Ανοσογονικότητα και άλλα κλινικά προβλήματα των βιο-ομοειδών παραγόντων;

Δεδομένα για τα πρώτα φάρμακα που έχουν λάβει άδεια κυκλοφορίας

Σπύρος Ν Νίκας

Ρευματολόγος

Ιωάννινα

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Conflict of interest (2y)

- BMS (6/12)
- Amgen (11/13)
- MSD (3/14)
- ABBVIE (3/13)

Τιμητική αμοιβή για την σημερινή παρουσίαση

Marketed "Biosimilars" Based On Biologic Agents Used To Treat Rheumatic Diseases

Drug*	Manufacturer (location)	Marketed in
Rituximab biosimilar		
Reditux™	Dr. Reddy's Laboratories (India)	Bolivia, Chile, India and Peru
Kikuzubam™	Probiomed (Mexico)	Bolivia, Chile, Mexico, and Peru
Etanercept biosimilar		
Yisaipu	Shanghai CP Goujian Pharmaceutical Co. (China)	China
Etanar®	Shanghai CP Goujian Pharmaceutical Co. (China)	Colombia
Infliximab biosimilar		
Remsima™ (CT–P13)	Celltrion (South Korea)	Approved in South Korea (EMA application pending)

MA Scheinberg & J Kay. *Nat Rev Rheumatol*. 2012; 8:430–36

Human medicines
- European public assessment reports
- Patient safety
- Pending EC decisions
- Withdrawn applications
- Paediatrics
- Rare disease designations
- Medicines under evaluation
- Medicines for use outside the EU
- Referrals
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- Veterinary medicines
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European public assessment reports

This page allows you to find the European public assessment reports (EPAR) for human medicines published by the European Medicines Agency (EMA).

The EMA publishes an EPAR for every medicine granted a central marketing authorisation by the European Commission following an assessment by the EMA's Committee for Medicinal Products for Human Use (CHMP). EPARs are full scientific assessment reports of medicines authorised at a European Union level.

Use this search to find information including a public-friendly summary in question-and-answer format and the package leaflet. You can also find information on medicines that have been refused a marketing authorisation or that have been suspended or withdrawn after being approved.

The Agency does not evaluate all medicines currently in use in Europe. If you cannot find the medicine you need through this search, please visit the website of your national health authority.

More information is available on the Central authorisation procedure and in EPARs: background and context.

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- ◉ Biosimilars
- ○ Conditional approval
- ○ Exceptional circumstances
- ○ Orphan medicines

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SCIENCE MEDICINES HEALTH

first biosimilar **monoclonal** antibody (mAb) therapy

Abseamed	epoetin alfa	Anemia Cancer Kidney Failure, Chronic	28/08/2007		Authorised
Alpheon	recombinant human interferon alfa-2a	Hepatitis C, Chronic	05/09/2006		Refused
Binocrit	epoetin alfa	Anemia Kidney Failure, Chronic	28/08/2007		Authorised
Biograstim	filgrastim	Cancer Hematopoietic Stem Cell Transplantation Neutropenia	15/09/2008		Authorised
Epoetin Alfa Hexal	epoetin alfa	Anemia Cancer Kidney Failure, Chronic	28/08/2007		Authorised
Filgrastim Hexal	filgrastim	Cancer Hematopoietic Stem Cell Transplantation Neutropenia	06/02/2009		Authorised
Filgrastim ratiopharm	filgrastim	Cancer Hematopoietic Stem Cell Transplantation Neutropenia	15/09/2008		Withdrawn
Grastofil	filgrastim	Neutropenia	18/10/2013	▼	Authorised
Inflectra	infliximab	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, Rheumatoid Colitis, Ulcerative Crohn Disease Psoriasis Spondylitis, Ankylosing	10/09/2013	▼	Authorised
Retacrit	epoetin zeta	Anemia Blood Transfusion, Autologous Cancer Kidney Failure, Chronic	18/12/2007		Authorised
Silapo	epoetin zeta	Anemia Blood Transfusion, Autologous Cancer Kidney Failure, Chronic	18/12/2007		Authorised
Tevagrastim	filgrastim	Cancer Hematopoietic Stem Cell	15/09/2008		Authorised

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Expand all items in this list

What is Remsima and what is it used for?

How is Remsima used?

How does Remsima work?

What benefits of Remsima have been shown in studies?

What are the risks associated with Remsima?

Why is Remsima approved?

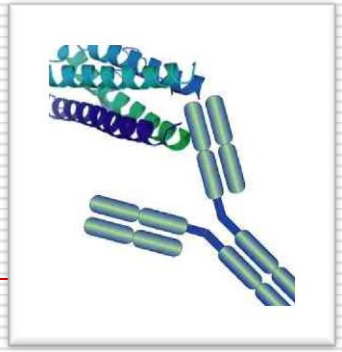
The Agency's Committee for Medicinal Products for Human Use (CHMP) decided that, in accordance with EU requirements, Remsima has been shown to have a comparable quality, safety and efficacy profile to Remicade. Therefore, the CHMP's view was that, as for Remicade, the benefit outweighs the identified risks. The Committee recommended that Remsima be approved for use in the EU.

What measures are being taken to ensure the safe and effective use of Remsima?

Other information about Remsima

Ιρλανδία , Πορτογαλία, Νορβηγία , Φιλανδία
Κορέα, Γουατεμάλα, Γεωργία, Μολδαβία , Λευκορωσία

Ανοσογονικότητα
και άλλα κλινικά προβλήματα των βιο-ομοειδών παραγόντων?



η ικανότητα μιας ουσίας να επάγει χυμική ή/και κυτταρική ανοσολογική απόκριση

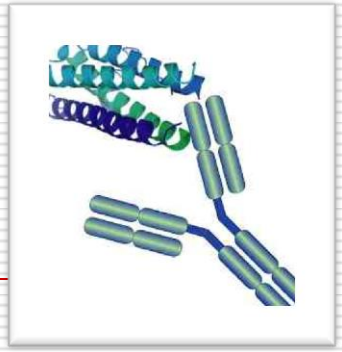
- γενετικό υπόβαθρο του ασθενούς
- η φύση του νοσήματος
- ο τύπος της πρωτεΐνης (οι ανθρώπινες είναι λιγότερο ανοσογόνες από τις ζωικής προέλευσης πρωτεΐνες)
- η οδός χορήγησης (υποδόρια πολύ ανοσογόνος, ενδοφλέβια ελάχιστα ανοσογόνος)
- η συχνότητα χορήγησης
- η διάρκεια της θεραπείας
- η επαναχορήγηση μετά από μακρά διακοπή
- ο τρόπος παρασκευής, ο χειρισμός και η αποθήκευση του φαρμάκου

ADA

περιοχής σύνδεσης του αντιγόνου **Άλλων περιοχών που δεν επηρεάζουν τη σύνδεση**

ανοσοσυμπλέγματα

Ανοσογονικότητα
και άλλα κλινικά προβλήματα των βιο-ομοειδών παραγόντων?



drug induces an unwanted immune reaction in the human body

- Immunogenicity of monoclonal antibodies in biologic therapeutics may have **negative** impacts on treatment response

- treatment **discontinuance** and higher disease **activity** with antidrug antibody formation in more than a quarter (28%) of patients over a 3-year period

Bartelds GM, Krieckaert CL, Nurmohamed MT, et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. JAMA. 2011;305(14):1460–1468.

Ανοσογονικότητα
και άλλα κλινικά προβλήματα
των βιο-ομοειδών παραγόντων?

Μελέτες

Registries

Κίτρινη κ

Προ-έγκρισης φαρμάκου

Μετά-έγκρισης φαρμάκου

CT-P13

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 CT-P13 and Remicade at Weeks 0, 2 and 6 Secondary: PK profile, PD, efficacy, and safety of CT-P13 in comparison to Remicade up to Week 102.	CT-P13 plus MTX or Remicade plus MTX	RA patients with active disease while receiving MTX Planned: 20 Randomised: 19 CT-P13: 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_T, $C_{max,ss}$ between CT-P13 and Remicade determined between Weeks 22 and 30. Secondary: long-term efficacy, PK and overall safety up to Week 54	CT-P13 or Remicade	AS patients with active disease Planned: 246 (ratio: 1:1) Randomised: 250 CT-P13: 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 CT-P13 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	CT-P13 plus MTX or Remicade plus MTX	RA patients with active disease while receiving MTX Planned: 584 (ratio: 1:1) Randomised: 606 CT-P13: 302 Remicade: 304

ACR20=20% improvement according to the ACR criteria; AS=Ankylosing spondylitis; AUC_T=Area under the concentration-time curve over the dosing interval; Cmax=maximum serum concentration; i.v.=intravenous; MTX=methotrexate; PK=Pharmacokinetics; PD=Pharmacodynamics; RA=Rheumatoid arthritis

Annals of the
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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

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]

Published Online First 17 May 2013

EXTENDED REPORT

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

ασθενείς με ενεργό PA και αποτυχία στην MTX (12.5–25 mg/week) τυχαιοποιήθηκαν:

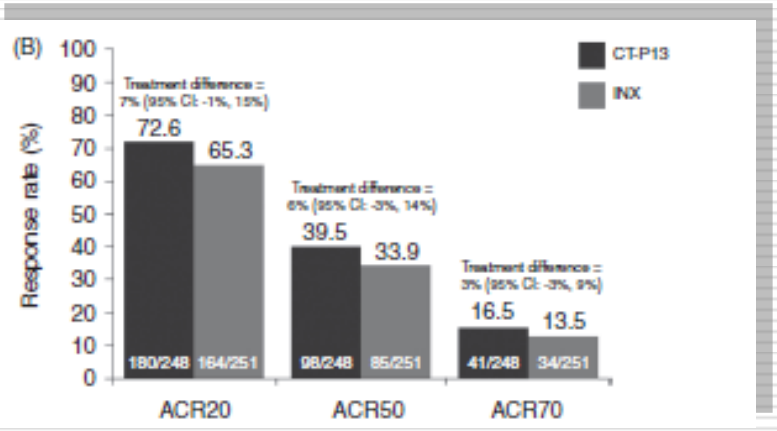
- **CT-P13** (n=302) 3 mg/kg
- **INX** (n=304) 3 mg/kg

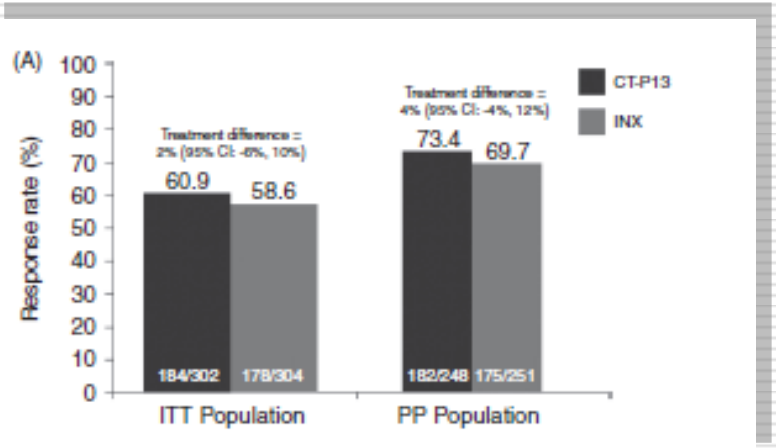
Σε συνδυασμό με MTX και folic acid

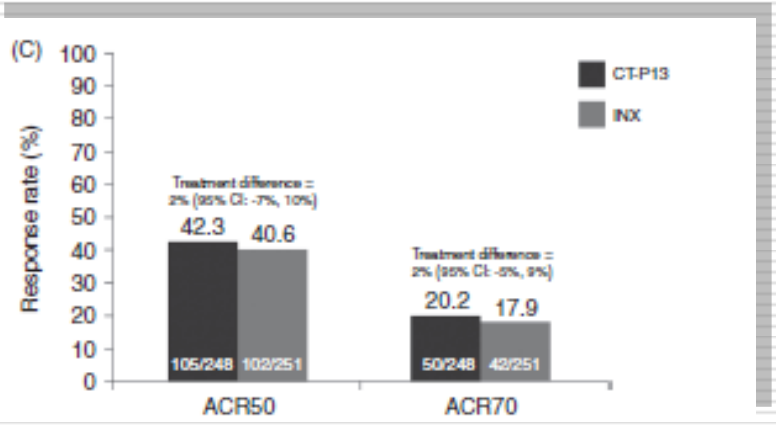
Εκτίμηση στις 30 εβδομάδες (ACR20)

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

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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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

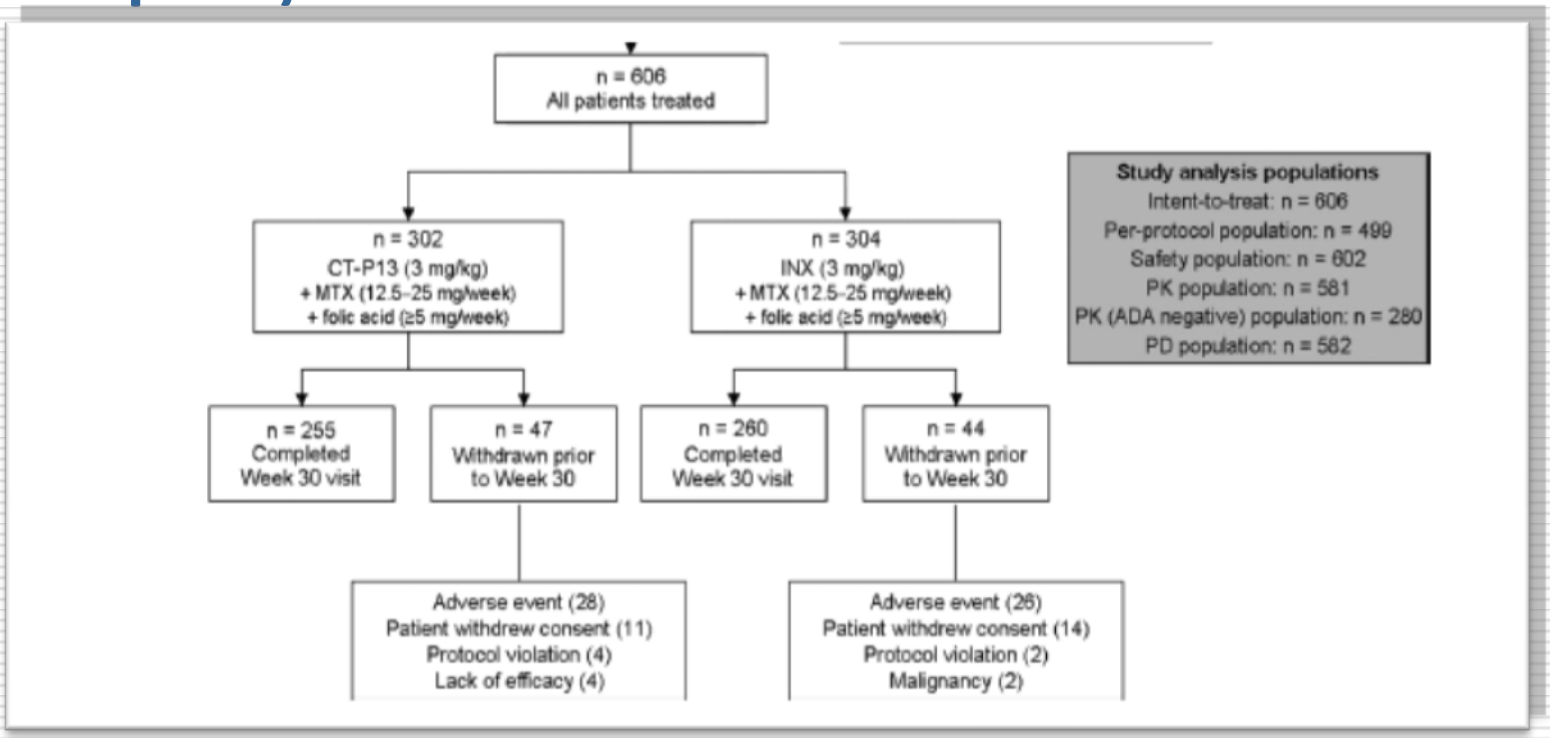
αποτελεσματικότητα

SF-36	Week 14			
	Physical component summary	7.5 (7.1)	5.8 (6.8)	0.007
	Mental component summary	6.6 (10.2)	6.5 (10.4)	0.925
	Week 30			
	Physical component summary	7.1 (7.9)	6.5 (7.6)	0.372
	Mental component summary	7.1 (10.0)	6.6 (10.4)	0.561
CRP	Week 14	−0.6 (2.5)	−0.8 (1.9)	0.413
	Week 30	−0.6 (2.0)	−0.8 (1.9)	0.323
HAQ	Week 14	−0.6 (0.6)	−0.5 (0.5)	0.053
	Week 30	−0.6 (0.6)	−0.5 (0.6)	0.082

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

Αποσύρσεις ασθενών

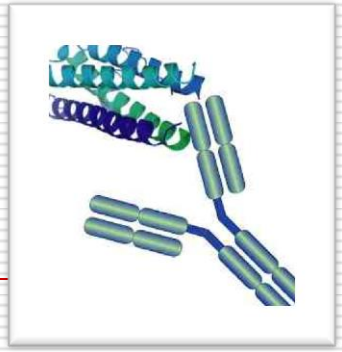


INFLECTRA® INFLIXIMAB

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



Ανοσογονικότητα

Εβδομάδα 14: Antibodies στο infliximab στο

- 25.4% (n=69) CT-P13
- 25.8% (n=70) INX

Εβδομάδα 30 :

- 48.4% (n=122) CT-P13
- 48.2% (n=122) INX

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

Ανεπιθύμητες δράσεις

Related TEAEs reported in at least 1% of patients in either treatment group	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)
Anaemia	2 (0.7)	3 (1.0)	5 (0.8)
Neutropenia	3 (1.0)	2 (0.7)	5 (0.8)
Leucopenia	1 (0.3)	3 (1.0)	4 (0.7)
Bone pain	3 (1.0)	0	6 (1.0)
Hypertension	5 (1.7)	3 (1.0)	8 (1.3)

Serious TEAEs

30 (10.0%) CT-P13

21 (7.0%) INX

[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]I 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; additic 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

positive for anti-drug antibodies (ADAs) :
CT-P13 (52.3%) και INX (49.5%)

◂ Previous Abstract: #L1 Next ▸

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

Abstract: #L1

Date: Tuesday, October 29, 2013

Time: 2:30 PM

Location: 6 A

Session Title: ACR Late-Breaking Abstract Oral Session

Abstract Category: Type: Late-Breaking Oral

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

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
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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

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Scientific Sessions: October 26-30, 2013

DAS28-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 (85.9)
	Wk 102	123 (81.5)	109 (76.8)

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

		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)

Είναι η ΡΑ κατάλληλο μοντέλο για την έλεγχο ενός biosimilar ?

The AAPS Journal, Vol. 16, No. 1, January 2014 (© 2013)
DOI: 10.1208/s12248-013-9534-y

Regulatory Note

Is Extrapolation of the Safety and Efficacy Data in One Indication to Another Appropriate for Biosimilars?

Howard Lee[1,2]

If the difference in efficacy between a treatment and placebo is small, it is difficult (i.e., less sensitive) to show a difference between the treatment and another treatment similar

Είναι η PA κατάλληλο μοντέλο για την έλεγχο ενός biosimilar ?

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Regulatory Note

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Howard Lee[1,2]

low immunogenicity in RA / IBD

Annals of the
RHEUMATIC DISEASES
The EULAR Journal

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

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]

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

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

- Φάσης Ι
- Τυχαιοποιημένη
- Διπλά τυφλή
- Πολυκεντρική
- 5 mg/kg **CT-P13** (n=125)
- **INX** (n=125)

•area under the concentration-time curve (AUC) at steady state
•observed maximum steady state serum concentration (Cmax,ss) between weeks 22 and 30

ASAS20 and ASAS40
safety outcomes

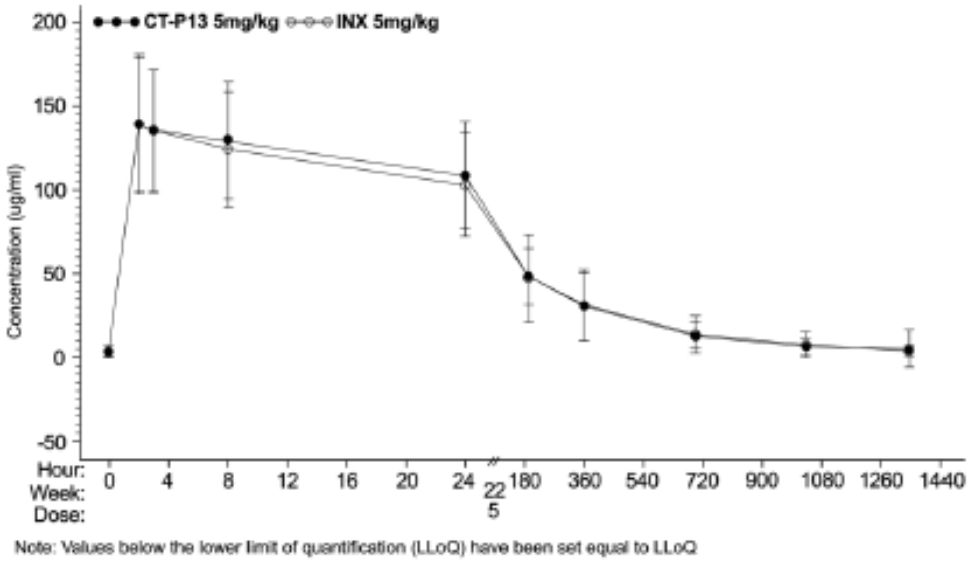
A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study

Parameter	Treatment	n	Geometric mean	Ratio (%) of geometric means	90% CI of ratio (%)
PK population					
AUC	CT-P13	112	32765.8	104.5	94.3 to 115.8
(μgh/ml)	INX	110	31359.3		
$C_{max,ss}$	CT-P13	113	147.0	101.5	94.7 to 108.9
(μg/ml)	INX	110	144.8		
ADA-negative subset					
AUC	CT-P13	84	37505.2	103.4	94.6 to 113.1
(μgh/ml)	INX	86	36266.9		
$C_{max,ss}$	CT-P13	85	153.9	104.7	97.2 to 112.9
(μg/ml)	INX	86	146.9		

The primary PK endpoints of the observed AUC and $C_{max,ss}$ in patients treated with CT-P13 and INX at steady state were analysed using an analysis of covariance with treatment as a fixed effect and region and baseline BASDAI score fitted as covariates. Point estimates and 90% CI for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale.

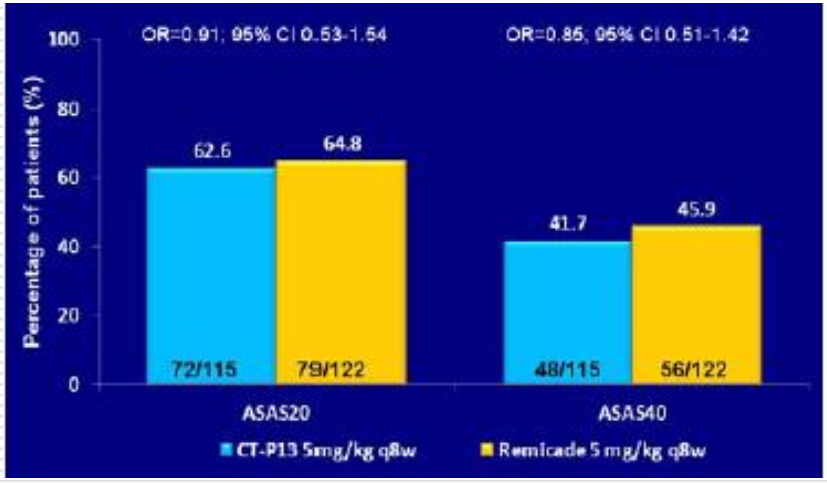
ADA, anti-drug antibodies; AUC, area under the concentration-time curve; $C_{max,ss}$, observed maximum steady state serum concentration; CI, confidence interval; INX, innovator infliximab; PK, pharmacokinetics.

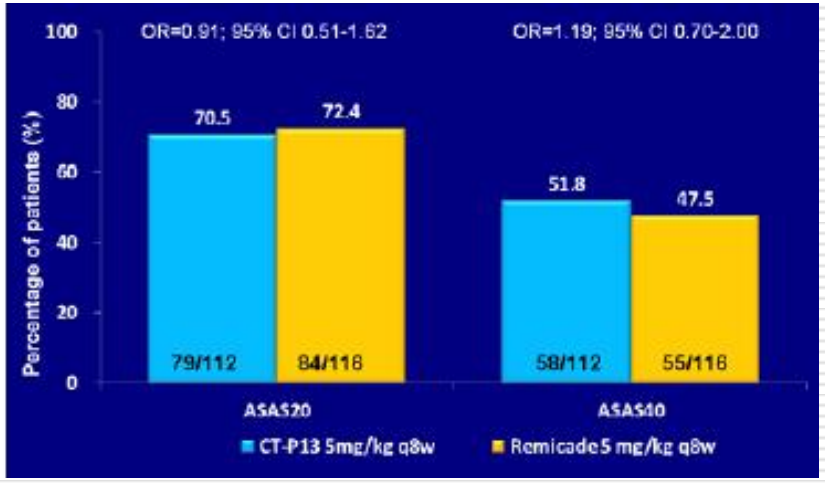
A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study



Mean serum drug concentration following administration of Dose 5

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





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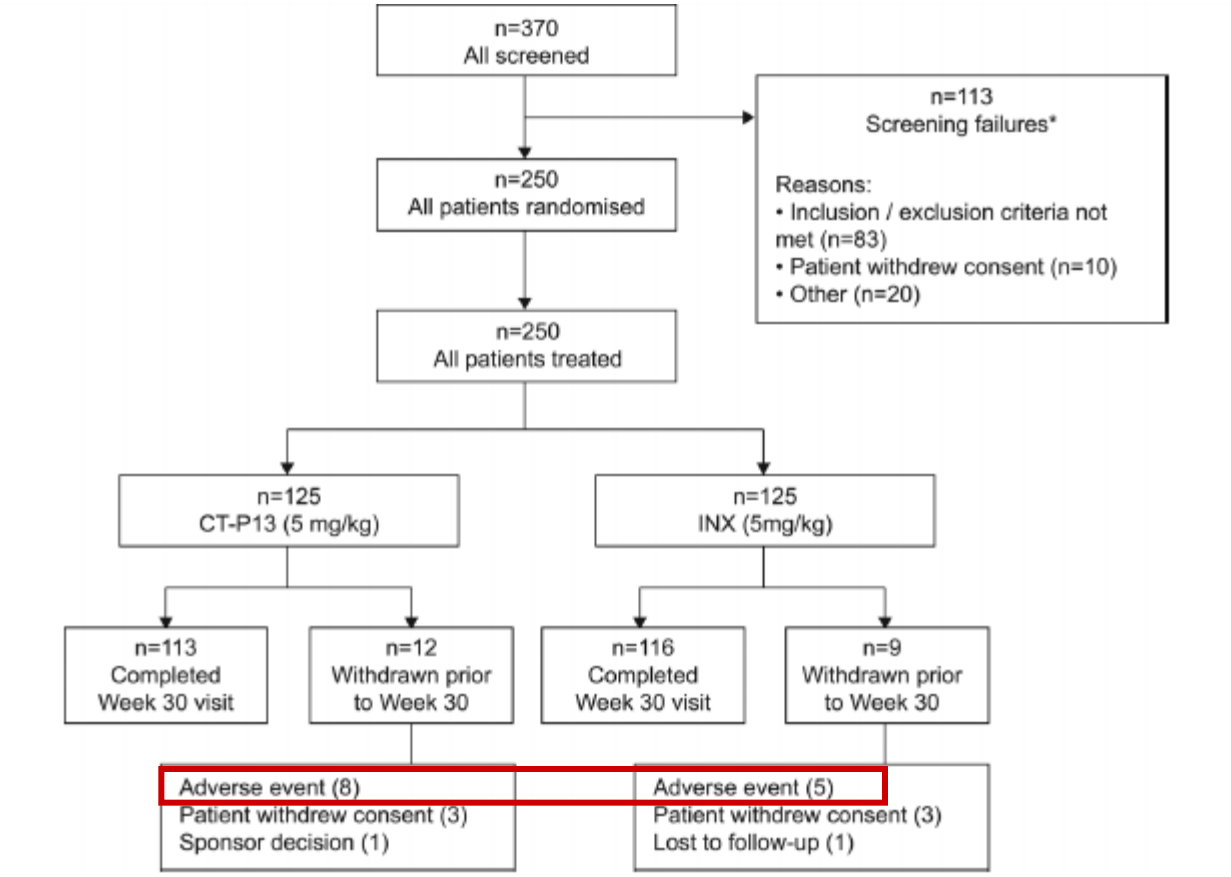
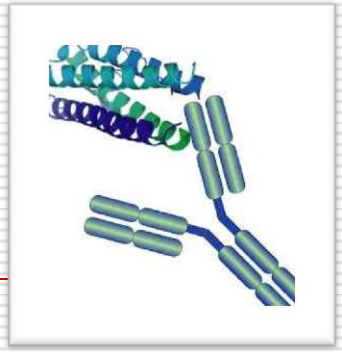


A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study

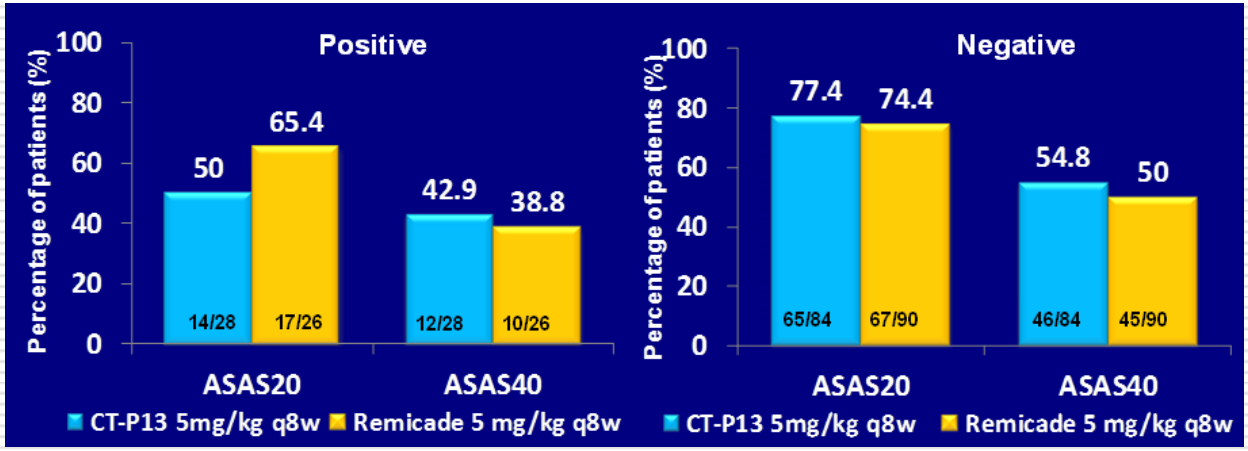
	CT-P13 5 mg/kg (N=128)	INX 5 mg/kg (N=122)	Total (N=250)
Alanine aminotransferase increased	14 (10.9)	13 (10.7)	27 (10.8)
Aspartate aminotransferase increased	12 (9.4)	10 (8.2)	22 (8.8)
γ-glutamyltransferase increased	4 (3.1)	5 (4.1)	9 (3.6)
Latent tuberculosis*	5 (3.9)	4 (3.3)	9 (3.6)
Upper respiratory tract infection	3 (2.3)	2 (1.6)	5 (2.0)
Nasopharyngitis	3 (2.3)	2 (1.6)	5 (2.0)
Pharyngitis	2 (1.6)	3 (2.5)	5 (2.0)
Urinary tract infection	5 (3.9)	0	5 (2.0)
Bacteriuria	0	2 (1.6)	2 (0.8)
Tonsillitis	0	2 (1.6)	2 (0.8)
Tuberculosis	2 (1.6)	1 (0.8)	3 (1.2)
Infusion-related reaction	5 (3.9)	6 (4.9)	11 (4.4)
Serum creatinine phosphokinase increased	4 (3.1)	1 (0.8)	5 (2.0)
Neutropenia	2 (1.6)	2 (1.6)	4 (1.6)
Leukopenia	0	2 (1.6)	2 (0.8)
Pyrexia	2 (1.6)	1 (0.8)	3 (1.2)
Headache	3 (2.3)	1 (0.8)	4 (1.6)
Rash	0	3 (2.5)	3 (1.2)
Urticaria	0	2 (1.6)	2 (0.8)
Nausea	1 (0.8)	2 (1.6)	3 (1.2)

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



Antibodies στο infliximab:

- 9.1% (n=11) και 11.0% (n=13) σε ασθενείς υπό CT-P13 and INX την **εβδομάδα 14**
- 27.4% (n=32) 22.5% (n=25) υπό CT-P13 και INX**, εβδομάδα 30**



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

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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)

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ASAS40 και ASAS **partial remission** ήταν παρόμοια στις 2 ομάδες

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

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%)

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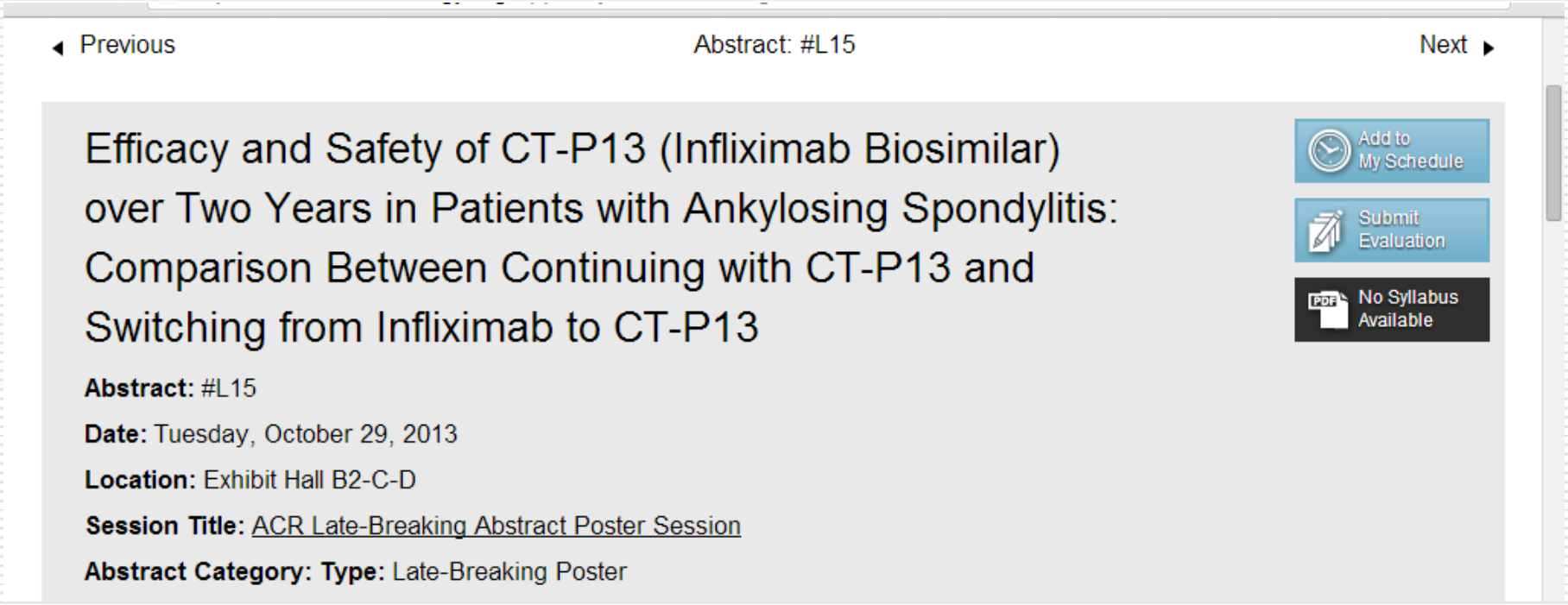
	CT-P13 (n=128)	INX (n=122)
No. (%) of patients with at least 1 related TEAE	62 (48.4)	63 (51.6)
No. (%) of patients with at least 1 STEAE	10 (7.8)	8 (6.6)
No. (%) of patients with at least 1 infusion-related reaction	4 (3.1)	11 (9.0)
- Positive for ADA, No. (%)	3 (75.0)	9 (81.8)
No. (%) of patients with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

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

174 ασθενείς με 54 εβδομάδες

88 έμειναν στο CT-P13

86 άλλαξαν από INX σε CT-P13

Για ακόμη 1 χρόνο

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

San Diego ACR/ARHP 13 Annual Meeting
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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

Ανοσογονικότητα και άλλα κλινικά προβλήματα των βιο-ομοειδών παραγόντων;

Δεδομένα για τα πρώτα φάρμακα που έχουν λάβει άδεια κυκλοφορίας

Σπύρος Ν Νίκας

Ρευματολόγος

Ιωάννινα

Musculoskeletal US specialist

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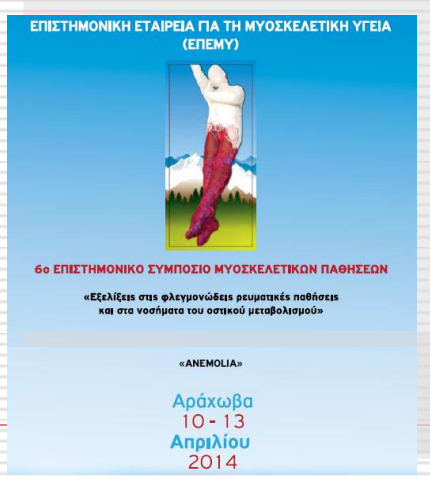


Level of Overall Experience: Remicade vs CT-P13

	REMICADE (infliximab)			CT-P13 (SEB to infliximab)		
	Patients	Number of Studies [1-34]		Patients	Number of Studies[35,36]	
		Phase I/II	Phase III/IV		Phase I	Phase III
Rheumatoid Arthritis	3,293	5	6	302		1
Ankylosing Spondylitis	385	1	1	125	1	
Psoriatic Arthritis	311		3			
Crohn's Disease (Adult)	1393	4	3			
Crohn's Disease (Pediatric)	133	1	1			
Ulcerative Colitis	647	1	3			
Ulcerative Colitis (Pediatric)	60		1			
Psoriasis	2,496	1	4			
Total	**8,718**	35		**427**	2	

Patient registries
INFLIXIMAB

- Pediatric IBD registry (DEVELOP; US & EU)
- Pregnancy registry (birth outcome data)
- Swedish Psoriasis Tumor registry
- Psoriasis registry (PSOLAR; US, Canada, EU)
- Ulcerative colitis registry (OPUS)
- Four National rheumatoid arthritis registries
- Crohn's disease registry (ENCORE)
- Two National Psoriasis registries
- Crohn's disease registry (TREAT; US)

→ Regular reports, ad hoc investigations of safety signals

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

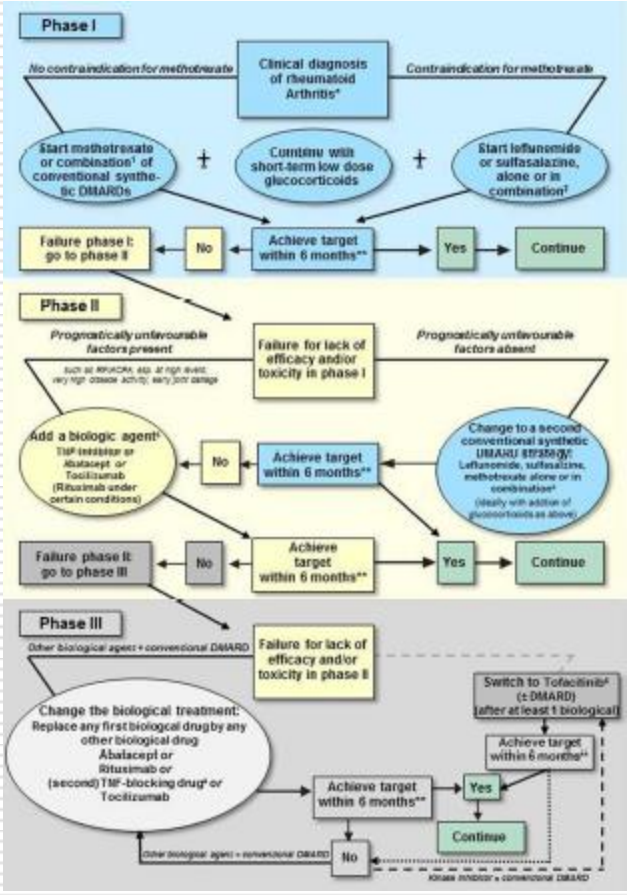
(adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, **biosimilars**), abatacept, tocilizumab

και υπο περιπτώσεις το rituximab

Θεωρείται ότι έχουν

ΤΗΝ ΙΔΙΑ ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ

one biosimilar infliximab product was placed alongside



Molecule	Phase		Trial name and Title	Condition
Adalimumab	Phase III	ADACCESS	Efficacy and Safety of GP2017 and adalimumab (ADACCESS)	Chronic Stable Plaque Psoriasis
Etanercept	Phase III	EGALITY	Efficacy and Safety of GP2015 and Etanercept (EGALITY)	Chronic Stable Plaque Psoriasis
Rituximab	Phase III	ASSIST-FL	GP2013 in the Treatment of Patients With Previously Untreated, Advanced Stage Follicular Lymphoma (ASSIST)	Follicular Lymphoma (FL)
Rituximab	Phase II	ASSIST-RA	GP2013 in the Treatment of RA Patients Refractory to or Intolerant of Standard Therapy	Rheumatoid Arthritis (RA)
Epoetin-alfa	Phase III (US)	access	Safety and Efficacy of HX575 Epoetin Alfa and US-licensed Epoetin Alfa (ACCESS)	Anemia due to Chronic Kidney Disease (CKD)
Epoetin-alfa	Phase III (EU)	sense	HX575 Epoetin Alfa Subcutaneously in Chronic Kidney Disease (SENSE)	Anemia due to Chronic kidney disease (CKD)
Filgrastim	Phase III (US)	PIONEER	Efficacy and Safety of EP2006 and Filgrastim (PIONEER)	Chemotherapy induced febrile neutropenia
PegFilgrastim	Phase III	PROTECT	Efficacy and Safety of LA-EP2006 and Peg-Filgrastim (PROTECT)	Chemotherapy induced febrile neutropenia