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 Mie Jin Lim,1 Yeon-Ah Lee,3 Sang Joon Lee,10 Ho Ung Kim,11 Dae Hyun Yoo,12 Jürgen Braun13

ABSTRACT

Objectives To compare the pharmacokinetics (PK), safety and efficacy of innovator infliximab (INX) and CT-P13, a biosimilar to INX, in patients with active ankylosing spondylitis (AS).

Methods Phase 1 randomised, double-blind, multicentre, multinational, parallel-group study. Patients were randomised to receive 5 mg/kg of CT-P13 (n=125) or INX (n=125). Primary endpoints were area under the concentration-time curve (AUC) at steady state and observed maximum steady state serum concentration (Cmax,ss) between weeks 22 and 30. Additional PK, efficacy endpoints, including 20% and 40% improvement response according to Assessment in Ankylosing Spondylitis International Working Group criteria (ASAS20 and ASAS40), and safety outcomes were also assessed.

Results Geometric mean AUC was 32 765.8 μg/ml/day for CT-P13 and 31 359.3 μg/ml/day for INX. Geometric mean Cmax,ss was 147.0 μg/ml for CT-P13 and 144.8 μg/ml for INX. The ratio of geometric means was 104.5% (90% CI 94% to 116%) for AUC and 101.5% (90% CI 95% to 109%) for Cmax,ss. ASAS20 and ASAS40 responses at week 30 were 70.5% and 51.8% for CT-P13 and 72.4% and 47.4% for INX, respectively. In the CT-P13 and INX groups more than one adverse event occurred in 64.8% and 63.9% of patients, infusion reactions occurred in 3.9% and 4.9%, active tuberculosis occurred in 1.6% and 0.8%, and 27.4% and 22.5% of patients tested positive for anti-drug antibodies, respectively.

Conclusions The PK profiles of CT-P13 and INX were equivalent in patients with active AS. CT-P13 was well tolerated, with an efficacy and safety profile comparable to that of INX up to week 30.

INTRODUCTION

Innovator infliximab (INX), a chimeric monoclonal antibody (mAb) to tumour necrosis factor-α (TNFα), was the first TNF antagonist shown to be efficacious in ankylosing spondylitis (AS).1 INX significantly improved the signs, symptoms, functional status, and quality of life (QOL) of patients with AS in clinical trials, with clinical improvement seen as early as 2 weeks after initiation of therapy and an acceptable safety profile.2–4 In the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) trial, patients receiving INX also showed significant improvement versus placebo in 20% and 40% improvement response according to Assessment in Ankylosing Spondylitis International Working Group criteria (ASAS20/ASAS40), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index (BASMI), chest expansion and physical component summary score of the SF-36.2 INX and other anti-TNF agents have become important components of the management of patients with active AS.5 6 With current biologic therapies approaching patent expiration, there has been considerable interest in developing biosimilar products, which are highly similar but not identical and not ‘bioequivalent’, to approved ‘reference’ agents.7

CT-P13 is an IgG1 chimeric human-murine mAb 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 to human TNFβ and TNFα from a range of different species known not to bind infliximab; relative binding affinities to complement protein C1q; and 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 tmhTNF-α-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 INX.

According to biosimilar guidelines from European Medicines Agency (EMA) and US Food and Drug Administration (FDA), comparative clinical trials for pharmacokinetics (PK) and efficacy are required for demonstration of clinical comparability, preferably double-blind, normally equivalence trials. Programme evLaTuating the Autoimmune disease iNvEstigational drug cT-p13 in AS patients (PLANETAS) was conducted with the approval of the regulatory authorities, including the EMA. PLANETAS was not a conventional dose finding Phase 1 clinical trial but a Phase 1 biosimilar study designed to demonstrate PK equivalence and efficacy and safety comparability of CT-P13 and INX in active AS patients. Efficacy equivalence of CT-P13 and INX in a phase 3 study named Programme evLaTuating the Autoimmune disease iNvEstigational drug cT-p13 in rheumatoind arthritis (RA) patients (PLANETRA).8 PK and PD endpoints were also assessed, as the indications for the PLANETAS and PLANETRA trials were different.

PATIENTS AND METHODS

Patients

Patients with active AS according to the 1984 modified New York classification criteria for ≥3 months prior to screening, with BASDAI score of ≥4 (range 0–10) and a visual analogue scale score for spinal pain of ≥4 (range 0–10) were eligible for PLANETAS study. Patients were permitted to receive both oral glucocorticoids (equivalent to ≤10mg daily prednisolone) and nonsteroidal 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

This study (ClinicalTrials.gov NCT01220518) was conducted according to the Declaration of Helsinki and International Committee on Harmonisation good clinical practices. 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 46 sites across 10 countries in Europe, Asia and Latin America.

Patients were randomly assigned 1:1 to receive either 5 mg/kg of CT-P13 (CELLTRION INC, Incheon, Republic of Korea) or INX (Jansen Biotech Inc, Horsham, Pennsylvania, USA), both administered 2-h IV infusion, at weeks 0, 2, 6 and then q8 weeks up to week 30. Patients were premedicated with anti-histamine (chlorpheniramine 2–4 mg or dose of equivalent antihistamine, eg, 10 mg of cetirizine) 30–60 min prior to the start of infusion at the investigator’s discretion.

Patients underwent clinical assessments and blood sampling at baseline, weeks 14 and 30. At each visit, patients were questioned about adverse events (AEs) and concomitant medications and were monitored for any clinical signs and symptoms of tuberculosis (TB). Additional study details are provided in (see online supplementary appendix C).

Study endpoints

The primary endpoint was to demonstrate PK equivalence at steady state (area under the concentration-time curve (AUC) and observed maximum serum concentration (Cmax)) between CT-P13 and INX assessed between weeks 22 and 30 (doses 5 and 6). Serum blood samples for PK analysis were obtained immediately prior to the study treatment infusion, at the end of the infusion and 1 h after the study treatment infusion. For primary PK analysis, a total of 10 serum blood samples were obtained between weeks 22 and 30. All PK analyses were conducted using a flow-through immunoassay platform (PyrolybaxP; Gyros AB, Sweden).

In an equivalence trial, we conclude that two treatments are equivalent if the observable difference (ΔE) between them lies within an established interval for predefined clinical equivalence margin (−d, d). In general, the ‘null hypothesis’ is that the difference (ΔE) is outside of the equivalence margin, that is, either ΔE>d or ΔE<-d. If collected data on the true difference ΔE reject the null hypothesis of ‘non-equivalence’ then we can accept the alternative explanation (−d≤ΔE≤d) that the two treatments work equally well.9 An equivalence margin of 80–125% was selected based on recommendations for bioequivalence trials.10–13 The use of 90% confidence intervals (CIs), lying within the equivalence margin of 80–125%, was therefore considered to be the best available method of determining bioequivalence for PK comparative trials. In our PK analysis, the predetermined difference is defined by its corresponding ratio since we use the ratio of geometric means of PK endpoints.

Secondary endpoints included additional PK, efficacy, immunogenicity and safety parameters. The secondary PK endpoints included assessments of observed maximum serum concentration (Cmax), minimum serum concentration (Cmin), time to reach Cmax (Tmax) up to week 30 and the comparison of the following parameters from week 22 to 30: average concentration at steady state (Cavss); minimum concentration at steady state immediately before the next infusion (Cmin,ss); swing ((Cmax,ss–Cmin,ss)/Cmin,ss); degree of fluctuation (Cmax,ss–Cmin,ss)/Cavss; mean residence time (MRT); terminal elimination half-life calculated between doses 5 and 6 (T1/2); total body clearance (CLss) and volume of distribution at steady state (Vss).

Efficacy endpoints were assessed at weeks 14 and 30 and included: proportion of patients achieving ASAS20 or ASAS40 responses; Ankylosing Spondylitis Disease Activity Score (ASDAS) score; change in BASDAI, BASFI and BASMI scores versus baseline; change in chest expansion score versus baseline; and QOL (assessed using the Medical Outcomes Study Short-Form Health Survey (SF-36)).

Blood samples were assessed for anti-drug antibodies (ADA) at weeks 14 and 30. Antibodies against CT-P13 or INX were measured using an electrochemiluminescent immunoassay method utilising the Meso Scale Discovery platform (MSD, Rockville, Maryland, USA).

Safety endpoints included incidence and type of AEs, serious AEs (SAEs) and incidence of infusion-related reactions, infection and changes in clinical laboratory parameters from baseline. AEs were coded using the Medical Dictionary for Regulatory Activities and severity was characterised as mild, moderate or severe. ECGs were recorded at week 30.

All patients were screened for latent or active TB by an interferon gamma release assay (IGRA) utilising Quantiferon-TB Gold in tube (Cellestis Ltd, Australia) and chest x-ray. Patients with latent TB received prophylactic medication according to the local guidelines. For countries with an increased incidence of TB, IGRA was used to identify positive conversion from negative results at weeks 14 and 30, in line with the WHO recommendations for sole use of IGRA in non-HIV adults receiving anti-TNF therapy.14–15

Statistical analysis

Sample size was determined using the following criteria: a coefficient of variation (CV) of 50%, expected ratio of means=1,
2-sided α=0.1, power=90%, and a 2-sided equivalence margin of 80–125% for AUC and C_{max,α}. Recruitment of 196 patients were required to demonstrate an effect. Allowing for a drop-out rate of 20%, a minimum of 246 patients were required for randomisation.

The PK population consisted of all patients who received at least the first five doses of study treatment and provided an end of infusion sample and at least one post-treatment PK sample to facilitate calculation of AUC and C_{max,α}. The PK population included only patients who did not have any major protocol deviations (see online supplementary appendix D).

Primary endpoints were assessed by statistical comparison of AUC and C_{max,α}. Serum concentrations and PK parameters were summarised using quantitative descriptive statistics (including geometric mean and CV) by actual treatment group and study visit (and by time point for serum concentrations).

Efficacy analysis assessed the proportion of patients achieving clinical response (ASAS20/ASAS40) by logistic regression modelling including all randomised patients, with treatment as a fixed effect and the stratification factors (region, baseline BASDAI score) as covariates. Treatment effect was estimated by calculating the OR and 95% CI. Descriptive statistics for actual result and change from baseline were calculated for the following quantitative parameters: ASDAS, BASDAI, BASFI, BASMI, chest expansion and SF-36.

The 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.

Safety analysis was performed by presenting data on hypersensitivity, ECG results, physical examination, vital sign measurements, clinical laboratory tests (haematology, clinical chemistry and urinalysis), AEs, concomitant medications and immunogenicity.

RESULTS
Patients
The first patient was screened in November 2010; the week 30 evaluation of the last patient was performed in December 2011. Baseline demographics are shown in table 1. Of the 250 randomised patients, 229 completed the 30-week study period and 21 discontinued study treatment prior to week 30, primarily due to AEs (5.2%) and patient withdrawal of consent (2.4%) (figure 1).

PK analyses included 223 patients. Efficacy and safety analysis were performed in all 250 patients.

Pharmacokinetics
Steady state PK (AUC and C_{max}) was equivalent for CT-P13 (32765.8 μg/ml and 147.0 μg/ml) and INX (31359.3 μg/ml and 144.8 μg/ml) in the overall PK population (table 2 and figure 2). The ratio of geometric means was near 100% for AUC and C_{max,α}. In the ADA-negative subset of patients (n=171), geometric means of AUC and C_{max,α} were higher than in the overall PK population, but the ratios of geometric means in this subgroup remained near 100% for both measures. The mean secondary PK endpoints—C_{min,ss}, swing, degree of fluctuation, MRT, T_{1/2}, CL_{ss}, V_{ss}, C_{max,α}, C_{min,α} and T_{max,ss}—were also highly similar between CT-P13 and INX (table 3).

Table 1 Baseline demographics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CT-P13 5 mg/kg (N=125)</th>
<th>INX 5 mg/kg (N=125)</th>
<th>Total (N=250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (years)</td>
<td>38.0 (18–69)</td>
<td>38.0 (18–66)</td>
<td>38.0 (18–69)</td>
</tr>
<tr>
<td>Gender, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>99 (79.2)</td>
<td>103 (82.4)</td>
<td>202 (80.8)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (20.8)</td>
<td>22 (17.6)</td>
<td>48 (19.2)</td>
</tr>
<tr>
<td>Ethnicity, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>97 (77.6)</td>
<td>92 (73.6)</td>
<td>189 (75.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>16 (12.8)</td>
<td>13 (10.4)</td>
<td>29 (11.6)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (9.6)</td>
<td>20 (16.0)</td>
<td>32 (12.8)</td>
</tr>
<tr>
<td>Height, cm (cm)</td>
<td>172.0 (148–198)</td>
<td>171.0 (147–193)</td>
<td>172.0 (147–198)</td>
</tr>
<tr>
<td>Weight, kg (kg)</td>
<td>72.70 (45.0–120.0)</td>
<td>76.00 (45.5–122.7)</td>
<td>73.75 (45.0–122.7)</td>
</tr>
<tr>
<td>Body mass index, kg/m² (kg/m²)</td>
<td>24.39 (18.0–38.7)</td>
<td>25.64 (17.5–42.0)</td>
<td>25.12 (17.5–42.0)</td>
</tr>
<tr>
<td>ASDAS, mean (SD)</td>
<td>3.8 (0.8)</td>
<td>3.9 (1.1)</td>
<td>3.9 (1.0)</td>
</tr>
<tr>
<td>BASDAI (stratification factor), no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–8</td>
<td>92 (73.6)</td>
<td>95 (76.0)</td>
<td>187 (74.8)</td>
</tr>
<tr>
<td>&gt;8–10</td>
<td>33 (26.4)</td>
<td>30 (24.0)</td>
<td>63 (25.2)</td>
</tr>
<tr>
<td>BASDAI score, 0–10</td>
<td>6.8 (3.4–10.0)</td>
<td>6.6 (1.8–10.0)</td>
<td>6.7 (1.8–10.0)</td>
</tr>
<tr>
<td>BASFI score, 0–10</td>
<td>6.3 (0.7–9.8)</td>
<td>6.3 (0.1–10.0)</td>
<td>6.3 (0.1–10.0)</td>
</tr>
<tr>
<td>BASMI score, 0–10</td>
<td>4.0 (0.0–9.0)</td>
<td>4.0 (0.0–9.0)</td>
<td>4.0 (0.0–9.0)</td>
</tr>
<tr>
<td>Chest expansion, cm</td>
<td>3.0 (0.5–9.0)</td>
<td>2.5 (0.0–7.0)</td>
<td>3.0 (0.0–9.0)</td>
</tr>
<tr>
<td>SF-36 summary scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical component</td>
<td>34.1 (16.2–49.7)</td>
<td>33.1 (15.3–54.3)</td>
<td>33.4 (15.3–54.3)</td>
</tr>
<tr>
<td>Mental component</td>
<td>38.2 (15.1–63.7)</td>
<td>37.2 (12.5–63.6)</td>
<td>37.8 (12.5–63.7)</td>
</tr>
<tr>
<td>CRP level, mg/dl</td>
<td>1.1 (0.0–13.0)</td>
<td>1.4 (0.0–17.4)</td>
<td>1.3 (0.0–17.4)</td>
</tr>
<tr>
<td>ESR level, mm/h</td>
<td>33.0 (2.0–110.0)</td>
<td>34.0 (1.0–119.0)</td>
<td>34.0 (1.0–119.0)</td>
</tr>
</tbody>
</table>

*Except where indicated otherwise, values are the median (minimum, maximum).

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; INX, innovator infliximab; SF-36, quality-of-life questionnaire (Medical Outcomes Study Short-Form Health Survey).
Clinical efficacy

Efficacy was highly similar between the two groups, as measured by all efficacy endpoints. ASAS20 response was achieved in 62.6% and 70.5% for CT-P13 and 64.8% and 72.4% for INX at weeks 14 (OR=0.91, 95% CI 0.53 to 1.54) and 30 (OR=0.91, 95% CI 0.51 to 1.62), respectively. ASAS40 response was achieved in 41.7% and 51.8% for CT-P13 and 45.9% and 47.4% for INX at weeks 14 (OR=0.85, 95% CI 0.51 to 1.42) and 30 (OR=1.19, 95% CI 0.70 to 2.00), respectively (see online supplementary appendix E).

The mean change from baseline in the ASDAS-CRP score was highly similar for both treatment groups at weeks 14 (−1.8; SD=1.1 vs −1.8; SD=1.1) and 30 (−1.8; SD=1.2 vs −1.7; SD=1.2) for CT-P13 and INX, respectively.

The median change from baseline to weeks 14 and 30 for CT-P13 and INX was noted in the following secondary endpoints: BASDAI score (week 14: −2.7 vs −2.7 and 30: −3.1 vs −2.5); BASFI score (week 14: −2.2 vs −2.4 and 30: −2.6 vs −2.2); BASMI score (week 14: 0.0 vs 0.0 and 30: −1.0 vs −1.0); and chest expansion score (week 14: +0.2 vs +0.5 and 30: +0.5 vs

### Table 2 Overall steady state PK between weeks 22 and 30

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>n</th>
<th>Geometric mean</th>
<th>Ratio (%) of geometric means</th>
<th>90% CI of ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK population</td>
<td>AUC (μg/ml)</td>
<td>CT-P13</td>
<td>112</td>
<td>32765.8</td>
<td>104.5</td>
</tr>
<tr>
<td></td>
<td>INX</td>
<td>110</td>
<td>31359.3</td>
<td>101.5</td>
<td>94.7 to 108.9</td>
</tr>
<tr>
<td></td>
<td>C_{max,ss} (μg/ml)</td>
<td>CT-P13</td>
<td>113</td>
<td>147.0</td>
<td>101.5</td>
</tr>
<tr>
<td></td>
<td>INX</td>
<td>110</td>
<td>144.8</td>
<td>100.5</td>
<td>94.7 to 108.9</td>
</tr>
<tr>
<td>ADA-negative subset</td>
<td>AUC (μg/ml)</td>
<td>CT-P13</td>
<td>84</td>
<td>37505.2</td>
<td>103.4</td>
</tr>
<tr>
<td></td>
<td>INX</td>
<td>86</td>
<td>36266.9</td>
<td>101.4</td>
<td>97.2 to 112.9</td>
</tr>
<tr>
<td></td>
<td>C_{max,ss} (μg/ml)</td>
<td>CT-P13</td>
<td>85</td>
<td>153.9</td>
<td>104.7</td>
</tr>
<tr>
<td></td>
<td>INX</td>
<td>86</td>
<td>146.9</td>
<td>101.4</td>
<td>97.2 to 112.9</td>
</tr>
</tbody>
</table>

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.
SF-36 score increased from baseline to week 14 and 30 similarly at both time points and in both treatment groups. At week 30, a significant improvement from baseline in the physical component score of the SF-36 (median change from baseline 7.6 vs 8.5, respectively) was observed in both treatment groups. A similar effect was observed for the mental component score of the SF-36 (6.5 vs 5.2).

An ASAS20 response for CT-P13 and INX at week 30, assessed according to baseline C-reactive protein (CRP) levels, was achieved in 75.2% and 77.6% of patients with a baseline CRP of >3 times the upper limit of normal (ULN) (OR=0.76: 95% CI 0.32 to 1.84) and in 68.9% and 67.2% of patients with a baseline CRP ≤3×ULN, respectively (OR=0.99: 95% CI 0.45 to 2.17). The median change from baseline to week 30 in CRP and erythrocyte sedimentation rate was −0.7 mg/dl and −21.0 mm/h for CT-P13 and −0.8 mg/dl and −19.5 mm/h for INX, respectively.

Overall, no statistical significance in clinical response between the treatment groups at weeks 14 and 30 was found.

Immunogenicity

Antibodies to infliximab with active AS patients were detected in 9.1% (n=11) and 11.0% (n=13) of patients for CT-P13 and INX at week 14 and 27.4% (n=32) and 22.5% (n=25) of patients for CT-P13 and INX, respectively, at week 30.

The efficacy results were analysed for ADA-positive and ADA-negative patients in a post-hoc analysis, and it was found that ADA-positive patients had a less robust ASAS20 response (see online supplementary appendix F). No statistically significant difference between the CT-P13 and INX treatment groups was observed at week 14 and 30.

Safety

Overall treatment-emergent AEs (TEAEs) were reported in 83 (64.8%) patients and 78 (63.9%) patients from the CT-P13 and INX treatment arms, respectively (table 4). The majority of TEAEs was 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: increased alanine transaminase (ALT) (n=14, 10.9%) and aspartate transaminase (AST) (n=12, 9.4%), urinary tract infection (n=5, 3.9%), serum creatine phosphokinase elevation (n=4, 3.1%), serum creatine phosphokinase elevation (n=4, 3.1%), and γ-glutamyltransferase elevation (n=4, 3.1%); INX: increased ALT (n=13, 10.7%) and AST (n=10, 8.2%), γ-glutamyltransferase elevation (n=5, 4.1%) and latent TB (n=4, 3.3%). Infusion-related reactions occurred in five (3.9%) and six (4.9%) patients in CT-P13 and INX groups, respectively.

Similar rates of SAEs were reported between treatment groups, regardless of the relationship with the study drug (see online supplementary appendix G). No deaths were reported during the study.

DISCUSSION

This randomised, double-blind, multicentre and multinational, parallel-group, prospective PLANETAS study assessed the PK equivalence and safety and efficacy comparability of multiple doses of CT-P13 (5 mg/kg) versus INX (5 mg/kg) administered up to week 30 in active AS patients.

The primary outcome, steady-state PK (AUC and Cmax,ss), was shown to be equivalent for CT-P13 and INX (90% CIs for the
mean AUC and C\text{max,ss} were 94–116% and 95–109%, respectively). These values were within the predefined margins for equivalence (80–125%), thereby satisfying the criteria set for PK equivalence of CT-P13 to INX. This predefined margin is considered appropriate from a clinical perspective because of the broad therapeutic window and high variability of INX.18,19 AUC and C\text{max,ss} were higher in the ADA-negative subset of patients in this study, versus values for the overall PK population. Published PK data for the 5mg/kg dose of INX in AS is sparse,20 but the values for AUC and C\text{max,ss} reported in this study are similar to those reported in previous studies of INX monotherapy using a similar dosing pattern in Crohn’s disease.21 The coadministration of methotrexate (MTX) is thought to increase concentrations of INX in patients with rheumatoid arthritis (RA).22–25 Although coadministration of MTX with INX in AS is not recommended,26 the effect of coadministration on CT-P13 should be further studied—especially in patients with peripheral arthritis. In patients with AS, the possible influence of ADA on circulating concentrations of INX, including the potential consequence, an impaired clinical response, has been studied but yielded conflicting results.26–28 Nevertheless, INX monotherapy remains a useful treatment for the majority of patients with AS, for which long-term data are available.29,30

The mean secondary PK endpoints were also highly similar between CT-P13 and INX groups. CT-P13 was also equivalent to INX up to week 30 in terms of efficacy as assessed by ASAS20/ASAS40 criteria. The median change from baseline in BASDAI, BASFI, BASMI, chest expansion and SF-36 score was highly similar at weeks 14 and 30, underlining the benefit of CT-P13 and INX in both physician-measured and patient-reported outcomes.

The efficacy outcomes of this trial were comparable to those reported previously in pivotal randomised controlled trials of INX in AS.3,2 The ASAS20 and ASAS40 responses at week 30 in this study for INX (72.4% and 47.4%, respectively) are similar to those reported at week 24 in the ASSERT trial (61.2% and 47.0%, respectively). The magnitude of improvements in secondary efficacy endpoints with INX in this trial were also comparable to those reported in ASSERT.2 Improvements from baseline to week 30 of the physical component of the SF-36 in the INX group in this study were comparable to those reported in ASSERT (8.5 vs 10.2, respectively), as were the median baseline scores of the physical component of the SF-36 (28.8 vs 33.1, respectively).2 However, the improvements from baseline to week 30 of the mental component of the SF-36 in this study were not seen in ASSERT (5.2 vs 2.7, respectively), likely reflecting the higher baseline median scores of the mental component of SF-36 in ASSERT (37.2 vs 47.6, respectively).2 ASDAS C was assessed in this study, and values were found to be highly similar between treatment groups at both weeks 14 and 30.31

---

**Table 3** Mean (CV) Serum pharmacokinetic parameters of INX: pharmacokinetic population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CT-P13 (N=113)</th>
<th>INX (N=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{max} (µg/ml)</td>
<td>n=109 155.8 (37.2)</td>
<td>n=107 145.3 (25.3)</td>
</tr>
<tr>
<td>C\text{min} (µg/ml)</td>
<td>n=109 29.1 (40.1)</td>
<td>n=108 29.8 (40.8)</td>
</tr>
<tr>
<td>T\text{max} (h)</td>
<td>n=109 2.0 (1.9, 3.2)</td>
<td>n=107 2.1 (2.0, 3.5)</td>
</tr>
</tbody>
</table>

---

T\text{max} was reported as median (minimum, maximum).

C\text{max} was set to missing if the concentration was below the lower limit of quantification or the same as other concentrations.

C\text{min} was set to missing if the concentration was below the lower limit of quantification or the same as other concentrations.

Swing

Mean residence time (h)

C\text{max,ss}, minimum concentration immediately before the next application at steady state; CV, coefficient of variation; INX, innovator infliximab; MRT, mean residence time; T1/2, terminal elimination half-life; Tmax, time to reach C\text{max}; Vss, volume of distribution at steady state.

---

Dose 1 (Week 0)

- C\text{max,ss} (µg/ml) n=109 155.8 (37.2)
- C\text{min,ss} (µg/ml) n=109 29.1 (40.1)
- T\text{max} (h) n=109 2.0 (1.9, 3.2)

Dose 2 (Week 2)

- C\text{max,ss} (µg/ml) n=112 175.6 (20.9)
- C\text{min,ss} (µg/ml) n=110 20.1 (56.1)
- T\text{max} (h) n=112 2.1 (1.8, 3.1)

Dose 3 (Week 6)

- C\text{max,ss} (µg/ml) n=113 172.3 (26.8)
- C\text{min,ss} (µg/ml) n=112 6.9 (80.2)
- T\text{max} (h) n=113 2.1 (2.0, 3.2)

Dose 4 (Week 14)

- C\text{max,ss} (µg/ml) n=113 158.4 (24.0)
- C\text{min,ss} (µg/ml) n=112 4.5 (83.6)
- T\text{max} (h) n=113 3.0 (2.0, 3.3)

Dose 5 (Week 22)

- C\text{max,ss} (µg/ml) n=111 26.0 (34.2)
- C\text{min,ss} (µg/ml) n=108 4.2 (139.5)
- Swing n=108 102.9 (108.1)

Degree of fluctuation

Mean residence time (h) n=103 353.7 (38.1) n=98 368.2 (37.3)

T\text{max} (h) n=113 3.0 (2.0, 3.3) n=110 2.1 (2.0, 3.2)

T\text{max} (h) n=112 2.1 (1.8, 3.1) n=108 2.2 (1.8, 3.2)

T\text{max} (h) n=110 2.1 (2.0, 3.2)

Mean residence time (h) n=103 3830.8 (30.8) n=98 4294.9 (78.3)

Swing

Degree of fluctuation

Mean residence time (h) n=110 3830.8 (30.8) n=98 4294.9 (78.3)

Swing

Mean residence time (h) n=110 3830.8 (30.8) n=98 4294.9 (78.3)

Swing

Mean residence time (h) n=110 3830.8 (30.8) n=98 4294.9 (78.3)
Comparison of ASAS20 and ASAS40 values for CT-P13 and INX by ADA status showed no statistical significance despite the observational difference in the ADA-positive subset, the latter probably due to the lack of patient numbers.

Overall, CT-P13 and INX were well-tolerated and their safety profiles were comparable. The majority of patients had negative immunogenicity results according to the electrochemiluminescent immunoassay method at weeks 14 and 30. Extra-articular manifestations such as uveitis, psoriasis and inflammatory bowel disease were not assessed in this study, but the single cases of uveitis and psoriasis observed were comparable. The majority of patients had negative tuberculin skin test and became positive subsequently. These cases were considered as an AE as patients were treated for the reasons related to latent TB.

### CONCLUSIONS
CT-P13 and INX were shown to be equivalent in terms of AUC and $C_{\text{max,ss}}$ in patients with active AS. Clinical efficacy endpoints, including ASAS20 and ASAS40 responses, were highly similar between CT-P13 and INX groups. CT-P13 was well-tolerated with an immunogenicity and safety profile comparable to that of INX up to week 30.

### Author affiliations
1Division of Rheumatology, Department of Internal Medicine, Inha University Hospital, Incheon, Republic of Korea
2Department of Rheumatology and Clinical Immunology, Poznan University of Medical Sciences, Poznań, Poland
3Department of Rheumatology and Connective Tissue Diseases, "NASZ LEKARZ." Praktyka Grupowa Lekarzy Rodzinnych z Przychodni, Toruń, Poland
4Section of Non-coronarogenic Myocardial Diseases and Clinical Rheumatology, National Scientific Center, Kiev, Ukraine
5Department of Family Medicine, Kyiv Regional Clinical Hospital, Kiev, Ukraine
6Rheumatology Department, Centro de Estudios Reumatológicos, Santiago, Chile
7Outpatient Clinic ORTO, Riga, Latvia
8Rheumatology Department, Antiguo Hospital Civil de Guadalajara, Guadalajara, Mexico
9Division of Rheumatology, Department of Internal Medicine, Kyung Hee University Hospital, Seoul, Republic of Korea
10Division of Biostatistics, Department of Internal Medicine, University of New Mexico, Albuquerque, New Mexico, USA
11Clinical Planning and Medical Affairs Department, CELLTRION, Inc, Incheon, Republic of Korea
12Division of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Republic of Korea
13Medical Director of Rheumazentrum Ruhrgebiet, a Medical Center specialised for rheumatic diseases, Rheumazentrum Ruhrgebiet, Herne, Germany

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### Contributors
WP, 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. DWK and IFL 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, SJ, VK, GL, PM, HM, SGU, MJL and YAL 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.

Ethics approval The protocol was reviewed and approved by each site's institutional review board or independent ethics committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data available for this paper are included in the manuscript and online supplementary appendices.

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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 EC₅₀ values of CT-P13 and INX were compared with the reference standard EC₅₀. *Relative neutralizing potency (%) of drug was calculated as a percentage of the reference standard EC₅₀. 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 AS according to the 1984 modified New York classification criteria [van der Linden et al 1984] for at least 3 months prior to Screening.
3. Patients had active disease as defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4 (range 0 to 10) at Screening in spite of following conventional treatment for AS for at least 3 months prior to Screening.
4. Patients had a visual analogue scale (VAS) score for spinal pain of ≥4 (range 0 to 10).
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/µL (SI [Système International d’Unités] units: ≥3.5 × 10^9/L)
   - Neutrophil count ≥1.5 × 10^3/µL (SI units: ≥1.5 × 10^9/L)
   - Platelet count ≥100 × 10^3/µL (SI units: ≥100 × 10^9/L)
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.

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.

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 AS.
2. Patients had total ankylosis of the spine, as defined by syndesmophytes present on the lateral views of spinal radiographs (cervical, thoracic, and lumbar) at all intervertebral levels from T6 to S1 within 3 months before Screening.
3. Patients had allergies to any of the excipients of infliximab or to any other murine and human proteins, and patients with a hypersensitivity to immunoglobulin product.
4. 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 had a positive result to the screening test for those infections.
5. 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.
6. Patients had recent exposure to persons with active TB, or had a positive result to the screening test for latent TB defined as a positive result of interferon-γ release assay with negative examination of chest x-ray, and 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 discussed with the medical monitor before randomization.
7. 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.

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

9. 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, RA, 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 American College of Rheumatology 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
   - Any other serious acute or chronic medical or psychiatric condition that might increase the risk associated with study participation or investigational product administration and that might interfere with the interpretation of study results

10. 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), including hydroxychloroquine, chloroquine, sulfasalazine, or methotrexate, 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 AS

11. 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.

12. 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.

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

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

Additional Study Details:

Sample size

- Sample size was determined by
  
  ▶ A total of 246 male and female patients will be enrolled in the study. Assuming a coefficient of variation (CV) of 50%, expected ratio of means equal to 1, 2-sided alpha equal to 0.1, power equal to 90%, and a 2-sided equivalence margin of 80% to 125% for AUC\textsubscript{r} and C\textsubscript{max,ss}, recruitment of 196 patients would be required. Allowing for a drop-out rate of 20% would mean that 246 patients would need to be randomized in total.

Randomisation

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

- The random allocation sequence was implemented using
  
  ▶ An interactive voice response system (IVRS) will be used for the randomization. Biostatistics will generate the randomization schedule for IVRS which will link sequential patient randomization numbers to treatment codes. The randomization will be stratified by region and baseline BASDAI score.

  ▶ The randomization 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 randomization 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 randomization code has been broken, the study can be considered open-label. While the study data are analyzed 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 (eg, 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 D.

Table S1. Protocol Violation: All-Randomised Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>CT-P13 (N=125)</th>
<th>INX (N=125)</th>
<th>Total (N=250)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%) of patients</td>
<td>Number (%) of patients</td>
<td>Number (%) of patients</td>
</tr>
<tr>
<td>Misrandomisations(^1)</td>
<td>1 (0.8)</td>
<td>3 (2.4)</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>Noncompliance with inclusion/exclusion criteria</td>
<td>3 (2.4)</td>
<td>2 (1.6)</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>Receipt of prohibited therapy</td>
<td>1 (0.8)</td>
<td>0 (0.0)</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

\(^1\) Misrandomisations defined as patients who received the opposite treatment to which they were assigned at any point during the study.
Appendix E.
Proportion of patients achieving ASAS responses (20% and 40%) with CT-P13 (5 mg/kg) or INX (5 mg/kg) at week 14 and week 30 in the all randomised population (CT-P13: N=125; INX: N=125).

Figure S2-1. ASAS20 rates at weeks 14 and 30

Figure S2-2. ASAS40 rates at weeks 14 and 30
### Table S2. ASAS20 and ASAS40 responses according to ADA status at week 30.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>N</th>
<th>(%)</th>
<th>Odds ratio [1]</th>
<th>95% CI of the odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADA positive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASAS20 CT-P13 5 mg/kg</td>
<td>14</td>
<td>28</td>
<td>50.0</td>
<td>0.47</td>
<td>(0.14, 1.53)</td>
</tr>
<tr>
<td>INX 5 mg/kg</td>
<td>17</td>
<td>26</td>
<td>65.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goodness-of-fit test (p-value 0.487) [2]</td>
<td>.</td>
<td>.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASAS40 CT-P13 5 mg/kg</td>
<td>12</td>
<td>28</td>
<td>42.9</td>
<td>1.45</td>
<td>(0.45, 4.70)</td>
</tr>
<tr>
<td>INX 5 mg/kg</td>
<td>10</td>
<td>26</td>
<td>38.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goodness-of-fit test (p-value 0.939) [2]</td>
<td>.</td>
<td>.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ADA negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASAS20 CT-P13 5 mg/kg</td>
<td>65</td>
<td>84</td>
<td>77.4</td>
<td>1.15</td>
<td>(0.57, 2.31)</td>
</tr>
<tr>
<td>INX 5 mg/kg</td>
<td>67</td>
<td>90</td>
<td>74.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goodness-of-fit test (p-value 0.488) [2]</td>
<td>.</td>
<td>.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASAS40 CT-P13 5 mg/kg</td>
<td>46</td>
<td>84</td>
<td>54.8</td>
<td>1.18</td>
<td>(0.65, 2.15)</td>
</tr>
<tr>
<td>INX 5 mg/kg</td>
<td>45</td>
<td>90</td>
<td>50.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goodness-of-fit test (p-value 0.93) [2]</td>
<td>.</td>
<td>.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

[1] The odds ratio was estimated using a logistic regression model with treatment as a fixed effect, and region and baseline BASDAI score as covariates. An odds ratio of >1 indicates an increased odds in favor of CT-P13 5mg/kg.

[2] The 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.
## Appendix G

### Table S3. Treatment-emergent serious adverse events, no (%)

<table>
<thead>
<tr>
<th>Event</th>
<th>CT-P13 5 mg/kg (N=128)</th>
<th>INX 5 mg/kg (N=122)</th>
<th>Total (N=250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>1 (0.8)</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>1 (0.8)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Oesophageal perforation</td>
<td>1 (0.8)*</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>0</td>
<td>2 (1.6)*</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>0</td>
<td>1 (0.8)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>0</td>
<td>1 (0.8)*</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Disseminated tuberculosis#</td>
<td>1 (0.8)*</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>0</td>
<td>1 (0.8)*</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1 (0.8)*</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>0</td>
<td>1 (0.8)*</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Vascular pseudoaneurysm</td>
<td>0</td>
<td>1 (0.8)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>1 (0.8)</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>1 (0.8)*</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

* indicate SAEs considered by the investigator to be related to the study treatment
# the baseline chest x-ray at screening of this patient showed “pneumofibrosis”. The patient had been registered with a TB centre during childhood following a positive tuberculin-skin-test, but without further details. Furthermore, the patient failed to disclose relevant previous TB history during recruitment.

Regardless of relationship with study drug, 6 cases and 8 cases were reported from the CT-P13 and INX group, respectively. Among them, 4 cases were related to study drug in the CT-P13 group; Tuberculosis, Disseminated tuberculosis, Oesophageal perforation and Dyspnoea and 5 cases were related to study drug in the INX group; 2 Infusion related reaction, Pulmonary tuberculosis, Cellulitis and Wound infection.