to evaluate biosimilarity.[17,19]. The guidelines on biosimilar evaluation issued by the World Health Organization consider a non-inferiority design to be acceptable.[20]

- Accordingly, several countries will accept such a non-inferiority approach. In Canada, regulatory authorities have acknowledgedthat an equivalence trial design is preferred. However, if clearly justified, a non-inferiority approach may be acceptable under certain conditions.

- Evidence must be provided that an eventual superiority has no clinical meaning and that there is no increase in adverse reactions with regard to the reference product.[21] In comparative effectiveness clinical trials designed using a non-inferiority approach, the test product can be superior to the reference product but it cannot be inferior.

Adalimumab similar biologic launched in India

- Indian generics maker Zydus Cadila announced on 9 December 2014 the launch of its adalimumab similar biologic in India.
- The similar biologic has been approved by the Drug Controller General of India for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis. The drug will be marketed under the brand name Exemptia (adalimumab).
- Zydus Cadila claims to be 'the first company anywhere in the world to launch a biosimilar of adalimumab'. They add that Exemptia is a 'fingerprint match with the originator in terms of safety, purity and potency of the product'.
- AbbVie's blockbuster arthritis and psoriasis treatment Humira (adalimumab) was first approved globally in 2002 and is the world's top selling prescription drug. Humira had sales of almost US$10.7 billion in 2013, accounting for almost 60% of AbbVie's total sales. Patents on Humira expire in the US in December 2016 and in Europe April 2018 [1].
- Despite the fact that more than 12 million patients in India suffer from these chronic conditions the therapy has not been available to patients in India. 'This therapy will offer a new lease of life to millions in India who did not have access to this therapy so far,' according to Dr Sharvil P Patel, Deputy Managing Director of Zydus Cadila.
- Exemptia will be offered at a fifth of Humira's price in the country (which costs around US$1,000 a vial in the US). Although a price of US$200 a vial would still keep the drug out of reach for most people in India, where more than 70% of the population lives on less than US$2 a day and health insurance is scarce.
- Exemptia will be marketed by Zydus Biovation – a new division launched to exclusively market this 'ground breaking therapy'. Dr Patel expects sales of between Rupees 1 billion (US$16.16 million) and Rupees 2 billion for Exemptia in the Indian market.
- The company expects to launch the medicine in the US in 2019 and already has meetings scheduled with Europe and US regulators for 2015.

Table 1. Summary of global phase III clinical efficacy studies for biosimilar adalimumab[1].

Company	IMP	Indication	Study Start	Status	Number of Patients	EudraCT Number
Amgen	ABP-501	PsO	2013	Completed	350	NCT01970488
		RA	2013	Completed	526	NCT01970475
Boehringer Ingelheim	BI 695501	RA	2014	Recruiting	650	NCT02137226 2012-002945-40
FujiFilm Kyowa Kirin Biologics	FKB327	RA	2014	Recruiting	600	NCT02260791 2014-000109-11
Pfizer	PF-06410293	RA	2014	Recruiting	560	2014-000352-29
Samsung Bioepis	SB5	RA	2014	Ongoing, not recruiting.	490	NCT02167139 2013-005013-13
Sandoz/Novartis	GP2017	PsO	2013	Ongoing, not recruiting.	448	NCT02016105 2013-000747-11

- Yisaipu® is an etanercept biomimic that is manufactured and marketed in China. It also is commercialized as Etanar® in Colombia, as Etart® in Mexico,and as Etacept®in India.[2,8,12,25,26].

- Clinical experience in China has found Yisaipu® to be effective.[26]However, it is surprising that, despite this product having been used in China for over a decade, no data have been published about drug survival or on the incidence of tuberculosis and other adverse effects. Furthermore, no head-to-head studies have been conducted to comparing Yisaipu® to innovator etanercept. Thus, this product cannot be considered to be an etanercept biosimilar.

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Rheumatol Int (2009) 29:297–303
DOI 10.1007/s00296-008-0681-x

ORIGINAL ARTICLE

A comparison study of a recombinant tumor necrosis factor receptor:Fc fusion protein (rhTNFR:Fc) and methotrexate in treatment of patients with active rheumatoid arthritis in China

Dawei Hu · Chunde Bao · Shunle Chen · Jieruo Gu · Zhanguo Li · Lingyun Sun · Xinghai Han · Liqing Ni

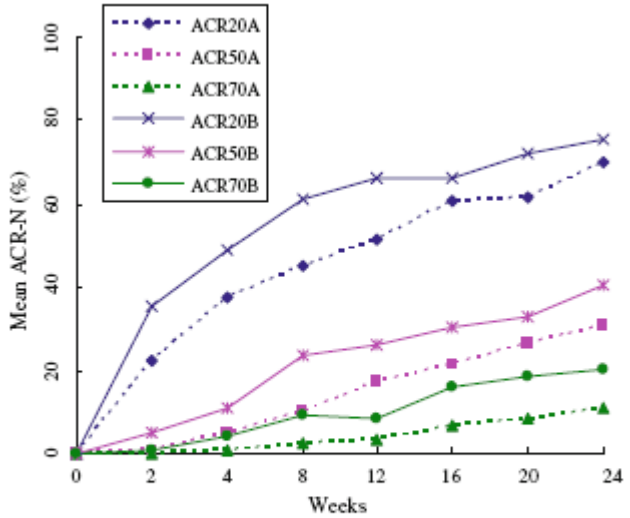


Fig. 1 Mean response of patients with RA to treatment with rhTNFR:Fc or MTX according to the percent improvement from base line as measured by the American College of Rheumatology criteria (ACR-N, *symbols*). A: MTX, B: rhTNFR:Fc

- An abstract describing an open-label study of Etanar® treatment in 110patients with rheumatoid arthritis was presented at the 2010 ACR Annual Scientific meeting,.[27] The patients enrolled were receiving a variety of antirheumatic drug regimens concomitantly with Etanar. The number of patients studied was small, considering the variety of treatment regimens that were allowed. Etanar® was not compared to innovator etanercept.

COMPARATIVE, RANDOMIZED, SIMPLE BLIND TO EVALUATE EFFICACY AND SAFETY OF INFINITAM® (ETANERCEPT), ASSOCIATED WITH METHOTREXATE COMPARED WITH ENBREL® (ETANERCEPT) ASSOCIATED WITH METHOTREXATE IN PATIENTS WITH MODEATE AND SEVERE RHEUMATOID ARTHRITIS

J. F. Moctezuma 1,*, A. Martinez 2, H. Enkerlin 3, C. Garcia 1, B. Chavez 2, N. Salazar-Teran 4, A. Molina 4, J. Revilla 4

1Rheumatology Service, Hospital De Jesus IAP, 2Rheumatology Service, Hospital

San Jose, Mexico City, 3Rheumatology Service, Instituto Mexicano de Investigación Clínica, mexico City, 4Medical Management, Probiomed S.A. de C.V., Mexico City, Mexico

- Objectives: To evaluate the efficacy and safety of Infinitam®(biosimilar
- etanercept) compared with Enbrel®(reference etanercept) after 12 and
- 24 weeks of treatment.
- Methods: This is a three treatment group randomized study: first and
- second group were in a PK sub population. First group received
- methotrexate plus *biosimilar Etanercept* 25 mg twice weekly (n=12)
- during 24 weeks. Second group initially received methotrexate
- plus *reference Etanercept*25 mg twice weekly (n=12) followed by 12
- weeks with methotrexate plus *biosimilar Etanercept* 25 mg twice
- weekly. Third group received methotrexate plus *biosimilar*
- *Etanercept* 25 mg twice weekly (n=30) during 24 weeks. Primary end
- point was to evaluate the average on patients who achieved on the
- Disease Activity Score 28 joint assessment (DAS28) at weeks 12 and
- 24.

- Conclusions: Clinical response, procedures and observations at the end
- of treatment was as expected in all group of patients. Study drug safety
- was similar for both drugs. All patients improved DAS28 evaluations.

- Infinitam® is a non-innovator etanercept that is manufactured and marketedby the Mexican company, Probiomed.[25] An abstract describing a study comparing Infinitam® to innovator etanercept (Enbrel®) was presented in the 2013 EULAR Annual Scientific meeting.[28] The design of this study is confusing.

- Three groups of patients were studied. In the first group, 12 patients received Infinitam® and methotrexate for 24 weeks. In the second group, 12 patients initially received Infinitam® and methotrexate for 12 weeks, followed by innovator etanercept and methotrexate for the subsequent 12 weeks.

- Patients in these two groups were participating in a pharmacokinetic study. In the third group, 30 patients received Infinitam®and methotrexate for 24 weeks. The stated primary endpoint was DAS28 at weeks 12 and 24. The authors concluded that DAS28 improved and thatdrug safety was similar in all treatment groups. However, it appears that onlypatients enrolled in the first and third groups had the same treatmentregimen.

- The only distinction between these groups was that patients in the first group were participating in a pharmacokinetic study, whereas those in the third group were not. The authors concluded that “none [**sic**] significant difference was observed in the pharmacokinetic groups (p=0.355)”.

- As mentioned earlier, failure to detect a significant difference is neitherevidence of equivalence nor of biosimilarity. This is particularly true when the sample size is evidently small (12 patients per group), yielding high standard deviation values

- **BIOMIMICS OR INTENDED COPIES**

- Biomimics, also known as jntended copies, are non-innovator biologics that had been approved before biosimilar regulations were put in place. Theycurrently are available in some Asian and Latin American countries.

A Phase I Pharmacokinetic Study Comparing SB4, na Etanercept Biosimilar, and Etanercept Reference Product (Enbrel®) In Healthy Male Subjects

Yoon Jung Lee[1], Donghoon Shin[1], Youngdoe Kim[1], Jung Won Kang[1], Rainard Fuhr[2], A Gauliard[2]

[1]Samsung Bioepis Co., Incheon, Korea, Republic of, [2]PAREXEL International Early Phase Clinical Unit, Berlin, Germany

A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy

- *Paul Emery,1 Jiří Vencovský,2 Anna Sylwestrzak,3 Piotr Leszczyński,4 Wieslawa Porawska,5 Asta Baranauskaite,6 Vira Tseluyko,7 Vyacheslav M Zhdan,8 Barbara Stasiuk,9 Roma Milasiene,10 Aaron Alejandro Barrera Rodriguez,11 Soo Yeon Cheong,12 Jeehoon Ghil12*

- http://ard.bmj.com/ on July 6, 2015

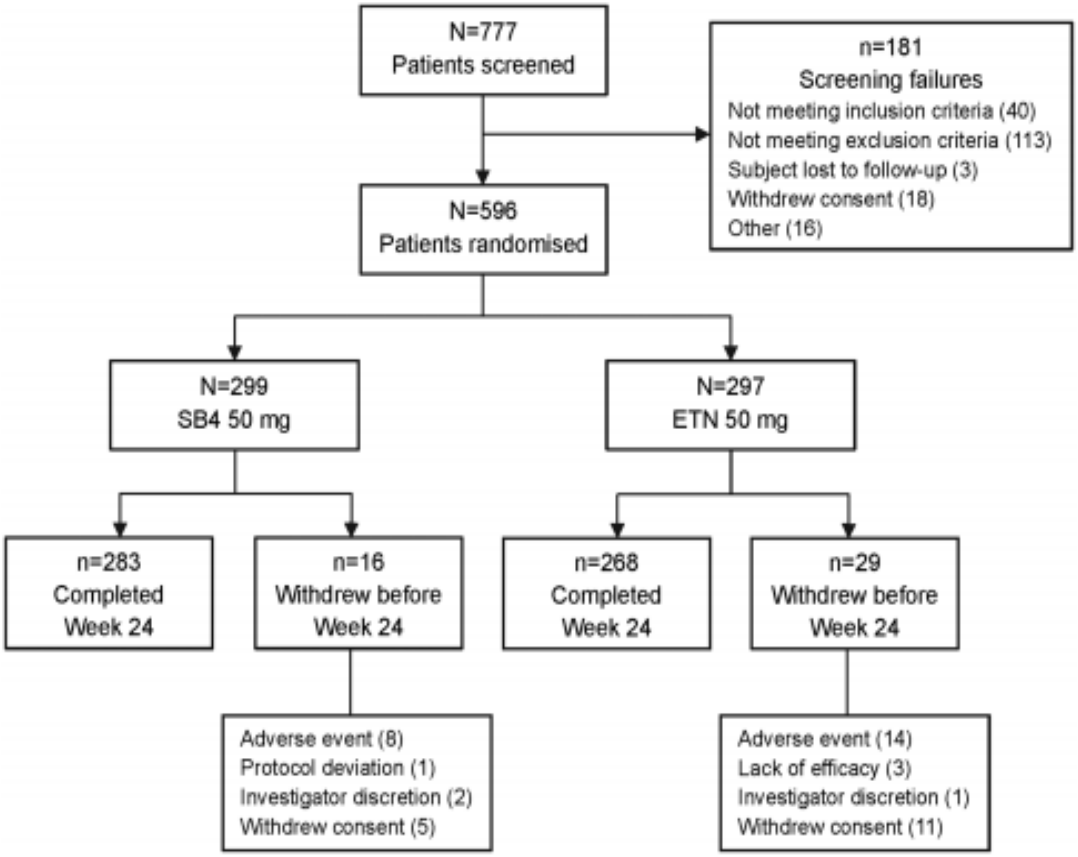
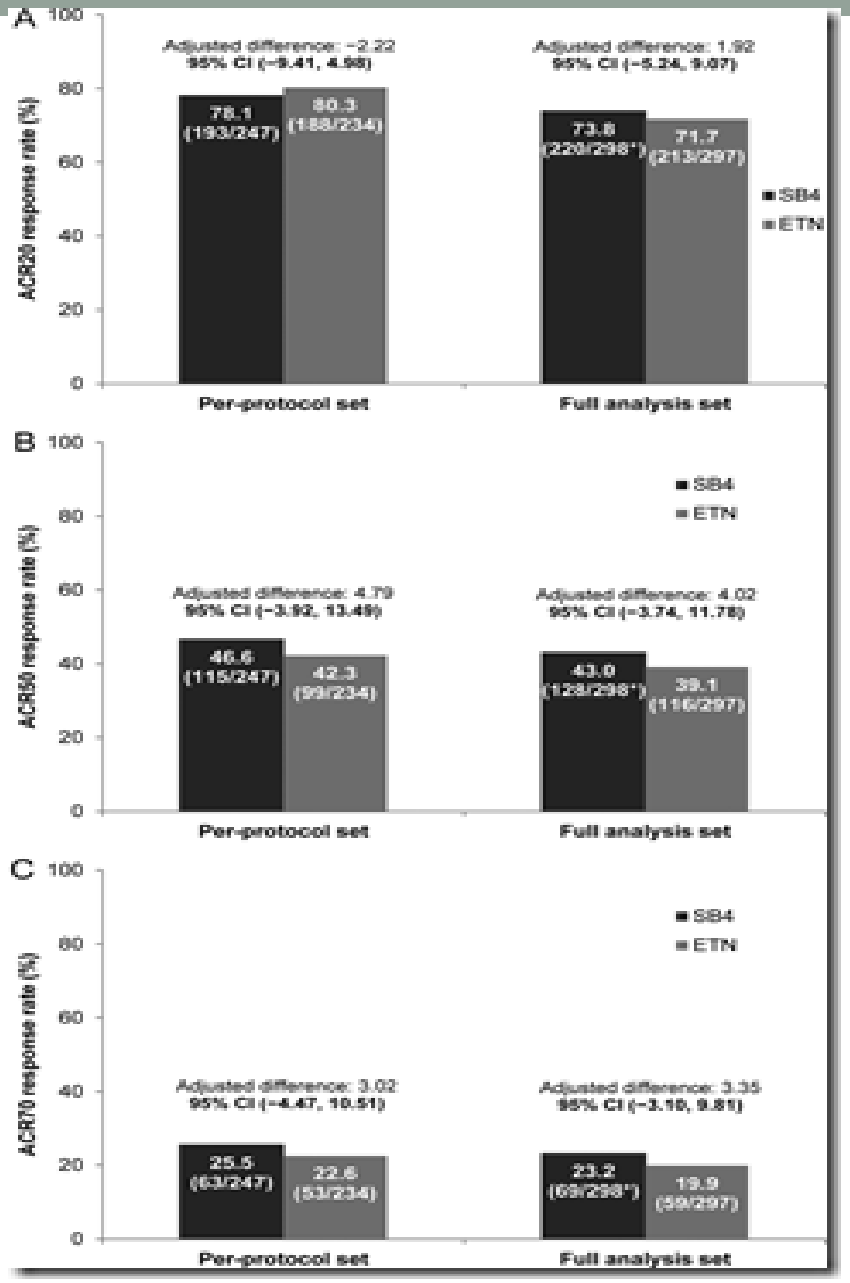


Figure 1 Summary of patient disposition. A total of 777 patients were screened and 181 patients were excluded mainly due to not meeting the exclusion criteria. Multiple screening failure reasons were possible. All patients randomised were included in the full analysis set and the safety set. Of the 551 patients who completed 24 weeks of treatment, 481 patients were included in the per-protocol set. ETN, etanercept.


A
ACR20 response rate (%)
100
80
60
40
20
0
Adjusted difference: −2.22
95% CI (−9.41, 4.98)
78.1
(193/247)
80.3
(188/234)
Adjusted difference: 1.92
95% CI (−5.24, 9.07)
73.8
(220/298*)
71.7
(213/297)
SB4
ETN
Per-protocol set
Full analysis set
B
ACR50 response rate (%)
Adjusted difference: 4.79
95% CI (−3.92, 13.49)
46.6
(115/247)
42.3
(99/234)
Adjusted difference: 4.02
95% CI (−3.74, 11.78)
43.0
(128/298*)
39.1
(116/297)
C
ACR70 response rate (%)
Adjusted difference: 3.02
95% CI (−4.47, 10.51)
25.5
(63/247)
22.6
(53/234)
Adjusted difference: 3.35
95% CI (−3.10, 9.81)
23.2
(69/298*)
19.9
(59/297)

- Kikuzubam® is a rituximab biomimic that was manufactured and marketedin Mexico by Probiomed.[2,8,25] In 2012, the Mexican Program of Pharmacovigilance issued a communication to health professionals warningthem of anaphylactic reactions that occurred in several patients who were switched from innovator rituximab (Mabthera®) to the biomimic, or vice versa.[29] This was surprising, since innovator rituximab had exhibited a very favorable peri-infusion safety profile among Mexican patients.[30]Because of these anaphylactic reactions and the lack of clinical data documenting the efficacy and safety of Kikuzubam®, approval to marketKikuzubam® in Mexico was withdrawn by the regulatory authority on March 28, 2014.[31]

- Reditux® is a rituximab biomimic manufactured in India and marketed inIndia and in several Latin American countries.[2,8] To our knowledge, no clinical trial has been performed to demonstrate equivalent efficacy and safety of Reditux® with innovator rituximab (Mabthera®) in patients with arheumatologic disease. However, analytical studies have demonstratedsignificant differences in physicochemical properties between Reditux® andinnovator rituximab.[32] Thus, Reditux® cannot be considered to be a rituximab biosimilar.

UNDERSTANDING BIOSIMILARS AND ORIGINATOR BIOLOGICS

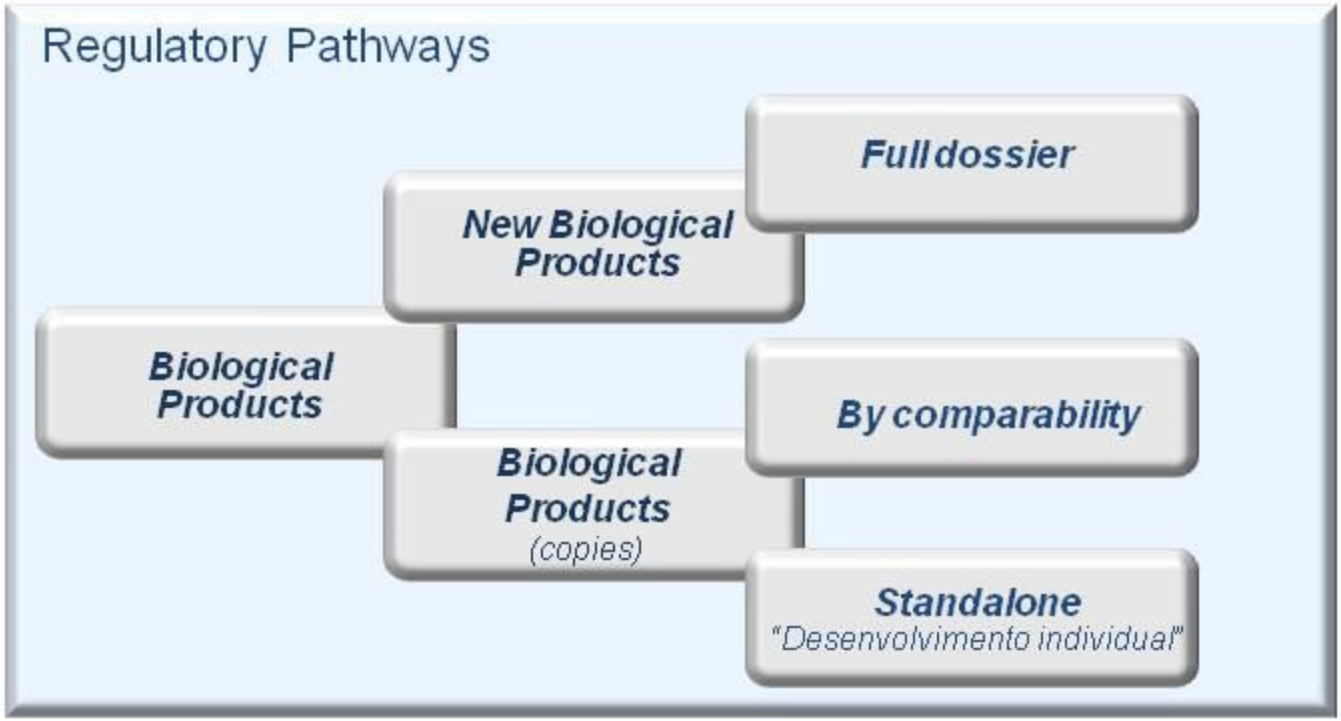
ISSUES AND CONSIDERATIONS

- *Regulatory pathways for the approval of biosimilars and the heterogeneity.*

Brazil

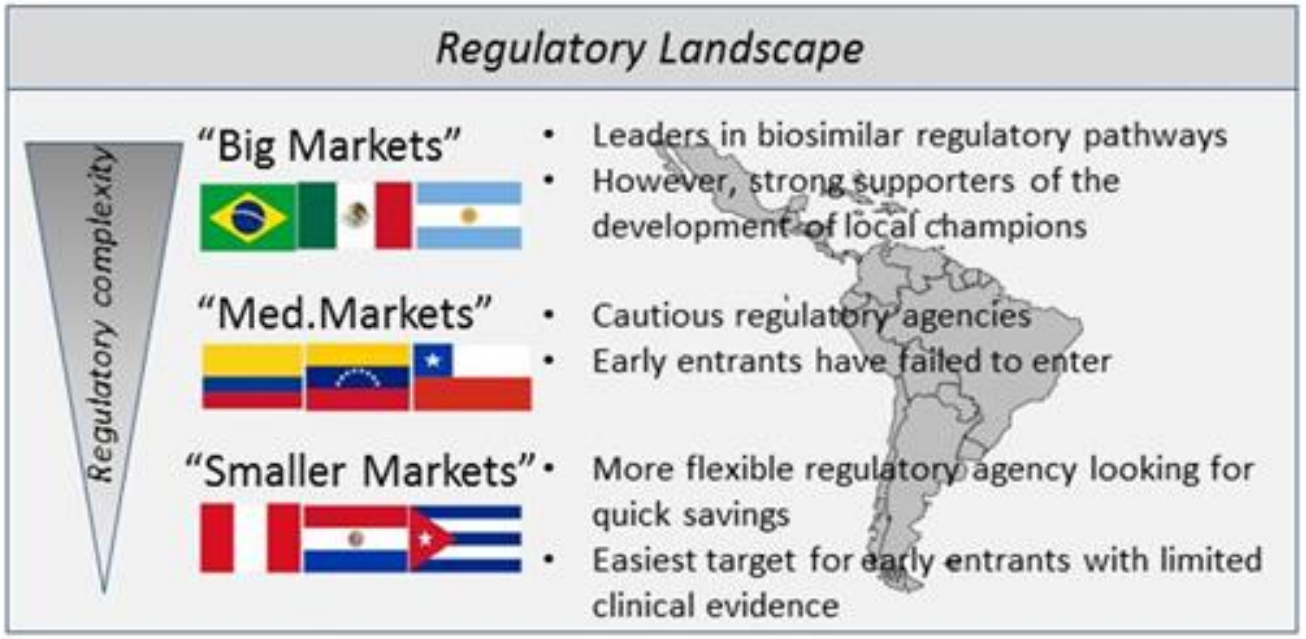
ANVISA

"Produtos Biológicos"
(RDC 55/2010)



HOSPITAL ABREU SODRÉ

ALBERT EINSTEIN
SOCIEDADE BENEFICENTE ISRAELITA BRASILEIRA



Biosimilar regulations

- EU guidelines for the development and approval of similar biologic medicinal products have been available since 2005[1]
- The FDA issued draft guidance on biosimilar product development in February 2012 to assist the industry in developing such products in the US[2]
- Biosimilarity is based on data directly comparing the proposed product with the reference product[2]
- The FDA plans to consider the **totality of the evidence submitted to** support biosimilarity demonstration[2]
- The FDA recommends sponsors use a stepwise approach in their development of biosimilar products including:[2]
  - Structural analysis, functional assays, animal data (toxicity, PK, PD, immunogenicity),clinical studies (human pharmacology, immunogenicity, clinical safety and effectiveness data, and postmarketing safety monitoring)

1. European Medicines Agency.www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf;
2. US DHHS, FDA, CDER, CBER. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.

PD: pharmacodynamics; PK: pharmacokinetics

EMA policy on automatic substitution

- *"The Agency's (EMA) evaluations do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine. For questions related to switching from one biological medicine to another, patients should speak to their doctor and pharmacist"*

European Medicines Agency. www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf .

Automatic substitution is regulated by European country guidelines

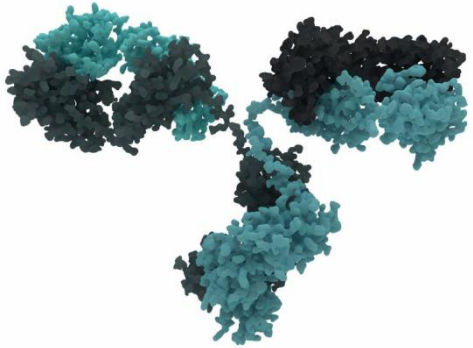
Automatic substitution regulation	Country
Automatic substitution not allowed	France, Germany, Greece, Italy, Slovenia, Spain, Sweden, UK
Automatic substitution must be actively prohibited by the physician	Czech Republic
Official list stating which products cannot be substituted	Denmark, Finland, Hungary, Norway, Slovakia
Physicians obliged to prescribe by brand name	Austria

Niederwieser D, et al. Eur J Haematol 2011;86:277–288.

Indication extrapolation

2

Approval in Indication **A**



1 Clinical safety and efficacy studies of a biosimilar in a single disease or specific patient population (Indication **A**)

3 Extrapolation to other diseases or patient populations?

Indication **B**

Indication **C**

Indication **D**

1. UA FDA website. Biosimilars. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ Accessed 01 July 2013.
2. EMA website. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp. Accessed 01 July 2013.

- Biosimilar Crohn s Disease

- J Crohns Colitis. 2013 Dec 20. pii: S1873-9946(13)00435-2. doi: 10.1016/j.crohns.2013.12.002. [Epub ahead of print]

- **Biosimilars in Crohn's disease.**

- Scheinberg M.

FDA policy on automatic substitution

- For a biosimilar to be considered“interchangeable” with the reference biologic,the US FDA requires evidence that:
  - demonstrates biosimilarity **AND**
  - Demonstrates that it produces the **SAME clinical** results at the same dose as the reference biologic in any given patient **AND**
  - Demonstrates no greater risk in terms of safety and efficacy if the biosimilar is used alternatively with reference biologic compared with continuous therapy with the reference biologic

US DHHS, FDA, CDER, CBER. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf.

EMA and FDA approve biosimilars on the totality of data

Study	EMA and FDA Guidance[1,2]
Non-clinical studies	• Head-to-head comparative approach evaluates biosimilars on a case-by-case basis • Physicochemical characterisation; PK, PD studies • In vivo animal studies, biologic testing, and toxicology
Clinical studies	
Human PK and PD studies	• PK comparability in a sufficiently sensitive and homogenous population, PD studies if possible: dose-concentration response curve
Efficacy studies	• Similar efficacy and safety in adequately powered, randomised, parallel-groupcomparative trials
Extrapolation	• Yes if biosimilarity is confirmed in the comparability studies, there is adequate justification, and the mechanism of action is the same
Safety and immunogenicity	• Comparable safety (type, frequency, and severity of AEs) including immunogenicity
Pharmacovigalence	• Pharmacovigillance and risk management plan for the post-authorisation phase(safety in extrapolated indications; rare and SAEs described for reference product; detection of novel safety signals, long-term immunogenicity and safety) • Traceability – recording the brand name used by physician

1. European Medicines Agency. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC500099361.pdf;
2. US DHHS, FDA, CDER, CBER. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.

AEs: adverse events; PD: pharmacodynamics; PK: pharmacokinetics

- *Biosimilars are becoming a reality in Rheumatology.*

- *Analytical and non clinical procedures to establish similarity*
- *Design of trials to demonstrate equivalence and non inferirority*
- *Clinical evidence for biosimilars that have been approved*
- *Lack of clinical evidence for intended copies , biocopies, biomimics risk for the continuous use of intended copies.*

SAT0152

A Randomised, Double-blind, Phase III Study Comparing SB2, An Infliximab Biosimilar, To The Infliximab Reference Product (Remicade®) In Patients With Moderate To Severe Rheumatoid Arthritis Despite Methotrexate Therapy

J.-Y. Choe[1], N. Prodanovic[2], J. Niebrzydowski[3], I. Staykov[4], E. Deksnupilova[5], A. Baranauskaite[6], R. Yatsyshyn[7], M. Mekic[8], W. Porawska[9], H. Ciferska[10], K. Jedrychowicz-Reniak[11], A. Zielinska[12], J.Y. Bang[13], Y.H. Rho[13], J. S. Smolen[14]

[1]Daegu Catholic University Medical Center, Daegu, Korea, Republic Of, [2]Clinical Center Banja Luka, Banja Luka, Bosnia and Herzegovina, [3]Medica Pro Familia, Gdynia, Poland, [4]MHAT "Dr. Ivan Seliminski", AD, Sliven, Bulgaria, [5]MEDICAL PLUS s.r.o, Ulbenske Hradiste, Czech Republic, [6]Lithuanian University of Health Sciences, Kaunas, Lithuania, [7]SHEI Ivano-Frankivsk NMU, Ivano-Frankivsk, Ukraine, [8]University Clinic Centre Sarajevo, Sarajevo, Bosnia and Herzegovina, [9]Poznanski Osrodek Medycyny NOVAMED, Poznan, Poland, [10]Revmatologicky ustav, Praha 2, Czech Republic, [11]MCRK S.C., Grodzisk Mazowiecki, [12]Medica Pro Familia Sp. z o.o. Spolka Komandytowo-Akcyjna, Warszawa, Poland, [13]Samsung Bioepis Co., Ltd., Incheon, Korea, Republic Of, [14]Medical University of Vienna, Vienna, Austria

Establishing Margins to Demonstrate Equivalence in Efficacy for Biosimilar Clinical Trials in Rheumatoid Arthritis Patients: a Meta-Analysis Approach

Steven Y. Hua[1], Kerry Barker[2], Peng Qu[3], Muhammad I. Rehman[2], Rob Schaum[4], Shivanthy Visvalingam[5], Joseph McClellan[6], Stephanie Salts[1], Ahmad AL-Sabbagh[6]

[1]Pfizer Inc, San Diego, CA, USA; [2]Pfizer Inc, Cambridge, MA, USA; [3]Pfizer Inc, Shanghai, China; [4]Pfizer Inc, Groton, CT, USA; [5]Pfizer Ltd Walton Oaks, UK; [6]Pfizer Inc, New York, NY, USA

Immunogenicity Assessment of PF-06438179, a Potential Biosimilar to Infliximab, in Healthy Volunteers

Chandrasekhar Udata[1], Donghua Yin[1], Chun-Hua Cai[2], Steven Y. Hua[1], Stephanie Salts[1], Muhammad I. Rehman[3], Ahmad AL-Sabbagh[4], Joseph E. McClellan[4], Xu Meng[1]

[1]Pfizer Inc, San Diego, CA, USA; [2]Pfizer Inc, Groton, CT, USA; [3]Pfizer Inc, Cambridge, MA, USA; [4]Pfizer Inc, New York, NY, USA

Relationship Between Pharmacokinetics and Antidrug Antibody Status of ABP 501, a Biosimilar Candidate to Adalimumab

Primal Kaur,[1] Vincent Chow,[2] Nan Zhang,[3] Richard Markus[1]

[1]Clinical Development, Amgen Inc., Thousand Oaks, CA, USA; [2]Clinical Pharmacology, Modeling and Simulation, Amgen Inc., Seattle, WA, USA; [3]Biostatistics, Amgen Inc., Thousand Oaks, CA, USA

Latin-American situation

- The need for cheaper drugs will help to close that gap
- At the same time the need to provide safe and efficacious drugs is also a requirement for the health departments in our countries
- The harm that could be done could outweigh the benefits
- The academia and health institutes in these countries should be part of the discussion for the development of local guideline

Issues affecting approval differ between biosimilars and generic drugs

Generic drug[1]	Biosimilar[1]
Has identical active substance	Has similar but not identical active substance
Has identical biologic activity	Establishing bioequivalence alone not adequate
Rate and extent of absorption is only possible variation	**Main issues[1,2]**
Establishing bioequivalence is adequate for approval	Safety and immunogenicity risks
	Need for pharmacovigilance
	Whether biosimilars can be substituted with their reference biologic for approval
	Additional issues[1,3]
	Risk–benefit assessment
	Naming conventions (same INN?)
	Appropriate design and reference products in clinical trials

1. Schellekens H. NDT Plus 2009;2 (Suppl 1):i27–i36;
2. Barlas S. Biotechnol Healthc 2012;9(2):28–29;
3. Simoens S. Clinicoecon Outcomes Res 2011;3:29–36.

INN: international nonproprietary name.

Incidence of Adverse Events in Patients Treated with Intended Copies of Biologic Therapeutic Agents in Colombia and Mexico

Incidence of Adverse Events in Patients Treated with Intended Copies of Biologic Therapeutic Agents in Colombia and Mexico

- **Abstract Number:** 1506
- **Program:** Abstract Submissions (ACR)
- **Session:** Rheumatoid Arthritis - Small Molecules, Biologics and Gene
- **Therapy:** Novel therapies, Biosimilars, Strategies and Mechanisms in Rheumatoid Arthritis
- **Keywords:** Biologic agents and adverse events
- **Year:** 2014

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Results

- A preliminary analysis was performed of 219 patients with various diagnoses treated with Infinitam/Etanar (14) or Kikuzubam (205) in the four hospitals. Among patients receiving treatment, 10 (4.6%) on Infinitam/Etanar and 101 (46.1%) on Kikuzubam experienced at least one treatment-related adverse event (AE). Of these, 86.7% were female, and the median age was 51.9 years (range: 22 – 93 years). The median duration of disease was 14.5 years (range: 1 – 67 years). Overall, although the majority of the AEs reported (98/118, 83.1%) were Grade 2 or less, there were several reports of Grade 3 (13/118; 11.0%) and Grade 4 (7/118; 5.9%) AEs; there were no Grade 5 AEs reported for any agent. The time to the first experience of an AE from initiation of intended copy therapy was ranged from 0 – 50 months with 38 (36.2%) patients experiencing AEs on the same day as the first treatment.

Conclusion

- A significant percent (14.3%) of patients receiving Infinitam/Etanar or Kikuzubam, intended copies of etanercept and rituximab, respectively, experience Grade 3/4 AEs with a very short time to onset.

- **Etacept:** use Etanercept in their PI even though they import it from Chinese manufacturer Shanghai CP Guojian Pharmaceutical Co who have called their product Yisaipu, as a "Recombinant Human Tumor Necrosis Factor Receptor - IgG1 Fc (rhTNFR:Fc) Fusion Protein" and not Etanercept.

- Intacept PI also shows differences in excipients. There is no explanation of differences.

Constituent	ENBREL 25	ENBREL 50	INTACEPT 25	INTACEPT 50
ETANERCEPT (mg)	25 mg	50 mg	25 mg	50 mg
Sucrose	5.1 mg	10.2 mg	10.0 mg	20.0 mg
L-Lysine Monohydrate	L-arginine (2.7 mg)	L-arginine (5.4 mg)	0.75 mg	1.50 mg
DL-aspartic acid	Absent	Absent	0.65 mg	1.30 mg
Sodium chloride	3.0 mg	6.0 mg	2.9 mg	5.8 mg
Polysorbate 25		Mannitol	0.1 mg	0.2 mg
Disodium EDTA	Disodium hydrogen phosphate (0.6 mg)	Disodium hydrogen phosphate (1.2 mg)	0.185 mg	0.370 mg
Sodium phosphate monobasic	Sodium dihydrogen phosphate (1.5 mg)	Sodium dihydrogen phosphate (3.0 mg)	0.75 mg	1.50 mg
Potassium phosphate dibasic	Absent	Absent	1.65 mg	3.30 mg
Orthophosphoric acid	Absent	Absent	q.s. to pH 6.3	q.s. to pH 6.3
Sodium hydroxide	Absent	Absent	q.s. to pH 6.3	q.s. to pH 6.3
Water for injection	q.s.	q.s.	q.s. to 0.5 ml	q.s. to 1.0 ml
pH	7.4	7.4	6.3 ± 0.3	6.3 ± 0.3

- Why to avoid comparability trials . What are they afraid off?

1) Costs on trials *

2) Immunogenicity challenges

3) Decreased efficacy

4) Purchase the innovator if trials are ahead.

*Reduce costs by increasing the margin of difference

Table 1 Intended copies of biologics licensed without biosimilar regulations

Year	Rituximab	Etanercept	Adalimumab
2007	India		
2008	Peru	Colombia	
2010	Chile, Bolivia and Mexico		
2011	Jamaica and Ecuador		
2012	Paraguay	Mexico	
2013		India	
2014			India

- **Biosimilars in Rheumatology: What Clinicians Should Know**

- **Gilberto Castañeda-Hernández[1,2], Rodrigo González-Ramírez[1], Jonathan Kay[3] and Morton A. Scheinberg[4,5]**
- **Review**: **Biosimilars in rheumatology: what the clinician should know**
- o Gilberto Castañeda-Hernández,
- o Rodrigo González-Ramírez,
- o Jonathan Kay,
- o Morton A Scheinberg
- *RMD Open 2015;**1**:1 e000010 doi:10.1136/rmdopen-2014-000010*

Select item 274323541.
Difference between Enbrel and Benepali treatment groups in 'hepatobiliary disorders'.
Scheinberg M, Azevedo V.
Ann Rheum Dis. 2016 Jul 18. pii: annrheumdis-2016-210101

Is Etanar a new biologic?

Scheinberg M.

Clin Exp Rheumatol. 2016 Jun 22. [Epub ahead of print]

PMID:
27383125

Bio……similars????

Or are they all great players (drugs) similar but not identical?

Thank you for your attention.