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ORIGINAL ARTICLE

Evaluation of the pharmacokinetic equivalence and 54-week efficacy and safety of CT-P13 and innovator infliximab in Japanese patients with rheumatoid arthritis

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Abstract

Objectives. To demonstrate the pharmacokinetic equivalence of CT-P13 and its innovator infliximab (IFX) in Japanese patients with rheumatoid arthritis (RA), and to compare the efficacy and safety of these drugs, administered for 54 weeks.

Methods. In a randomized, double-blind, parallel-group, multicenter study, 3 mg/kg of CT-P13 or IFX, in combination with methotrexate (MTX) (6–16 mg/week), was administered for 54 weeks to Japanese active RA patients with an inadequate response to MTX, to demonstrate the pharmacokinetic equivalence, based on the area under the curve (AUC_τ) (weeks 6–14) and C_{max} (week 6) of these drugs, and to compare their efficacy and safety.

Results. The CT-P13-to-IFX ratios (90% confidence intervals) of the geometric mean AUC_τ and C_{max} values in patients negative for antibodies to infliximab at week 14 were 111.62% (100.24–124.29%) and 104.09% (92.12–117.61%), respectively, demonstrating the pharmacokinetic equivalence of these drugs. In the full analysis set, CT-P13 and IFX showed comparable therapeutic effectiveness, as measured by the American College of Rheumatology, Disease Activity Score in 28 joints, the European League Against Rheumatism, and other efficacy criteria, at weeks 14 and 30. The incidence of adverse events was similar for these drugs.

Conclusion. CT-P13 and IFX, administered at a dose of 3 mg/kg in combination with MTX to active RA patients, were pharmacokinetically equivalent and comparable in efficacy and safety.

Keywords

Biosimilar, CT-P13, Infliximab, PK equivalence, Rheumatoid arthritis

History

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Introduction

Infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha (anti-TNF-α antibody), is a biotechnology-derived pharmaceutical that has brought about a dramatic change in rheumatoid arthritis (RA) treatment.

CT-P13 is a biosimilar (biotherapeutic product that is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product [1]) of innovator infliximab (IFX), developed by Celltrion, Inc. (Republic of Korea). This product was first approved in the Republic of Korea in July 2012, and is currently available in 26 countries, including the EU member states (as of September 22, 2014).

CT-P13 has been demonstrated to be comparable in terms of quality attributes to IFX, based on its primary and higher-order structure, microheterogeneity, biological activity, and impurities [2]. *In vitro* pharmacology studies comparing the biological activity of CT-P13 and IFX have demonstrated the pharmacological comparability of these drugs, in terms of binding affinity for TNF-α, neonatal Fc receptor and human complement protein (C1q), TNF-α-neutralizing effect, complement-dependent cytotoxicity, and apoptosis-inducing activity through reverse signaling.

Based on the results of the pilot phase I study in active RA patients—which was conducted in the Philippines to evaluate the preliminary pharmacokinetic (PK) profiles and to compare the efficacy and safety of CT-P13 and IFX, and represented the second study performed in Asia and the EU—the equivalence of the PK profiles of CT-P13 and IFX in patients with active ankylosing spondylitis was demonstrated (PLANETAS study) [3]. The phase III study included patients from the EU and Asia, excluding Japan, and enrolled 606 active RA patients and demonstrated the equivalence, in terms of clinical efficacy of CT-P13 (302 patients) and IFX (304 patients), when administered in combination with methotrexate (MTX) (PLANETRA study) [4].

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Since PK equivalence between CT-P13 and IFX had not heretofore been formally assessed in RA patients, the present study was planned with a primary objective of demonstrating the equivalence of the PK parameters of these drugs. Secondary objectives included comparisons of the efficacy and safety.

Patients and methods

Patient population

The study was conducted at 20 medical institutions across Japan, between October 2011 and June 2013, in active RA patients who had an inadequate response to MTX. Patients with active RA, according to the revised 1987 American College of Rheumatology (ACR) classification criteria [5] for ≥ 1 year prior to study entry, aged ≥ 20 years and ≤ 75 years were enrolled. Within 6 weeks prior to the start of the study treatment, patients were required to have ≥ 6 tender and ≥ 6 swollen joints and at least two of the following: morning stiffness lasting ≥ 45 min, erythrocyte sedimentation rate (ESR) ≥ 28 mm/h, and a serum C-reactive protein (CRP) concentration ≥ 2.0 mg/dL. Oral MTX therapy had to have continued for ≥ 12 weeks at 6–16 mg/week, with a stable dosage during the 4 weeks just prior to study drug administration.

Study design

This is a multicenter, randomized, double-blind, parallel-group study to demonstrate PK equivalence between CT-P13 and IFX; its reference infliximab product is approved in the EU.

Patients who were confirmed to be eligible for study entry based on the screening assessment were randomly assigned (1:1) to receive a 2-hour intravenous infusion of 3 mg/kg CT-P13 or IFX at weeks 0, 2, and 6, and each 8 weeks afterward up to week 54. A dynamic allocation procedure using the participating medical institutions and the CRP level stratified by baseline level (≤ 2 mg/dL and > 2 mg/dL) as allocation factors was employed. Throughout the study, MTX (stable dose of 6–16 mg/week administered 4 weeks prior to study enrollment should be maintained; oral dose) and folic acid (≤ 5 mg/week; oral dose) were coadministered.

To utilize the efficacy equivalence data and safety results from the PLANETRA study for the application in Japan, extrapolability of the PLANETRA study data to Japanese patients must be considered. We have therefore maintained the same conditions, including the inclusion and exclusion criteria, allocation factors, and administration schedule, as in the PLANETRA study.

This study was conducted in accordance with ethical principles derived from the Declaration of Helsinki, and in compliance with good clinical practice guidelines. The study protocol and informed consent form were reviewed and approved by the Institutional Review Board at each site. Written informed consent was obtained from all patients. This study was registered with the JAPIC Clinical Trials Information Center (http://www.clinicaltrials.jp/user/cteSearch_e.jsp) (JapicCTI-111620).

Pharmacokinetic assessments

The primary objective was to demonstrate PK equivalence between CT-P13 and IFX based on the primary endpoints, area under the curve (AUC_τ) (weeks 6–14) and C_{max} (week 6), and the secondary PK objective was to compare the following PK parameters between the drugs: peak serum concentration (C_{max}), average serum concentration (C_{av}), trough serum concentration (C_{min}), peak-to-trough fluctuation ratio (PTF), time to reach C_{max} (T_{max}), mean residence time (MRT), terminal elimination half-life ($T_{1/2}$), total clearance (CL), and distribution volume at steady state (V_{dss}).

Blood samples for PK analyses were collected immediately before dosing, at the end (± 15 minutes) of infusion, and at 1 hour (± 15 mins) after completion of infusion, at weeks 0, 2, 6, 14, 22, 30, 38, 46, and 54, and at one time point each at weeks 8 and 10, when the study drug was not scheduled to be administered.

Efficacy assessments

Efficacy endpoints were assessed at weeks 14, 30, and 54, and included the ACR 20%, 50%, and 70% response rates (ACR20, ACR50, and ACR70) [6,7], change from baseline in disease activity score using a 28-joint count (DAS28) [8], proportion of patients achieving moderate or good response according to the European League Against Rheumatism (EULAR) response criteria [9], simplified disease activity index (SDAI) [10], clinical disease activity index (CDAI) [11], and Health Assessment Questionnaire Disability Index (HAQ-DI) [12].

Safety assessments

Safety endpoints included adverse events (AEs), serious AEs (SAEs), vital signs (systolic and diastolic blood pressure while sitting, pulse rate, respiratory rate, and body temperature), physical findings, laboratory test results, infections (including tuberculosis), infusion reactions, antibodies to infliximab, proportion of patients whose interferon-gamma (INF-γ) release assay result became positive, and electrocardiogram findings; the results of these endpoints were compared between the CT-P13 and IFX groups.

Serum antidrug antibodies (ADAs) were measured using an electrochemiluminescent immunoassay method utilizing the Meso Scale Discovery platform (MSD, Rockville, Maryland, USA) and neutralizing activity of ADA was detected using Gyros assay at weeks 0, 14, 30, and 54, and at the end of the observation. Serum samples for ADA were collected before drug administration to avoid possible drug interference [4].

Statistical analysis

The sample size was determined in order to demonstrate the equivalence of AUC_τ (weeks 6–14) and C_{max} (week 6) between CT-P13 and IFX with appropriate precision. Based on the PK results of a phase II/III study using IFX coadministered with MTX and a phase II study using IFX alone, both conducted in Japan, the coefficients of variations of AUC_τ (weeks 6–14) and C_{max} (week 6) were assumed to be not more than 35%. Given a power of 80%, a two-sided significance level of 0.1, and an equivalence margin of 80% to 125%, at least 41 patients were required in each group. Allowing for a 20% dropout rate, total enrollment was set at 50 patients in each group (100 in total).

All patients who received at least one dose of either study drug were included in the safety analysis set. Efficacy analyses were performed on the full analysis set (FAS), which consisted of all patients who were eligible and received at least one dose of the study drug.

Among the FAS patients, those who received the study drug at weeks 0, 2, and 6, had both AUC_τ (weeks 6–14) and C_{max} (week 6) data, and had not experienced the development of antibodies to infliximab up to week 14 were included in the PK analysis set (anti-infliximab antibody-negative patients only), which was used for assessment of the primary endpoint (PK equivalence of CT-P13 and IFX).

CT-P13 and IFX were concluded to be pharmacokinetically equivalent if the 90% confidence interval (CI) for the ratios of the geometric mean AUC_τ (weeks 6–14) and C_{max} (week 6) values between the treatment groups were within an equivalence margin of 80–125% in the PK analysis set (anti-infliximab antibody-negative patients only). Additional analysis was performed on the FAS, including both anti-infliximab antibody-positive and -negative patients. All of the secondary PK endpoints were analyzed using the FAS.

Efficacy analyses were performed on the FAS. The treatment groups were compared using the Fisher's exact test for the ACR and EULAR response data, and the Student's *t*-test for the DAS28,

SDAI, CDAI, and HAQ-DI data. The non-responder imputation procedure was applied for patients who were withdrawn due to insufficient response or adverse reactions, whereby missing continuous data were imputed by baseline data. Missing data generated due to other reasons were imputed using the last observation carried forward method. All significance tests for efficacy were performed based on a significance level of 0.05.

Safety analyses were performed on the safety analysis set. All AEs that developed from the start of study treatment through the time point of assessment for the completion/discontinuation of study treatment (at 8 weeks ± 1 week after the last administration of study drug) were collected, and summarized by the number and percentage of patients experiencing each AE, as well as severity and relation to the study drug. For laboratory parameters, the changes from baseline were summarized using descriptive statistics. The development of antibodies to infliximab was represented as the proportion of antibody-positive patients.

Results

Patient disposition and disease characteristics

A total of 108 patients were enrolled and randomized into the CT-P13 group or the IFX group, and 104 (51 in the CT-P13 group and 53 in the IFX group) of these patients received study drug. Among these 104 patients, 3 (1 in the CT-P13 group and 2 in the IFX group) were found to have deviated from the inclusion criteria or matched the exclusion criteria (e.g., use of disease-modifying antirheumatic drugs other than MTX) after the study treatment was started. These 3 patients were excluded from the FAS for eligibility violations, but included in the safety analysis set. Accordingly, the FAS comprised 101 patients (50 in the CT-P13 group and 51 in the IFX group).

The PK analysis set (anti-infliximab antibody-negative patients only), which was used for the primary analysis, comprised 78 patients (39 each in the CT-P13 and IFX groups) from the FAS, excluding 5 patients (1 in the CT-P13 group and 4 in the IFX group) who had no PK parameter data for weeks 6–14 and 18 patients (10 in the CT-P13 group and 8 in the infliximab group) who had antibodies to IFX by week 14.

Nine patients (17.6%) in the CT-P13 group and 14 patients (26.4%) in the IFX group discontinued study treatment before week 62, when the safety data were finalized. The reasons for discontinuation included AEs [9 (17.6%) in the CT-P13 group and 6 (11.3%) in the IFX group], consent withdrawal [2 (3.8%) in the IFX group], protocol deviations [1 (1.9%) in the IFX group], insufficient response [4 (7.5%) in the IFX group], and poor compliance with MTX therapy [1 (1.9%) in the IFX group].

The baseline demographics in the FAS are shown in Table 1. The patient age [mean ± standard deviation (SD)] was 54.5 ± 13.0 years in the CT-P13 group and 53.8 ± 13.4 years in the IFX group, and body weight was 57.1 ± 10.9 kg and 53.4 ± 10.1 kg, with no significant differences between the groups. Both the CT-P13 and IFX groups contained more females (80.0% and 80.4%, respectively) than males. The duration of disease (mean ± SD) was similar, at 7.1 ± 7.3 years in the CT-P13 group and 8.0 ± 7.3 years in the IFX group.

The baseline demographics in the PK analysis set (anti-infliximab antibody-negative patients only) were also similar between groups (Supplementary Table 1 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2015.1022297).

According to the protocol, all patients had been treated with MTX prior to study entry. The initial and final doses of MTX administered during the study were similar in the CT-P13 and IFX groups, with initial doses (mean ± SD) of 9.7 ± 2.7 mg/week and 9.5 ± 2.8 mg/week, and final doses of 9.5 ± 3.0 mg/week and 9.0 ± 3.2 mg/week, respectively.

Table 1. Baseline patient demographics and disease characteristics—FAS.

Characteristics		CT-P13 (N = 50)	IFX (N = 51)
Age (years), mean ± SD		54.5 ± 13.0	53.8 ± 13.4
Gender (male/female), n (%)		10 (20.0)/40 (80.0)	10 (19.6)/41 (80.4)
Body weight (kg), mean ± SD		57.1 ± 10.9	53.4 ± 10.1
Duration of disease (years), mean ± SD		7.1 ± 7.3	8.0 ± 7.3
Dose of MTX at the first dose of study drug (mg/week), mean ± SD		9.7 ± 2.7	9.5 ± 2.8
Use of corticosteroids at baseline, n (%)		18 (36.0)	24 (47.1)
Dose of corticosteroids (mg/day as prednisolone equivalent), mean ± SD (n)		4.6 ± 1.9 (17)	4.8 ± 2.2 (24)
Anti-CCP antibody-positive, n (%)		42 (84.0)	48 (94.1)
Rheumatoid factor-positive, n (%)		43 (86.0)	45 (88.2)
CRP (mg/dL), mean ± SD		2.09 ± 1.55	2.27 ± 2.42
≤ 2 mg/dL, n (%)		29 (58.0)	29 (56.9)
> 2 mg/dL, n (%)		21 (42.0)	22 (43.1)
ESR (mm/h), mean ± SD		55.9 ± 28.0	54.6 ± 24.1
Steinbrocker class	Class I, n (%)	5 (10.0)	6 (11.8)
	Class II, n (%)	37 (74.0)	34 (66.7)
	Class III, n (%)	8 (16.0)	11 (21.6)
	Class IV, n (%)	0	0
Tender joint count (0–68), mean ± SD		14.7 ± 11.0	17.8 ± 12.3
Swollen joint count (0–66), mean ± SD		12.1 ± 7.6	12.8 ± 7.0
Patient's assessment of pain (VAS, 0–100), mean ± SD		52.7 ± 23.3	49.4 ± 22.3
Patient's global assessment of disease activity (VAS, 0–100), mean ± SD		55.0 ± 22.6	51.0 ± 23.1
Physician's global assessment of disease activity (VAS, 0–100), mean ± SD		56.1 ± 18.9	53.9 ± 18.2
DAS28 (ESR), mean ± SD		5.929 ± 1.005	6.104 ± 0.841
DAS28 (CRP), mean ± SD		5.190 ± 1.012	5.301 ± 0.900
SDAI, mean ± SD		31.43 ± 13.12	34.06 ± 10.91
CDAI, mean ± SD		29.34 ± 12.53	31.79 ± 10.19
HAQ-DI, mean ± SD		1.03 ± 0.67	1.12 ± 0.65

CCP cyclic citrullinated peptide, *CDAI* clinical disease activity index, *CRP* C-reactive protein, *DAS28 (CRP)* disease activity score using a 28-joint count and CRP level, *DAS28 (ESR)* disease activity score using a 28-joint count and ESR, *ESR* erythrocyte sedimentation rate, *FAS* full analysis set, *HAQ-DI* health assessment questionnaire disability index, *IFX* innovator infliximab, *MTX* methotrexate, *SDAI* simplified disease activity index, *VAS* visual analog scale.

The disease activity score of RA (mean ± SD), as evaluated by DAS28 (ESR), was 5.929 ± 1.005 in the CT-P13 group and 6.104 ± 0.841 in the IFX group, with no significant difference between the groups. The results of other disease activity endpoints were also generally similar for the groups.

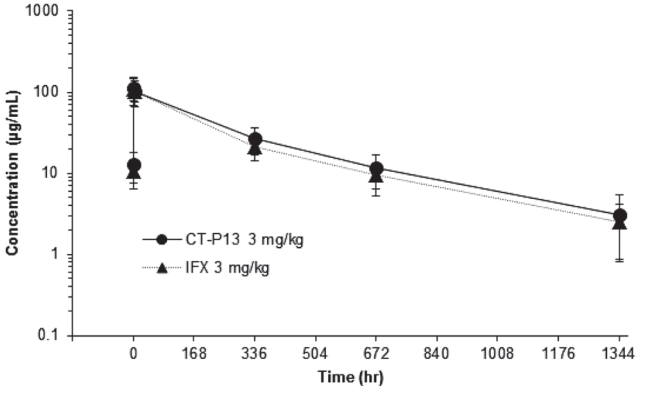
Pharmacokinetics

In the PK analysis set (anti-infliximab antibody-negative patients only), the CT-P13-to-IFX ratios (90% CIs) of the geometric mean AUC_τ (weeks 6–14) and C_{max} (week 6) values were 111.62% (100.24–124.29%) and 104.09% (92.12–117.61%), respectively, and the 90% CIs for both PK parameters were within the predefined equivalence margin of 80–125% (Figure 1). The PK equivalence of CT-P13 and IFX was also evaluated in 96 antibody-positive and -negative patients (49 in the CT-P13 group and 47 in the IFX group), excluding 5 patients with no PK data for weeks 6–14 (1 in the CT-P13 group and 4 in the IFX group) from the FAS, and both the 90% CIs of the ratios of geometric mean AUC_τ and C_{max} values fell inside the equivalence margin of 80–125% (Figure 2).

Other PK parameters (C_{max}, C_{AV}, C_{min}, PTF, T_{max}, MRT, $T_{1/2}$, CL, and V_{dss}) at weeks 6–14, which comprised the secondary endpoints, were similar in the CT-P13 and IFX groups (Supplementary Tables 2, 3 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2015.1022297). The serum infliximab concentrations up to week 54 are illustrated in Figure 3. The PK parameters (C_{max}, C_{av}, C_{min}, PTF, and T_{max}) appeared to remain stable from week 14 onward in both treatment groups, suggesting that a steady state was achieved by week 14. The proportion of patients whose serum trough concentration was 1 μg/mL or higher at each assessment point did not differ between the groups, except for that at week 54 (Table 2).

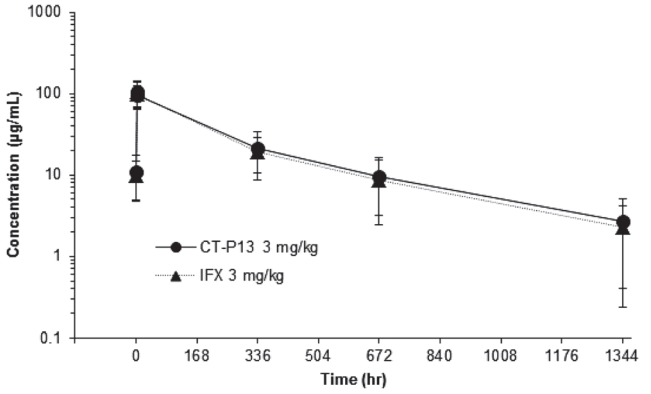
Clinical efficacy

The results of the efficacy endpoints in the FAS are shown in Table 3. The proportions of patients achieving ACR20 response in the CT-P13 and IFX groups were 74.0% (37/50 patients) and 70.6% (36/51 patients), at week 14, 78.0% (39/50 patients) and 64.7% (33/51 patients) at week 30, and 64.0% (32/50 patients) and 49.0% (25/51 patients) at week 54, respectively. There were no significant differences between the groups in the ACR20, ACR50, and ACR70 response rates at each assessment point, except for the ACR70 response rate at week 54. The proportion of EULAR (ESR and CRP) responders did not significantly differ between the groups at any of the assessment points. The improvements from baseline for other efficacy endpoints, including DAS28 (ESR and CRP), SDAI, CDAI, and HAQ-DI, were similar for the CT-P13 and IFX groups, except for those for DAS28 (CRP) and HAQ-DI at week 54.



Treatment group	n	Geometric mean	Ratio of the geometric means (%)	90% CI of the ratio (%)
AUC_τ (μg·hr/mL)				
CT-P13	39	27600	111.62	100.24 – 124.29
IFX	39	24700		
C_{max} (μg/mL)				
CT-P13	39	115	104.09	92.12 – 117.61
IFX	39	111		

Figure 1. PK equivalence between CT-P13 and IFX—pharmacokinetic analysis set (anti-infliximab antibody-negative patients only). Upper, Time course of mean (± SD) serum concentration of CT-P13 (closed circle) and IFX (closed triangle). Lower, PK parameters for PK equivalence. The CT-P13-to-IFX ratios of the geometric mean and their 90% CIs for AUC_τ (weeks 6–14) and C_{max} (week 6) values are shown.



Treatment group	n	Geometric mean	Ratio of the geometric means (%)	90% CI of the ratio (%)
AUC_τ (μg·hr/mL)				
CT-P13	49	21300	97.24	80.97 – 116.79
IFX	47	21900		
C_{max} (μg/mL)				
CT-P13	49	107	99.47	88.72 – 111.53
IFX	47	108		

Figure 2. PK equivalence between CT-P13 and IFX—FAS. Upper, Time course of mean (± SD) serum concentration of CT-P13 (closed circle) and IFX (closed triangle). Lower, PK parameters for PK equivalence. The CT-P13-to-IFX ratios of the geometric mean and their 90% CIs for AUC_τ (weeks 6–14) and C_{max} (week 6) values are shown.

Safety

Forty-five patients (88.2%) in the CT-P13 group and 46 patients (86.8%) in the IFX group reported at least one AE, and 43 patients (84.3%) in the CT-P13 group and 43 patients (81.1%) in the IFX group reported at least one adverse reaction. SAEs were reported in 8 patients (15.7%) in the CT-P13 group and 8 patients (15.1%) in

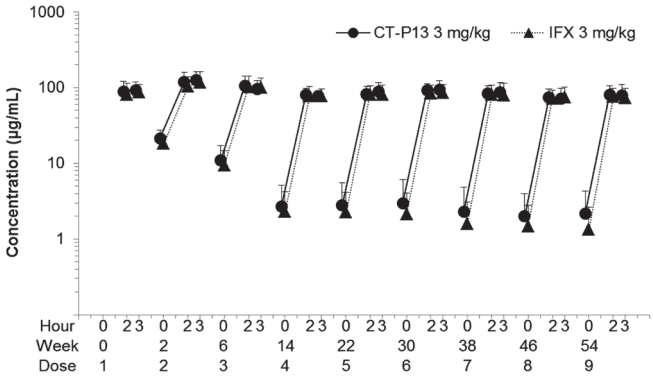


Figure 3. Mean (± SD) serum infliximab concentrations during a 54-week treatment with CT-P13 or IFX—FAS. Mean serum concentration of CT-P13 (closed circle) and IFX (closed triangle) following administration of doses 1–9.

Table 2. Proportions of patients with serum trough concentration of <1 μg/mL or ≥ 1 μg/mL—FAS.

Assessment point	CT-P13[a]			IFX[a]		
	n	<1 μg/mL	≥ 1 μg/mL	n	<1 μg/mL	≥ 1 μg/mL
week 2	49	0 (0.0)	49 (100.0)	50	0 (0.0)	50 (100.0)
week 6	49	4 (8.2)	45 (91.8)	50	2 (4.0)	48 (96.0)
week 14	49	16 (32.7)	33 (67.3)	47	15 (31.9)	32 (68.1)
week 22	45	15 (33.3)	30 (66.7)	44	18 (40.9)	26 (59.1)
week 30	44	14 (31.8)	30 (68.2)	42	18 (42.9)	24 (57.1)
week 38	41	16 (39.0)	25 (61.0)	40	20 (50.0)	20 (50.0)
week 46	42	21 (50.0)	21 (50.0)	39	21 (53.8)	18 (46.2)
week 54	41	16 (39.0)	25 (61.0)	38	21 (55.3)	17 (44.7)

IFX innovator infliximab, *FAS* full analysis set.
[a]Proportions of patient data are presented as n (%).

the IFX group, and infection-related SAEs were reported in 5 and 3 patients, respectively. Nine patients (17.6%) in the CT-P13 group and 6 patients (11.3%) in the IFX group discontinued study treatment due to AEs. Infusion-related reactions (including anaphylactic shock developing during infusion) occurred in 2 patients each in both groups, and infection-related AEs occurred in 4 patients in the CT-P13 group and 2 patients in the IFX group. There were no significant differences between the groups regarding the types and incidences of AEs, adverse reactions, SAEs/serious adverse reactions, and AEs/adverse reactions leading to the discontinuation of the study treatment (Table 4).

The AEs reported in $\geq 5\%$ of patients in either of the treatment groups are shown in Table 5. The common AEs were abnormal hepatic function [12 patients (23.5%) in the CT-P13 group and 16 patients (30.2%) in the IFX group], nasopharyngitis [10 patients (19.6%) and 13 patients (24.5%)], infusion-related reaction [7 patients (13.7%) and 7 patients (13.2%)], upper respiratory tract inflammation [7 patients (13.7%) and 2 patients (3.8%)], and eczema [2 patients (3.9%) and 6 patients (11.3%)]. There were no significant differences in the types and incidences of these AEs between the groups. The laboratory test results were generally similar for the groups.

Among the AEs that are not listed in Table 5, interstitial lung disease, which was reported in 1 patient each in both groups, and miscarriage, which was reported in 1 patient of the CT-P13 group, were considered to be clinically important.

Although the INF-γ release assay was positive in some patients, no development of tuberculosis was reported during the study. In addition, although anti-dsDNA antibodies were occasionally detected, none of the patients reported lupus or lupus-like syndrome.

Antibodies to infliximab occurred in 19.6% of patients in the CT-P13 group and 15.1% of patients in the IFX group at week 14, 25.5% and 26.4% at week 30, and 25.5% and 32.1% at week 54, respectively. The proportion of antibody-positive patients increased over time in both groups, and all of the antibody-positive patients had neutralizing antibodies.

Table 3. Changes over time in ACR response, disease activity, and physical performance assessment endpoints—FAS.

Endpoint	Assessment point	CT-P13[a] (N = 50)	IFX[a] (N = 51)	P value[b]
ACR20 response	14 W	37 (74.0)	36 (70.6)	0.825
	30 W	39 (78.0)	33 (64.7)	0.187
	54 W	32 (64.0)	25 (49.0)	0.161
ACR50 response	14 W	23 (46.0)	26 (51.0)	0.692
	30 W	27 (54.0)	24 (47.1)	0.553
	54 W	25 (50.0)	16 (31.4)	0.070
ACR70 response	14 W	14 (28.0)	12 (23.5)	0.654
	30 W	16 (32.0)	14 (27.5)	0.667
	54 W	21 (42.0)	7 (13.7)	0.002
EULAR responders (ESR)	14 W	42 (84.0)	42 (82.4)	1.000
	30 W	41 (82.0)	41 (80.4)	1.000
	54 W	36 (72.0)	34 (66.7)	0.667
EULAR responders (CRP)	14 W	42 (84.0)	41 (80.4)	0.796
	30 W	41 (82.0)	41 (80.4)	1.000
	54 W	38 (76.0)	32 (62.7)	0.196
Change from baseline in DAS28 (ESR)	14 W	-2.142 ± 1.494	-1.966 ± 1.232	0.519
	30 W	-2.142 ± 1.471	-1.961 ± 1.326	0.518
	54 W	-2.097 ± 1.691	-1.537 ± 1.368	0.071
Change from baseline in DAS28 (CRP)	14 W	-2.094 ± 1.495	-1.897 ± 1.184	0.466
	30 W	-2.080 ± 1.456	-1.955 ± 1.331	0.652
	54 W	-2.077 ± 1.650	-1.431 ± 1.346	0.033
Change from baseline in SDAI	14 W	-18.93 ± 14.36	-18.53 ± 12.20	0.880
	30 W	-18.67 ± 14.01	-18.06 ± 13.20	0.822
	54 W	-18.43 ± 15.77	-14.14 ± 12.24	0.131
Change from baseline in CDAI	14 W	-17.86 ± 13.35	-17.41 ± 11.71	0.859
	30 W	-17.55 ± 13.02	-17.08 ± 12.37	0.855
	54 W	-17.39 ± 14.82	-13.66 ± 11.51	0.162
Change from baseline in HAQ-DI	14 W	-0.36 ± 0.48	-0.33 ± 0.40	0.742
	30 W	-0.47 ± 0.51	-0.36 ± 0.47	0.254
	54 W	-0.54 ± 0.59	-0.25 ± 0.47	0.007

ACR American College of Rheumatology, *CDAI* clinical disease activity index, *CRP* C-reactive protein, *DAS28 (CRP)* disease activity score using a 28-joint count and CRP level, *DAS28 (ESR)* disease activity score using a 28-joint count and ESR, *ESR* erythrocyte sedimentation rate, *EULAR* European League Against Rheumatism, *FAS* full analysis set, *HAQ-DI* health assessment questionnaire disability index, *IFX* innovator infliximab, *SDAI* simplified disease activity index.
[a]Clinical efficacy data are presented as n (%) or mean ± SD.
[b]Fischer's exact test for ACR responses and EULAR responders; Student's *t*-test for DAS28, SDAI, CDAI, and HAQ-DI.

Table 4. Adverse events—safety analysis set.

Adverse events	CT-P13 (N = 51) Adverse event n (%)	CT-P13 (N = 51) Adverse reaction n (%)	IFX (N = 53) Adverse event n (%)	IFX (N = 53) Adverse reaction n (%)
Any adverse event/adverse reaction	45 (88.2)	43 (84.3)	46 (86.8)	43 (81.1)
Serious adverse events/adverse reactions				
	8 (15.7)	7 (13.7)	8 (15.1)	6 (11.3)
Anemia			1 (1.9)[b]	
Large intestinal ulcer			1 (1.9)	1 (1.9)
Anaphylactic shock			1 (1.9)	1 (1.9)
Acute tonsillitis	1 (2.0)	1 (2.0)		
Pneumonia			2 (3.8)	2 (3.8)
Chlamydial pneumonia	1 (2.0)[a]	1 (2.0)[a]		
Sinusitis	1 (2.0)	1 (2.0)		
Urinary tract infection	1 (2.0)	1 (2.0)		
Listeria sepsis			1 (1.9)[b]	1 (1.9)[b]
Pneumocystis jiroveci pneumonia	1 (2.0)	1 (2.0)	1 (1.9)[b]	1 (1.9)[b]
Road traffic accident	1 (2.0)			
Infusion-related reaction	1 (2.0)	1 (2.0)		
Dehydration			1 (1.9)	
Miscarriage	1 (2.0)	1 (2.0)		
Cervical dysplasia			1 (1.9)	1 (1.9)
Interstitial lung disease	1 (2.0)[a]	1 (2.0)[a]	1 (1.9)[b]	1 (1.9)[b]
Cataract operation			1 (1.9)	
Adverse events/adverse reactions leading to study discontinuation				
	9 (17.6)	7 (13.7)	6 (11.3)	6 (11.3)
Anemia			1 (1.9)[b]	
Anaphylactic shock			1 (1.9)	1 (1.9)
Acute tonsillitis	1 (2.0)	1 (2.0)		
Pneumonia			1 (1.9)	1 (1.9)
Chlamydial pneumonia	1 (2.0)[a]	1 (2.0)[a]		
Urinary tract infection	1 (2.0)	1 (2.0)		
Listeria sepsis			1 (1.9)[b]	1 (1.9)[b]
P. jiroveci pneumonia	1 (2.0)	1 (2.0)	1 (1.9)[b]	1 (1.9)[b]
Infusion-related reaction	2 (3.9)	2 (3.9)	1 (1.9)	1 (1.9)
Rheumatoid arthritis	2 (3.9)			
Miscarriage	1 (2.0)	1 (2.0)		
Cervical dysplasia			1 (1.9)	1 (1.9)
Interstitial lung disease	1 (2.0)[a]	1 (2.0)[a]	1 (1.9)[b]	1 (1.9)[b]
Rash	1 (2.0)[a]	1 (2.0)[a]	1 (1.9)	1 (1.9)

[a]and [b]: developed in the same patient

Table 5. Adverse events reported in at least 5% of patients in either of the treatment groups—safety analysis set.

Adverse events	CT-P13 (N = 51) Total n (%)		Severity Mild	Moderate	Severe	IFX (N = 53) Total n (%)		Severity Mild	Moderate	Severe
Any adverse event	45	(88.2)				46	(86.8)			
Nausea	2	(3.9)	2			3	(5.7)	3		
Diarrhea	1	(2.0)	1			3	(5.7)	3		
Dental caries	3	(5.9)	3							
Influenza	3	(5.9)	1	2		2	(3.8)	2		
Pharyngitis	4	(7.8)	4			3	(5.7)	3		
Bronchitis	3	(5.9)	3			3	(5.7)	3		
Oral herpes	3	(5.9)	3			1	(1.9)	1		
Herpes zoster	3	(5.9)	3			1	(1.9)	1		
Pneumonia[a]	2	(3.9)			2	4	(7.5)	1		3
Nasopharyngitis	10	(19.6)	10			13	(24.5)	13		
Sinusitis	3	(5.9)	2	1						
Cystitis	3	(5.9)	3			2	(3.8)	2		
Upper respiratory tract inflammation	7	(13.7)	7			2	(3.8)	2		
Infusion-related reaction	7	(13.7)	5	2		7	(13.2)[b]	4	2	1[b]
Eczema	2	(3.9)	2			6	(11.3)	6		
Rash	5	(9.8)	3	2		5	(9.4)	5		
Hepatic function abnormal[c]	12	(23.5)	11	1		16	(30.2)	13	3	
Blood beta-D-glucan increased	3	(5.9)	3			3	(5.7)	2	1	

[a]Includes pneumonia, *P. jiroveci* pneumonia, and chlamydial pneumonia.
[b]Includes a patient experiencing anaphylactic shock during the infusion of the study drug.
[c]Includes hepatic function abnormal, liver disorder, ALT increased, AST increased, gamma GTP increased, liver function test abnormal, and hepatic enzyme increased.

Discussion

The primary endpoints, AUC_τ (weeks 6–14) and C_{max} (week 6), were demonstrated to be equivalent between CT-P13 and IFX, based on the fact that the 90% CIs for the geometric mean ratios of these PK parameters were within the equivalence margin of 80–125%. This is the first clinical study to demonstrate the PK equivalence of CT-P13 and IFX, when coadministered with MTX to RA patients. In the PLANETAS study, CT-P13 was shown to exhibit steady-state (weeks 22–30) PK characteristics equivalent to those of IFX in non-Japanese patients with ankylosing spondylitis [3].

Since anti-drug antibodies are less frequently measured during treatment in clinical settings, additional analysis was performed on the FAS, including both anti-infliximab antibody-positive and -negative patients. Although the geometric mean AUC_τ and C_{max} values in the FAS were lower than those in the PK analysis set (anti-infliximab antibody-negative patients only), these parameters were also equivalent for CT-P13 and IFX in the FAS. The lower values of AUC_τ and C_{max} observed in the FAS are consistent with a report that the serum IFX concentrations in patients who became positive for antibodies to infliximab during treatment with infliximab were lower than those who were negative [13].

The PK parameters (C_{max}, C_{av}, C_{min}, PTF, and T_{max}) appeared to remain stable from week 14 onward in both the treatment groups, suggesting that a steady state was achieved by week 14. Similar findings were reported in the ATTRACT study, in which the serum drug concentration was kept constant from pre-dose at week 14 to week 54 [14].

It has been reported that serum trough concentrations of IFX following the administration of infliximab should be higher than the threshold level of 1 μg/mL to achieve sufficient clinical outcomes [15,16]. The proportion of patients whose serum trough concentrations were 1 μg/mL or higher was similar in the CT-P13 and IFX groups, indicating that these drugs would produce therapeutic effects of similar magnitudes.

The efficacy equivalence of CT-P13 to IFX in RA patients has been demonstrated in a phase III clinical study (PLANETRA study), which reported an ACR20 response rate at week 30 of 60.9% in the CT-P13 group compared with 58.6% in the IFX group (intention-to-treat population) [4]. Similarly, in the present study, both CT-P13 and IFX showed excellent therapeutic effects, with ACR20 response rates at week 30 of 78.0% and 64.7%, respectively. Since MTX dose was the principal difference between the PLANETRA study (15.6 mg/week in the CT-P13 and IFX groups) and the current study (9.7 mg/week in the CT-P13 group and 9.5 mg/week in the IFX group), it is difficult to compare clinical efficacy between these studies. A clinical study of adalimumab coadministered with MTX in early RA patients (CONCERTO study) showed that the serum trough concentration of adalimumab, the incidence of antibodies to adalimumab, and clinical efficacy did not significantly differ between 10 mg/week and 20 mg/week doses of MTX [17]. These results suggest that the difference in the dose of MTX (10 mg/week and 20 mg/week) may be less likely to influence the PK/pharmacodynamic (PD) of antibody drugs. Although the MTX doses coadministered with CT-P13 or IFX differed between the PLANETRA study and this study, the range of MTX doses were approximately 10–20 mg/week. Similar PK/PD profiles were shown using these antibody drugs, indicating possible efficacy equivalence. Indeed, the efficacy of the drug in this study was generally consistent with that of the PLANETRA study. Thus, extrapolation of the data on the efficacy equivalence of CT-P13 and IFX generated from non-Japanese patients in the PLANETRA study to Japanese patients is considered to be possible.

CT-P13 showed a safety profile comparable to that of IFX. Accordingly, when using CT-P13, careful attention should be given to the occurrence of adverse reactions, such as infections and infusion-related reactions, which have been reported in association with treatment with IFX treatment. An extension study to evaluate the long-term safety and efficacy of CT-P13 (up to 158 weeks), as well as the safety and efficacy of CT-P13 following a switch from IFX, is ongoing. Postmarketing surveillance is important to further accumulate CT-P13 safety information, since CT-P13 is the first antibody biosimilar launched in Japan.

In conclusion, CT-P13 was demonstrated to be pharmacokinetically equivalent to IFX, and CT-P13 administered for 54 weeks was comparable in terms of efficacy and safety to IFX in Japanese RA patients. The efficacy equivalence between these drugs has already been demonstrated in the PLANETRA study. The results of this study, together with that of the PLANETRA study, support the conclusion that CT-P13, when coadministered with MTX, will produce clinical benefits equivalent or comparable to IFX.

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Conflict of interest

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Supplementary material available online

Supplementary Tables 1, 2, and 3.