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]

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For numbered affiliations see end of article.

Correspondence to
Professor Dae Hyun Yoo, Division of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, 220 Wangsimni-Ro, Seongdong-Gu, Seoul 133-792, Republic of Korea; dhyoo@hanyang.ac.kr; Professor Ulf Müller-Ladner, Department of Rheumatology and Clinical Immunology, Justus Liebig University Giessen, Kerckhoff-Klinik GmbH, Benekestrasse 2–8, 61231 Bad Nauheim, Germany; u.mueller-ladner@kerckhoff-klinik.de

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ABSTRACT

Objectives To compare the efficacy and safety of innovator infliximab (INX) and CT-P13, an INX biosimilar, in active rheumatoid arthritis patients with inadequate response to methotrexate (MTX) treatment.

Methods Phase III randomised, double-blind, multicentre, multinational, parallel-group study. Patients with active disease despite MTX (12.5–25 mg/week) were randomised to receive 3 mg/kg of CT-P13 (n=302) or INX (n=304) with MTX and folic acid. The primary endpoint was the American College of Rheumatology 20% (ACR20) response at week 30. Therapeutic equivalence of clinical response according to ACR20 criteria was concluded if the 95% CI for the treatment difference was within ±15%. Secondary endpoints included ACR response criteria, European League Against Rheumatism (EULAR) response criteria, change in Disease Activity Score 28 (DAS28), Medical Outcomes Study Short-Form Health Survey (SF-36), Simplified Disease Activity Index, Clinical Disease Activity Index, as well as pharmacokinetic (PK) and pharmacodynamic (PD) parameters, safety and immunogenicity.

Results At week 30, ACR20 responses were 60.9% for CT-P13 and 58.6% for INX (95% CI −6% to 10%) in the intention-to-treat population. The proportions in CT-P13 and INX groups achieving good or moderate EULAR responses (C reactive protein (CRP)) at week 30 were 85.8% and 87.1%, respectively. Low disease activity or remission according to DAS28–CRP, ACR–EULAR remission rates, ACR50/ACR70 responses and all other PK and PD endpoints were highly similar at week 30. Incidence of drug-related adverse events (35.2% vs 35.9%) and detection of antidrug antibodies (48.4% vs 48.2%) were highly similar for CT-P13 and INX, respectively.

Conclusions CT-P13 demonstrated equivalent efficacy to INX at week 30, with a comparable PK profile and immunogenicity. CT-P13 was well tolerated, with a safety profile comparable with that of INX.

ClinicalTrials.gov Identifier NCT01217086

INTRODUCTION

Innovator infliximab (INX), a chimeric monoclonal antibody to tumour necrosis factor-α (TNFα), with demonstrated beneficial effects in rheumatoid arthritis (RA) patients, was approved in 1999. The approval of INX was based on data from the ATTRACT study.[1]

The availability of targeted biological therapies has revolutionised the treatment of RA. However, the significant cost of these medications creates a major barrier that limits universal access to these effective therapeutic agents. This has led to interest in developing biosimilar products, which are highly similar, but not identical and not 'bioidentical', to approved 'reference' agents.[2]

CT-P13 is an immunoglobulin (Ig)G1 chimeric human–murine monoclonal antibody biosimilar to INX. CT-P13 is produced in the same type of cell-line (Sp2/0-AG14—purchased from ATCC, Cat. CRL-1581) and has an identical amino acid sequence to INX. CT-P13 and INX have demonstrated comparable in vitro primary pharmacodynamics (PD) in a range of studies (CELLTRION, Inc unpublished data; see online supplementary appendix A). CT-P13 and INX showed comparable binding affinities to monomeric and trimeric forms of human TNFα (hTNFα), transgenic mouse hTNFα (tmhTNFα) expressed by Jurkat cells and to Fcγ receptors and FcRn. Comparable hTNFα neutralising activity against a TNFα-sensitive mouse sarcoma cell-line (WEHI-164) has also been demonstrated. CT-P13 and INX are also comparable in terms of: lack of binding activity with hTNFβ and TNFα from a range of different species known not to bind infliximab; relative binding affinities to complement protein C1q; complement dependent cytotoxicity effects and apoptotic effects against a Jurkat T cell-line expressing tmhTNFα. Comparable cytotoxic activities have been achieved as a result of antibody-dependent cellular cytotoxicity evaluation of human peripheral blood mononuclear cells against tmhTNFα–Jurkat T cells, demonstrating biosimilarity of CT-P13 and INX. Highly comparable human tissue cross-reactivity results have been observed for biotinylated CT-P13 and biotinylated INX. CT-P13 was also assessed for bioequivalence to INX in a phase 1 trial in ankylosing spondylitis (AS).[3]

Based on the data described, this trial, PLANETRA (*P*rogramme eva*L*uating the *A*utoimmune disease i*N*v*E*stigational drug c*T*-p13 in *RA* patients), was conducted with the approval of the regulatory authorities including EMA. PLANETRA was designed to assess efficacy equivalence and to evaluate pharmacokinetics (PK), PD and overall safety of multiple doses of CT-P13 versus INX in active RA patients.

PATIENTS AND METHODS

Patients

Patients with active RA according to the revised 1987 American College of Rheumatology (ACR) classification criteria for ≥1 year prior to screening were recruited. Patients had to have ≥6 swollen and ≥6 tender joints and at least two of the following: morning stiffness lasting ≥45 min; serum C reactive protein (CRP) concentration >2.0 mg/dl and erythrocyte sedimentation rate (ESR) >28 mm/h despite methotrexate (MTX) therapy for ≥3 months (stable dose of 12.5–25 mg/week for ≥4 weeks prior to screening). Patients were permitted to receive both oral glucocorticoids (equivalent to ≤10 mg daily prednisolone) and non-steroidal anti-inflammatory drugs, if they had received a stable dose for ≥4 weeks prior to screening. Additional details of patient eligibility criteria are provided online (see online supplementary appendix B).

Study design

The study (ClinicalTrials.gov NCT01217086) was conducted according to the Declaration of Helsinki and the International Committee on Harmonisation good clinical practice. The protocol was reviewed and approved by regulatory authorities and the ethics committees of each study site. Written informed consent was obtained from all patients. The study was conducted at 100 centres across 19 countries in Europe, Asia, Latin America and Middle East.

Patients were randomly assigned 1:1 to receive 2 h intravenous infusion of either 3 mg/kg of CT-P13 (CELLTRION INC, Incheon, Republic of Korea) or INX (Janssen Biotech Inc, Horsham, Pennsylvania, USA) at weeks 0, 2 and 6 and then

Table 1 Baseline demographics and disease characteristics*

	CT-P13 3 mg/kg (N=302)	INX 3 mg/kg (N=304)	Total (N=606)
Age (years)			
Median (range)	50 (18–75)	50 (21–74)	50 (18–75)
Gender, no (%)			
Female	245 (81.1)	256 (84.2)	501 (82.7)
Male	57 (18.9)	48 (15.8)	105 (17.3)
Ethnicity, no (%)			
Asian	34 (11.3)	37 (12.2)	71 (11.7)
Black	2 (0.7)	1 (0.3)	3 (0.5)
White	220 (72.8)	222 (73.0)	442 (72.9)
Other	46 (15.2)	44 (14.5)	90 (14.9)
Height (cm), median (range)	162.3 (144.0–186.0)	162.0 (124.0–190.0)	162.0 (124.0–190.0)
Weight (kg), median (range)	69.0 (36.5–134.0)	68.0 (36.0–136.0)	68.6 (36.0–136.0)
BMI (kg/m^2), median (range)	26.3 (13.9–49.8)	25.4 (15.0–53.1)	25.9 (13.9–53.1)
Anti-CCP antibody-positive, no (%)	205 (67.9)	213 (70.1)	418 (69.0)
Joint count			
TJC (68 joints)	25.6 (13.9)	24.0 (12.9)	24.8 (13.4)
SJC (66 joints)	16.2 (8.7)	15.2 (8.3)	15.7 (8.5)
TJC (28 joints)	15.9 (6.4)	15.1 (6.1)	15.5 (6.2)
SJC (28 joints)	12.0 (4.9)	11.2 (4.7)	11.6 (4.8)
Duration of prior MTX therapy (weeks)	97.7 (141.2)	89.4 (96.5)	93.6 (120.8)
MTX dose (mg)	15.6 (3.1)	15.6 (3. 2)	15.6 (3.1)
CDAI	40.9 (11.5)	39.3 (11.1)	40.1 (11.3)
SDAI	42.8 (11.9)	41.2 (11.7)	42.0 (11.8)
CRP (mg/dl)	1.9 (2.5)	1.9 (2.2)	1.9 (2.4)
ESR (mm/h)	46.6 (22.4)	48.5 (22.6)	47.5 (22.5)
Anti-CCP (IU/ml)	190.4 (124.1)	197.9 (122.7)	194.1 (123.3)
IgA RF (IU/ml)	54.9 (88.9)	65.8 (99.3)	60.3 (94.3)
IgM RF (IU/ml)	123.3 (114.6)	129.5 (113.8)	126.4 (114.1)
IgG RF (IU/ml)	68.4 (89.4)	66.2 (85.4)	67.3 (87.3)
DAS28–CRP	5.9 (0.8)	5.8 (0.9)	5.8 (0.9)
HAQ	1.6 (0.6)	1.6 (0.6)	1.6 (0.6)
Patient's assessment of pain	65.9 (17.4)	65.5 (17.2)	65.7 (17.3)
Patient global assessment of disease activity	65.7 (17.2)	65.4 (17.0)	65.5 (17.1)
Physician global assessment of disease activity	64.7 (14.3)	65.0 (13.5)	64.8 (13.9)

*Except where indicated otherwise, values are the mean (SD).
BMI, body mass index; CCP, cyclic citrullinated peptide; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; Ig, immunoglobulin; INX, innovator infliximab; MTX, methotrexate; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; SJC, swollen joint count; TJC, tender joint count.

q8 weeks up to week 30. Patients were premedicated with antihistamine (chlorpheniramine 2–4 mg or dose of equivalent antihistamine) 30–60 min prior to the start of infusion at the investigator's discretion. Weekly MTX (12.5–25 mg/week, oral or parenteral dose) and folic acid (≥5 mg/week, oral dose) were coadministered. Rescue therapy was only allowed with tramadol and/or acetaminophen. Salvage therapy was defined as an antirheumatoid drug, such as disease-modifying antirheumatic drugs, non-steroidal anti-inflammatory drugs and any biological agent for the treatment of RA, received on or after the day of the first dose of study treatment.

Study endpoints

The primary endpoint was to demonstrate equivalent efficacy of CT-P13 to INX at week 30, as determined by ACR20 response criteria. Equivalence of efficacy was concluded if the 95% CIs for treatment difference were within ±15% at week 30.

Secondary endpoints included additional efficacy, immunogenicity, safety, PK and PD parameters. Clinical assessments of disease activity, including the additional measures: ACR individual component scores; ACR20/ACR50/ACR70; time-to-onset of ACR20; mean decrease in Disease Activity Score 28 (DAS28); European League Against Rheumatism (EULAR) response criteria; Clinical Disease Activity Index (CDAI); Simplified Disease Activity Index (SDAI) and general health status (Medical Outcomes Study Short-Form Health Survey (SF-36)), were performed before infusion at baseline, weeks 14 and 30. A post hoc analysis of ACR–EULAR remission rate at week 30 was also performed.[4]

Blood samples collected at screening and weeks 14 and 30 were assessed for antidrug antibodies (ADA), and a post hoc analysis of endpoints by ADA status was conducted. Immunogenicity testing used both the CT-P13 tag and INX tag (see online supplementary appendix C). Antibodies against CT-P13 or INX were measured using an electrochemiluminescent immunoassay method using the Meso Scale Discovery platform (MSD, Rockville, Maryland, USA).

Safety endpoints included incidence and type of adverse events (AEs) and infection, serious AEs, incidence of infusion-related reactions and changes from baseline in clinical laboratory parameters. AEs were coded using the Medical Dictionary for Regulatory Activities and severity was characterised as mild, moderate or severe.

All patients were screened for latent or active tuberculosis (TB) by an interferon γ-release assay using QuantiFERON-TB Gold in tube (QTF-TB Gold-IT, Cellestis, Australia) and chest x-ray and monitored for any clinical signs and symptoms of TB at each planned visit. Patients with latent TB received prophylactic medication before and during the study period according to country-specific guidelines. For countries with an increased incidence of TB, QTF-TB Gold-IT was used at weeks 14 and 30 to identify positive conversion from negative results at baseline, according to WHO recommendations for sole use of interferon γ-release assay in non-HIV adults receiving anti-TNF therapy.[5 6]

PK endpoints included C_{max}, C_{min}, $C_{av,ss}$, peak to trough fluctuation ratio and time to reach C_{max} (T_{max}). PD endpoints included concentrations of serum CRP, rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP) and ESR. Serum blood samples were obtained immediately before each dosing for PK and PD analyses, and at the end and 1 h after the end of each treatment infusion for PK analysis. All PK analyses were conducted using a flow-through immunoassay platform (GyrolabxP; Gyros AB, Sweden).

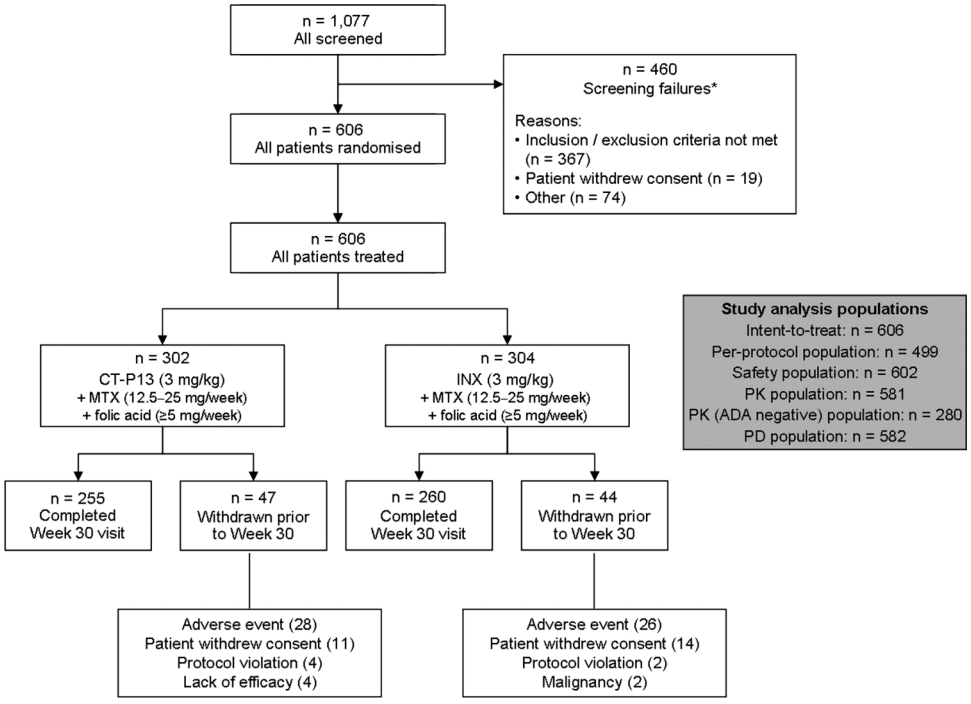

Figure 1 Flowchart of patient disposition. A total of 1077 patients were screened for the study, and 606 eligible patients were randomised into a CT-P13 group (N=302) or an innovator infliximab (INX) group (N=304) to receive 3 mg/kg of CT-P13 or INX, respectively, coadministered with methotrexate (MTX) and folic acid. All 606 randomly assigned patients were included in the intention-to-treat population. A total of 107 out of 606 randomised patients were excluded from the per-protocol population due to the various protocol violations. *Eleven patients from a potentially fraudulent study site were excluded from analyses.

Statistical analysis

Sample size was determined using the following criterion: therapeutic equivalence to INX in the all randomised population was based on expected responder rates of 50% in the test and control groups.[1] Specifying a two-sided α level of 0.05, power of 80% and a two-sided equivalence margin of 15% required 468 patients in the per-protocol (PP) population final analysis. Assuming exclusion of 20% of patients from the PP population, this required a minimum of 584 randomised patients. In an equivalence trial, we conclude that two treatments are equivalent if the observable difference (Δ_E) between them lies within an established interval for predefined clinical equivalence margin, (−d, d). The 'null hypothesis' is that the difference Δ_E is outside of the equivalence margin, that is, either $\Delta_E > d$ or $\Delta_E < -d$. If collected data on the true difference Δ_E reject the null hypothesis of 'non-equivalence' then we can accept the alternative explanation ($-d \leq \Delta_E \leq d$) that the two treatments work equally well.[7]

All primary efficacy analyses were performed on both the intention-to-treat (ITT) and PP populations. All other efficacy analyses were performed on the PP population only. The proportion of patients achieving ACR20 response at week 30 was analysed by the exact binomial approach, calculating a point estimate and 95% CIs for the difference in proportion between the two treatment groups. The equivalence margin within ±15% at week 30 was selected based on recommendations from regulatory bodies[8 9] and historical data from clinical trials of INX plus MTX in RA.[1 10–13] A weighted average for the treatment difference in ACR20 response between the INX plus MTX and placebo plus MTX was nearly 30%, and so the equivalence margin of 15% was considered appropriate.

A sensitivity analysis considering stratification factors was also performed, accounting for region (EU or non-EU) and serum CRP (≤2 mg/dl or >2 mg/dl). The exact binomial and sensitivity analyses were repeated for the secondary ACR response criteria. Time-to-onset of ACR20 response was analysed by survival analysis. Descriptive statistics for change from baseline were presented by randomised treatment group and study visit for DAS28, EULAR response, SDAI, CDAI and SF-36 subscales.

An analysis of covariance for DAS28 was performed with treatment group as a fixed effect and baseline DAS28 score, region and CRP as covariates. A point estimate and 95% CI for the treatment difference were provided. The EULAR response criteria were analysed using a relative risk (RR) with 95% CI for the difference in response between the two treatment groups. The number of patients requiring salvage retreatment was summarised by randomised treatment group and visit.

Safety endpoints analysed in safety population consisted of all patients who received at least one (full or partial) dose of either of the study treatments during any dosing period. In this population, patients were included in the CT-P13 group for safety analyses, irrespective of their randomisation if they received at least one (full or partial) dose of CT-P13.

The PK–PD population consisted of all patients who received either CT-P13 or INX during the 30-week blinded study period and had at least one PK–PD concentration data value. PK–PD parameters were summarised using quantitative descriptive statistics by actual treatment group and study visit.

RESULTS

Patients

The first patient was screened in November 2010; the last week 30 evaluation was performed in November 2011. Baseline demographics and disease status were comparable between treatment groups (table 1). Of the 606 randomised patients, 515 completed the 30-week study period and, of these, 16 patients were excluded from the PP population due to major protocol violations. Discontinuation in randomised patients was primarily due to AEs (8.9%) and patient withdrawal of consent (4.1%) (figure 1).

Efficacy

The primary endpoint, ACR20 response at week 30, was equivalent between treatment groups and achieved in 60.9% and 58.6% in ITT (n=606, 95% CI −6% to 10%) and 73.4%

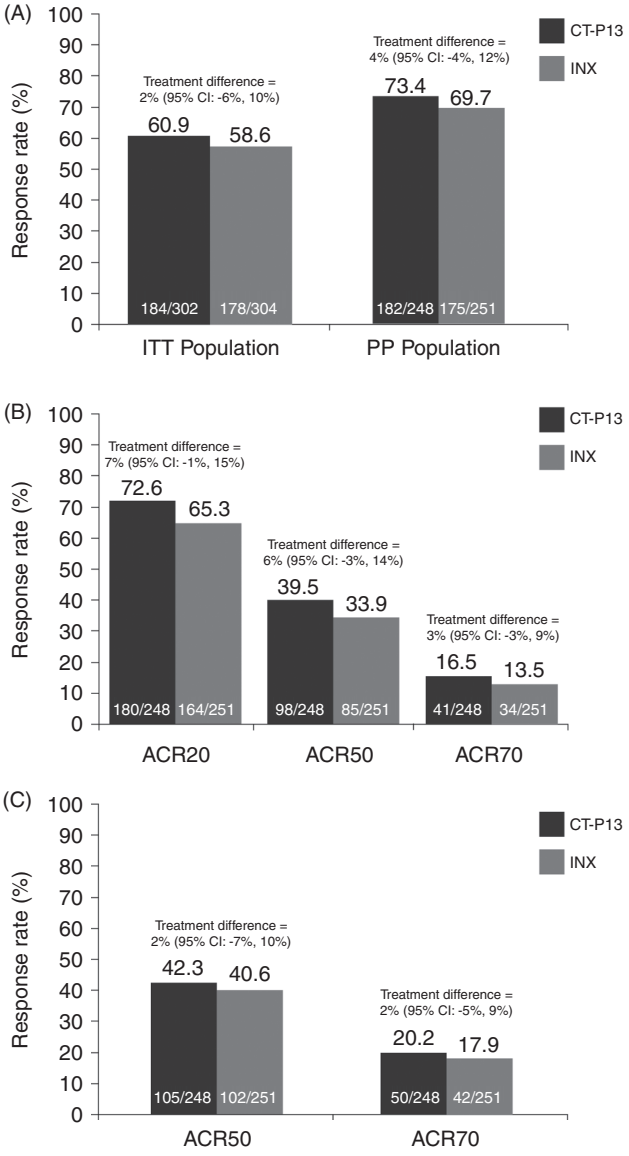

Figure 2 American College of Rheumatology (ACR) response rates. (A) ACR20 improvement criteria at week 30 (primary efficacy endpoint) for the intention-to-treat (ITT) (N=302 and 304 in CT-P13 and innovator infliximab (INX) groups, respectively) and per-protocol (PP) populations (N=248 and 251 patients in CT-P13 and INX groups, respectively). (B) ACR20, ACR50 or ACR70 improvement criteria at week 14 for the PP population. (C) ACR50 or ACR70 improvement criteria at week 30 for the PP population. ACR20, ACR50 and ACR70 are the ACR 20%, 50% and 70% improvement criteria, respectively. 95% CI was calculated by the exact binomial method.

Table 2 Mean changes of secondary outcome measures from baseline

Secondary outcome measure, mean (SD)	Timepoint	CT-P13 3 mg/kg	INX 3 mg/kg	p Value*
TJC (68 joints)	Week 14	−14.6 (11.1)	−14.0 (11.4)	0.559
	Week 30	−16.5 (11.7)	−15.7 (12.6)	0.458
SJC (66 joints)	Week 14	−10.9 (8.1)	−10.2 (8.0)	0.331
	Week 30	−12.4 (8.9)	−11.4 (9.1)	0.219
TJC (28 joints)	Week 14	−9.2 (6.4)	−8.4 (6.0)	0.149
	Week 30	−10.1 (6.7)	−9.5 (6.4)	0.378
SJC (28 joints)	Week 14	−7.8 (5.1)	−7.2 (5.0)	0.173
	Week 30	−8.8 (5.3)	−7.9 (5.6)	0.073
CDAI	Week 14	−23.5 (12.4)	−21.6 (11.6)	0.076
	Week 30	−25.2 (13.3)	−23.6 (13.0)	0.182
SDAI	Week 14	−24.0 (13.0)	−22.4 (11.9)	0.141
	Week 30	−25.8 (14.0)	−24.4 (13.6)	0.247
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
Patient's assessment of pain	Week 14	−29.5 (23.2)	−27.2 (23.2)	0.253
	Week 30	−29.5 (25.5)	−27.8 (24.9)	0.443
Patient global assessment of disease activity	Week 14	−29.5 (22.1)	−25.5 (24.4)	0.057
	Week 30	−28.1 (25.9)	−27.0 (25.6)	0.658
Physician global assessment of disease activity	Week 14	−35.4 (19.3)	−33.7 (19.5)	0.314
	Week 30	−35.6 (20.6)	−35.3 (21.2)	0.910

*Student's t test.
CDAI, Clinical Disease Activity Index; CRP, C reactive protein; HAQ, health assessment questionnaire; INX, innovator infliximab; SDAI, Simplified Disease Activity Index; SF-36, Short-Form Health Survey 36; SJC, swollen joint count; TJC, tender joint count.

and 69.7% in PP population (n=499, 95% CI −4% to 12%) for CT-P13 and INX, respectively (figure 2A).

Equivalent results were also shown for ACR responses in the PP population at weeks 14 and 30 (figure 2B,C) for CT-P13 and INX, respectively. ACR50 and 70 responses in the ITT population at week 30 were comparable (35.1% and 16.6% vs 34.2% and 15.5% for CT-P13 and INX, respectively). Post hoc analysis by baseline CRP demonstrated highly similar ACR20 responses in the ITT population for CT-P13 and INX, respectively (CRP >2 mg/dl: 58.7% and 58.6%; ≤2 mg/dl: 61.9% and 58.5%).

Mean improvements from baseline for additional secondary efficacy endpoints including CDAI and SDAI (CT-P13 (25.2 and 25.8) vs INX (23.6 and 24.4) at week 30, respectively) were equivalent at weeks 14 and 30 between treatment groups (table 2). The proportion in each group achieving good or moderate EULAR responses (CRP) at week 30 was highly similar (CT-P13 85.8%; INX 87.1%, RR=0.98, 95% CI 0.92 to 1.06). Low disease activity or remission according to DAS28-CRP was achieved in 40.9% and 39.0% with CT-P13 and INX, respectively (figure 3). The proportion of patients requiring salvage therapy at week 30 was also highly similar between CT-P13 (3.2%) versus INX (4.0%). The medians of time-to-onset of ACR20 of the two treatment groups were almost identical (median CT-P13, 99 days; INX, 100 days).

In addition, ACR/EULAR remission rates were comparable for CT-P13 and INX at week 30 (Boolean: 6.9% (17/248) and 6.8% (17/251); SDAI: 9.7% (24/248) and 9.6% (24/251)). Efficacy criteria were also analysed according to ADA status at week 30 (see online supplementary appendix D).

Overall, no statistically significant differences in responses between the two treatment groups were found.

Immunogenicity

Antibodies to infliximab were detected using INX tag in 25.4% (n=69) and 25.8% (n=70) of patients for CT-P13 and INX at week 14 and 48.4% (n=122) and 48.2% (n=122) of patients for CT-P13 and INX, respectively, at week 30.

Safety

Overall treatment-emergent AEs (TEAEs) were reported in 181 (60.1%) patients and 183 (60.8%) patients for CT-P13 and INX, respectively. TEAEs considered related to study treatment were reported in 106 (35.2%) and 108 (35.9%) patients for CT-P13 and INX, respectively (table 3). The majority of TEAEs were mild-to-moderate in intensity. The TEAEs considered by the investigator to be related to the study treatment and most frequently reported for patients were—CT-P13: latent TB (positive conversion of QTF, n=13), increased ALT (n=12), increased AST (n=8) and a flare of RA activity (n=7); INX: latent TB (n=14), increased ALT (n=11), increased AST (n=8) and urinary tract infection (n=7). Two patients were withdrawn due to malignancies in the INX group (figure 1), breast cancer and cervix carcinoma.

Patients with latent TB were recommended for prophylactic TB medication, and latent TB in patients receiving prophylactic TB medication did not convert to active TB. There were three cases of active TB in the CT-P13 group and none in the INX group (see online supplementary appendix E).

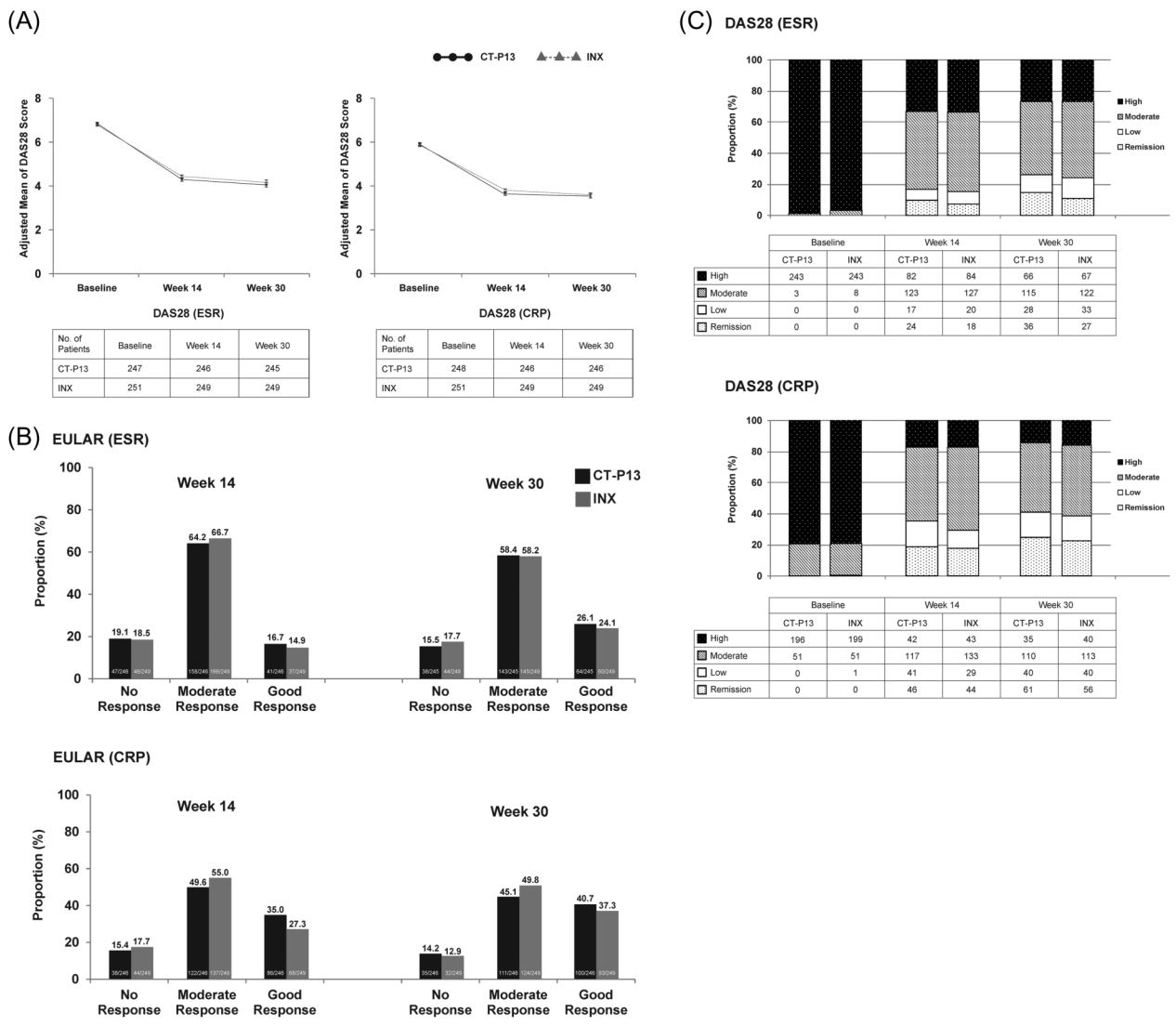

Figure 3 Changes over time in the Disease Activity Score in 28 joints (DAS28) and European League Against Rheumatism (EULAR) responses for CT-P13 (3 mg/kg) and innovator infliximab (INX) (3 mg/kg) treatment in the per-protocol population. (A) Adjusted mean DAS28 score based on erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) at baseline, weeks 14 and 30. Error bars represent SE. (B) EULAR response criteria based on DAS28 score at weeks 14 and 30 following treatment. (C) Disease activity based on DAS28 (ESR) and DAS28 (CRP) at baseline, weeks 14 and 30.

Infusion-related reactions occurred in 20 (6.6%) and 25 (8.3%) patients for CT-P13 and INX, respectively. The proportions of infusion-related reactions for CT-P13 and INX groups were 6.7% (n=9) versus 13.3% (n=18) in ADA-positive group and 4.2% (n=6) versus 2.8% (n=4) in ADA-negative group, respectively. Serious TEAEs were reported in 30 (10.0%) and 21 (7.0%) patients for CT-P13 and INX, respectively (see online supplementary appendix F). There were no deaths reported during the study.

Pharmacokinetics and pharmacodynamics

The PK and PD endpoint results were highly similar for each treatment group. In the PK population, geometric means and peak serum concentrations (C_{max}) were highly similar after each infusion of study treatment for doses 1–6, as was the overall range of geometric means across all doses (CT-P13, range 83.9–111.9 μg/ml; INX, range 83.8–105.1 μg/ml). The mean secondary PK endpoints were highly similar for CT-P13 and INX (see online supplementary appendix G).

In the ADA-negative subset, geometric mean C_{max} values were 96.7 and 91.6μg/ml (90% CI of ratio 97% to 115%), and C_{min} values were 1.9 and 1.8 μg/ml (90% CI of ratio 85% to 132%) for CT-P13 and INX at dose 5, respectively. In the ADA-positive subset, geometric mean C_{max} values were 85.1 and 76.7 μg/ml (90% CI of ratio 99% to 124%), and C_{min} values were 0.6 and 0.6 μg/ml (90% CI of ratio 82% to 107%) for CT-P13 and INX at dose 5, respectively.

CT-P13 and INX had comparable mean CRP (1.2 vs 1.1 mg/dl and 1.1 vs 1.0 mg/dl), ESR (32.8 vs 31.0 mm/h and 30.6 vs 32.1 mm/h), anti-CCP (186.5 vs 195.4 IU/ml and 189.8 vs 174.6 IU/ml), IgA RF (41.2 vs 45.8 IU/ml and 33.9 vs 38.3 IU/ml), IgG RF (40.5 vs 33.4 IU/ml and 33.5 vs 29.5 IU/ml) and IgM RF (90.0 vs 88.0 IU/ml and 83.9 vs 82.5 IU/ml) at weeks 14 and 30, respectively.

DISCUSSION

In this randomised, double-blind, multicentre, multinational, parallel-group, prospective PLANETRA study, we assessed the equivalence of efficacy and comparability of safety, PK and PD of multiple doses of CT-P13 (3 mg/kg) versus INX (3 mg/kg) administered up to week 30 in active RA patients with inadequate response to MTX treatment. Equivalence of efficacy was

Table 3 Treatment-emergent adverse events (TEAEs) reported as related in at least 1% of patients in either treatment group, no (%)

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)
Headache	4 (1.3)	6 (2.0)	10 (1.7)
Pyrexia	0	3 (1.0)	4 (0.7)
Rash	1 (0.3)	4 (1.3)	5 (0.8)
Nausea	1 (0.3)	3 (1.0)	4 (0.7)
Flare in RA activity	7 (2.3)	4 (1.3)	11 (1.8)
Bone pain	3 (1.0)	0	6 (1.0)
Hypertension	5 (1.7)	3 (1.0)	8 (1.3)

The total number of treatment-emergent adverse events count included all related patient events. At each level of summarisation, a patient was counted once if he or she reported one or more related events. Only the most severe event was counted.
*Patients who received at least one (full or partial) dose of CT-P13 were included in the CT-P13 group for safety analyses, irrespective of their randomisation.
INX, innovator infliximab; RA, rheumatoid arthritis.

demonstrated, and there was no clinically meaningful difference in safety data. Only comparability of PK data was shown in this study, as coadministration of MTX could affect PK data; PK bioequivalence has been assessed in a phase I study for ankylosing spondylitis patients in the absence of MTX.[3]

The primary outcome, ACR20 response at week 30, was shown to be equivalent for CT-P13 and INX: the 95% CIs for treatment difference were within the predefined margins for equivalence of ±15%. To ensure a credible comparison with existing INX data, the disease definition for enrolment in our study was identical to ATTRACT[1] and a separate phase III trial of INX in RA,[12] and was similar to a further, more recent trial.[13] The finding that baseline CRP levels in the equivalent INX arm of the ATTRACT study (3 mg/kg, every 8 weeks) were higher than in both groups of this study (3.1 vs 1.9 mg/dl), raising the possibility that our study had enrolled a population with less severe disease, led us to conduct a post hoc sensitivity analysis of patients with baseline CRP >2 or ≤2 mg/dl. This analysis demonstrated that responses by baseline CRP level were highly similar between treatment groups regardless of baseline CRP level. The ACR responses observed in this study were higher than those reported at week 30 in ATTRACT (ACR20, 50 and 70: 60.9%, 35.1% and 16.6% for CT-P13 and 58.6%, 34.2% and 15.5% for INX, respectively, vs 50%, 27% and 8% for INX in ATTRACT[1]). However, they were similar to INX responses in the START study (ACR20, 50 and 70 at week 30: 58.0%, 32.1% and 14.0%), which included similar baseline tender joint count, swollen joint count and CRP.[13]

It is also interesting to note that although CRP is regarded as the better marker of inflammation, ESR may have utility in reflecting disease severity.[14 15] However, as ESR data are not available for ATTRACT or any other placebo-controlled INX plus MTX studies in the literature, we rely on assessment of CRP to ensure appropriate comparison of patient populations.

Although the point estimates of medians for time-to-onset of ACR20 were very similar, we have observed faster tendency of ACR 20 response among CT-P13 group compared with the INX group based on log-rank test result (p=0.02). ACR20 responses were measured only at weeks 14 and 30; therefore, we have a limitation to adapt statistical survival methods on a very small number of evaluation time points and conclude log-rank test results from our data.

Efficacy criteria were also analysed according to ADA status at week 30, and no statistically significant difference in responses between the two treatment groups was found. However, as this was a post hoc analysis, interpretation of these results should be done with care and to a limited extent.

In our study, PK and PD endpoint results were highly similar for each treatment group and antibody status had a minimal effect on the PK of infliximab. A difference was noted in the change from baseline in anti-CCP at week 30 and IgG RF at week 14. However, these two parameters are more indicative of disease severity rather than a direct marker of anti-TNFα effect. In addition, it should be noted that the assumptions of normality and homogeneity of variance were assessed for each parameter for the ANCOVA analysis. Both assumptions did not hold for anti-CCP, IgA RF, IgG RF and IgM RF, and valid conclusions for these parameters beyond investigating trends cannot be drawn.

The objective with regard to safety was to demonstrate comparability of CT-P13 and INX, not equivalence. Overall, CT-P13 was well tolerated, and its safety profile was comparable with INX. The rate of infusion reactions in both treatment groups was approximately 7.5%, lower than the 20% incidence listed in the INX product information, although the incidence of severe infusion reactions was 1.3%, slightly higher than the <1% listed.[16] The safety results were similar to those observed in the ATTRACT and ASPIRE trials.[1 17] The incidence of active TB in patients receiving INX or CT-P13 in this study (0% and 1.0%, respectively) was similar to that described in ATTRACT (0.3%) and ASPIRE (0.5%)[1 17] and was not considered significant, as 42% of patients in our study were from countries listed in WHO Global tuberculosis report as having higher TB incidence,[18] whereas ATTRACT and ASPIRE included only centres in North America and Western Europe.[1 17]

Immunogenicity testing demonstrated a comparable profile for CT-P13 and INX in terms of proportion of ADA-positive patients at weeks 14 and 30. Although the proportion of ADA-positive patients was slightly higher than that observed in previous studies,[1] the method used to detect immunogenicity was more sensitive than those previously used, and the proportion of ADA-positive patients was similar to that observed in more recent studies of INX.[19 20]

Assessment of efficacy and safety of CT-P13 in patients with RA for up to 1 year is ongoing, and the positive results of this study provide a rationale for future studies of CT-P13 in the treatment of other TNF-mediated inflammatory diseases.

CONCLUSIONS

CT-P13 and INX were shown to be equivalent in terms of ACR20 response at week 30 in active RA patients with inadequate response to MTX treatment. Overall, CT-P13 was well tolerated and the safety profile of CT-P13 was comparable with that of INX.

Author affiliations
[1]Division of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Republic of Korea
[2]Department of Rheumatology and Clinical Immunology, Poznan University of Medical Sciences, Poznan, Poland
[3]Rheumatology Department, Centro de Estudios Reumatologicos, Santiago, Chile
[4]Department of Internal Medicine, Brokenshire Memorial Hospital, Davao City, Philippines
[5]Reumed, Lublin, Poland
[6]Scientific and Research Institute of Invalid Rehabilitation of MoH of Ukraine, Kiev, Ukraine
[7]Section of Non-coronarogenic Myocardial Diseases and Clinical Rheumatology, National Scientific Center, Kiev, Ukraine
[8]Department of Rheumatology and Clinical Immunology, Clinic of Internal Diseases, Clinical Center Banja Luka, Banja Luka, Bosnia and Herzegovina
[9]Centro Integral de Reumatologia del Caribe, Barranquilla, Colombia
[10]Rheumatology Department, Antiguo Hospital Civil de Guadalajara, Guadalajara, Mexico
[11]Rheumatology Department, Hospital Maria Auxiliadora, Lima, Peru
[12]Department of Medicine, Medical Center Manila, Manila, Philippines
[13]Rheumatology Department, Centro de Estudios Investigaciones Clinicas, Viña del Mar, Chile
[14]Rheuma Zentrum Favoriten, Vienna, Austria
[15]Division of Biostatistics, Department of Internal Medicine, University of New Mexico, Albuquerque, New Mexico, USA
[16]Clinical Planning and Medical Affairs Department, CELLTRION Inc, Incheon, Republic of Korea
[17]Division of Rheumatology, Department of Internal Medicine, Inha University Hospital, Incheon, Republic of Korea
[18]Department of Rheumatology and Clinical Immunology, Justus-Liebig University Giessen, Kerchoff-Klinik GmbH, Bad Nauheim, Germany

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Contributors DHY, SJL and HUK were involved in the conception and design of the study, acquisition of data and/or analysis and interpretation of data; drafting of manuscript and revising it critically for important intellectual content; final approval of the version to be published. WP and UM-L were involved in the conception and design of the study; drafting of manuscript and revising it critically for important intellectual content; final approval of the version to be published. PH, PM, ER, MP, SS, VK, NP, MA-B, SG-U, LM-O, MT, RJ and OZ were involved in the acquisition of data; drafting of manuscript and revising it critically for important intellectual content; final approval of the version to be published. The project management, clinical and medical monitoring, pharmacovigilance (PVG), data management, analysis of pharmacokinetic (PK) data, biostatistical analysis, and medical writing were performed under contract with PPD, Inc. in collaboration with the CELLTRION, Inc.

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Patient consent Obtained.

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Appendix A.

Figure S1-1. Comparative Fourier transform infrared (FTIR) between CT-P13 and INX.

CT-P13 and INX were analysed in a FTIR spectrometer and spectral data was plotted as a function of % transmission. CT-P13 A, B and C represent three different batches of CT-P13 drug.

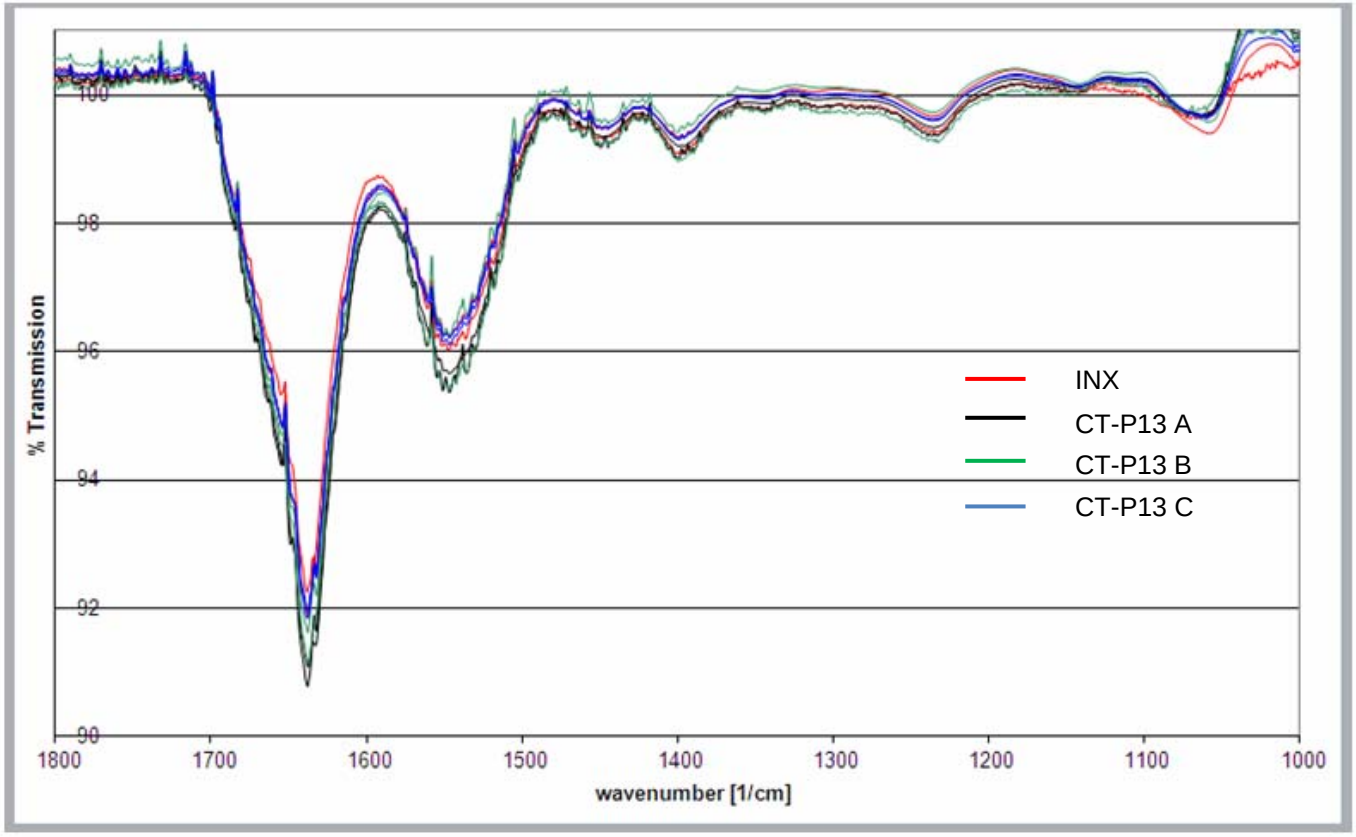


Figure S1-2. Comparative TNFα neutralizing assay between CT-P13 and INX

CT-P13 compounds and INX were used in a TNFα neutralising assay. The EC_{50} values of CT-P13 and INX were compared with the reference standard EC_{50}. *Relative neutralizing potency (%) of drug was calculated as a percentage of the reference standard EC_{50}.The bold line indicates the average value for INX drug in this assay. CT-P13 A, B and C represent three different campaign batches of CT-P13 drug substance.

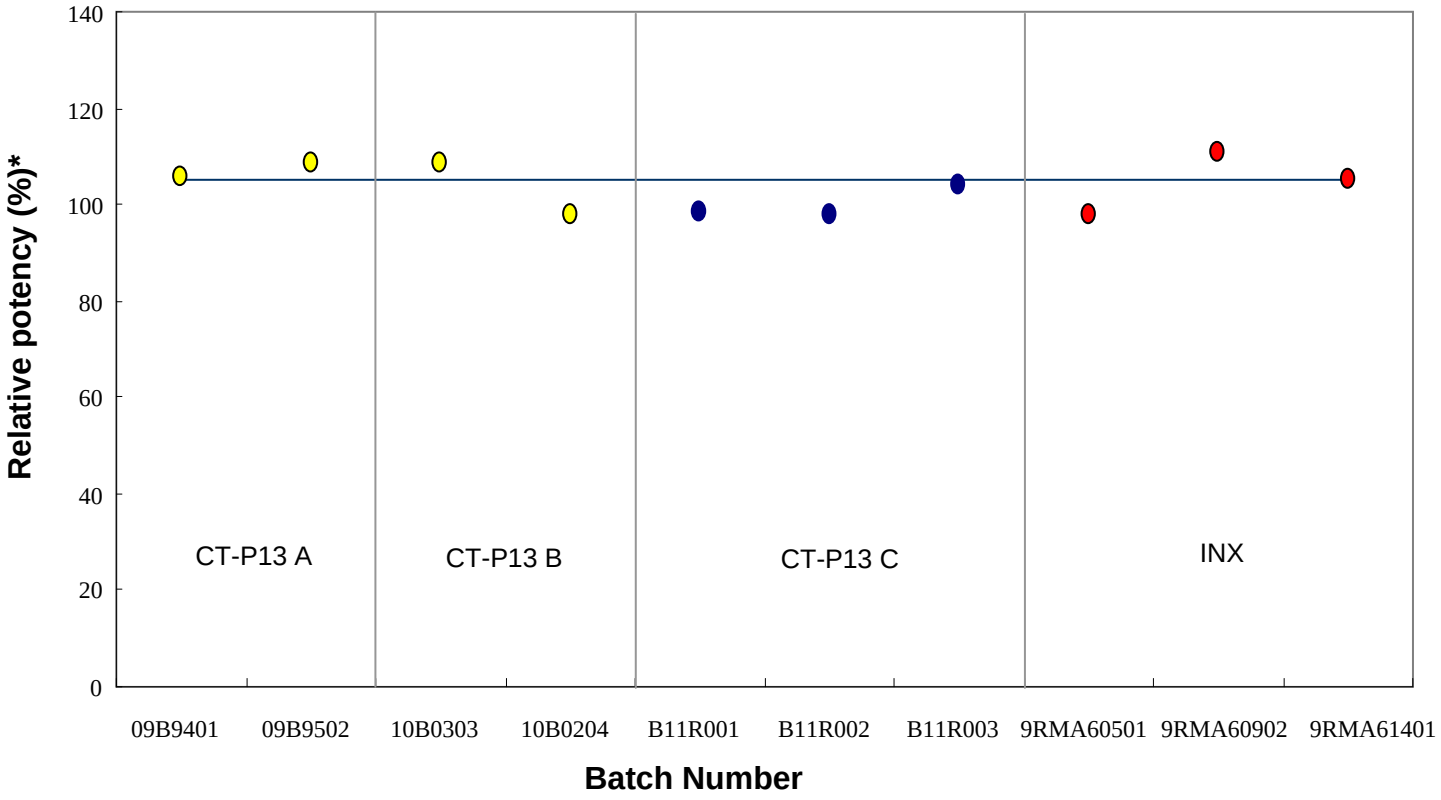
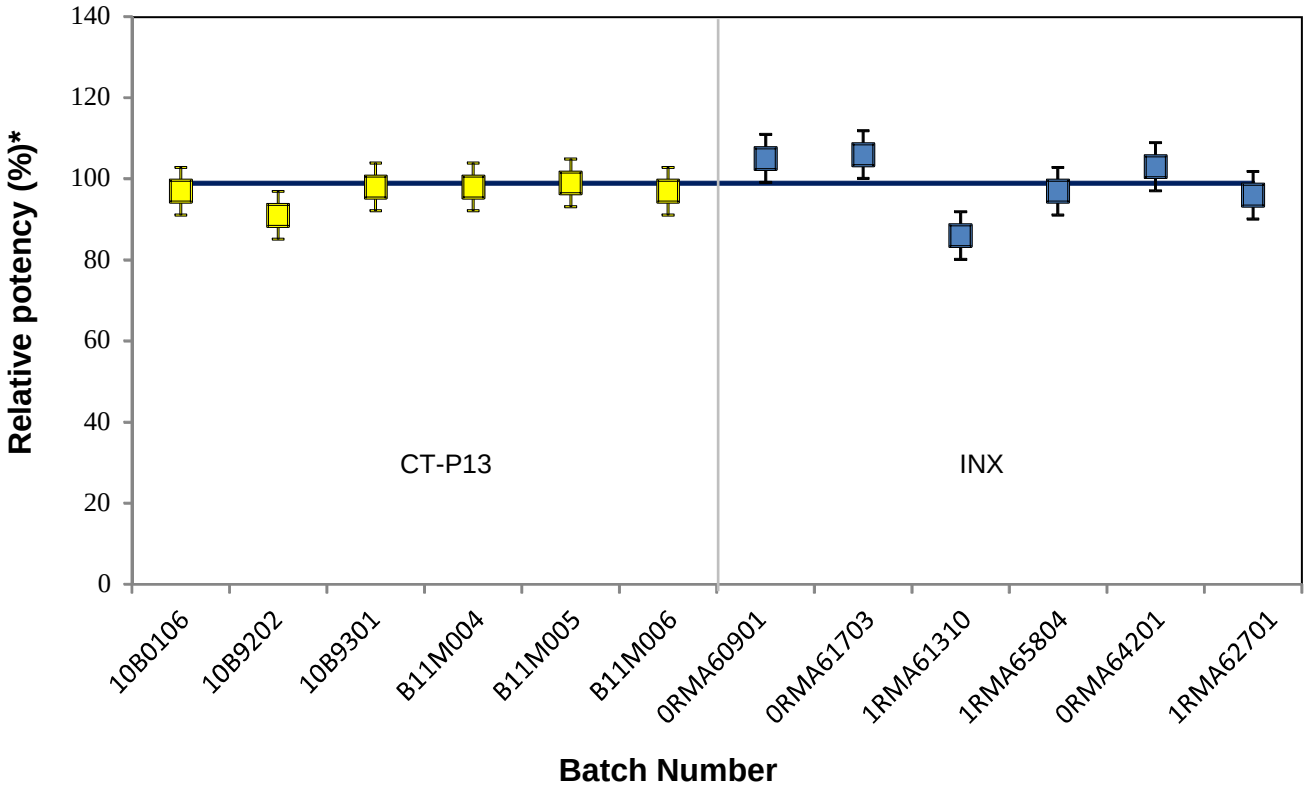


Figure S1-3. Comparative complement dependent cytotoxicity (CDC) between CT-P13 and INX

CT-P13 and INX were used in a CDC assay. *The relative CDC bioactivities of CT-P13 and INX were calculated as a percentage of the EC_{50} of each sample curve Vs the EC_{50} of the reference standard curve. Error bars represent standard deviation of each sample analysed in duplicate. The bold line indicates the average value for INX drug in this assay.



Appendix B.

Inclusion Criteria

Patients had to meet all of the following criteria to be enrolled in this study:

1. Patient was male or female aged 18 to 75 years old, inclusive.

2. Patient had a diagnosis of RA according to the revised 1987 ACR classification criteria [Arnett et al 1988] for at least 1 year prior to Screening.

3. Patients had active disease as defined by the presence of 6 or more swollen joints, 6 or more tender joints, and at least 2 of the following: morning stiffness lasting at least 45 minutes, an ESR greater than 28 mm/h, and a serum CRP concentration greater than 2.0 mg/dL [Maini et al 1998].

4. Patients had completed at least 3 months of treatment of oral or parenteral dosing with MTX between 12.5 to 25 mg/week and were on stable dosing with MTX between 12.5 to 25 mg/week for at least 4 weeks prior to Screening.

5. Both male and female patients and their partners of childbearing potential who had agreed to use 2 medically accepted methods of contraception (eg, barrier contraceptives [male condom, female condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], and intrauterine devices) during the course of the study and for 6 months following discontinuation of study treatments (excluding women who were not of childbearing potential and men who had been sterilized).

6. Male or female patients and their partners who had been surgically sterilized for less than 6 months prior to study entry had agreed to use 2 medically accepted methods of contraception as per inclusion criterion 5.

7. Menopausal females had to have experienced their last period more than 12 months prior to study entry to be classified as not of childbearing potential.

8. Patients had adequate renal and hepatic function at Screening as defined by the following clinical chemistry results:

    - Serum creatinine <1.7 × upper limit of normal (ULN) or an estimated creatinine clearance level >75 mL/min.
    - Serum alanine aminotransferase (ALT) <2 × ULN.
    - Serum aspartate aminotransferase (AST) <2 × ULN.

9. Patients had the following hematology laboratory test results at Screening:

- Hemoglobin ≥8.0 g/dL
- White blood cell count ≥3.5 × 10^3 cells/μL (SI [Système International d'Unités] units: ≥3.5 × 10^9 cells/L)
- Neutrophil count ≥1.5 × 10^3 cells/μL (SI units: ≥1.5 × 10^9 cells/L)
- Platelet count ≥100 × 10^3 cells/μL (SI units: ≥100 × 10^9 cells/L)

10. Patients were permitted to receive both oral glucocorticoids equivalent to ≤10 mg daily prednisolone and nonsteroidal anti-inflammatory drugs, if they had received a stable dose for at least 4 weeks prior to Screening. In addition, patients were permitted to receive low-potency topical, otic, and ophthalmic glucocorticoid preparations provided the preparations were administered per the instructions on the product label.

11. Patients had the ability to comprehend the full nature and purpose of the study, including possible risks and side effects, to cooperate with the investigator, to understand verbal and written instructions, and to comply with the requirements of the entire study.

12. Patient (or legal guardian, if applicable) was informed of the full nature and purpose of the study, including possible risks and side effects, and given ample time and opportunity to read and understand this information, signed and dated the written informed consent before inclusion in the study.

Exclusion Criteria

Patients meeting any of the following criteria were excluded from the study:

1. Patients had previously been administered a biological agent for the treatment of RA.

2. Patients had allergies to any of the excipients of INX or any other murine and human proteins, and patients with a hypersensitivity to Ig product.

3. Patients had a current or past history of chronic infection with hepatitis B, hepatitis C, or infection with human immunodeficiency virus (HIV)-1 or-2 or who had a positive result to the screening test for those infections.

4. Patients had a current diagnosis of TB or other severe or chronic infection (such as sepsis, abscess or opportunistic infections, or invasive fungal infection such as histoplasmosis) or a past diagnosis without sufficient documentation of complete resolution following treatment.

5. Patients had recent exposure to persons with active TB, or who had a positive result to the screening test for latent TB defined as a positive result of interferon-γ release assay with a negative examination of chest x-ray, and who had not received at least the first 30 days of country-specific TB therapy and did not intend to complete the entire course of that therapy. Patients with an abnormal chest x-ray were to have been discussed with the medical monitor before randomization.

6. Patients had an infection requiring oral antibiotics in the 2 weeks before Screening, parenteral injection of antibiotics in the 4 weeks before Screening, or other serious infection in the 6 months before Screening or who had a history of recurrent herpes zoster or other chronic or recurrent infection.

7. Patients had a current or past history of drug or alcohol abuse.

8. Patients had a medical condition including one or more of the following:

    - Classified as obese
    - Bone marrow hypoplasia
    - Diabetes mellitus unless on a stable dosing regimen for at least 4 weeks prior to Screening
    - Hypertension at Screening
    - Any other inflammatory or rheumatic diseases, including but not limited to psoriatic arthritis, AS, spondyloarthritis, systemic lupus erythematosus, Lyme disease, or fibromyalgia, that could confound the evaluation of the effect of study treatment
    - History of any malignancy within the previous 5 years except completely excised and cured squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma
    - History of lymphoma or lymphoproliferative disease
    - History of congestive heart failure (New York Heart Association class III/IV) or unstable angina
    - History of organ transplantation
    - History of severe hypersensitivity
    - Severe physical incapacitation (unable to perform routine self-care, has RA ACR functional status class 4 [Arnett et al 1988], or who could not benefit from medication)
    - Any clinically significant respiratory disease, including but not limited to chronic obstructive pulmonary disease, asthma, bronchiectasis, or pleural effusion.
    - Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain-Barré syndrome
    - Any conditions significantly affecting the nervous system (ie, neuropathic conditions or nervous system damage) if it might interfere with the investigator's assessment on disease activity scores including joint counts
    - Any other serious acute or chronic medical or psychiatric condition that might increase the risk associated with study participation or investigational product administration or that might interfere with the interpretation of study results

9. Patients taking any of the following concomitant medications:

    - Corticosteroids, except oral glucocorticoids, of maximum equivalent daily dose of 10 mg of prednisolone within 4 weeks prior to Screening. (Patients were permitted to receive low-potency topical, otic, and ophthalmic glucocorticoid preparations

provided the preparations were administered per the instructions on the product label.)

- Disease-modifying antirheumatic drugs (DMARDs), other than MTX, including hydroxychloroquine, chloroquine, or sulfasalazine, within 4 weeks prior to Screening. Patients who discontinued leflunomide and had successful chelation with 8 g of cholestyramine (3 times daily) for 11 days had to wait 4 weeks prior to Screening. Patients who discontinued leflunomide and did not have cholestyramine washout had to wait 12 weeks after last dose of leflunomide before Screening.
- Alkylating agents within 12 months prior to Screening
- Live or live-attenuated vaccine within 8 weeks of Screening
- Any biological agents for the treatment of RA

10. Patients had participated in a study with an investigational drug within 6 months of Screening or who were currently receiving treatment with any other investigational drug or device.

11. Female patients who were currently pregnant or breastfeeding, or were planning to become pregnant or breastfeed within 6 months of the last dose of CT-P13 or Remicade reference product.

12. Patients had received a live or live-attenuated vaccination within 8 weeks of Screening or who were scheduled to receive a live or live-attenuated vaccination. Killed vaccines were acceptable during the study.

13. Patients who, in the opinion of their general practitioner or investigator, should not participate in the study.

Appendix C.

Table S1-1a. Analysis of Agreement of Immunogenicity testing between Anti-drug Antibody (ADA) CT-P13 tag and ADA INX tag assays

Actual treatment group: CT-P13 3 mg/kg

		ADA INX tag outcome					Cohen's Kappa		
Visit	ADA CT-P13 Tag outcome	Positive	Negative	Missing	PPA (%)	NPA (%)	Statistic	95% CI	p-value
Screening	**Positive**	9	3	0	100.00	98.97	0.85	(0.69, 1.00)	<0.001
	Negative	0	289	0					
	Missing	0	0	0					
Week 14	**Positive**	68	4	0	98.55	98.02	0.95	(0.91, 0.99)	<0.001
	Negative	1	198	0					
	Missing	0	1	0					
Week 30	**Positive**	120	6	0	98.36	95.38	0.94	(0.89, 0.98)	<0.001
	Negative	2	124	0					
	Missing	0	0	0					

Note: PPA = Positive Percent Agreement; NPA = Negative Percent Agreement. The p-value is significant at the 5% level.
Counts of missing values are for information purposes only and are not used in calculation of PPA, NPA or Cohen's Kappa. The ADA INX tag outcome is that outcome at the same visit which is displayed in the Visit column. Patients with a Quantity Not Sufficient (QNS) outcome are categorized as Missing for this analysis.
PPA = (Number of patients with positive outcome for both ADA CT-P13 and INX tags)/ (Number of patients with positive outcome for ADA INX tag) * 100.
NPA = (Number of patients with negative outcome for both ADA CT-P13 and INX tags)/ (Number of patients with negative outcome for ADA INX tag) * 100.

Table S1-1b. Analysis of Agreement of Immunogenicity testing between Anti-drug antibody (ADA) CT-P13 tag and ADA INX tag assays

Actual treatment group: INX 3 mg/kg

		ADA INX tag outcome					Cohen's Kappa		
Visit	ADA CT-P13 Tag outcome	Positive	Negative	Missing	PPA (%)	NPA (%)	Statistic	95% CI	p-value
Screening	**Positive**	6	1	0	100.00	99.66	0.92	(0.77, 1.00)	<0.001
	Negative	0	291	0					
	Missing	0	0	0					
Week 14	**Positive**	66	4	0	95.65	98.01	0.93	(0.88, 0.98)	<0.001
	Negative	3	197	0					
	Missing	1	0	0					
Week 30	**Positive**	118	2	0	96.72	98.47	0.95	(0.91, 0.99)	<0.001
	Negative	4	129	0					
	Missing	0	0	0					

Note: PPA = Positive Percent Agreement; NPA = Negative Percent Agreement. The p-value is significant at the 5% level.
Counts of missing values are for information purposes only and are not used in calculation of PPA, NPA or Cohen's Kappa. The ADA INX tag outcome is that outcome at the same visit which is displayed in the Visit column. Patients with a Quantity Not Sufficient (QNS) outcome are categorized as Missing for this analysis.
PPA = (Number of patients with positive outcome for both ADA CT-P13 and INX tags)/ (Number of patients with positive outcome for ADA INX tag) * 100.
NPA = (Number of patients with negative outcome for both ADA CT-P13 and INX tags)/ (Number of patients with negative outcome for ADA INX tag) * 100.

Table S1-1c. Analysis of Agreement of Immunogenicity testing between Anti-drug antibody (ADA) CT-P13 tag and ADA INX tag assays

Actual treatment group: Total

		ADA INX tag outcome					Cohen's Kappa		
Visit	ADA CT-P13 Tag outcome	Positive	Negative	Missing	PPA (%)	NPA (%)	Statistic	95% CI	p-value
Screening	**Positive**	15	4	0	100.00	99.32	0.88	(0.76, 1.00)	<0.001
	Negative	0	580	0					
	Missing	0	0	0					
Week 14	**Positive**	134	8	0	97.10	98.01	0.94	(0.91, 0.97)	<0.001
	Negative	4	395	0					
	Missing	1	1	0					
Week 30	**Positive**	238	8	0	97.54	96.93	0.94	(0.92, 0.97)	<0.001
	Negative	6	253	0					
	Missing	0	0	0					

Note: PPA = Positive Percent Agreement; NPA = Negative Percent Agreement. The p-value is significant at the 5% level.
Counts of missing values are for information purposes only and are not used in calculation of PPA, NPA or Cohen's Kappa. The ADA INX tag outcome is that outcome at the same visit which is displayed in the Visit column. Patients with a Quantity Not Sufficient (QNS) outcome are categorized as Missing for this analysis.
PPA = (Number of patients with positive outcome for both ADA CT-P13 and INX tags)/ (Number of patients with positive outcome for ADA INX tag) * 100.
NPA = (Number of patients with negative outcome for both ADA CT-P13 and INX tags)/ (Number of patients with negative outcome for ADA INX tag) * 100.

Table S1-2a. Analysis of Agreement of Immunogenicity testing between Neutralising Antibody (NAb) CT-P13 tag and NAb INX tag assay

Actual treatment group: CT-P13 3 mg/kg

		INX tag outcome							Cohen's Kappa		
Visit	CT-P13 Tag outcome	Positive	Negative[1]	QNS	NR	Missing	PPA (%)	NPA (%)	Statistic	95% CI	p-value
Screening	Positive	1	1	0	0	0	33.33	99.66	0.40	(-0.15, 0.94)	<0.001
	Negative	2	297	0	0	0					
	QNS	0	0	0	0	0					
	NR	0	0	0	0	0					
	Missing	0	0	0	0	0					
Week 14	Positive	67	4	0	0	0	97.10	98.02	0.94	(0.90, 0.99)	<0.001
	Negative	2	198	0	0	0					
	QNS	0	0	0	0	0					
	NR	0	0	0	0	0					
	Missing	0	1	0	0	0					

[1]The NAb negative population constitutes both (1) patients who were originally tested for ADA using tagged CT-P13 or tagged INX assay and who were found to be negative (therefore these patients were not further tested for NAb using either assay NAb-A or NAb-B, but are included in the NAb negative data group), and (2) patients who were originally tested for ADA using tagged CT-P13 or tagged INX assay and who were found to be positive; these patients were then tested for NAb using tagged CT-P13 and found to be negative.

Note: PPA = Positive Percent Agreement; NPA = Negative Percent Agreement. QNS = Quantity Not Sufficient, NR = No Result. The p-value is significant at the 5% level. Counts of Missing, QNS, and NR values are for information purposes only and are not used in calculation of PPA, NPA or Cohen's Kappa. The INX tag outcome is that outcome at the same visit which is displayed in the Visit column. N.E. = Non-estimable.

PPA = (Number of patients with positive outcome for both CT-P13 and INX tags)/ (Number of patients with positive outcome for INX tag) * 100.

NPA = (Number of patients with negative outcome for both CT-P13 and INX tags)/ (Number of patients with negative outcome for INX tag) * 100.

Table S1-2a. Analysis of Agreement of Immunogenicity testing between Neutralising Antibody (NAb) CT-P13 tag and NAb INX tag assay

Actual treatment group: CT-P13 3 mg/kg

		INX tag outcome							Cohen's Kappa		
Visit	CT-P13 Tag outcome	Positive	Negative[1]	QNS	NR	Missing	PPA (%)	NPA (%)	Statistic	95% CI	p-value
Week 30	Positive	117	6	0	0	0	96.69	95.42	0.92	(0.87, 0.97)	<0.001
	Negative	4	125	0	0	0					
	QNS	0	0	0	0	0					
	NR	0	0	0	0	0					
	Missing	0	0	0	0	0					

[1]The NAb negative population constitutes both (1) patients who were originally tested for ADA using tagged CT-P13 or tagged INX assay and who were found to be negative (therefore these patients were not further tested for NAb using either assay NAb-A or NAb-B, but are included in the NAb negative data group), and (2) patients who were originally tested for ADA using tagged CT-P13 or tagged INX assay and who were found to be positive; these patients were then tested for NAb using tagged CT-P13 and found to be negative.

Note: PPA = Positive Percent Agreement; NPA = Negative Percent Agreement. QNS = Quantity Not Sufficient, NR = No Result. The p-value is significant at the 5% level. Counts of Missing, QNS, and NR values are for information purposes only and are not used in calculation of PPA, NPA or Cohen's Kappa. The INX tag outcome is that outcome at the same visit which is displayed in the Visit column. N.E. = Non-estimable.

PPA = (Number of patients with positive outcome for both CT-P13 and INX tags)/ (Number of patients with positive outcome for INX tag) * 100.

NPA = (Number of patients with negative outcome for both CT-P13 and INX tags)/ (Number of patients with negative outcome for INX tag) * 100.

Table S1-2b. Analysis of Agreement of Immunogenicity testing between Neutralising Antibody (NAb) CT-P13 tag and NAb INX tag assay

Actual treatment group: INX 3 mg/kg

		INX tag outcome							Cohen's Kappa		
Visit	CT-P13 Tag outcome	Positive	Negative[1]	QNS	NR	Missing	PPA (%)	NPA (%)	Statistic	95% CI	p-value
Screening	**Positive**	2	1	0	0	0	100.00	99.66	0.80	(0.41, 1.00)	<0.001
	Negative	0	295	0	0	0					
	QNS	0	0	0	0	0					
	NR	0	0	0	0	0					
	Missing	0	0	0	0	0					
Week 14	**Positive**	63	4	2	0	0	95.45	98.02	0.93	(0.88, 0.98)	<0.001
	Negative	3	198	0	0	0					
	QNS	1	0	0	0	0					
	NR	0	0	0	0	0					
	Missing	0	0	0	0	0					

[1]The NAb negative population constitutes both (1) patients who were originally tested for ADA using tagged CT-P13 or tagged INX assay and who were found to be negative (therefore these patients were not further tested for NAb using either assay NAb-A or NAb-B, but are included in the NAb negative data group), and (2) patients who were originally tested for ADA using tagged CT-P13 or tagged INX assay and who were found to be positive; these patients were then tested for NAb using tagged CT-P13 and found to be negative.

Note: PPA = Positive Percent Agreement; NPA = Negative Percent Agreement. QNS = Quantity Not Sufficient, NR = No Result. The p-value is significant at the 5% level. Counts of Missing, QNS, and NR values are for information purposes only and are not used in calculation of PPA, NPA or Cohen's Kappa. The INX tag outcome is that outcome at the same visit which is displayed in the Visit column. N.E. = Non-estimable.

PPA = (Number of patients with positive outcome for both CT-P13 and INX tags)/ (Number of patients with positive outcome for INX tag) * 100.

NPA = (Number of patients with negative outcome for both CT-P13 and INX tags)/ (Number of patients with negative outcome for INX tag) * 100.

Table S1-2b. Analysis of Agreement of Immunogenicity testing between Neutralising Antibody (NAb) CT-P13 tag and NAb INX tag assay

Actual treatment group: INX 3 mg/kg

		INX tag outcome							Cohen's Kappa		
Visit	CT-P13 Tag outcome	Positive	Negative[1]	QNS	NR	Missing	PPA (%)	NPA (%)	Statistic	95% CI	p-value
Week 30	Positive	117	2	0	0	0	95.90	98.47	0.94	(0.90, 0.99)	<0.001
	Negative	5	129	0	0	0					
	QNS	0	0	0	0	0					
	NR	0	0	0	0	0					
	Missing	0	0	0	0	0					

[1]The NAb negative population constitutes both (1) patients who were originally tested for ADA using tagged CT-P13 or tagged INX assay and who were found to be negative (therefore these patients were not further tested for NAb using either assay NAb-A or NAb-B, but are included in the NAb negative data group), and (2) patients who were originally tested for ADA using tagged CT-P13 or tagged INX assay and who were found to be positive; these patients were then tested for NAb using tagged CT-P13 and found to be negative.

Note: PPA = Positive Percent Agreement; NPA = Negative Percent Agreement. QNS = Quantity Not Sufficient, NR = No Result. The p-value is significant at the 5% level. Counts of Missing, QNS, and NR values are for information purposes only and are not used in calculation of PPA, NPA or Cohen's Kappa. The INX tag outcome is that outcome at the same visit which is displayed in the Visit column. N.E. = Non-estimable.

PPA = (Number of patients with positive outcome for both CT-P13 and INX tags)/ (Number of patients with positive outcome for INX tag) * 100.

NPA = (Number of patients with negative outcome for both CT-P13 and INX tags)/ (Number of patients with negative outcome for INX tag) * 100.

Table S1-2c. Analysis of Agreement of Immunogenicity testing between Neutralising Antibody (NAb) CT-P13 tag and NAb INX tag assay

Actual treatment group: Total

		INX tag outcome							Cohen's Kappa		
Visit	CT-P13 Tag outcome	Positive	Negative[1]	QNS	NR	Missing	PPA (%)	NPA (%)	Statistic	95% CI	p-value
Screening	**Positive**	3	2	0	0	0	60.00	99.66	0.60	(0.24, 0.96)	<0.001
	Negative	2	592	0	0	0					
	QNS	0	0	0	0	0					
	NR	0	0	0	0	0					
	Missing	0	0	0	0	0					
Week 14	**Positive**	130	8	2	0	0	96.30	98.02	0.94	(0.90, 0.97)	<0.001
	Negative	5	396	0	0	0					
	QNS	1	0	0	0	0					
	NR	0	0	0	0	0					
	Missing	0	1	0	0	0					

[1]The NAb negative population constitutes both (1) patients who were originally tested for ADA using tagged CT-P13 or tagged INX assay and who were found to be negative (therefore these patients were not further tested for NAb using either assay NAb-A or NAb-B, but are included in the NAb negative data group), and (2) patients who were originally tested for ADA using tagged CT-P13 or tagged INX assay and who were found to be positive; these patients were then tested for NAb using tagged CT-P13 and found to be negative.

Note: PPA = Positive Percent Agreement; NPA = Negative Percent Agreement. QNS = Quantity Not Sufficient, NR = No Result. The p-value is significant at the 5% level. Counts of Missing, QNS, and NR values are for information purposes only and are not used in calculation of PPA, NPA or Cohen's Kappa. The INX tag outcome is that outcome at the same visit which is displayed in the Visit column. N.E. = Non-estimable.

PPA = (Number of patients with positive outcome for both CT-P13 and INX tags)/ (Number of patients with positive outcome for INX tag) * 100.

NPA = (Number of patients with negative outcome for both CT-P13 and INX tags)/ (Number of patients with negative outcome for INX tag) * 100.

Table S1-2c. Analysis of Agreement of Immunogenicity testing between Neutralising Antibody (NAb) CT-P13 tag and NAb INX tag assay

Actual treatment group: Total

		INX tag outcome							Cohen's Kappa		
Visit	CT-P13 Tag outcome	Positive	Negative[1]	QNS	NR	Missing	PPA (%)	NPA (%)	Statistic	95% CI	p-value
Week 30	Positive	234	8	0	0	0	96.30	96.95	0.93	(0.90, 0.96)	<0.001
	Negative	9	254	0	0	0					
	QNS	0	0	0	0	0					
	NR	0	0	0	0	0					
	Missing	0	0	0	0	0					

[1]The NAb negative population constitutes both (1) patients who were originally tested for ADA using tagged CT-P13 or tagged INX assay and who were found to be negative (therefore these patients were not further tested for NAb using either assay NAb-A or NAb-B, but are included in the NAb negative data group), and (2) patients who were originally tested for ADA using tagged CT-P13 or tagged INX assay and who were found to be positive; these patients were then tested for NAb using tagged CT-P13 and found to be negative.

Note: PPA = Positive Percent Agreement; NPA = Negative Percent Agreement. QNS = Quantity Not Sufficient, NR = No Result. The p-value is significant at the 5% level. Counts of Missing, QNS, and NR values are for information purposes only and are not used in calculation of PPA, NPA or Cohen's Kappa. The INX tag outcome is that outcome at the same visit which is displayed in the Visit column. N.E. = Non-estimable.

PPA = (Number of patients with positive outcome for both CT-P13 and INX tags)/ (Number of patients with positive outcome for INX tag) * 100.

NPA = (Number of patients with negative outcome for both CT-P13 and INX tags)/ (Number of patients with negative outcome for INX tag) * 100.

Appendix D.

Table S2-1. ACR20, ACR50 and ACR70 responses according to ADA status at week 30

	Treatment			n	N	(%)	Estimate [1]	Treatment difference estimate [2]	95% CI of treatment difference	
ADA positive										
ACR20	CT-P13 3 mg/kg			79	122	64.8	0.65	0.01	(-0.11,	0.13)
	INX 3 mg/kg			78	121	64.5	0.64	.		
	Goodness-of-fit test (p-value	0.986	[3])	.	.	.	.	.		
ACR50	CT-P13 3 mg/kg			36	122	29.5	0.29	-0.04	(-0.16,	0.08)
	INX 3 mg/kg			41	121	33.9	0.34	.		
	Goodness-of-fit test (p-value	0.984	[3])	.	.	.	.	.		
ACR70	CT-P13 3 mg/kg			9	122	7.4	0.07	-0.06	(-0.13,	0.02)
	INX 3 mg/kg			16	121	13.2	0.13	.		
	Goodness-of-fit test (p-value	0.850	[3])	.	.	.	.	.		
ADA negative										
ACR20	CT-P13 3 mg/kg			103	126	81.7	0.82	0.06	(-0.04,	0.16)
	INX 3 mg/kg			97	129	75.2	0.75	.		
	Goodness-of-fit test (p-value	0.769	[3])	.	.	.	.	.		
ACR50	CT-P13 3 mg/kg			69	126	54.8	0.54	0.07	(-0.06,	0.19)
	INX 3 mg/kg			61	129	47.3	0.48	.		
	Goodness-of-fit test (p-value	0.960	[3])	.	.	.	.	.		

	Treatment	n	N	(%)	Estimate [1]	Treatment difference estimate [2]	95% CI of treatment difference
ACR70	CT-P13 3 mg/kg	41	126	32.5	0.33	0.10	(-0.01, 0.21)
	INX 3 mg/kg	29	129	22.5	0.22	.	
	Goodness-of-fit test (p-value 0.996 [3])	.	.	.	.	.	

Note: N = the number of subjects with an assessment. n = the number of subjects with the event. (%)= n/N*100.

[1] Estimates of proportions are calculated using a logistic regression model with treatment as a fixed effect, and region and CRP category as covariates.

[2] The estimate of treatment difference of proportions (CT-P13 — INX) and corresponding 95% confidence interval were estimated from the logistic regression results using the Delta method. This method assumes independence between treatment groups.

[3] P-value is calculated using the Hosmer-Lemeshow test for the goodness-of-fit of the logistic regression model. The test is significant at the 5% level.

Table S2-2. EULAR responses (moderate and good) according to ADA status at week 30

Parameter	Treatment	n	N	(%)	Relative Risk Estimate	95% CI of Relative Risk
ADA positive						
EULAR(CRP)	CT-P13 3 mg/kg	97	122	79.51	0.96	(0.85, 1.09)
	INX 3 mg/kg	99	120	82.50	.	
EULAR(ESR)	CT-P13 3 mg/kg	94	122	77.05	1.03	(0.89, 1.18)
	INX 3 mg/kg	90	120	75.00	.	
ADA negative						
EULAR(CRP)	CT-P13 3 mg/kg	114	124	91.94	1.01	(0.93, 1.08)
	INX 3 mg/kg	117	128	91.41	.	
EULAR(ESR)	CT-P13 3 mg/kg	113	123	91.87	1.03	(0.95, 1.12)
	INX 3 mg/kg	114	128	89.06	.	

Note: The estimate of treatment difference of proportions (CT-P13 – INX) and corresponding 95% confidence interval were estimated from the logistic regression results using the Delta method. This method assumes independence between treatment groups. A relative risk (RR) of 1 indicates 'no difference' in risk between treatment groups. A RR of >1 indicates the EULAR response is more likely to occur in the CT-P13 group than in the INX group. A RR of <1 indicates the EULAR response is less likely to occur in the CT-P13 group than in the INX group. N = the number of subjects with an assessment. n = the number of subjects with the event. (%) = n/N*100.

Table S2-3. DAS28 according to ADA status at week 30

Parameter	Treatment	n	Adjusted mean	(SE)	Estimate of treatment difference	95% CI of treatment difference
ADA positive						
DAS28(CRP)	CT-P13 3 mg/kg	122	-1.82	(0.109)	0.11	(-0.19, 0.42)
	INX 3 mg/kg	120	-1.93	(0.110)	.	
DAS28(ESR)	CT-P13 3 mg/kg	122	-2.02	(0.115)	0.07	(-0.25, 0.39)
	INX 3 mg/kg	120	-2.09	(0.115)	.	
ADA negative						
DAS28(CRP)	CT-P13 3 mg/kg	124	-2.61	(0.108)	-0.21	(-0.51, 0.08)
	INX 3 mg/kg	128	-2.40	(0.107)	.	
DAS28(ESR)	CT-P13 3 mg/kg	123	-2.83	(0.114)	-0.27	(-0.58, 0.05)
	INX 3 mg/kg	128	-2.57	(0.114)	.	

Note: Analysis of covariance (ANCOVA) model with DAS28 as the response, treatment as a fixed effect, and baseline DAS28, region and CRP category as covariates. Adjusted least squares means and standard error, estimate of treatment difference (CT-P13 — INX) and 95 Confidence Interval calculated from the ANCOVA model. A treatment difference >0 implies that a subject treated with CT-P13 has on average a higher increase in post-baseline DAS28 at the scheduled visit in comparison to a INX-treated subject.

Appendix E.

Table S3. Individual Patient Listings and Details for Treatment-Related SAEs and AEs of Active Tuberculosis Cases for PLANETRA study

	CT-P13 3 mg/ kg		
Patient No.	0306-3026*	1208-3002	2201-3005
Age/Sex/ Race[1]	27/F/A	58/F/W	37/F/O: Hispanic
Geographical area	Non-European region - Philippines	European region – Eastern Europe (Poland)	Non-European region - Latin America (Mexico)
Indication	Rheumatoid arthritis	Rheumatoid Arthritis	Rheumatoid arthritis
Interferon-gamma release assay	Screening – Negative Week 14 – Positive End-of-Study – Positive	Screening - Negative	Screening – Negative Unscheduled - Positive
Condition / Diagnosis	Pulmonary TB	Miliary TB (Diseminated TB)	Disseminated TB[2]
Severity	Moderate	Moderate	Severe
Related / Unrelated to Drug	Definite	Probable	Definite
BCG vaccination	Yes	Yes	Yes
Treatment	Anti-TB drugs	Anti-TB drugs	Anti-TB drugs
Outcome to Treatment	Recovered/Resolved	Recovered/Resolved	Recovering/Resolving
Action	Permanently discontinued	Permanently discontinued	Permanently discontinued
Medical history	Osteonecrosis	Cholelithiasis Cholecystectomy	Sjogren's syndrome Ulcerative keratitis
Immunosupressants used	METHOTREXATE(JAN2007)	METHOTREXATE(22JUN2010) METHYLPREDNISOLONE(05MAY2009~)	METHOTREXATE(03MAY2007) PREDNISONE(03MAY2007~)

[1] F = Female, W = White, A = Asian, O = Other

[2] Disseminated TB was reported as a TEAE for this patient as a recovering/resolving condition of the SAE

* Unconfirmed TB diagnosis defined as clinical symptoms compatible with TB in the absence of an alternative diagnosis without evidence of M. tuberculosis culture growth, molecular diagnostics or histopathological examination

Two of the cases were considered moderate and one severe in severity. As these numbers are generally low these events are likely chance findings. All of these cases came from regions or countries with an increased prevalence and incidence of TB: Estimated rates in the Philippines of 275, Mexico 16, Latvia 39, Republic of Korea 97 and Poland of 23 per 100,000 population compared to Western Europe countries: e.g. France 9.3, and Germany 4.8 per 100,000 population (WHO TB cases by region, 2010, WHO TB cases by country, 2010).

Appendix F.

Table S4. Treatment-emergent serious adverse events reported as related to study treatment, no (%)

	CT-P13 3 mg/kg (N=301)			INX 3 mg/kg (N=301)		
N (%)	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Neutropenia			1 (0.3)			
Vestibular disorder			1 (0.3)			
Infusion-related reaction		2 (0.7)	2 (0.7)	2 (0.7)	1 (0.3)	1 (0.3)
Hepatitis toxic			1 (0.3)			
Appendicitis						1 (0.3)
Arthritis infective						1 (0.3)
Disseminated TB		1 (0.3)	1 (0.3)			
Pulmonary TB		1 (0.3)				
Herpes zoster						1 (0.3)
Lobar pneumonia	1 (0.3)					
Pneumonia		1 (0.3)				
Wound infection staphylococcal		1 (0.3)				
Musculoskeletal chest pain			1 (0.3)			

Flare in RA activity			1 (0.3)			
Breast cancer						1 (0.3)
Ovarian cancer metastatic						1 (0.3)
Renal neoplasm	1 (0.3)					
Cerebrovascular disorder			1 (0.3)			
Endometrial hyperplasia		1 (0.3)				
Metrorrhagia					1 (0.3)	
Thrombophlebitis			1 (0.3)			

Active TB was reported for three patients and none (0 patients) in the CT-P13 and INX treatment groups, respectively. Latent TB was observed in 13 patients receiving CT-P13 and 14 patients in INX.

The number of patients who were reported to be seroconverted to positive after the study drug exposure with negative results at screening from IGRA test was similar in the CT-P13 (30 patients) and INX treatment groups (28 patients).The three patients with active TB at screening, had negative IGRA results and prophylactic TB medication was not given to them. These patients were from Philippines, Mexico and Poland respectively, and future follow-up on social environment seems to be required.

Appendix G.

Table S5. Mean (CV) Serum Pharmacokinetic Parameters of Infliximab: Pharmacokinetic population

Parameter	CT-P13 3 mg/kg (N=292)		INX 3 mg/kg (N=289)	
Dose 1 (Week 0)				
C_{max} (µg/mL)	n=290	91.50 (35)	n=285	88.53 (37)
C_{min} (µg/mL)	n=284	15.76 (58)	n=278	16.76 (44)
T_{max} (h)	n=290	3.00 (1.83, 4.08)	n=285	2.12 (1.50, 5.17)
Dose 2 (Week 2)				
C_{max} (µg/mL)	n=288	111.88 (32)	n=285	105.07 (35)
C_{min} (µg/mL)	n=278	6.15 (75)	n=278	7.65 (85)
T_{max} (h)	n=288	2.25 (0.25, 4.03)	n=285	3.00 (0.50, 3.75)
Dose 3 (Week 6)				
C_{max} (µg/mL)	n=277	97.91 (40)	n=277	96.20 (33)
C_{min} (µg/mL)	n=267	1.51 (301)	n=262	1.42 (187)
T_{max} (h)	n=277	2.25 (0.08, 7.33)	n=277	2.97 (1.00, 3.33)
Dose 4 (Week 14)				
C_{max} (µg/mL)	n=269	90.25 (36)	n=263	85.25 (40)
C_{min} (µg/mL)	n=261	1.05 (136)	n=251	1.07(140)
T_{max} (h)	n=269	3.00 (1.17, 3.20)	n=263	2.42 (0.22, 4.00)
Dose 5 (Week 22)				
C_{max} (µg/mL)	n=258	90.82 (40)	n=253	86.26 (44)
C_{min} (µg/mL)	n=240	0.99 (390)	n=243	1.02 (297)
T_{max} (h)	n=258	3.00 (2.00, 3.25)	n=253	2.25 (2.00, 4.50)
$C_{av,ss}$(µg/mL)	n=240	47.10 (40)	n=241	44.37 (44)
PTF	n=240	1.86 (12)	n=241	1.90 (8)
Dose 6 (Week 30)				
C_{max} (µg/mL)	n=243	83.87 (38)	n=245	83.78 (35)
T_{max} (h)	n=243	2.08 (2.00, 3.58)	n=245	2.25 (0.10, 3.33)

Note: Note: C_{max} represents the observed maximum serum drug concentration; C_{min} represents minimum serum drug concentration immediately prior to next dose; T_{max} represents time to reach C_{max} and is reported here as the median (minimum, maximum). CV, coefficient of variation.

Appendix H.

Additional Study Details:

Sample size

- Sample size was determined by

    - A total of 584 male and female patients will be enrolled in the study. Therapeutic equivalence to Remicade in the all randomised population will be based on expected responder rates of 50% in the test and control groups [Maini et al 1999]. Specifying a 2-sided alpha level of 0.05, power of 80%, and a 2-sided equivalence margin of 15% would require 468 patients to be included in the per-protocol population for the final analysis. Assuming that 20% of patients will be excluded from the per-protocol population would require 584 patients in total to be randomised.

Randomisation

- The random allocation sequence was generated by PPD unblended biostatistics team.

- The random allocation sequence was implemented using

    - An interactive voice recognition system (IVRS) will be used for the randomisation. Biostatistics will generate the randomisation schedule for IVRS, which will link sequential patient randomisation numbers to treatment codes. The randomisation will be stratified by region (European and non-European) and CRP. The randomisation numbers will be blocked, and within each block the same number of patients will be allocated to each treatment group. The block size will not be revealed.

- Participants were enrolled by investigators in each institution, and participants were assigned to their interventions by each institution.

Blinding

- As this is a double-blind study, the overall randomisation code will be broken only for reporting purposes, which will occur once all final clinical data up to Week 30 have been entered into the database and the database up to Week 30 is finalized for analysis. Final determination of the analysis sets will occur prior to finalizing the database. Once the overall randomisation code has been broken, the study can be considered open-label. While the study data are analysed at Week 30, the study will remain blinded to the investigators and patients until the end of the study to reduce bias.

- **Breaking the Blind**

- The study blind should not be broken except in a medical emergency (where knowledge of the study treatment received would affect the treatment of the emergency) or regulatory requirement (e.g., for SAEs or death). Any unblinding by study centre personnel will be documented in the eCRF, and statistical analysis will examine the potential impact of the unblinding. The blind must only be broken following discussion on a case-by-case basis, at the discretion of the sponsor or medical monitor. If the blind is broken, the date, time, and reason must be recorded in the patient's eCRF and any associated AE report.

- The investigator should notify the sponsor or medical monitor prior to contacting IVRS. All calls resulting in an unblinding event will be recorded and reported by the IVRS to the medical monitor and the sponsor.

Appendix I.

Per-protocol (PP) population

The PP population consisted of all randomly assigned patients who fully complied with the inclusion and exclusion criteria, received all doses of study treatment up to Week 30, not received any prohibited therapies, and had an ACR assessment at Week 30.

For the following reason, 107 patients (54 patients from CT-P13 group, 53 patients from INX group) were excluded from all randomised population (N=606) in the PP population (N=499).

Table S6. The number (%) of patients excluded due to protocol violations.

	Number (%) of Patients		
	CT-P13 3 mg/kg (N=302)	**INX 3 mg/kg (N=304)**	**Total (N=606)**
Misrandomisations[1]	0	1 (0.3)	1 (0.2)
Noncompliance with inclusion/exclusion criteria	2 (0.7)	3 (1.0)	5 (0.8)
An assessment out of window by more than 2 weeks for Dose 6	2 (0.7)	3 (1.0)	5 (0.8)
Receipt of corticosteroids	4 (1.3)	5 (1.6)	9 (1.5)
Patients who did not receive all doses of study treatment up to Week 30	48 (15.9)[a]	44 (14.5)[a]	92 (15.2)
– Patients who did not have an ACR assessment at Week 30	45 (14.9)	43 (14.1)	88 (14.5)
Patients who discontinued or reduced their methotrexate dose for more than 2 consecutive weeks up to Week 30	2 (0.7)[b]	1 (0.3)	3 (0.5)

Note: PP = per-protocol population.

[1] Misrandomisations defined as patients who received the opposite treatment to which they were assigned at any point during the study.

a. Two patients from CT-P13 group and a patient from INX group due to noncompliance with inclusion/exclusion criteria and 2 patients from both groups due to receipt of corticosteroids were already excluded from the PP population. One patient in the CT-P13 group skipped Dose 4 and received Dose 5 and 6, therefore considered that did not receive all doses of study treatment up to Week 30.

b. One patient was already excluded from PP due receipt of corticosteroids.

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Rheumatoid arthritis: cheaper biological treatments on the horizon?

INTRODUCTION

In recent years the so-called 'biological' treatments have marked a major step forward in the treatment of rheumatoid arthritis. Now a new study has looked at a similar treatment that may be cheaper and, therefore, available to more people.

WHAT DO WE KNOW ALREADY?

Research into rheumatoid arthritis has moved very quickly in the last 10 years or so. New medicines-and even new types of medicines-have become available. This is important because there seems to be no one drug that helps everyone who has the condition. Treating rheumatoid arthritis often involves a process of trial and error to see which medicine or combination of medicines suits individual people, and which causes the least-serious side effects.

One major advance has been the development of the so-called 'biological' medicines. (You may have heard some of these medicines referred to as TNF [tumour necrosis factor] inhibitors.) Biological treatments, which are made from genetically engineered human proteins, have been shown to help many people who don't respond much to more established treatments such as methotrexate. But these newer treatments are expensive, which means they are often only recommended when other drugs haven't worked. This can be extremely frustrating for people who want to get the most effective treatment as soon as possible.

The new study looked at a medicine called CT-P13. This is a kind of drug known as a monoclonal antibody. It is produced from human cells in a similar but not identical way to the innovator infliximab (INX, brand name Remicade), and it works in a similar way. So CT-P13 is called a 'biosimilar' biological disease-modifying antirheumatic drug. Biosimilar biological drugs are expected to be cheaper than the originator biological agents..

In the study, the researchers randomly divided about 600 people with active rheumatoid arthritis who were not responding well to methotrexate into two groups. One group was given INX in addition to methotrexate. The second group was given methotrexate alongside the new drug, CT-P13. After 30 weeks, the researchers looked to see how many people in each group had improved using a measurement called the American College of Rheumatology 20%, or ACR 20.

People being treated for rheumatoid arthritis may not have heard of this measurement, as it's usually only used by researchers comparing treatments in studies, and usually not by doctors treating patients. The ACR 20 assesses how many people have 20 percent fewer tender and swollen joints (and 20% improvement in at least 3 of 5 other measures) at the end of a study.

WHAT DOES THE NEW STUDY SAY?

The new study found that CT-P13 worked just as well as INX. For both medicines, about 60 in 100 people met the ACR 20 target. However, the researchers found that CT-P13 worked slightly more quickly than INX. There were no major differences in side effects between the two groups, which suggests that the new medicine is no less safe to use than INX.

HOW RELIABLE ARE THE FINDINGS?

This was a well-conducted study that was big enough for the results to carry quite a lot of weight. Indeed, the European Medicines Agency (EMA) approved CT-P13 for use in people with rheumatoid arthritis based on its findings, which suggest that CT-P13 works as well as the originator infliximab and that its side effects are no worse. However, longer-lasting studies will also be needed, as well as studies into how biosimilar drugs compare with originator biologicals with regard to what's called 'antidrug antibodies'. In some people, the immune system produces antidrug antibodies to fight the medicine, the way they would fight an infection. This then stops the medicine from working.

WHAT DOES THIS MEAN FOR ME?

New treatments for rheumatoid arthritis that work as well as established biological medicines would be very welcome-especially if they prove cheaper and easier to access. CT-P13 is still being tested. Its availability in different countries will depend on when the patent for Remicade expires.

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