INFLECTRA

Το 1ο βιο-ομοειδές mab στη παγκόσμια κλινική πράξη

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ΣΥΓΚΡΟΥΣΗ ΣΥΜΦΕΡΟΝΤΩΝ 2 ΕΤΗ

- **BMS (4/15)**
- **Amgen (11/13)**
- **MSD (4/14)**
- **ABBVIE (3/13)**
- **ΒΙΑΝΕΞ (10 /14)**

ΤΙΜΙΤΙΚΗ ΑΜΟΙΒΗ

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MEDICAL INTELLIGENCE ARCHIVE

Treatment of B-Cell Lymphoma with Monoclonal Anti-Idiotype Antibody

Richard A. Miller, M.D., David G. Maloney, B.S., Roger Warnke, M.D., and Ronald Levy, M.D.
N Engl J Med 1982; 306:517-522 | March 4, 1982 | DOI: 10.1056/NEJM198203043060906

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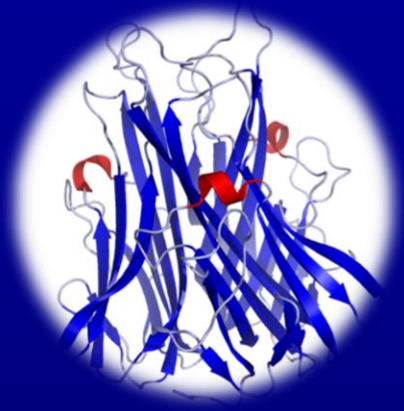

First recognised in the 1960s and 1970s for its toxic effects on cancer cells

early 1990s, Professor Ravinder Maini, Professor Marc Feldmann and colleagues (Arthritis Research Campaign's Kennedy Institute) demonstrated that excessive production of a particular type of TNF, TNF alpha => damaging inflammation characteristic of inflammatory joint disease.

Proceedings of the National Academy of Sciences of the United States of America

> Current Issue > vol. 89 no. 20 > R O Williams, 9784–9788, doi: 10.1073/pnas.89.20.9784

Anti-tumor necrosis factor ameliorates joint disease in murine collagen-induced arthritis.

R O Williams, M Feldmann, and R N Maini

Author Affiliations

Abstract

There is considerable evidence implicating tumor necrosis factor alpha (TNF-alpha) in the pathogenesis of rheumatoid arthritis. This evidence is based not only on the universal presence of TNF-alpha in arthritic joints accompanied by the upregulation of TNF-alpha receptors but also on the effects of neutralizing TNF-alpha in joint cell cultures. Thus, neutralization of TNF-alpha in vitro results in inhibition of the production of interleukin 1, which like TNF-alpha, is believed to contribute to joint inflammation and erosion. To determine the validity of this concept in vivo, the effect of administering TNF-neutralizing antibodies to mice with collagen-induced arthritis has been studied. This disease model was chosen because of its many immunological and pathological similarities to human rheumatoid arthritis. TN3-19.12, a hamster IgG1 monoclonal antibody to murine TNF-alpha/beta, was injected i.p. into mice either before the onset of [illegible]itis or after the establishment of clinical disease. Anti-TNF administered prior to disease onset

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Repeated therapy with monoclonal antibody to tumour necrosis factor α (cA2) in patients with rheumatoid arthritis

M.J. Elliott, PhD, Prof R.N. Maini, FRCP, Prof M. Feldmann, PhD, A. Long-Fox, RGN, P. Charles, FIBMS, J.A. Bijl, MD, J.N. Woody, MD

Altmetric 0

DOI: http://dx.doi.org/10.1016/S0140-6736(94)90632-7

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Infliximab

- Έγκριση EU το 8/1999 για την Crohn’s disease
- Ενδείξεις για UC, RA, AS , Psoriatic Arthritis
- Το 2011, ένδειξη για παιδιατρική UC (6-17 yrs)

EUROPEAN MEDICINES AGENCY

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Abasaglar (previously Abasria)	insulin glargine	Diabetes Mellitus	09/09/2014	▼	
Abseamed	epoetin alfa	Anemia Cancer Kidney Failure, Chronic	28/08/2007		
Accofil	filgrastim	Neutropenia	18/09/2014	▼	
Bemfola	follitropin alfa	Anovulation	27/03/2014	▼	
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Biograstim	filgrastim	Cancer Hematopoietic Stem Cell Transplantation Neutropenia	15/09/2008		
Epoetin Alfa Hexal	epoetin alfa	Anemia Cancer Kidney Failure, Chronic	28/08/2007		Authorise
Filgrastim Hexal	filgrastim	Cancer Hematopoietic Stem Cell Transplantation Neutropenia	06/02/2009		Authorised
Grastofil	filgrastim	Neutropenia	18/10/2013	▼	Authorised

Inflectra	infliximab	Arthritis, Psoriatic Arthritis, Rheumatoid Colitis, Ulcerative Crohn Disease Psoriasis Spondylitis, Ankylosing	10/09/2013	▼	Authorised
Nivestim	filgrastim	Cancer Hematopoietic Stem Cell Transplantation Neutropenia	08/06/2010		Authorised
Omnitrope	somatropin	Dwarfism, Pituitary Prader-Willi Syndrome Turner Syndrome	12/04/2006		Authorised
Ovaleap	follitropin alfa	Anovulation	27/09/2013	▼	Authorised
Ratiograstim	filgrastim	Cancer Hematopoietic Stem Cell Transplantation Neutropenia	15/09/2008		Authorised
Remsima	infliximab	Arthritis, Psoriatic Arthritis, Rheumatoid Colitis, Ulcerative Crohn Disease Psoriasis Spondylitis, Ankylosing	10/09/2013	▼	Authorised
Tevagrastim	filgrastim	Cancer Hematopoietic Stem Cell Transplantation Neutropenia	15/09/2008		Authorised
Zarzio	filgrastim	Cancer Hematopoietic Stem Cell Transplantation Neutropenia	06/02/2009		Authorised


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March 6, 2015
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The company Sandoz got approval (6/3/15) to market its drug Zarxio (filgrastim) as a biosimilar product to Amgen's Neupogen, originally licensed in 1991

- A biosimilar product is a biological product that is approved based on a showing that it is **highly similar** to an already-approved biological product, known as a reference product
- The biosimilar also must show it has no clinically meaningful differences in terms of **safety** and **effectiveness** from the reference product
- Only minor differences in clinically inactive components are allowable in biosimilar products

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm

ΕΡΩΤΗΜΑ 1ο


9 lit/100 km
40 lit
1,2 E => 48E
1,6 E / lit
Βενζίνη - 25%
64 E
ΕΡΩΤΗΜΑ ?
5 ώρ. 55 λεπτ.
447 χλμ.
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Πάτρα
Αθήνα
Λάρισα
Βόλος
Χαλκίδα
Πύργος
Τρίπολη
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ΕΡΩΤΗΜΑ 2ο

Πόσο ίδια σε
ασφάλεια & αποτελεσματικότητα
είναι αυτή η «βενζίνη»

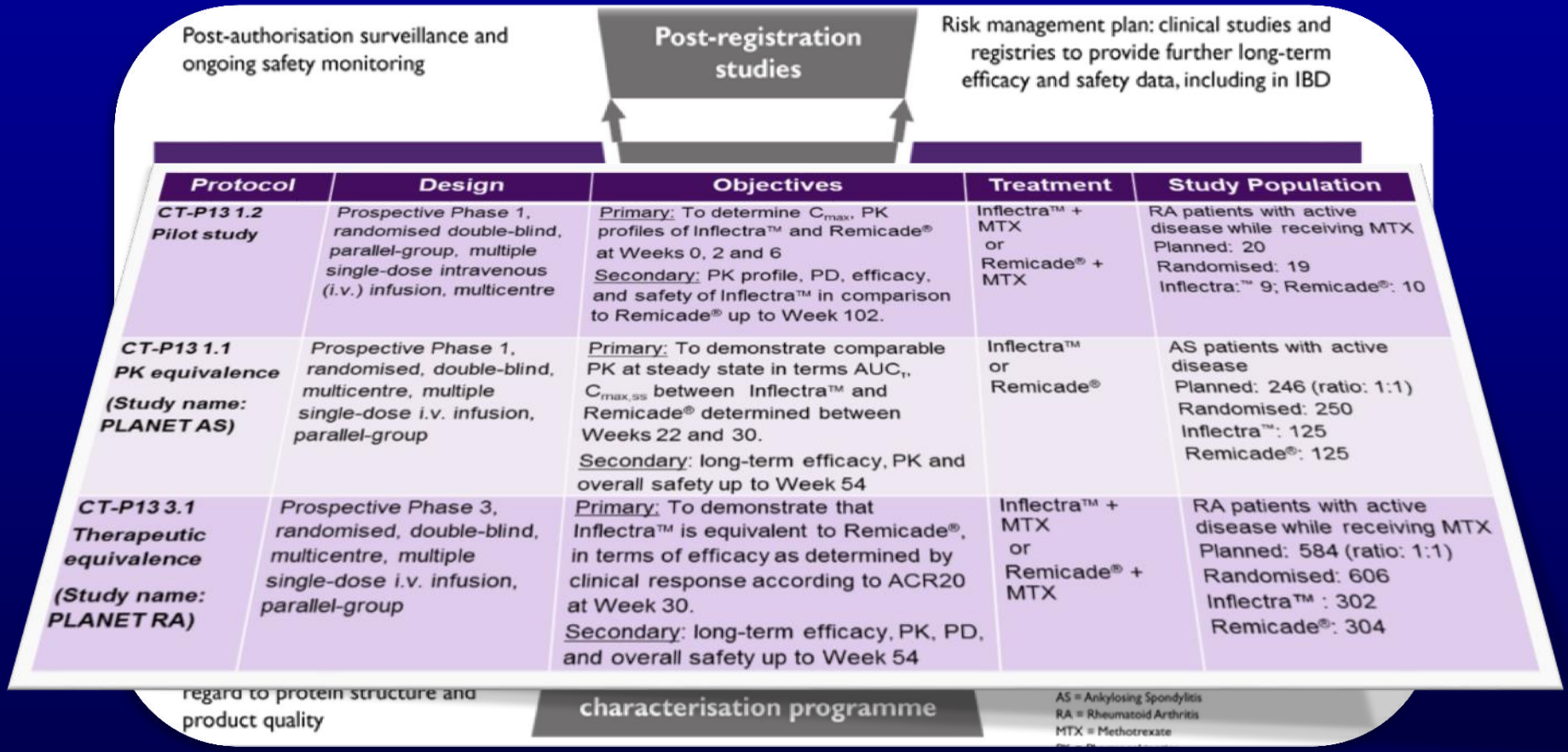
ΕΡΩΤΗΜΑ 2ο

Πόσο ίδιο σε

ασφάλεια & αποτελεσματικότητα

είναι αυτό το «biosimilar»

Πρόγραμμα ανάπτυξης Inflectra



Post-authorisation surveillance and ongoing safety monitoring

Post-registration studies

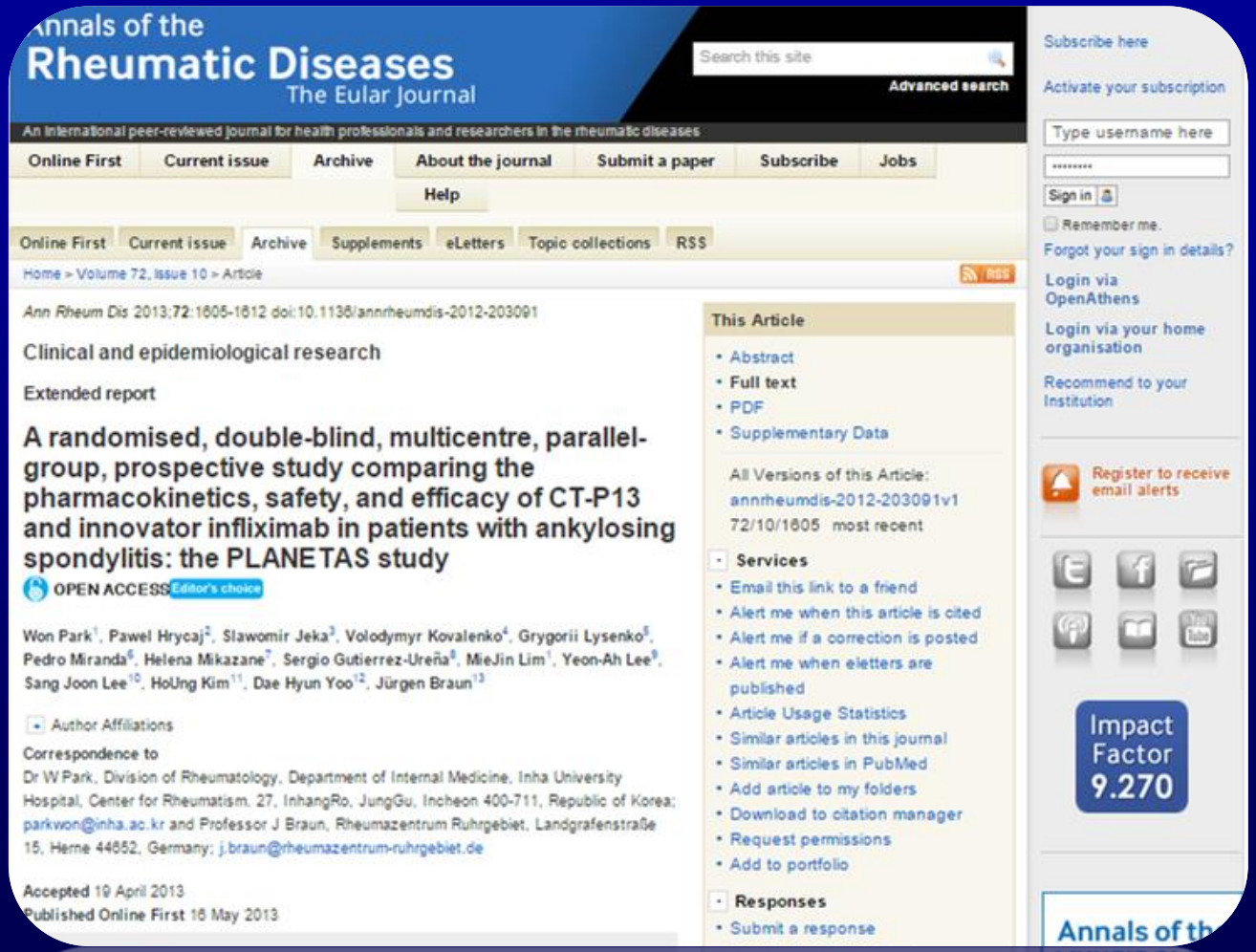
Risk management plan: clinical studies and registries to provide further long-term efficacy and safety data, including in IBD

Protocol	Design	Objectives	Treatment	Study Population
CT-P13 1.2 Pilot study	*Prospective Phase 1, randomised double-blind, parallel-group, multiple single-dose intravenous (i.v.) infusion, multicentre*	Primary: To determine C_{max}, PK profiles of Inflectra™ and Remicade® at Weeks 0, 2 and 6 Secondary: PK profile, PD, efficacy, and safety of Inflectra™ in comparison to Remicade® up to Week 102.	Inflectra™ + MTX or Remicade® + MTX	RA patients with active disease while receiving MTX Planned: 20 Randomised: 19 Inflectra:™ 9; Remicade®: 10
CT-P13 1.1 PK equivalence (Study name: PLANET AS)	*Prospective Phase 1, randomised, double-blind, multicentre, multiple single-dose i.v. infusion, parallel-group*	Primary: To demonstrate comparable PK at steady state in terms AUC_{τ}, $C_{max,ss}$ between Inflectra™ and Remicade® determined between Weeks 22 and 30. Secondary: long-term efficacy, PK and overall safety up to Week 54	Inflectra™ or Remicade®	AS patients with active disease Planned: 246 (ratio: 1:1) Randomised: 250 Inflectra™: 125 Remicade®: 125
CT-P13 3.1 Therapeutic equivalence (Study name: PLANET RA)	*Prospective Phase 3, randomised, double-blind, multicentre, multiple single-dose i.v. infusion, parallel-group*	Primary: To demonstrate that Inflectra™ is equivalent to Remicade®, in terms of efficacy as determined by clinical response according to ACR20 at Week 30. Secondary: long-term efficacy, PK, PD, and overall safety up to Week 54	Inflectra™ + MTX or Remicade® + MTX	RA patients with active disease while receiving MTX Planned: 584 (ratio: 1:1) Randomised: 606 Inflectra™ : 302 Remicade®: 304

regard to protein structure and product quality

characterisation programme

AS = Ankylosing Spondylitis
RA = Rheumatoid Arthritis
MTX = Methotrexate



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Ann Rheum Dis 2013;**72**:1605-1612 doi:10.1136/annrheumdis-2012-203091

Clinical and epidemiological research

Extended report

A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study

OPEN ACCESS Editor's choice

Won Park[1], Pawel Hrycaj[2], Slawomir Jeka[3], Volodymyr Kovalenko[4], Grygorii Lysenko[5], Pedro Miranda[6], Helena Mikazane[7], Sergio Gutierrez-Ureña[8], MieJin Lim[1], Yeon-Ah Lee[9], Sang Joon Lee[10], HoUng Kim[11], Dae Hyun Yoo[12], Jürgen Braun[13]

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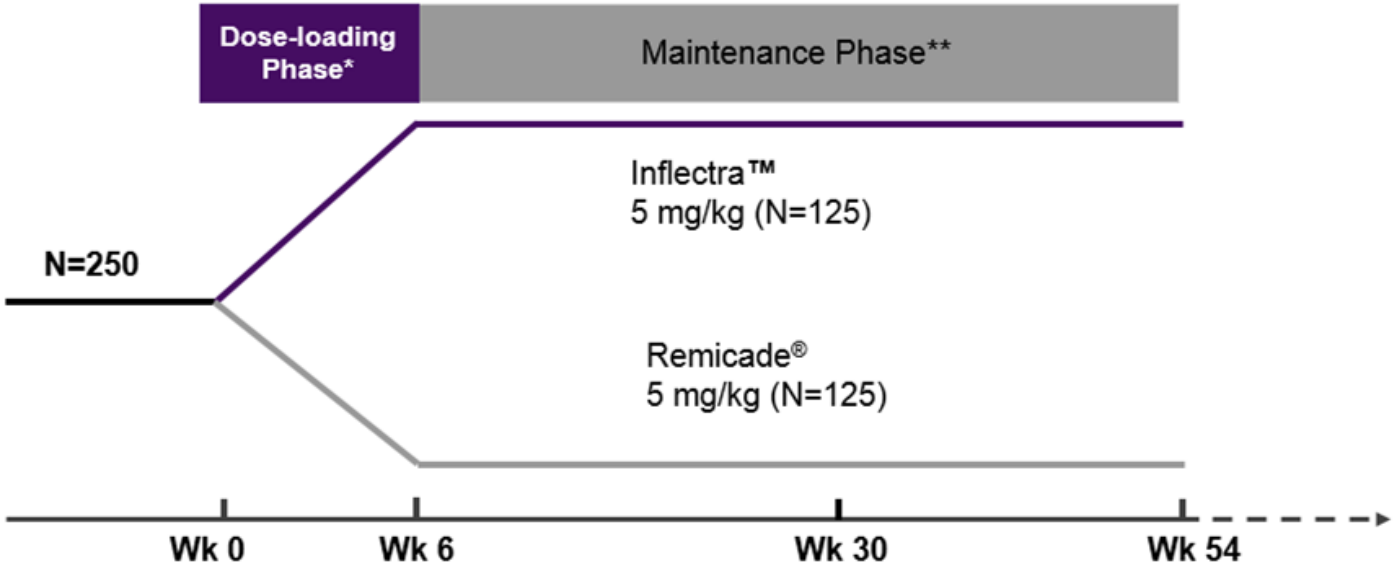
Annals of th

PLANETAS

Κύριος στόχος	**Να δειχθεί η παρόμοια PK (*at steady state in terms* AUC_{τ}, $C_{max,ss}$) μεταξύ Inflectra™ (CT-P13) και Remicade® για τις εβδομάδες 22 και 30 σε ασθενείς με ενεργό AS**
Άλλοι στόχοι	**Μακροχρόνια αποτελεσματικότητα, PK και ασφάλεια μέχρι Week 30-54**

PLANETAS

Randomised Double-blind Study in Patients with AS



*Doses at weeks 0, 2 and 6 by 2-hr IV infusion

** Doses every 8 weeks up to 54 weeks by 2-hr IV infusion

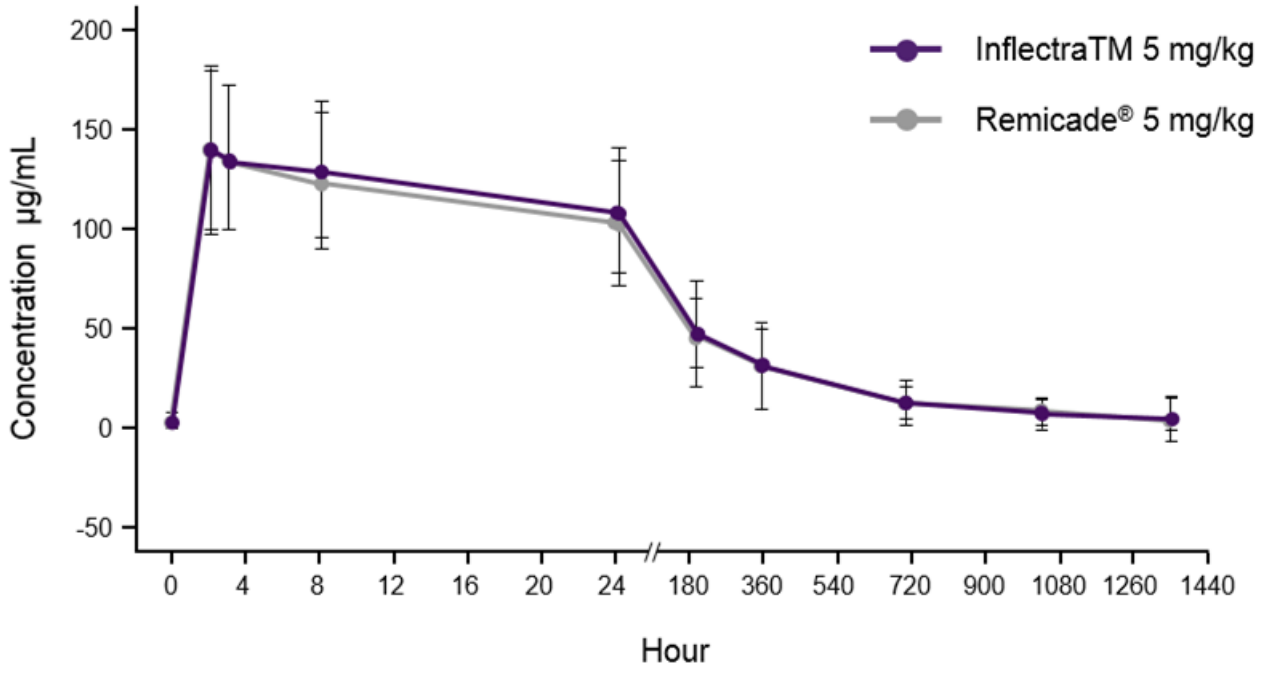
Biologics naïve patients diagnosed with AS according to the 1984 modified New York classification criteria [van der Linden *et al* 1984] for at least 3 months prior to Screening

Demographic Characteristics (All-randomised Population)

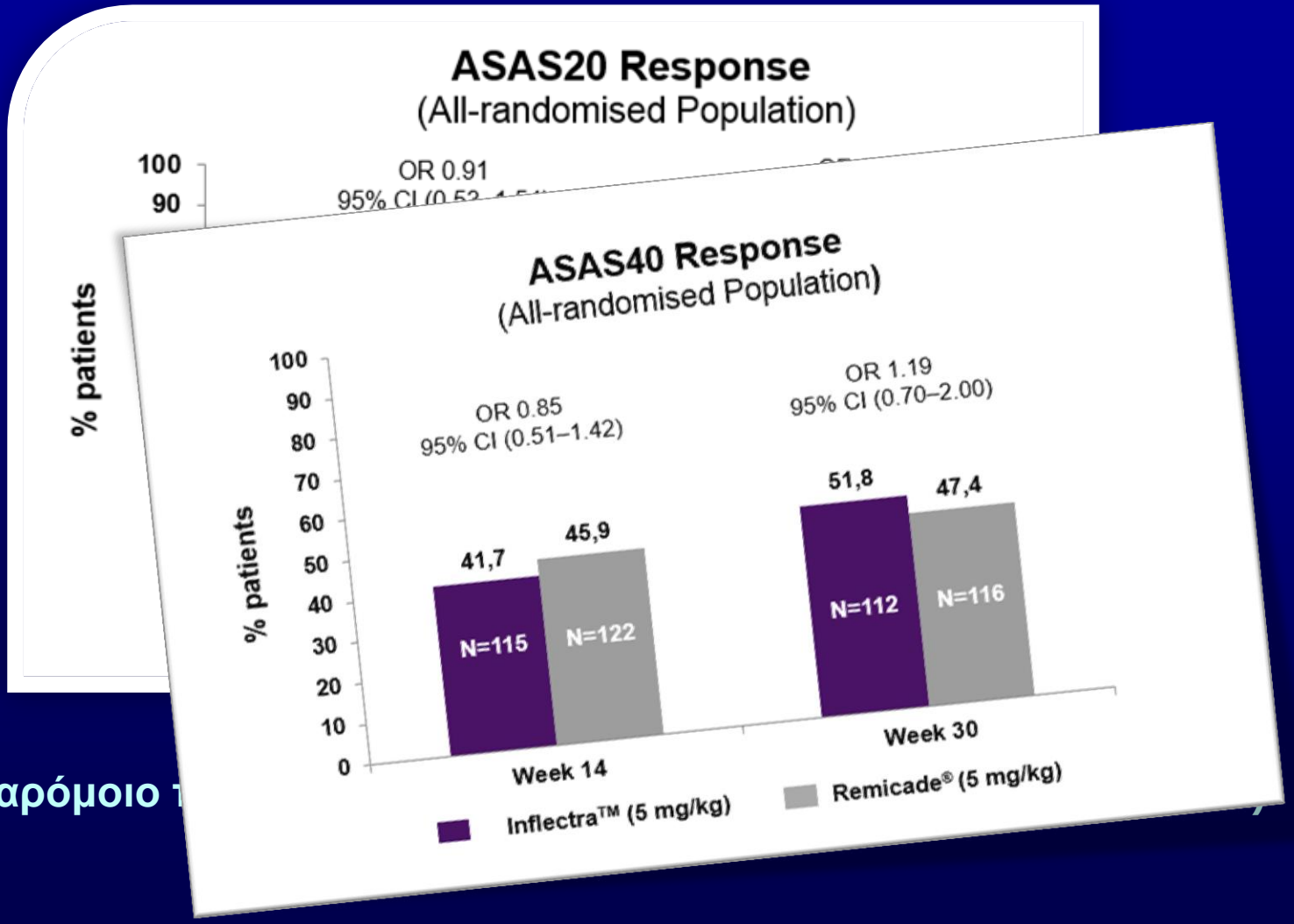
	Inflectra™ 5 mg/kg (N=125)	Remicade® 5 mg/kg (N=125)
Mean Age (years)	39.2	38.7
Sex (% male)	79.2	82.4
Race (%)		
White	77.6	73.6
Asian	12.8	10.4
Mean height (cm)	171.7	171.4
Mean weight (kg)	74.33	76.74
Mean BMI (kg/m^2)	25.09	26.09
Region (%)		
European	64.8	64.8
Non-European	35.2	35.2

Biologics naïve patients diagnosed with AS according to the 1984 modified New York classification criteria [van der Linden *et al* 1984] for at least 3 months prior to Screening

Συγκεντρώσεις infliximab ορού : παρόμοιες μεταξύ Inflectra™ και Remicade®

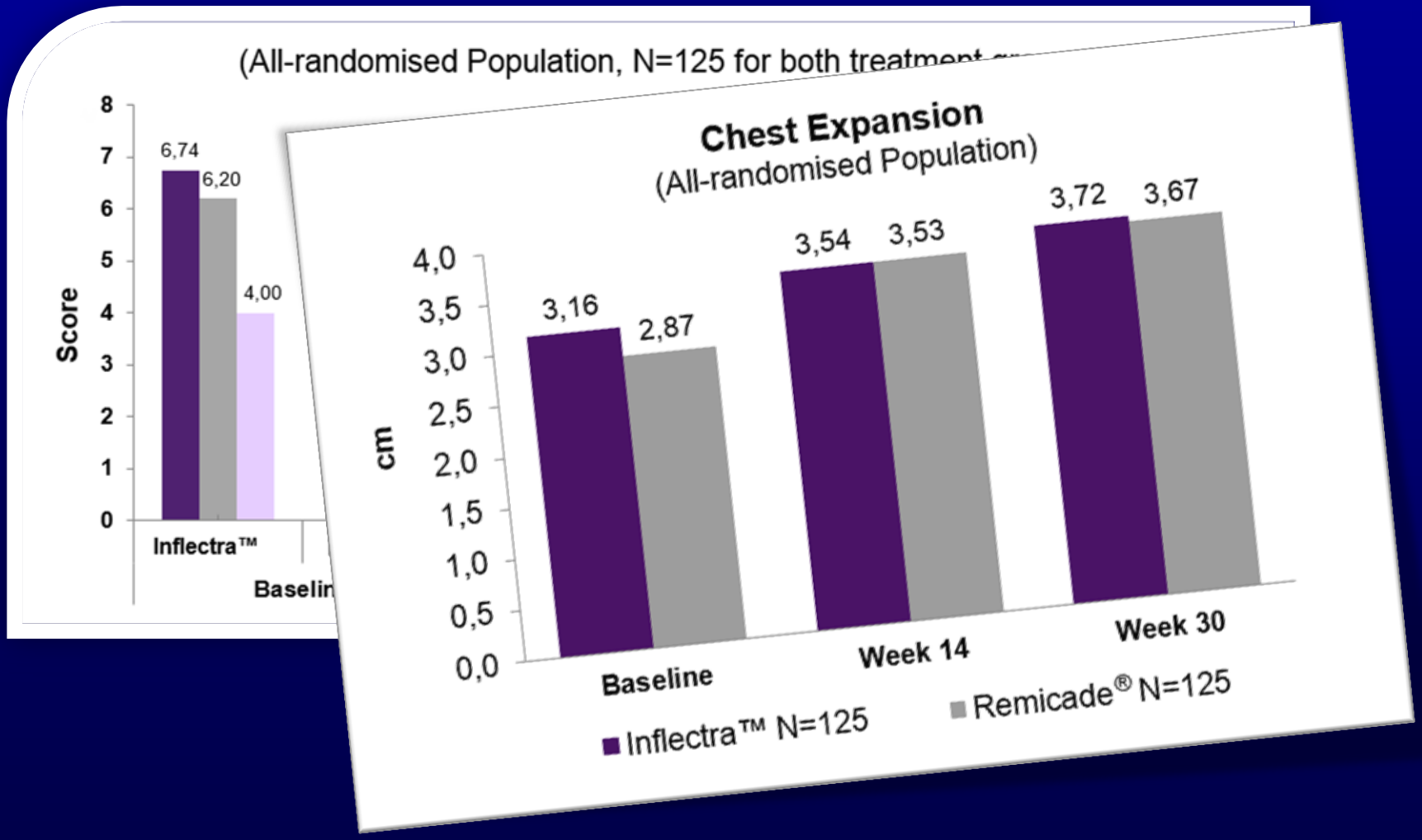


αποτελεσματικότητα



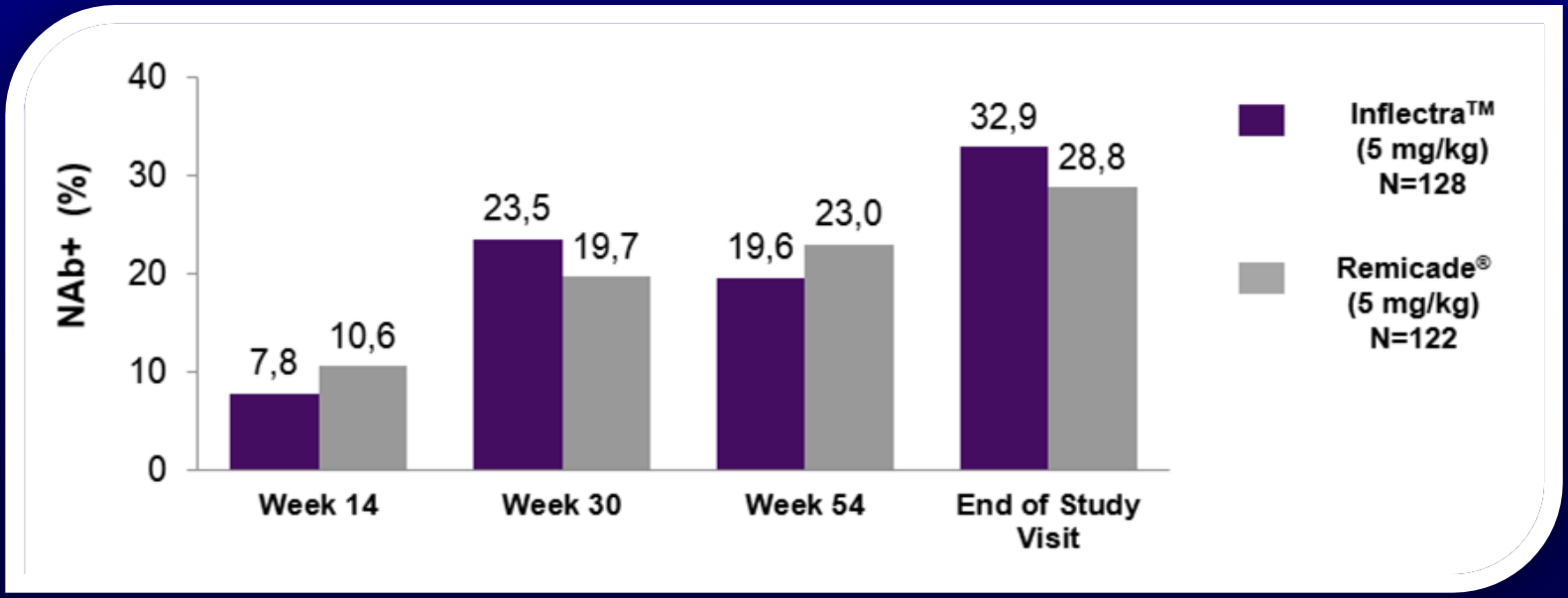
Παρόμοιο τ

Παρόμοια ευρήματα για with BASDAI, BASFI BASMI scores



ανοσογονικότητα

- Παρόμοιο ποσοστό ασθενών ανέπτυξε anti-infliximab antibodies (ADA)
- 34.4% (Inflectra™) vs. 32.0% (Remicade®) : 54 w
- Κυρίως ήταν εξουδετερωτικά (NAb)



Ασφάλεια (PLANETAS)

- Η αναλογία των ασθενών με drug-related TEAEs την εβδ 30 ήταν παρόμοια:
  - 44.5% (57/128) για Inflectra™
  - 47.5% (58/122) για Remicade®

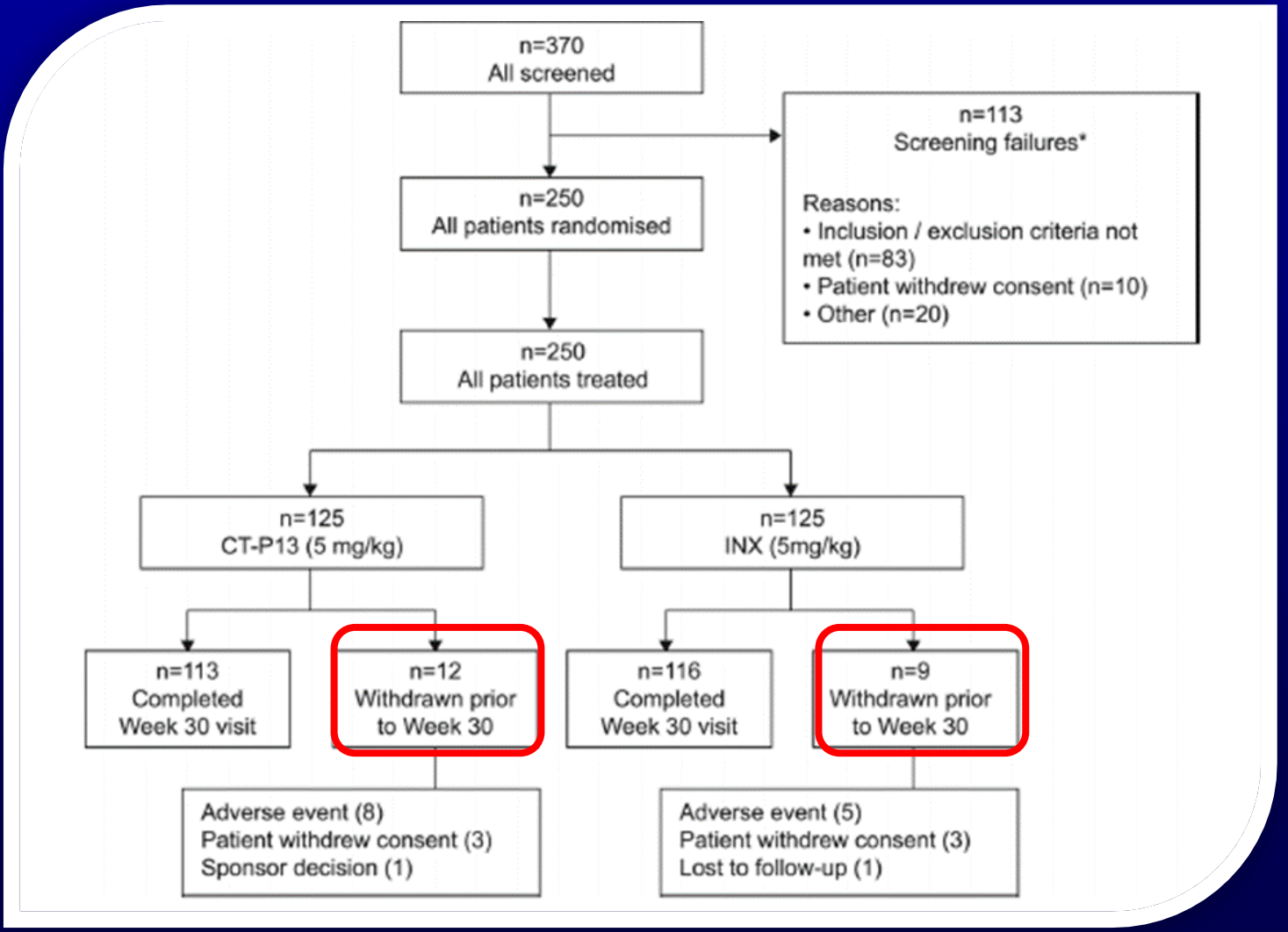
- Δεν αναφέρθηκαν
  - θάνατοι
  - Σοβαρές διαφορές για AE ή SAE μεταξύ Inflectra™ και Remicade®

Ασφάλεια (PLANETAS, 30w)

Adverse Event	Inflectra™ 5 mg/kg (N=128)	Remicade® 5 mg/kg (N=122)
Alanine aminotransferase increased (ALT)	9 (9.4%)	11 (9.0%)
Aspartrate aminotransferase increased (AST)	11 (8.6%)	8 (6.6%)
Gamma-glutamyltransferase increased (GGT)	3 (2.3%)	3 (2.5%)
Blood creatine phosphokinase (CPK) increased	4 (3.1%)	1 (0.8%)
Latent tuberculosis*	5 (3.9%)	4 (3.3%)
Urinary tract infection	5 (3.9%)	0
Nasopharyngitis	3 (2.3%)	2 (1.6%)
Pharyngitis	2 (1.6%)	3 (2.5%)
Upper respiratory tract infection		
Pyrexia		
Headac		
Infusion		
Rash		

	Inflectra™ (N=128)	Remicade® (N=122)
All patients with at least 1 TEAE due to hypersensitivity and infusion-related reactions (0–30 Weeks)	5 (3.9%)	6 (4.9%)
All patients with at least 1 TEAE due to hypersensitivity and infusion-related reactions (31–54 Weeks)	4 (3.1%)	11 (9.0%)

Ασφάλεια (PLANETAS, 30w)



Συμπεράσματα (PLANETAS)

Παρόμοιες συγκεντρώσεις infliximab για το Inflectra™ και το Remicade®

Φαρμακοκινητική ισοδυναμία Inflectra™ και Remicade® για AUC_{tau} και $C_{max,ss}$ στις 30 εβδ,
as the 90% CIs for the geometric mean ratios were fully contained within the 80–125% acceptance limits

Το Inflectra™ ήταν καλά ανεκτό, με προφίλ ασφάλειας και αποτελεσματικότητας παρόμοιας του Remicade® για 30 (54) εβδ

PLANETAS 1 χρόνο

[2013] [FRI0421] A RANDOMISED, DOUBLE-BLIND, PARALLEL-GROUP, PHASE 1 STUDY COMPARING THE PHARMACOKINETICS, SAFETY AND EFFICACY OF CT-P13 AND INFLIXIMAB IN PATIENTS WITH ACTIVE ANKYLOSING SPONDYLITIS: 54 WEEK RESULTS FROM THE PLANETAS STUDY

W. Park[1], J. Jaworski[2], J. Brzezicki[3], A. Gnylorybov[4], V. Kadinov[5], I. Goecke Sariego[6], C. Abud-Mendoza[7], W. J. Otero Escalante[8], S. W. Kang[9], D. Andersone[10], F. Blanco[11], D. H. Yoo[12], C. Ahn[13], H. U. Kim[14], J. Braun[15]. [1]Inha Univ. Hospital, Incheon, Republic of Korea; [2]Linea Corporis, Warszawa; [3]Wojewodzki Szpital Zespolony w Elblagu, Elblag, Poland; [4]Institute of Urgent and Recovery Surgery, Donetsk, Ukraine; [5]Univ. Hospital St. Marina, Varna, Bulgaria; [6]Prosalud y Cia Ltda, Santiago, Chile; [7]Hospital Central Dr. Ignacio Morones Prieto, San Luis Potosí, Mexico; [8]Servimed Empresa Unipersonal, Bucaramanga, Colombia; [9]Chungnam National Univ. Hospital, Daejeon, Republic of Korea; [10]P. Stradina Clinical Univ. Hospital, Riga, Latvia; [11]Hospital Universitario a Coruña, A Coruña, Spain; [12]Hanyang Univ. Hospital, Seoul, Republic of Korea; [13]UT Southwestern Medical Center, Dallas, United States; [14]CELLTRION, Incheon, Republic of Korea; [15]Rheumazentrum Ruhrgebiet, Herne, Germany

Background: CT-P13 is a biosimilar product of infliximab (INX). Data up to week 30 has been reported at EULAR 2012.[1]
Objectives: To assess the PK, efficacy and safety of CT-P13 in patients with active AS up to week 54 and to compare this with INX, also in relation to the formation of anti-drug antibodies (ADAs).
Methods: Patients with active AS (1984 modified NY criteria) were randomised (1:1) to receive either CT-P13 (5mg/kg) or INX (5mg/kg) at weeks 0, 2, 6 and then every 8 weeks up to week 54.
Results: Of 250 patients randomised at baseline, 213 patients were treated up to week 54. C_{max} of CT-P13 and INX were shown to be equivalent, since 90% CIs for the ratio of geometric means were within 80–125% at all doses (CT-P13, 128.1μg/mL–172.2μg/mL; INX, 123.0μg/mL–176.7μg/mL). At week 54, the proportion of patients testing positive for ADAs was comparable between CT-P13 and INX (22.9% [25/109] vs 26.7% [28/105]). ADAs had similar effects on PKs in both groups. Patients with negative ADA results had higher C_{max} values (CT-P13, 134.5μg/mL–177.2μg/mL; INX, 131.9μg/mL–177.4μg/mL) compared with patients with positive results (CT-P13, 101.8μg/mL–160.4μg/mL; INX, 104.0μg/mL–175.2μg/mL). At week 54, ASAS40 and ASAS partial remission were comparable between groups (CT-P13, 54.7% and 19.8%; INX, 49.1% and 17.6%, respectively). More patients with negative ADA results achieved ASAS40 responses (CT-P13, 61.0%; IFX, 54.7%) compared with patients with positive results (CT-P13, 37.9%; IFX, 36.4%). The safety profiles of CT-P13 and INX were also comparable (table). Active tuberculosis (TB) was reported in 3 patients (CT-P13, 2; INX, 1) and there were no malignancies.

[2013] [FRI0421] A RANDOMISED, DOUBLE-BLIND, PARALLEL-GROUP, PHASE 1 STUDY COMPARING THE PHARMACOKINETICS, SAFETY AND EFFICACY OF CT-P13 AND INFLIXIMAB IN PATIENTS WITH ACTIVE ANKYLOSING SPONDYLITIS: 54 WEEK RESULTS FROM THE PLANETAS STUDY

W. Park[1], J. Jaworski[2], J. Brzezicki[3], A. Gnylorybov[4], V. Kadinov[5], I. Goecke Sariego[6], C. Abud-Mendoza[7], W. J. Otero Escalante[8], S. W. Kang[9], D. Andersone[10], F. Blanco[11], D. H. Yoo[12], C. Ahn[13], H. U. Kim[14], J. Braun[15]. [1]Inha Univ. Hospital, Incheon, Republic of Korea; [2]Linea Corporis, Warszawa; [3]Wojewodzki Szpital Zespolony w Elblagu, Elblag, Poland; [4]Institute of Urgent and Recovery Surgery, Donetsk, Ukraine; [5]Univ. Hospital St. Marina, Varna, Bulgaria; [6]Prosalud y Cia Ltda, Santiago, Chile; [7]Hospital Central Dr. Ignacio Morones Prieto, San Luis Potosi, Mexico; [8]Servimed Empresa Unipersonal, Bucaramanga, Colombia; [9]Chungnam National Univ. Hospital, Daejeon, Republic of Korea; [10]P. Stradina Clinical Univ. Hospital, Riga, Latvia; [11]Hospital Universitario a Coruña, A Coruña, Spain; [12]Hanyang Univ. Hospital, Seoul, Republic of Korea; [13]UT Southwestern Medical Center, Dallas, United States; [14]CELLTRION, Incheon, Republic of Korea; [15]Rheumazentrum Ruhrgebiet, Herne, Germany

Cmax CT-P13 και INX ήταν ισοδύναμα:

- **90% CIs for the ratio of geometric means were within 80–125% at all doses**
- **CT-P13 128.1μg/mL–172.2μg/mL**
- **INX 123.0μg/mL–176.7μg/mL**

Ποσοστό ασθενών με θετικά ADAs ήταν παρόμοιο CT-P13 - INX

- **22.9% [25/109] vs 26.7% [28/105]**
- **ADAs παρόμοια δράση στην ΦΚ**

Ασθενείς με αρνητικά ADA είχαν υψηλότερες τιμές Cmax

(CT-P13, 134.5μg/mL–177.2μg/mL; INX, 131.9μg/mL–177.4μg/mL)

Σε σχέση με ασθενείς με θετικά

(CT-P13, 101.8μg/mL–160.4μg/mL; INX, 104.0μg/mL–175.2μg/mL)

[2013] [FRI0421] A RANDOMISED, DOUBLE-BLIND, PARALLEL-GROUP, PHASE 1 STUDY COMPARING THE PHARMACOKINETICS, SAFETY AND EFFICACY OF CT-P13 AND INFLIXIMAB IN PATIENTS WITH ACTIVE ANKYLOSING SPONDYLITIS: 54 WEEK RESULTS FROM THE PLANETAS STUDY

W. Park[1], J. Jaworski[2], J. Brzezicki[3], A. Gnylorybov[4], V. Kadinov[5], I. Goecke Sariego[6], C. Abud-Mendoza[7], W. J. Otero Escalante[8], S. W. Kang[9], D. Andersone[10], F. Blanco[11], D. H. Yoo[12], C. Ahn[13], H. U. Kim[14], J. Braun[15]. [1]Inha Univ. Hospital, Incheon, Republic of Korea; [2]Linea Corporis, Warszawa; [3]Wojewodzki Szpital Zespolony w Elblagu, Elblag, Poland; [4]Institute of Urgent and Recovery Surgery, Donetsk, Ukraine; [5]Univ. Hospital St. Marina, Varna, Bulgaria; [6]Prosalud y Cia Ltda, Santiago, Chile; [7]Hospital Central Dr. Ignacio Morones Prieto, San Luis Potosi, Mexico; [8]Servimed Empresa Unipersonal, Bucaramanga, Colombia; [9]Chungnam National Univ. Hospital, Daejeon, Republic of Korea; [10]P. Stradina Clinical Univ. Hospital, Riga, Latvia; [11]Hospital Universitario a Coruña, A Coruña, Spain; [12]Hanyang Univ. Hospital, Seoul, Republic of Korea; [13]UT Southwestern Medical Center, Dallas, United States; [14]CELLTRION, Incheon, Republic of Korea; [15]Rheumazentrum Ruhrgebiet, Herne, Germany

ASAS40 και ASAS partial remission ήταν παρόμοια στις 2 ομάδες

- **CT-P13 : 54.7% / 19.8%**
- **INX: 49.1% / 17.6%**

Περισσότεροι ασθενείς με αρνητικά ADA πέτυχαν ASAS40 responses (CT-P13, 61.0%; IFX, 54.7%) Σε σχέση με αυτούς με θετικά (CT-P13, 37.9%; IFX, 36.4%)

[2013] [FRI0421] A RANDOMISED, DOUBLE-BLIND, PARALLEL-GROUP, PHASE 1 STUDY COMPARING THE PHARMACOKINETICS, SAFETY AND EFFICACY OF CT-P13 AND INFLIXIMAB IN PATIENTS WITH ACTIVE ANKYLOSING SPONDYLITIS: 54 WEEK RESULTS FROM THE PLANETAS STUDY

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	CT-P13 (n=128)	INX (n=122)
No. (%) of patients with at least 1 related TEAE	62 (48.4)	63 (51.6)
No. (%) of patients with at least 1 STEAE	10 (7.8)	8 (6.6)
No. (%) of patients with at least 1 infusion-related reaction - Positive for ADA, No. (%)	4 (3.1) 3 (75.0)	11 (9.0) 9 (81.8)
No. (%) of patients with at least 1 related TEAE due to infection	30 (23.4)	24 (19.7)

TEAE, treatment-emergent adverse event; STEAE, serious TEAE

PLANETAS 2 χρόνια

◂ Previous Abstract: #L15 Next ▸

Efficacy and Safety of CT-P13 (Infliximab Biosimilar) over Two Years in Patients with Ankylosing Spondylitis: Comparison Between Continuing with CT-P13 and Switching from Infliximab to CT-P13

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Abstract: #L15

Date: Tuesday, October 29, 2013

Location: Exhibit Hall B2-C-D

Session Title: ACR Late-Breaking Abstract Poster Session

Abstract Category: Type: Late-Breaking Poster

Efficacy and Safety of CT-P13 (Infliximab Biosimilar) over Two Years in Patients with Ankylosing Spondylitis: Comparison Between Continuing with CT-P13 and Switching from Infliximab to CT-P13

174 ασθενείς με 54 εβδομάδες

88 έμειναν στο CT-P13

86 άλλαξαν από INX σε CT-P13

Για ακόμη 1 χρόνο

Συνολική παρακολούθηση : 2 χρόνια

Efficacy and Safety of CT-P13 (Infliximab Biosimilar) over Two Years in Patients with Ankylosing Spondylitis: Comparison Between Continuing with CT-P13 and Switching from Infliximab to CT-P13

Efficacy outcome		CT-P13 throughout study (N=88)	Switched from INX to CT-P13 in extension phase (N=86)
ASAS20, n (%)	Wk 54	62 (70.5)	65 (75.6)
	Wk 78	61 (70.1)	64 (77.1)
	Wk 102	67 (80.7)	60 (76.9)
ASAS40, n (%)	Wk 54	51 (58.0)	46 (53.5)
	Wk 78	50 (57.5)	43 (51.8)
	Wk 102	53 (63.9)	48 (61.5)
ASAS partial remission, n (%)	Wk 54	18 (20.5)	17 (19.8)
	Wk 78	19 (21.8)	18 (21.7)
	Wk 102	23 (27.7)	22 (28.2)
ASDAS-CRP	Baseline (BL)	3.86	3.85
	Mean Δ from BL at Wk 54	−1.77	−1.74

Efficacy and Safety of CT-P13 (Infliximab Biosimilar) over Two Years in Patients with Ankylosing Spondylitis: Comparison Between Continuing with CT-P13 and Switching from Infliximab to CT-P13

Safety outcome		CT-P13 throughout study (N=90)	Switched from INX to CT-P13 in extension phase (N=84)
TEAEs, n		103	162
pts with ≥1 TEAE, n (%)		44 (48.9)	60 (71.4)
Mild		20 (22.2)	27 (32.1)
Moderate		21 (23.3)	28 (33.3)
Severe		3 (3.3)	5 (6.0)
pts with ≥1 TESAE, n (%)		4 (4.4)	4 (4.8)
pts with ≥1 infection, n (%)		23 (25.6)	29 (34.5)
ADA positive, n (%)	Wk 54	20 (22.2)	22 (26.2)
	Wk 78	21 (24.4)	25 (31.3)
	Wk 102	21 (25.0)	23 (30.7)

ADA, anti-drug antibodies; ASAS, Assessment of SpondyloArthritis international Society; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score C-reactive protein; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

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Ann Rheum Dis 2013;**72**:1613-1620 doi:10.1136/annrheumdis-2012-203090

Clinical and epidemiological research

Extended report

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study

OPEN ACCESS Editor's choice

Dae Hyun Yoo[1], Pawel Hrycaj[2], Pedro Miranda[3], Edgar Ramiterre[4], Mariusz Piotrowski[5], Sergii Shevchuk[6], Volodymyr Kovalenko[7], Nenad Prodanovic[8], Mauricio Abello-Banfi[9], Sergio Gutierrez-Ureña[10], Luis Morales-Olazabal[11], Michael Tee[12], Renato Jimenez[13], Omid Zamani[14], Sang Joon Lee[15], HoUng Kim[16], Won Park[17], Ulf Müller-Ladner[18]

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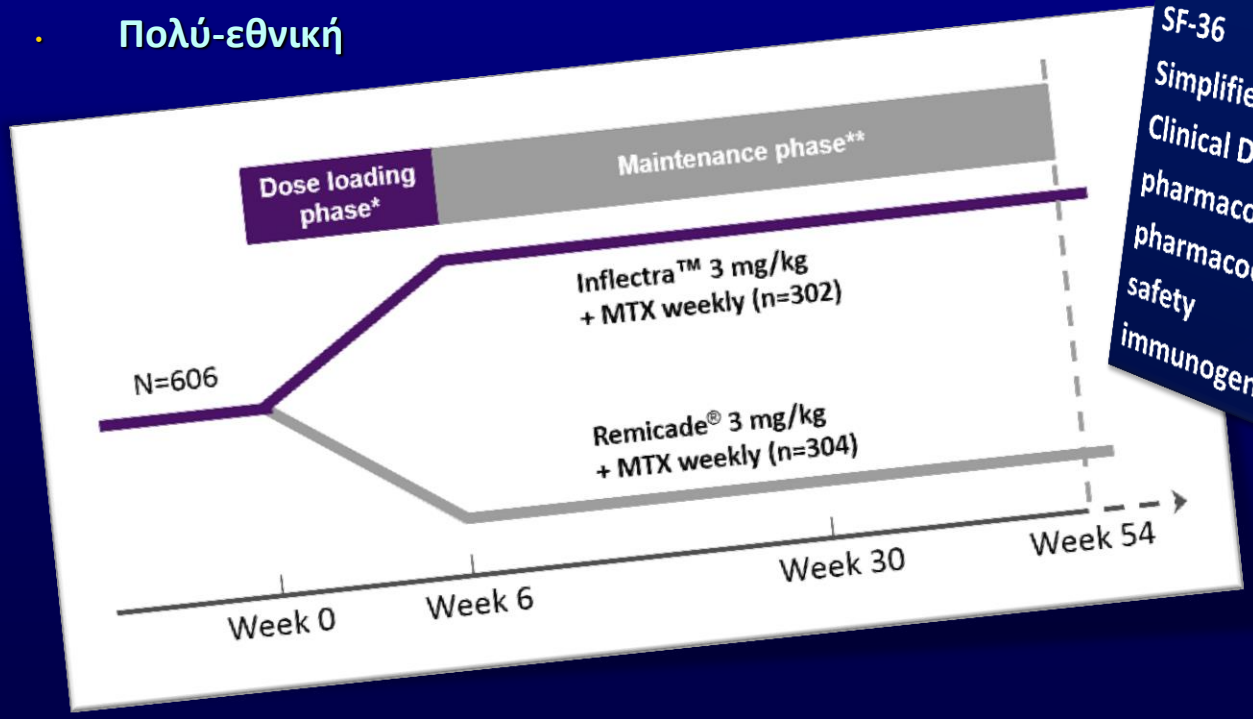
EXTENDED REPORT

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study

- **Phase III**
- **τυχαιοποιημένη**
- **Διπλά τυφλή**
- **Πολύ-κεντρική**
- **Πολύ-εθνική**



ACR response criteria
EULAR response criteria
DAS28
SF-36
Simplified Disease Activity Index
Clinical Disease Activity Index
pharmacokinetic (PK)
pharmacodynamic (PD)
safety
immunogenicity

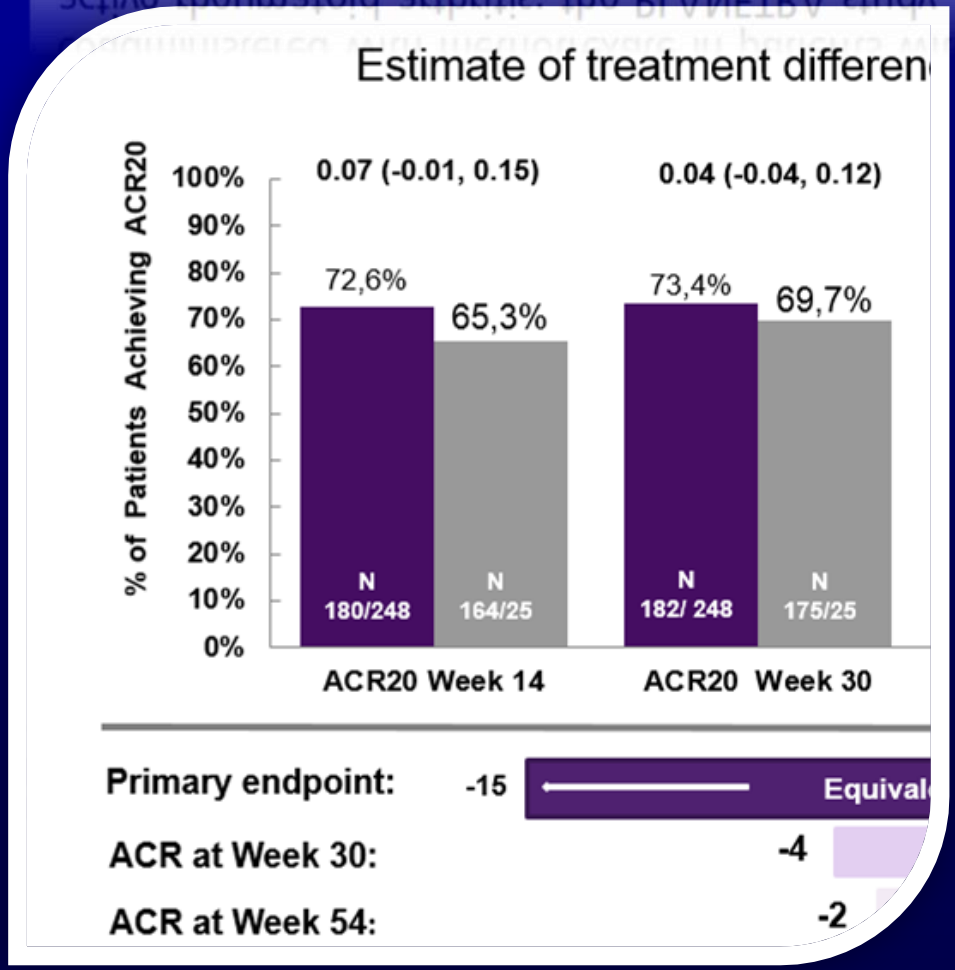
EXTENDED REPORT

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study

	Inflectra™ 3 mg/kg (N=302)	Remicade® 3 mg/kg (N=304)
Mean Age (years)	49.0	48.6
Sex (% female)	81.1	84.2
Race (%)		
White	72.8	73.0
Asian	11.3	12.2
Other	15.9	14.8
Mean height (cm)	163.15	162.89
Mean weight (kg)	70.74	69.86
Mean BMI (kg/m^2)	26.48	26.26
Concomitant oral corticosteroids (%)	68.8	59.8
Mean MTX dose, mg/week (SD)	15.62 (3.10)	15.61 (3.15)
Region (%)		
European	59.3	59.2
Non-European	40.7	40.8

EXTENDED REPORT

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study



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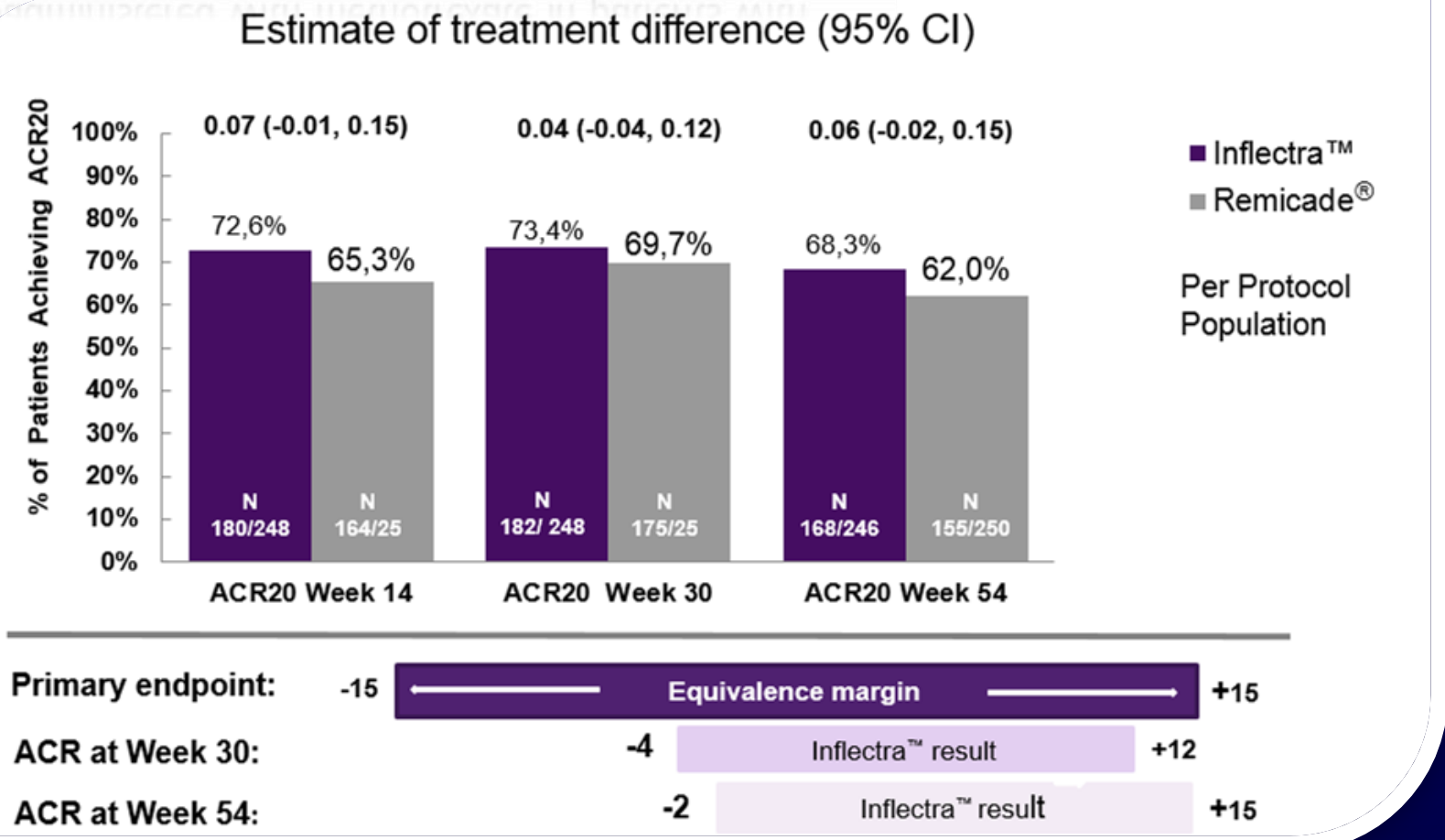

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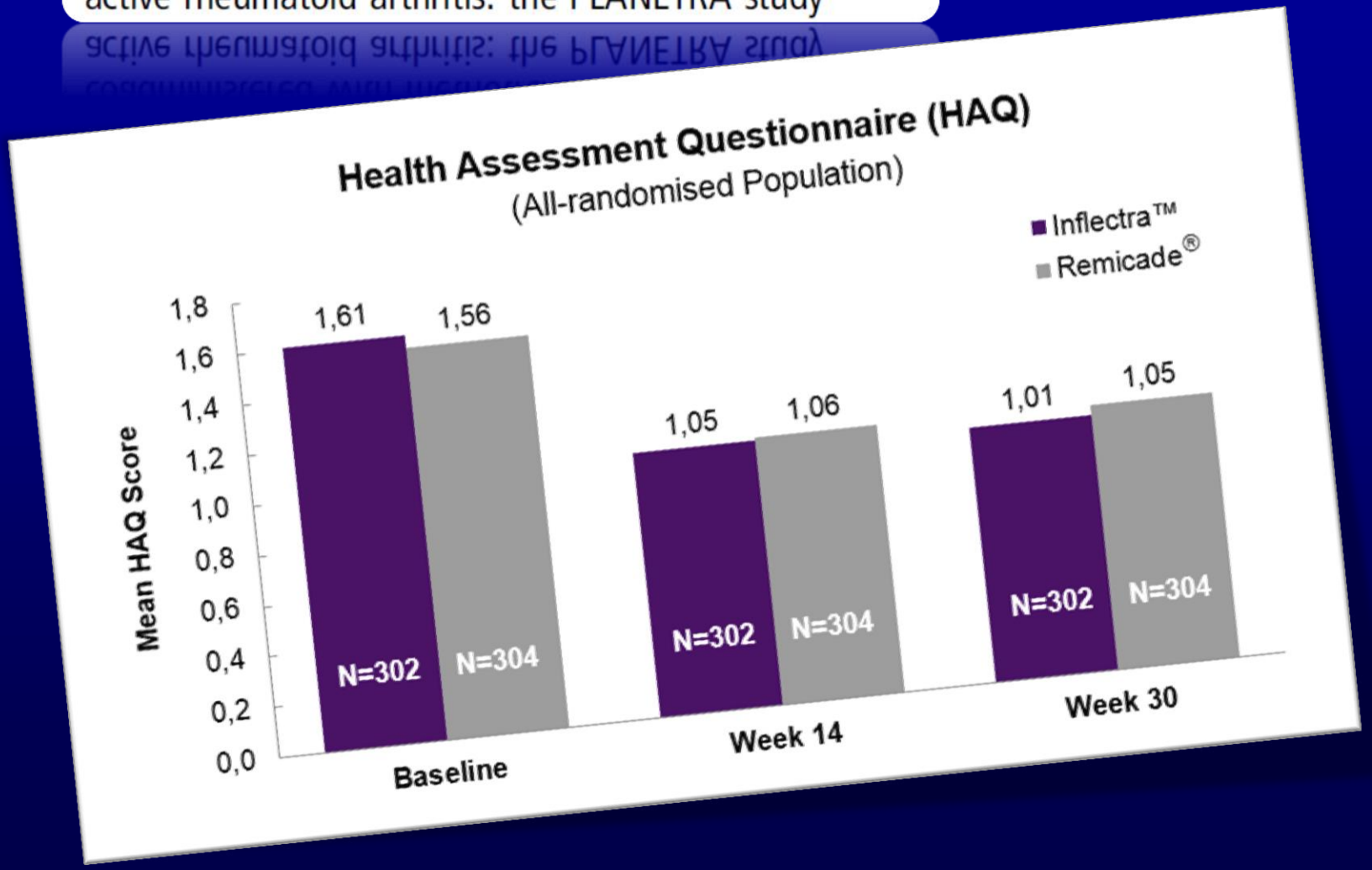

EXTENDED REPORT

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study

System Organ Class	Inflectra™ 3 mg/kg (N=301)	Remicade® 3 mg/kg (N=301)
TEAE	**Number of Patients / %**	
Latent tuberculosis	13 (4.3%)	14 (4.7%)
Alanine aminotransferase (ALT) increased	9 (3.0%)	9 (3.3%)
Aspartate aminotransferase increased	5 (1.7%)	7 (2.3%)
Flare in RA activity	7 (2.3%)	4 (1.3%)
Nasopharyngitis	6 (2.0%)	4 (1.3%)
Urinary tract infection	4 (1.3%)	7 (2.3%)
Drug hypersensitivity	5 (1.7%)	8 (2.7%)
Infusion-related reactions	3 (1.0%)	6 (2.0%)
Headache	4 (1.3%)	6 (2.0%)

Η ορο-μετατροπή (interferon-gamma release assay) ήταν παρόμοια και στις 2 ομάδες : 20%

EXTENDED REPORT

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study

System Organ Class	Inflectra™ 3 mg/kg (N=301)	Remicade® 3 mg/kg (N=301)
TEAE	**Number of Patients / %**	
Total infections reported	126 (41.7%)	136 (45.3%)
Infections in ≥5% patients	**Percentage**	
Latent TB	8.9%	8.3%
Upper respiratory tract infection	8.9%	5.3%
Nasopharyngitis	7.9%	5.7%
Urinary tract infection	6.0%	7.0%
Bronchitis (Inflectra % from general TEAE data)	2.7%	5.7%

EXTENDED REPORT

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study

ανοσογονικότητα

Time point	Inflectra™ (N=302)	Remicade® (N=300)
Screening	2 (0.6%)	3 (1.0%)
Week 14	71 (23.5%)	68 (22.7%)
Week 30	123 (40.7%)	119 (39.7%)

EXTENDED REPORT

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study

ανοσογονικότητα

Time point	Inflectra™ (N=302)	Remicade® (N=300)
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Week 14	71 (23.5%)	68 (22.7%)
Week 30	123 (40.7%)	119 (39.7%)
Week 54	124 (41.0%)	104 (34.7%)

EXTENDED REPORT

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study

Αντιδράσεις στην έγχυση

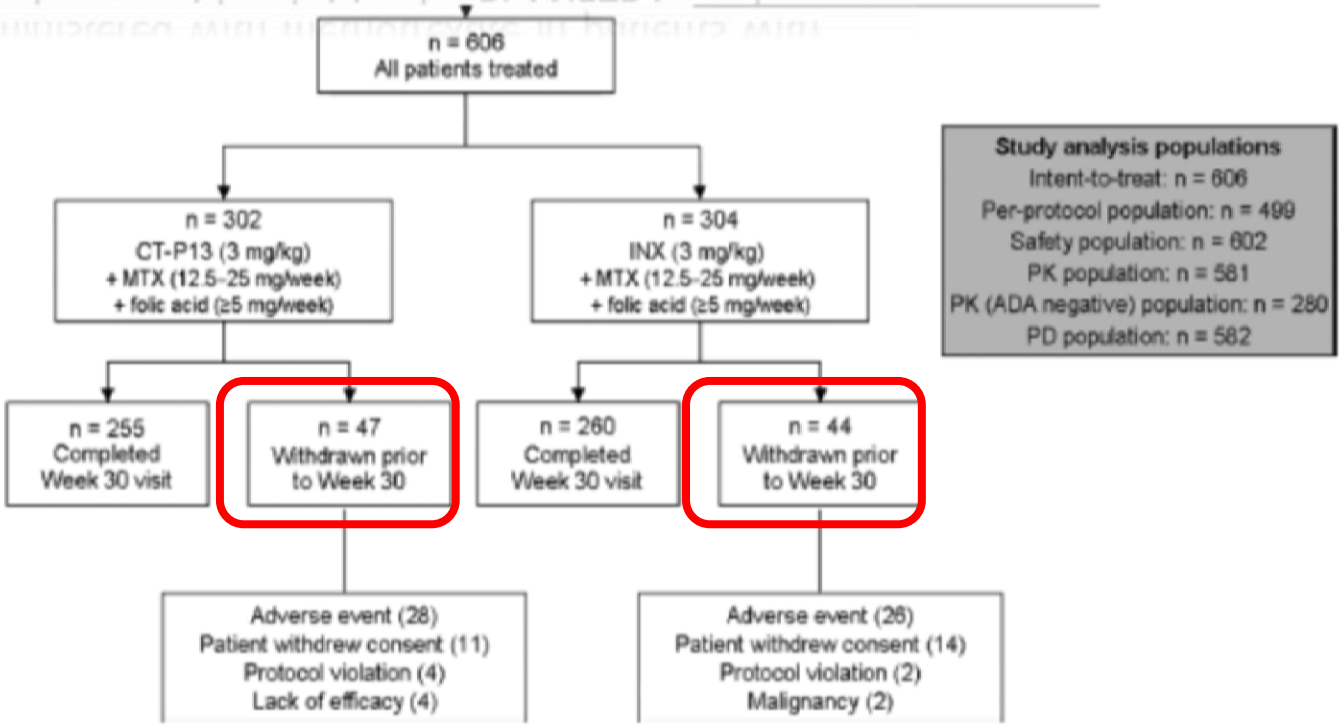
TEAE	INFLECTRA™ 3 mg/kg (N=301)	Remicade® 3 mg/kg (N=301)
No. (%) of patients with at least 1 TEAE due to hypersensitivity and infusion-related reactions at:		
Week 30	16 (5.3%)	18 (6.0%)
Week 54*	23 (8.0%)	31 (10.0%)
Serious infusion-related reactions including anaphylactic/anaphylactoid reactions leading to treatment discontinuation**	7 (2.3%)	7 (2.3%)

- In the safety update at Week 54, infusion-related reactions were reviewed based on a more comprehensive definition; this analysis showed fewer infusion-related reactions to Inflectra™ than Remicade®

** At week 54

EXTENDED REPORT

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study



INFLECTRA® INFLIXIMAB

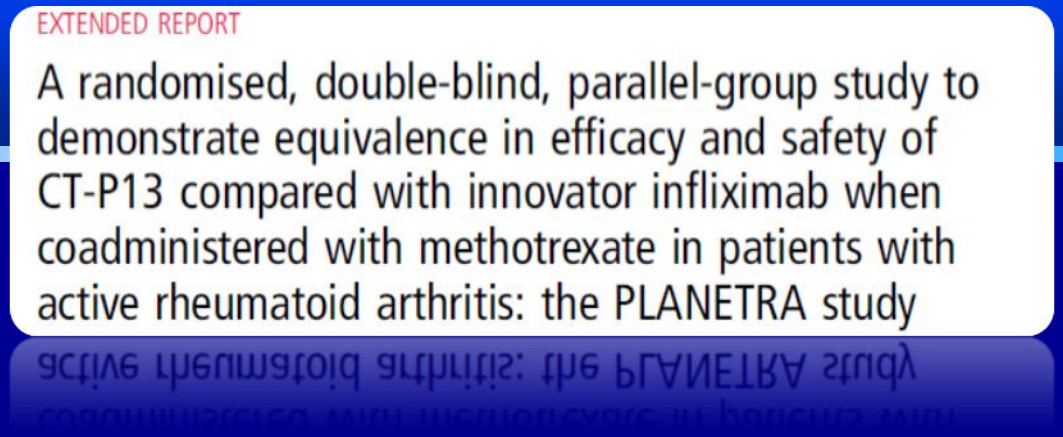
Remicade® INFLIXIMAB

EXTENDED REPORT

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study

- **Ο βασικός στόχος της μελέτης ήταν να επιδειχθεί θεραπευτική ισοδυναμία μεταξύ Inflectra™ και Remicade®**
- **(ACR20 response /Week 30)**
  - **Στον PP πληθυσμό η ACR20 απόκριση ήταν:**
    - **73.4% (182/248) για Inflectra™**
    - **69.7% (176/251) για Remicade®**

The 95% CI for the treatment difference in ACR20 was within the predefined equivalence margin of ± 15%, demonstrating therapeutic equivalence



- **Και για 2γενείς εκβάσεις (ACR criteria, DAS28 ,SF36) επίσης φάνηκε θεραπευτική ισοδυναμία μεταξύ Inflectra™ και Remicade®**

- **Δεν υπήρχαν κλινικά σημαντικές διαφορές μεταξύ Inflectra™ και Remicade® σχετικά με το προφίλ ασφάλειας**

Source: EMA Inflectra EPAR, June 2013

[2013] [OP0068] A PHASE 3 RANDOMISED CONTROLLED TRIAL TO COMPARE CT-P13 WITH INFLIXIMAB IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS: 54 WEEK RESULTS FROM THE PLANETRA STUDY

D. H. Yoo[1], A. Racewicz[2], J. Brzezicki[3], R. Yatsyshyn[4], E. Tobias Arteaga[5], A. Baranauskaite[6], C. Abud-Mendoza[7], S. Navarra[8], R. Eullaran[9], V. Kadinov[10], I. Goecke Sariego[11], P. Byrne[12], W. Park[13], S. J. Lee, H Kim[14], U. Müller-Ladner[16]. [1]Hanyang Univ. Hospital, Seoul, Republic of Korea; [2]NZOZ Osteo-Medic, Bialystok; [3]Wojewodzki Szpital Zespolony, Elblag, Poland; [4]Ivano-Frankivsk Regional Clinical Hospital, Ivan Frankivsk, Ukraine; [5]Hospital Militar Central, Bogota, Colombia; [6]Kaunas Medical Univ. Hospital, Kaunas, Lithuania; [7]Hospital Central Dr. Ignacio Morones Prieto, San Luis Potosi, Mexico; [8]St. Luke's Medical C Quezon City; [9]Chong Hua Hospital, Cebu City, Philippines; [10]Univ. Hospital St. Marina, Varna, Bulgaria; [11]Prosalud y Cia Ltda, Santiago, Chile; [12]Colchester General Hospital, Colchester, United Kingdom; [13] Hospital; [14]CELLTRION, Incheon, Republic of Korea; [15]Univ. of New Mexico, Albuquerque, United States; [16]Justus-Liebig Univ. Giessen, Bad Nauheim, Germany

Background: CT-P13 is a biosimilar product of infliximab (INX). Data up to week 30 has been reported at EULAR 2012.[1]
Objectives: To compare the efficacy and safety of CT-P13 and INX in active rheumatoid arthritis (RA) patients up to week 54.
Methods: Patients with active RA (1987 ACR criteria) and inadequate response to methotrexate (MTX) were randomised (1:1) to receive either CT-P13 (3mg/kg) or INX (3mg/kg) at weeks 0, 2, 6 and then every 8 weeks up to we combination with MTX (12.5–25mg/week).
Results: Of 606 patients randomised at baseline, 457 patients were treated up to week 54. At week 54, ACR20 was highly similar between groups (CT-P13, 57.0% [172/302]; INX, 52.0% [158/304]; 95% CI: -0.03–0.13). ACR50 a scores were also comparable between groups (CT-P13, 33.1% and 16.2%; INX, 31.6% and 15.1%, respectively). In the CT-P13 and INX groups respectively, 26.4% and 27.8% of patients reached remission with DAS28-CRP; additio 14.3% and 14.8% reached low disease activity compared to approximately 80% high disease activity in both groups at baseline. The proportion of patients testing positive for anti-drug antibodies (ADAs) was comparable between CT (52.3%) and INX (49.5%). More patients with negative ADA results achieved ACR20 responses (CT-P13, 73.9%; INX, 67.2%) compared with patients with positive results (CT-P13, 53.2%; INX, 48.1%). Total Sharp scores at baselin 54 were comparable (CT-P13, 104.6 and 70.4; INX, 103.6 and 73.0). C_{max} of CT-P13 or INX at all doses ranged from 66.1µg/mL–112.2µg/mL and 60.3µg/mL–104.5µg/mL, respectively. The safety profiles of CT-P13 and INX were a comparable (table).

PlanetRA 54 εβδ

ACR20

- CT-P13 57.0% [172/302]
- INX 52.0% [158/304]

95% CI: -0.03–0.13

ACR50 - ACR70

- CT-P13 33.1% 16.2%
- INX 31.6% 15.1%

ΥΦΕΣΗ DAS28-CRP

- CT-P13 26.4%
- INX 27.8%

Total Sharp scores στην αρχή και την εβδομάδα 54 ήταν παρόμοια

- CT-P13 104.6 - 70.4
- INX 103.6 - 73.0

Cmax of CT-P13 or INX at all doses ranged

66.1μg/mL–112.2μg/mL

60.3μg/mL–104.5μg/mL

PLANETRA 54 εβδ

	CT-P13 (n=302)	INX (n=300)
No. (%) of patients with at least 1 related TEAE	131 (43.4)	134 (44.7)
No. (%) of patients with at least 1 STEAE	42 (13.9)	31 (10.3)
No. (%) of patients with at least 1 infusion-related reaction	23 (7.6)	31 (10.3)
Positive for ADA, No. (%)	20 (87.0)	25 (80.6)
No. (%) of patients with at least 1 related TEAE due to infection	69 (22.8)	69 (23.0)

TEAE, treatment-emergent adverse event; STEAE, serious TEAE

San Diego ACR/ARHP 13 Annual Meeting
Pre-Meeting Courses: October 25-26, 2013
Scientific Sessions: October 26-30, 2013

Efficacy and Safety of CT-P13 (Infliximab biosimilar) over Two Years in Patients with Rheumatoid Arthritis: Comparison Between Continued CT-P13 and Switching from Infliximab to CT-P13

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Date: Tuesday, October 29, 2013

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Efficacy and Safety of CT-P13 (Infliximab biosimilar) over Two Years in Patients with Rheumatoid Arthritis: Comparison Between Continued CT-P13 and Switching from Infliximab to CT-P13

302 ασθενείς με 54 εβδομάδες

158 έμειναν στο CT-P13

144 άλλαξαν από INX σε CT-P13

Για ακόμη 48 εβδομάδες

Efficacy and Safety of CT-P13 (Infliximab biosimilar) over Two Years in Patients with Rheumatoid Arthritis: Comparison Between Continued CT-P13 and Switching from Infliximab to CT-P13

San Diego ACR/ARHP 13 Annual Meeting
Pre-Meeting Courses: October 25-26, 2013
Scientific Sessions: October 26-30, 2013

Efficacy outcome		CT-P13 throughout study (N=151)	Switched from INX to CT-P13 in extension phase (N=142)
ACR20, n (%)	Wk 54	116 (76.8)	110 (77.5)
	Wk 78	108 (71.5)	111 (78.2)
	Wk 102	109 (72.2)	102 (71.8)
ACR50, n (%)	Wk 54	69 (45.7)	71 (50.0)
	Wk 78	73 (48.3)	68 (47.9)
	Wk 102	73 (48.3)	73 (51.4)
ACR70, n (%)	Wk 54	33 (21.9)	34 (23.9)
	Wk 78	37 (24.5)	42 (29.6)
	Wk 102	37 (24.5)	37 (26.1

Efficacy and Safety of CT-P13 (Infliximab biosimilar) over Two Years in Patients with Rheumatoid Arthritis: Comparison Between Continued CT-P13 and Switching from Infliximab to CT-P13

San Diego ACR/ARHP 13 Annual Meeting
Pre-Meeting Courses: October 25-26, 2013
Scientific Sessions: October 26-30, 2013

·S28-CRP	Baseline (BL, wk 0)	5.8	5.8
	Δ from BL at Wk 54	-2.4	-2.4
	Δ from BL at Wk 78	-2.4	−2.6
	Δ from BL at Wk 102	-2.4	−2.5
DAS28-ESR	BL (wk 0)	6.6	6.6
	Δ from BL at Wk 54	-2.5	−2.6
	Δ from BL at Wk 78	−2.6	−2.8
	Δ from BL at Wk 102	−2.6	−2.7
EULAR-CRP good and moderate responses, n (%)	Wk 54	135 (89.4)	124 (87.3)
	Wk 78	120 (79.5)	122 (85
	Wk 102	123 (81.5)	109

Efficacy and Safety of CT-P13 (Infliximab biosimilar) over Two Years in Patients with Rheumatoid Arthritis: Comparison Between Continued CT-P13 and Switching from Infliximab to CT-P13

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		CT-P13 throughout study (N=151)	Switched from INX to CT-P13 in extension phase (N=142)
TEAEs, n		226	180
pts with ≥1 TEAE, n (%)		85 (53.5)	77 (53.8)
Mild		37 (23.3)	38 (26.6)
Moderate		39 (24.5)	31 (21.7)
Severe		7 (4.4)	8 (5.6)
Life-threatening		1 (0.6)	0
Death		1 (0.6)	0
pts with ≥1 TESAE, n (%)		12 (7.5)	13 (9.1)
pts with ≥1 infection, n (%)		50 (31.4)	47 (32.9)
ADA positive, n (%)	Wk 54	78 (49.1)	69 (49.3)
	Wk 78	71 (50.4)	66 (49.6)
	Wk 102	64 (46.4)	64 (49.6)

ΤΙ ΕΙΔΑΜΕ ΩΣ ΤΩΡΑ …

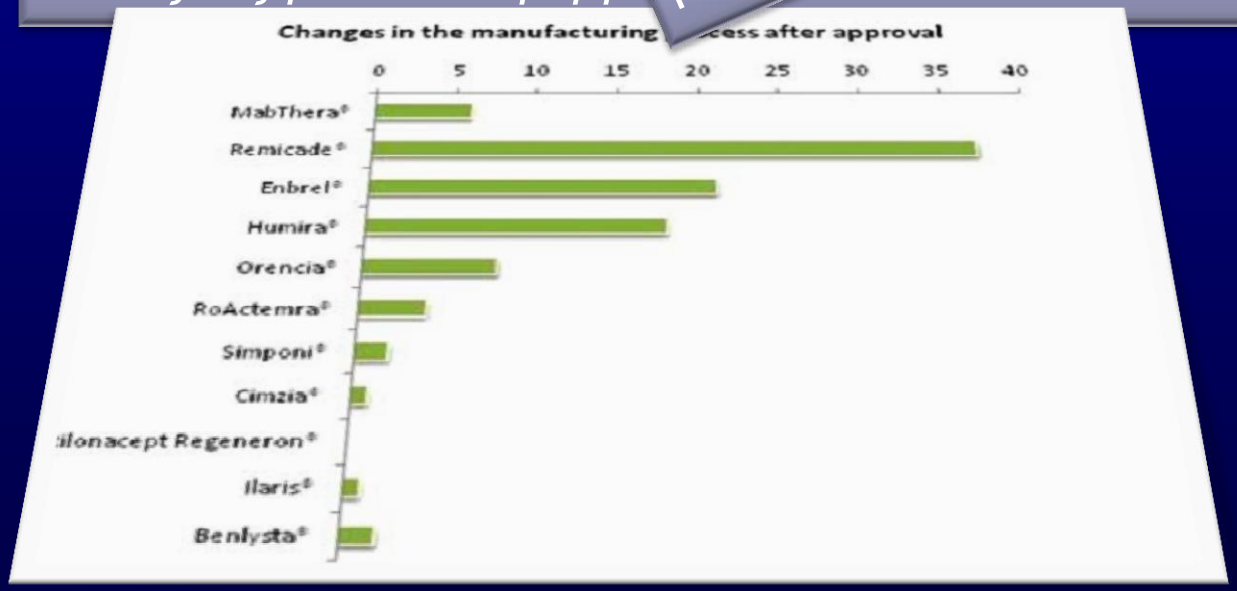
Προφανώς & ΑΠΟΔΕΔΕΙΓΜΕΝΑ, PK, η ασφάλεια και η αποτελεσματικότητα είναι ΙΔΙΑ

Είναι τα 2 φάρμακα ΕΝΤΕΛΩΣ ίδια ?

- *amount of afucosylat*
- *εξέλιξη στο ίδιο φάρμ*

Έχει αυτό κάποια ΚΛΙΝΙΚΗ σημασία ?

No!



ΘΕΜΑΤΑ ΓΙΑ ΣΥΖΗΤΗΣΗ

Υπάρχει έστω και ένας λόγος ώστε το biosimilar να μην χρησιμοποιείται πλέον ως 1η επιλογή σε νέους υποψήφιους για INX ασθενείς ?

Επέκταση σε άλλες ενδείξεις

Ανταλαξιμότητα ? (interchangeability/Substitutions)

INN (φαρμακοεπαγρύπνηση)

ne First, published on October 25, 2013 as 10.1136/annrheumdis-2013-204573

Recommendation

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update

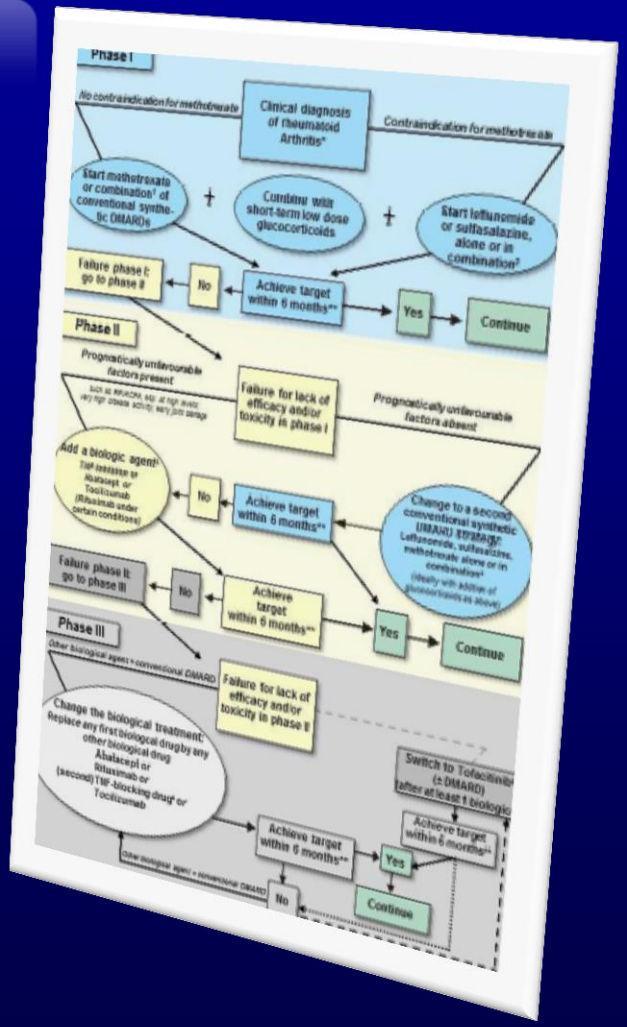
Tumour necrosis factor inhibitors

(adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, biosimilars), abatacept, tocilizumab

και υπο περιπτώσεις το rituximab

Θεωρείται ότι έχουν

ΤΗΝ ΙΔΙΑ ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ



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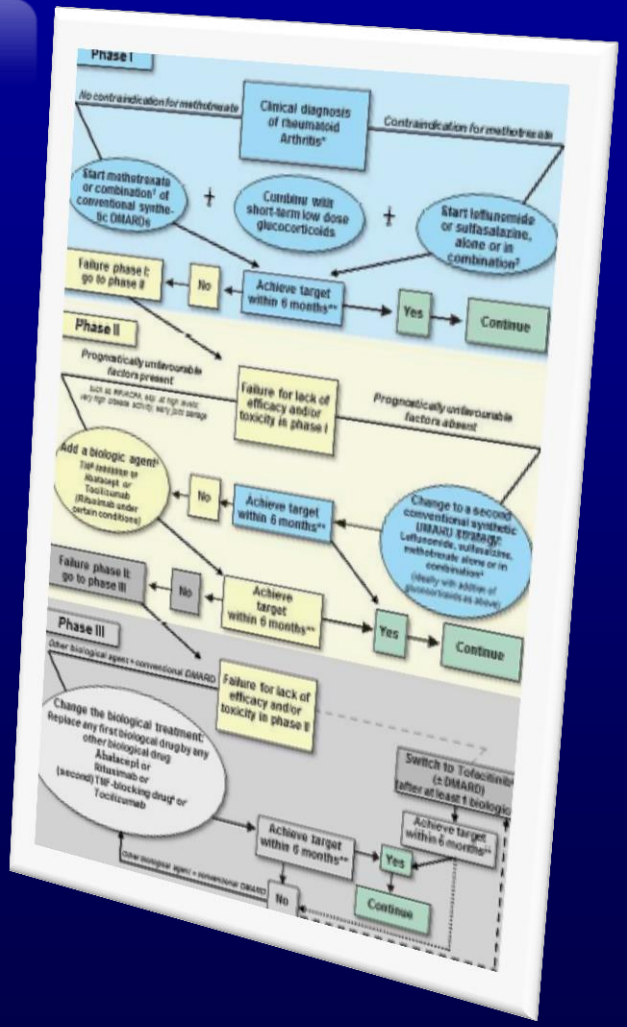
Θεωρείται ότι έχουν

ΤΗΝ ΙΔΙΑ ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ

one biosimilar infliximab product was placed alongside



ΙΩΑΝΝΙΝΑ

EMA Guideline on Biosimilars

- Required to compare biosimilar with reference product:
  - Preclinical *in vitro* assays & *in vivo* animal studies
  - Clinical studies in patients
- If available, single- and multiple-dose PK studies & PD studies using biomarkers relevant to the clinical efficacy of the drug
- In most cases, 'comparative clinical trials' are also needed
  - To demonstrate clinical equivalence between the biosimilar and the already approved reference product
  - To assess potential immunogenicity with chronic dosing
- Careful post-approval pharmacovigilance monitoring is expected
- Extrapolation of efficacy data for the biosimilar to another indication, if reference product acts by the same mechanism in each disease state

Committee for Medicinal Products for Human Use. *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.* London: European Medicines Agency; 2006.

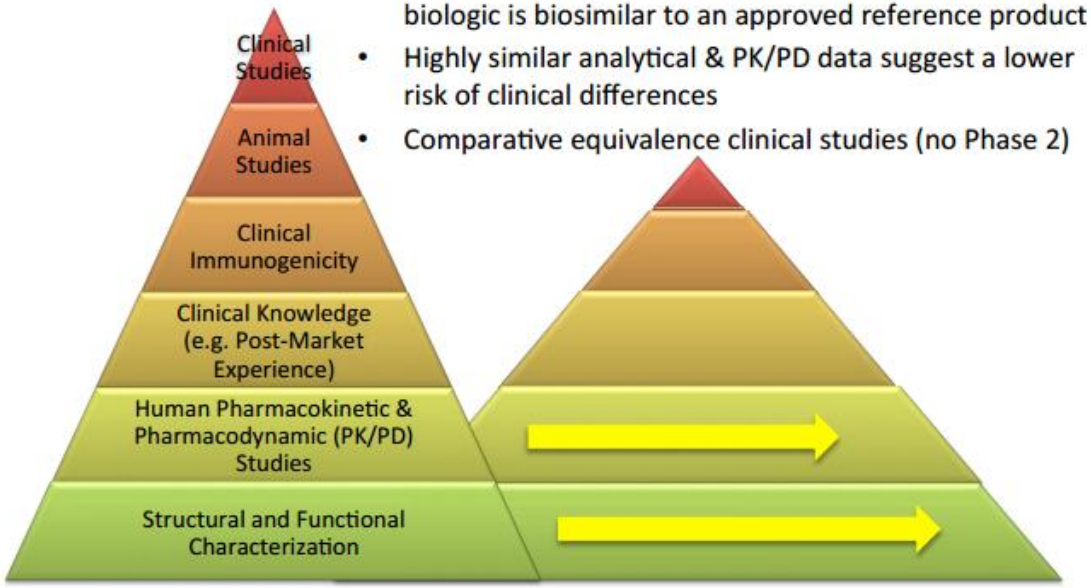
EMA Guideline on Biosimilars: 2011 Proposed Revisions

- Reduce size and number of animal studies required for evaluation of biosimilars.
- Streamline design of clinical testing in patients
  - When reference biopharmaceutical is approved for several indications, phase 2 studies of a biosimilar should be conducted in the disease setting that is most responsive to the innovator therapy
  - Non-inferiority trial design (trials designed to demonstrate therapeutic equivalence or superiority would require much larger numbers of participants)
- Extrapolation of safety & efficacy data from one indication to other indications
- 1-year follow-up immunogenicity data are expected to be requested for biopharmaceuticals intended for chronic administration

Committee for Medicinal Products for Human Use. *Concept paper on the revision of the guideline on similar biological medicinal products containing biotechnology-derived proteins as active*

FDA "Totality of the Evidence" Approach To Assessing Biosimilars

- FDA scientists will integrate various types of information to provide an overall assessment that a biologic is biosimilar to an approved reference product
- Highly similar analytical & PK/PD data suggest a lower risk of clinical differences
- Comparative equivalence clinical studies (no Phase 2)



S Koslowski et al. *N Engl J Med*. 2011;365:385-88

Biologics Price Competition and Innovation Act of 2009: Interchangeability

SEC. 7002. APPROVAL PATHWAY FOR BIOSIMILAR BIOLOGICAL PRODUCTS.

(a) LICENSURE OF BIOLOGICAL PRODUCTS AS BIOSIMILAR OR INTERCHANGEABLE.—Section 351 of the Public Health Service Act (42 U.S.C. 262) is amended—

"(4) SAFETY STANDARDS FOR DETERMINING INTERCHANGEABILITY.—Upon review of an application submitted under this subsection or any supplement to such application, the Secretary shall determine the biological product to be interchangeable with the reference product if the Secretary determines that the information submitted in the application (or a supplement to such application) is sufficient to show that—

"(A) the biological product—

"(i) is biosimilar to the reference product; and

"(ii) can be expected to produce the same clinical result as the reference product in any given patient; and

"(B) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.

FDA

February 2012: FDA Draft Guidance for Implementation of the Biologics Price Competition and Innovation Act of 2009

- A biosimilar agent need not be licensed for all routes of administration, doses and indications for which the reference product is approved
- Extrapolation of data from a clinical trial of the biosimilar conducted in one disease to support approval for additional indications, for which reference product is already licensed
- Does not specify requirements for clinical trial
  - Size or duration
  - Non-inferiority or equivalence design