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ORIGINAL RESEARCH ARTICLE

Efficacy and Safety of Biosimilar CT-P47 Versus Reference Tocilizumab: 1-Year Results of a Randomised, Active-Controlled, Double-Blind, Phase III Study in Patients with Rheumatoid Arthritis

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Abstract

Background and Objective This phase III study conducted in 22 centres in Poland assessed the efficacy equivalence of candidate tocilizumab biosimilar, CT-P47, and European Union-approved reference tocilizumab (r-TCZ) in rheumatoid arthritis. We report 1-year data, including switching from r-TCZ to CT-P47.

Methods This active-controlled, double-blind, multicentre trial randomised (1:1) adults (aged 18–75 years) with moderate-to-severe rheumatoid arthritis diagnosed for ≥ 24 weeks and treated with methotrexate for ≥ 12 weeks before the first study drug administration, to receive CT-P47 or r-TCZ every 4 weeks (8 mg/kg, intravenous) up to week 20. At week 24, those on CT-P47 continued maintenance treatment; those on r-TCZ were re-randomised (1:1) to continue r-TCZ (r-TCZ maintenance) or to switch to CT-P47 (CT-P47 switched) until week 48 (Treatment Period 2). After week 48, patients were followed up until week 52 (end of study). Efficacy, pharmacokinetics, safety and immunogenicity were evaluated.

Results In Treatment Period 2, 225 patients continued CT-P47 maintenance, 109 continued r-TCZ maintenance and 110 switched to CT-P47. During Treatment Period 2, efficacy findings were comparable between groups. At week 52, the mean change from baseline in Disease Activity Score in 28 joints-erythrocyte sedimentation rate was − 4.279, − 4.231 and − 4.376 in the CT-P47 maintenance, r-TCZ maintenance and CT-P47 switched groups, respectively. Joint damage progression over 1 year was minimal in all groups. Drug serum concentrations were relatively consistent throughout Treatment Period 2. The safety profile and antidrug antibody-positive conversion rate (< 5% in each group) were similar between groups.

Conclusions Week 52 results show maintained efficacy after switching from r-TCZ to CT-P47, and comparable efficacy, pharmacokinetics, safety and immunogenicity of CT-P47 versus r-TCZ over 1 year of treatment.

Clinical Trial Registration NCT05489224, 24 July 2022.

1 Introduction

Overproduction of the proinflammatory cytokine interleukin-6 (IL-6) is implicated in the pathogenesis of a number of autoimmune diseases, including rheumatoid arthritis (RA), in which IL-6 plays a pivotal role [1–3]. This pivotal role is confirmed by the clear long-term efficacy of the biologic disease-modifying antirheumatic drug tocilizumab, demonstrated over 4.5 years and six clinical trials [4].

Tocilizumab inhibits IL-6-mediated signalling by binding to both membrane and soluble forms of the IL-6 receptor [1]. This biologic agent is approved by various regulatory authorities, including the European Medicines Agency and the US Food and Drug Administration for indications including RA, giant cell arteritis and, in the USA only, systemic sclerosis-associated interstitial lung disease [5, 6]. As with many biologics, biosimilar agents are under evaluation. Biosimilars can reduce the costs associated with biologic disease-modifying antirheumatic drug therapy and their use

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Key Points

The candidate tocilizumab biosimilar, CT-P47, has previously been demonstrated to have equivalent efficacy to reference tocilizumab in a phase III study in patients with rheumatoid arthritis.

Here, we present 1-year data from the same phase III study, including from patients who switched from reference tocilizumab to CT-P47.

These week 52 data provide further supporting evidence for the equivalent efficacy and comparable pharmacokinetics, safety and immunogenicity of CT-P47 and reference tocilizumab. Additionally, the data demonstrate comparable outcomes after the switch from the reference agent to CT-P47, as shown in the primary analysis.

has long been encouraged by the European League Against Rheumatism (EULAR) [7]. However, long-term studies of biosimilars are relatively rare.

To date, two tocilizumab biosimilars have been approved [8–10]. The candidate tocilizumab biosimilar CT-P47 is in development, and has been examined in four randomised controlled trials [11–15]. As previously reported, efficacy equivalence of CT-P47 and reference tocilizumab (r-TCZ) was demonstrated in a randomised, active-controlled, double-blind, multicentre, phase III trial [15]. Efficacy equivalence was determined via evaluation of dual primary endpoints (for regulatory purposes) in the mean change from baseline in Disease Activity Score in 28 joints (DAS28-erythrocyte sedimentation rate [ESR]) at week 12 and at week 24. CT-P47 and r-TCZ were also found to be comparable with respect to secondary efficacy endpoints, pharmacokinetics (PK), safety and immunogenicity, up to week 32 [15].

Here, we present 1-year findings from this trial, with a particular focus on the results of a 'switching' treatment period. Efficacy, PK, safety and immunogenicity findings are reported from week 24 until the end of the study at week 52.

2 Methods

2.1 Study Design

This was a randomised, active-controlled, double-blind, multicentre, phase III study involving 22 study centres in Poland (NCT05489224) [15]. The study design has been reported previously (Fig. S1 of the Electronic Supplementary Material [ESM]) [15]. In brief, the study comprised two treatment periods. In Treatment Period 1 (TP1), spanning from week 0 (day 1) to pre-dose on week 24, eligible patients were randomised 1:1 (on day 1) to receive CT-P47 or r-TCZ every 4 weeks (Q4W) until week 20. In Treatment Period 2 (TP2), extending from the end of TP1 until the last visit prior to week 52 (end of study [EOS]), patients in the CT-P47 group continued on CT-P47 (CT-P47 maintenance) Q4W to week 48. Those in the r-TCZ group were re-randomised (1:1) prior to dosing at week 24, to either continue on r-TCZ (r-TCZ maintenance) or switch to CT-P47 (CT-P47 switched) Q4W until week 48.

Patients received 8 mg/kg of the study drug diluted with sodium chloride and given as an intravenous infusion over 1 h (±15 minutes), co-administered with methotrexate (MTX; 10–25 mg/week; oral or parenteral) and folic acid (≥ 5 mg/week; oral). On development of laboratory abnormalities in liver enzymes (aspartate aminotransferase and/or alanine aminotransferase), absolute neutrophil or platelet counts, serious or opportunistic infection, or sepsis, study drug and/or MTX dosing was to be modified or stopped until evaluation and control of the clinical situation, per study protocol and the r-TCZ label [5, 6].

Randomisation was carried out using an interactive web response system, and blinding was performed as previously described [15]. The first randomisation (day 1) was stratified by body weight (< 100 kg vs ≥ 100 kg), DAS28-ESR at screening (> 5.1 vs ≤ 5.1) and prior use of biologics approved for RA (yes vs no). The second randomisation (prior to dosing at week 24) was stratified by DAS28-ESR at week 20 (< 2.6 vs ≥ 2.6). Ethical obligations were fulfilled and written informed consent was obtained from all patients prior to enrolment, as described previously [15].

2.2 Patients

Briefly, patients eligible for the study were adults aged 18–75 years with moderate-to-severe RA diagnosed ≥ 24 weeks and treated with MTX for ≥ 12 weeks (stable dose and route of administration for ≥ 8 weeks) before the first study drug administration [15]. Key exclusion criteria were prior treatment with an investigational or licenced targeted disease-modifying antirheumatic drug for RA and/or an IL-6 inhibitor for any purpose; prior treatment with more than one biologic approved for RA; allergies to any study drug excipients or other murine or human proteins; and hypersensitivity to immunoglobulin products [15].

2.3 Study Endpoints and Assessments

Efficacy endpoints, PK, safety and immunogenicity of CT-P47 during TP2 are reported in this article, with a particular focus on the switch from r-TCZ to CT-P47. Efficacy

endpoints included changes from baseline in DAS28-ESR, DAS28-C-reactive protein (CRP), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), individual components of DAS28, the SDAI, CDAI and American College of Rheumatology (ACR) assessment, modified total Sharp score, Health Assessment Questionnaire estimate of physical ability, and 36-item Short Form Health Survey (SF-36) physical and mental component scores; and the proportion of patients achieving 20%, 50% or 70% improvement by ACR criteria (ACR20, ACR50 and ACR70, respectively). Baseline was defined in terms of the last non-missing value before the first study drug administration (week 0, which is in line with EULAR recommendations [16]). Post hoc efficacy endpoints evaluated DAS28-ESR < 2.6 and low disease activity (LDA; $2.6 \leq x \leq 3.2$), ACR-EULAR index-based (SDAI and CDAI) remission (SDAI: $x \leq 3.3$; CDAI: $x \leq 2.8$) and LDA (SDAI: $3.3 < x \leq 11.0$; CDAI: $2.8 < x \leq 10.0$), and ACR/EULAR Boolean-based remission (Boolean 2.0) [17]; DAS28-ESR by prior biologic status was also assessed. PK sampling and determination of serum tocilizumab concentrations were as previously described [15].

Safety assessments included treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events, treatment-emergent adverse events of special interest (TEAESIs), clinical laboratory testing and soluble IL-6 (sIL-6) [15]. TEAESIs comprised infection, hypersensitivity including anaphylaxis, hepatic event, haemorrhage, gastrointestinal perforation, malignancy and demyelinating disorder [15]. TEAEs were coded using the *Medical Dictionary for Regulatory Activities* (version 26.0) and graded for intensity per the *Common Terminology Criteria for Adverse Events* (version 5.0) [15]. Immunogenicity assessments comprised antidrug antibody (ADA)-positive conversion incidence (patients who did not have any ADA-positive results in TP1 but had at least one ADA-positive result in TP2) and titre, and neutralising antibody incidence, in pre-dose blood samples [15]. Post hoc analyses were conducted of tocilizumab serum concentrations by post-treatment ADA status, with ADA positive defined as at least one positive measurement of ADA.

The dual primary endpoints of TP1 (mean change from baseline in DAS28-ESR at week 12 and at week 24) have been reported previously, together with additional efficacy endpoints for TP1 and up to week 32 of TP2, as well as complete information on study assessments [15].

2.4 Statistical Analysis

The sample size and statistical testing for the primary endpoint were previously described [15]. Analysis sets for the present analyses included intent-to-treat (ITT), which comprised all patients randomised at day 1; ITT in TP2 (ITT-TP2), which comprised all patients in the ITT set who entered TP2; the PK-TP2 set, which comprised all patients randomised, administered at least one full dose of study drug and from whom at least one post-treatment PK sample was taken during TP2 (at or after week 24 treatment); and the safety-TP2 set, which comprised all randomised patients who received a full or partial dose of the study drug during TP2. All statistical analyses were performed using Statistical Analysis System (SAS) software (version 9.4; SAS Institute Inc., Cary, NC, USA).

3 Results

3.1 Patient Disposition

The first patient was randomised on 14 September 2022 and the last patient's EOS visit was on 23 November 2023. Of 471 initially randomised patients, 444 completed TP1, and all of these entered TP2, being randomly assigned to CT-P47 maintenance ($n = 225$), r-TCZ maintenance ($n = 109$) or CT-P47 switched ($n = 110$) treatment groups (Fig. 1). During TP2, a total of 31 patients discontinued the study drug; 14 (6.2%), 9 (8.3%) and 8 (7.3%) in the CT-P47 maintenance, r-TCZ maintenance and CT-P47 switched groups, respectively. This was most frequently because of adverse events (Fig. 1).

Patient demographics and baseline characteristics were comparable between treatment groups (Table 1). Briefly, the median (range) age for the ITT-TP2 subset was 56.5 (20–73) years. Most patients were female, weighed < 100 kg, had a high DAS28-ESR (> 5.1) and had received no prior biologic treatment for RA. Across treatment groups, DAS28-ESR at baseline was comparable between subgroups of patients with and without prior biologic treatment (Table S1 of the ESM). Mean [standard deviation] doses (mg/week) of MTX were comparable between treatment groups at the first drug administration in TP2 (CT-P47 maintenance: 17.48 [6.68]; r-TCZ maintenance: 17.13 [6.82]; CT-P47 switched: 17.91 [6.30]).

3.2 Efficacy

The secondary efficacy endpoints were generally maintained in TP2 and were comparable across the three treatment groups. During TP2, this included comparable results between CT-P47 maintenance, r-TCZ maintenance and CT-P47 switched groups for the mean change from baseline in DAS28-ESR, DAS28-CRP, SDAI, CDAI, ACR20, ACR50 and ACR70 (Fig. 2). At week 52, the mean change from baseline in DAS28-ESR was − 4.279, − 4.231 and − 4.376 in the CT-P47 maintenance, r-TCZ maintenance and

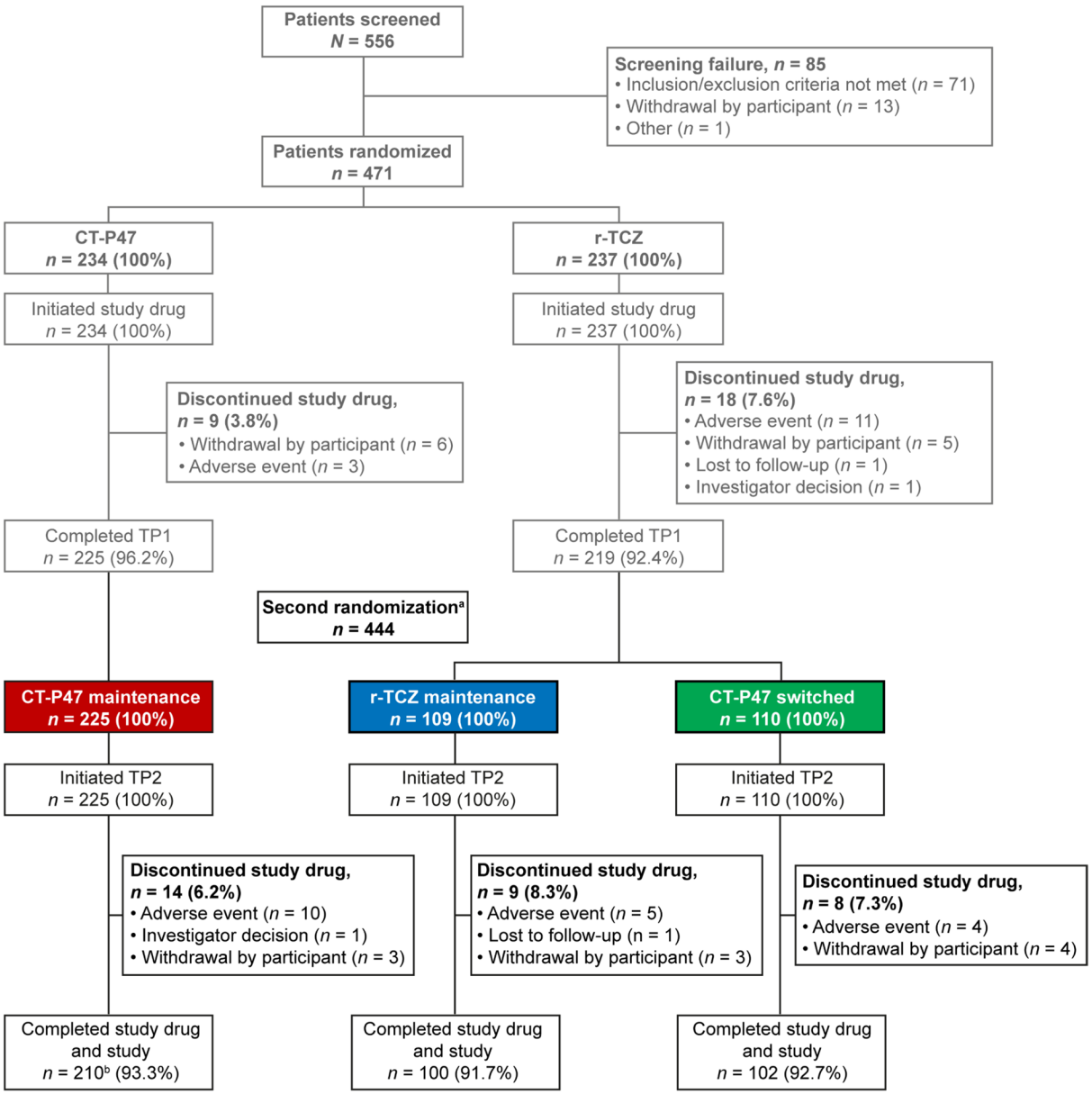

Fig. 1 Patient disposition (intent-to-treat set and intent-to-treat in Treatment Period 2 subset). [a]Prior to dosing at week 24, all patients underwent a second randomisation process. Patients who were initially randomised to reference tocilizumab (r-TCZ) were randomised (1:1) to either continue with r-TCZ (r-TCZ maintenance) or switch to CT-P47 (CT-P47 switched) every 4 weeks until week 48. Patients who were initially randomised to CT-P47 were to continue treatment with CT-P47 every 4 weeks until week 48. After week 48, all patients were followed up until week 52 (end of study). [b]One patient in the CT-P47 maintenance group is not included as the patient completed the study drug and then terminated the study. *TP1* Treatment Period 1, *TP2* Treatment Period 2

CT-P47 switched groups, respectively (Fig. 2). At week 52, the mean change from baseline in DAS28 component swollen joint count and tender joint count, Patient Global Assessment, Physician Global Assessment, Health Assessment Questionnaire estimate of physical ability, SF-36 (physical component score and mental component score), CRP and ESR were similar across all groups (Table 2).

Post hoc efficacy analyses showed that during TP2, rates of DAS28-ESR < 2.6 (Fig. 3a), ACR-EULAR index-based (SDAI and CDAI) remission rates (Fig. 3b, c) and ACR/EULAR Boolean-based remission (Boolean 2.0) rates (Fig. 3d) were generally comparable between the groups. Improvements from baseline in DAS28-ESR during TP2 were similar between the CT-P47 maintenance,

Table 1 Demographics and baseline characteristics (ITT-TP2 subset)

Parameter	CT-P47 maintenance ($n = 225$)	r-TCZ maintenance ($n = 109$)	CT-P47 switched ($n = 110$)
Age (years), median (range)	57.0 (20–73)	57.0 (27–73)	54.0 (22–73)
Sex, *n* (%)			
Male	49 (21.8)	35 (32.1)	21 (19.1)
Female	176 (78.2)	74 (67.9)	89 (80.9)
Race, *n* (%)			
White	225 (100)	109 (100)	110 (100)
Ethnicity, *n* (%)			
Hispanic or Latino	6 (2.7)	3 (2.8)	1 (0.9)
Non-Hispanic or non-Latino	219 (97.3)	106 (97.2)	109 (99.1)
Body weight (kg)[a], mean (SD)	76.70 (16.943)	75.85 (18.037)	75.48 (18.342)
Body weight ≥ 100 kg[b], *n* (%)	25 (11.1)	14 (12.8)	12 (10.9)
Prior biologic use approved for RA treatment, *n* (%)			
Yes	55 (24.4)	25 (22.9)	33 (30.0)
No	170 (75.6)	84 (77.1)	77 (70.0)
DAS28-ESR[b], mean (SD)	6.4 (0.61)	6.4 (0.71)	6.4 (0.70)
DAS28-ESR > 5.1[a], *n* (%)	220 (97.8)	108 (99.1)	105 (95.5)
SDAI, mean (SD)	39.1 (9.29)	38.6 (11.31)	38.2 (10.40)
CDAI, mean (SD)	38.1 (8.74)	37.6 (10.72)	37.2 (10.21)
SJC, mean (SD)	12.9 (5.50)	13.4 (6.32)	13.4 (6.04)
TJC, mean (SD)	19.5 (9.31)	19.2 (10.01)	18.8 (9.36)
mTSS, mean (SD)	31.2 (47.02)	36.1 (56.19)	35.7 (47.10)
CRP (mg/L), mean (SD)	9.9 (16.39)	10.0 (14.01)	9.1 (12.31)
ESR (mm/h), mean (SD)	38.3 (14.05)	39.4 (15.11)	38.2 (12.50)
PtGA score (VAS [mm]), mean (SD)	71.1 (14.47)	70.7 (15.50)	70.5 (13.48)
PGA score (VAS [mm]), mean (SD)	70.7 (12.38)	70.6 (12.72)	68.2 (12.35)
HAQ estimate of physical ability, mean (SD)	1.5 (0.48)	1.4 (0.47)	1.4 (0.52)
SF-36 PCS, mean (SD)	34.9 (5.59)	34.9 (5.91)	35.3 (5.79)
SF-36 MCS, mean (SD)	38.7 (9.19)	38.8 (10.14)	39.4 (9.85)
sIL-6R (ng/mL), mean (SD)	32.7 (9.93)	33.6 (13.02)	32.9 (11.24)

CDAI Clinical Disease Activity Index, *DAS28* Disease Activity Score in 28 joints, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *HAQ* Health Assessment Questionnaire, *ITT-TP2* intent-to-treat in Treatment Period 2, *MCS* mental component score, *mTSS* modified total Sharp score, *PCS* physical component score, *PGA* Physician Global Assessment, *PtGA* Patient Global Assessment, *RA* rheumatoid arthritis, *r-TCZ* reference tocilizumab, *SD* standard deviation, *SDAI* Simplified Disease Activity Index, *SF-36* 36-Item Short Form Health Survey, *sIL-6R* soluble interleukin-6 receptor, *SJC* swollen joint count, *TJC* tender joint count, *VAS* visual analogue scale

[a]Measured at screening

[b]Measured on day 1

r-TCZ maintenance and CT-P47 switched groups regardless of prior biologic use, and the degree of improvement in each treatment group was similar between the subgroups of patients with or without prior biologic use (Table S1 of the ESM).

3.3 Joint Damage Progression

At week 52, mean (standard deviation) change from baseline in the modified total Sharp score in the ITT set was 0.57 (2.45) in the CT-P47 maintenance group, 0.09 (1.17) in the r-TCZ maintenance group and 0.46 (2.14) in the CT-P47 switched group (Table 2). The proportions of patients with no radiographic progression were comparable across treatment groups (CT-P47 maintenance: 169/207 [81.64%]; r-TCZ maintenance: 85/99 [85.86%]; CT-P47 switched: 82/101 [81.19%]).

3.4 Pharmacokinetics

Study drug serum concentrations were relatively similar throughout TP2 in all three treatment groups (Table S2 of

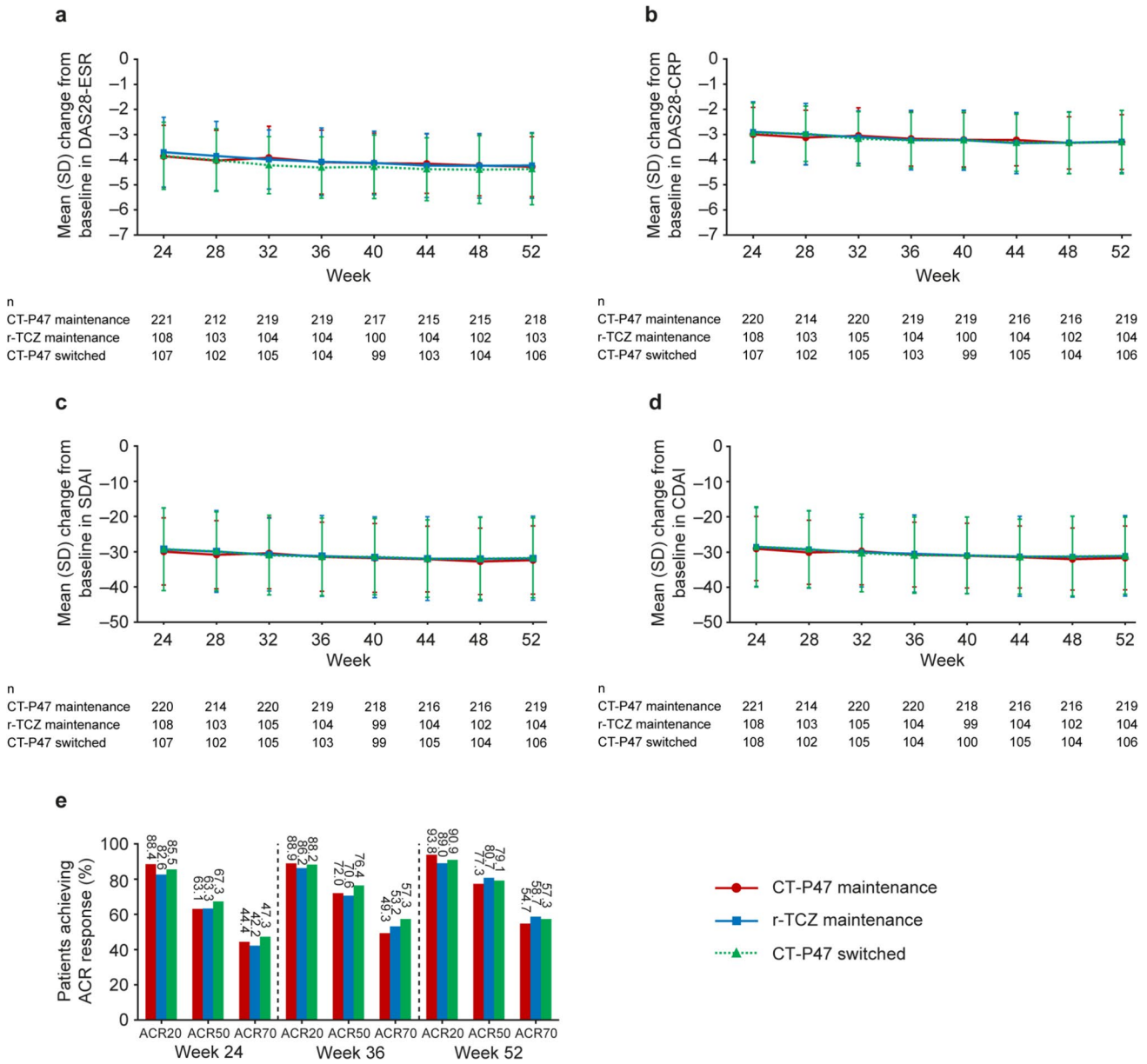

Fig. 2 Efficacy results in Treatment Period 2 (intent-to-treat Treatment Period 2 set). Mean change from baseline in Disease Activity Score in 28 joints-erythrocyte sedimentation rate (DAS28-ESR) [**a**]. Mean change from baseline in DAS28-C-reactive protein (CRP) [**b**]. Mean change from baseline in Simplified Disease Activity Index (SDAI) [**c**]. Mean change from baseline in Clinical Disease Activity Index (CDAI) [**d**]. 20% improvement according to American College of Rheumatology (ACR) criteria (ACR20), 50% improvement according to ACR criteria (ACR50) and 70% improvement according to ACR criteria (ACR70) response rates at weeks 24, 36 and 52 (end of study) [**e**]. Data are prior to administration of the study drug at each timepoint. Therefore, patients in the CT-P47 switched group had not yet received CT-P47 when week 24 measurements were taken. *r-TCZ* reference tocilizumab, *SD* standard deviation

the ESM). However, at week 40, the mean serum drug concentration in the CT-P47 switched group was higher than in the maintenance groups. Nevertheless, median values at week 40 were comparable between groups.

3.5 Safety and Immunogenicity

In TP2, both the mean (standard deviation) total number of study drug doses and the total dose received were consistent across treatment groups. The total number of study drug doses were 6.6 (1.16), 6.5 (1.30) and 6.4 (1.36) for the CT-P47 maintenance, r-TCZ maintenance

Table 2 Efficacy results at week 52 (ITT-TP2 subset)

Parameter	CT-P47 maintenance ($n = 225$)	r-TCZ maintenance ($n = 109$)	CT-P47 switched ($n = 110$)
SJC (DAS28 component)			
n	219	104	106
Change from baseline, mean (SD)	− 9.3 (3.97)	− 9.1 (4.00)	− 9.5 (4.51)
TJC (DAS28 component)			
n	219	104	106
Change from baseline, mean (SD)	− 11.6 (4.78)	− 10.9 (5.93)	− 11.1 (5.54)
mTSS			
n	207	99	101
Change from baseline, mean (SD)	0.57 (2.45)	0.09 (1.17)	0.46 (2.14)
CRP, mg/L			
n	219	104	106
Change from baseline, mean (SD)	− 7.2 (17.76)	− 7.7 (13.68)	− 7.2 (13.39)
ESR, mm/h			
n	219	104	106
Change from baseline, mean (SD)	− 30.2 (15.91)	− 30.7 (16.53)	− 31.1 (15.59)
PtGA score, VAS [mm]			
n	219	104	106
Change from baseline, mean (SD)	− 51.1 (23.50)	− 51.9 (27.01)	− 51.3 (24.53)
PGA score, VAS [mm]			
n	219	104	106
Change from baseline, mean (SD)	− 56.5 (18.23)	− 58.2 (18.88)	− 53.5 (19.69)
HAQ estimate of physical ability			
n	219	104	106
Change from baseline, mean (SD)	− 0.7 (0.55)	− 0.7 (0.53)	− 0.8 (0.62)
SF-36 scores, PCS			
n	219	104	106
Change from baseline mean (SD)	9.2 (7.44)	9.7 (7.46)	9.9 (7.81)
SF-36 scores, MCS			
n	219	104	106
Change from baseline mean (SD)	7.0 (9.85)	8.3 (8.88)	9.0 (10.02)

CRP C-reactive protein, *DAS28* Disease Activity Score in 28 joints, *ESR* erythrocyte sedimentation rate, *HAQ* Health Assessment Questionnaire, *ITT-TP2* intent-to-treat in Treatment Period 2, *MCS* mental component score, *mTSS* modified total Sharp score, *PCS* physical component score, *PGA* Physician Global Assessment, *PtGA* Patient Global Assessment, *r-TCZ* reference tocilizumab, *SD* standard deviation, *SF-36* 36-Item Short Form Health Survey, *SJC* swollen joint count, *TJC* tender joint count, *VAS* visual analogue scale

and CT-P47 switched groups, respectively. Total dose was 3632.5 (1184.29) mg, 3483.4 (1210.18) mg and 3578.5 (1218.77) mg, in the CT-P47 maintenance, r-TCZ maintenance and CT-P47 switched groups, respectively.

The proportions of patients reporting one or more TEAE were comparable across treatment groups. One hundred and forty-nine (66.2%), 74 (67.9%) and 71 (64.5%) patients reported one or more TEAE in the CT-P47 maintenance, r-TCZ maintenance and CT-P47 switched groups, respectively (Table 3). The most frequent TEAE overall and in all groups was alanine aminotransferase increased. The proportions of patients reporting treatment-emergent adverse events leading to study drug discontinuation were also similar across treatment groups; nine (4.0%), five (4.6%) and three (2.7%) patients in the CT-P47 maintenance, r-TCZ maintenance and CT-P47 switched groups, respectively.

Treatment-emergent serious adverse events were reported in 11 (4.9%), 8 (7.3%) and 6 (5.5%) patients in the CT-P47 maintenance, r-TCZ maintenance and CT-P47 switched groups, respectively (Table 3). One (0.4%) death (Table 3) owing to peritonitis deemed unrelated to the study drug occurred in the CT-P47 maintenance group, as previously reported [15]. This patient died 4 days after a scheduled gastroscopy, which had shown gastroesophageal reflux, gastritis with erosions in the antrum and *Helicobacter pylori* infection. On the death certificate, the direct cause of death was recorded as cardiac arrest, the secondary cause of death was

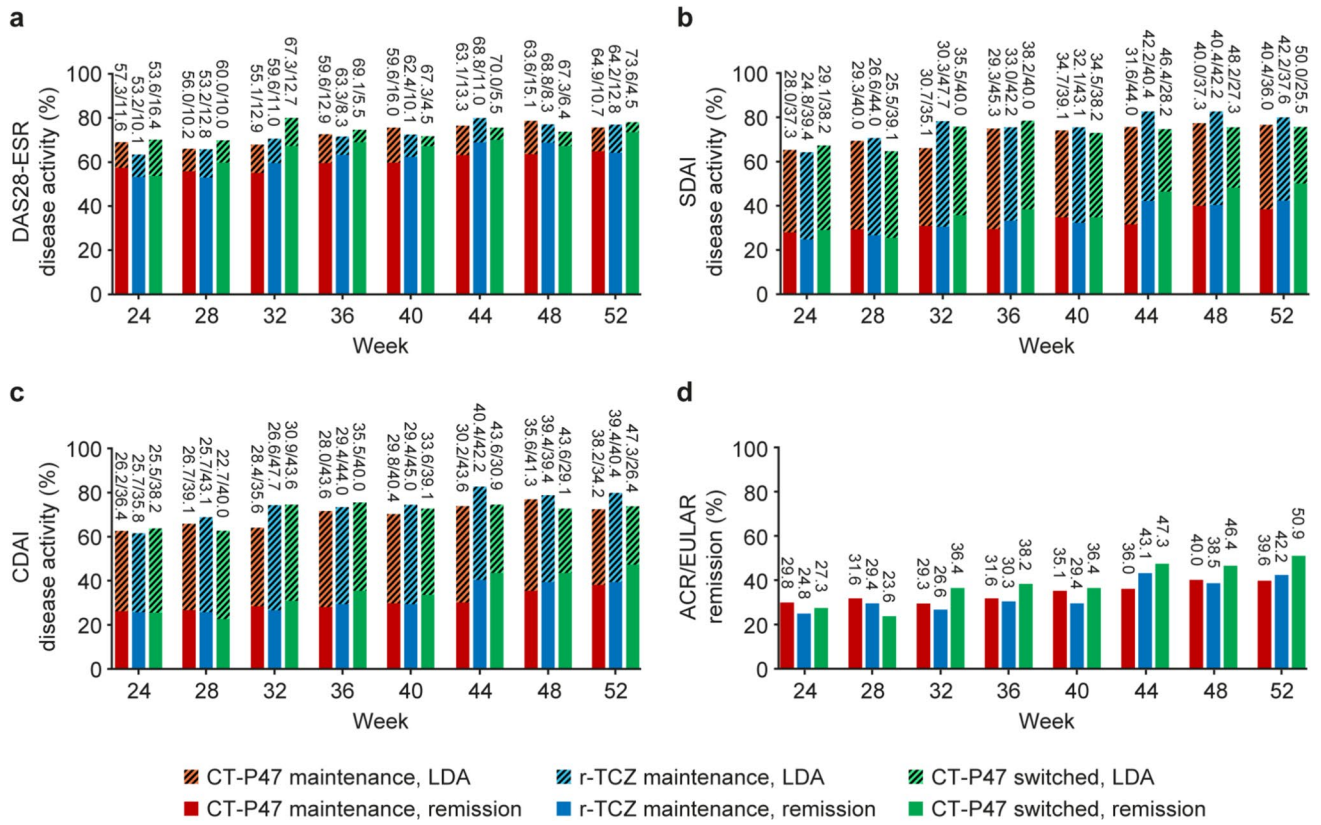

Fig. 3 Post hoc analysis of Disease Activity Score in 28 joints-erythrocyte sedimentation rate (DAS28-ESR) < 2.6 and low disease activity (LDA) [**a**], American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) index-based remission and LDA by Simplified Disease Activity Index (SDAI) [**b**] and Clinical Disease Activity Index (CDAI) [**c**] and ACR/EULAR Boolean-based remission (**d**) in Treatment Period 2 (intent-to-treat Treatment Period 2 subset). Data are prior to administration of the study drug at each timepoint. Therefore, patients in the CT-P47 switched group had not yet received CT-P47 when week 24 measurements were taken. **a** DAS28-ESR score categorised $x < 2.6$ and LDA ($2.6 \leq x \leq 3.2$). **b** SDAI score categorised as remission ($x \leq 3.3$) and LDA ($3.3 < x \leq 11.0$). **c** CDAI score categorised as remission ($x \leq 2.8$) and LDA ($2.8 < x \leq 10.0$). **d** ACR/EULAR remission using the Boolean-based 2.0 definition must satisfy all of the following: tender joint count ≤ 1 (of 28 assessed); swollen joint count ≤ 1 (of 28 assessed); C-reactive protein ≤ 1 mg/dL; patient's global assessment of disease activity (visual analogue scale) ≤ 2 (when converted to 0–10 cm). *r-TCZ* reference tocilizumab

respiratory arrest and the initial cause of death (primary) was generalised (acute) peritonitis.

Infections were the most common TEAESI, with comparable frequencies across treatment groups (CT-P47 maintenance: 64 [28.4%]; r-TCZ maintenance: 32 [29.4%]; CT-P47 switched: 31 [28.2%]) during TP2 (Table 3). The majority of TEAEs classified as infection were Grade 1 or 2 in intensity. Upper respiratory tract infection was the most commonly reported type of infection (reported in ≥ 5% of patients; Table 3). No active cases of tuberculosis were reported. Hepatic events were the next most common TEAESI, also with similar frequencies across treatment groups. Most treatment-emergent hepatic events were Grade 1 or 2. Three patients experienced a Grade 3 hepatic event (two patients [0.9%] in the CT-P47 maintenance group and one patient [0.9%] in the r-TCZ maintenance group). The most common hepatic event in all groups was alanine aminotransferase increased, reported in 58 (13.1%) patients (30 [13.3%], 13 [11.9%] and 15 [13.6%] patients in the CT-P47 maintenance, r-TCZ maintenance and CT-P47 switched groups, respectively). One (0.4%) patient in the CT-P47 maintenance group only reported a hypersensitivity TEAESI (study drug related, Grade 3). Similar proportions of TEAESIs classified as haemorrhage were reported across treatment groups (two [0.9%] with CT-P47 maintenance, one [0.9%] with r-TCZ maintenance and three [2.7%] in the CT-P47 switched group). All haemorrhage events were deemed non-medically significant, except for one Grade 3 event of uterine haemorrhage in the CT-P47 switched group. Two patients (both in the CT-P47 maintenance group) experienced a TEAESI of gastrointestinal perforation; one case of anal fistula of Grade 2 severity considered to be related to the study drug, and one case of peritonitis of Grade 5 severity considered to be unrelated

Table 3 Summary of TEAEs in TP2 (safety-TP2 subset)

Patients with TEAEs, by preferred term or TEAESI classification	CT-P47 maintenance ($n = 225$)	r-TCZ maintenance ($n = 109$)	CT-P47 switched ($n = 110$)
≥ 1 TEAE, *n* (%)	149 (66.2)	74 (67.9)	71 (64.5)
Related	95 (42.2)	50 (45.9)	45 (40.9)
Unrelated	112 (49.8)	52 (47.7)	47 (42.7)
TEAEs reported by ≥ 5% of patients in any treatment group, *n* (%)			
Alanine aminotransferase increased	30 (13.3)	13 (11.9)	15 (13.6)
Leukopenia	18 (8.0)	8 (7.3)	12 (10.9)
Neutropenia	14 (6.2)	8 (7.3)	12 (10.9)
Upper respiratory tract infection	16 (7.1)	10 (9.2)	8 (7.3)
Aspartate aminotransferase increased	14 (6.2)	8 (7.3)	9 (8.2)
Blood creatine phosphokinase MB increased	11 (4.9)	7 (6.4)	5 (4.5)
Latent tuberculosis	16 (7.1)	3 (2.8)	5 (4.5)
≥ 1 TESAE, *n* (%)	11 (4.9)	8 (7.3)	6 (5.5)
Related	3 (1.3)	1 (0.9)	2 (1.8)
Unrelated	8 (3.6)	7 (6.4)	4 (3.6)
Patients with ≥ 1 TEAE leading to study drug discontinuation, *n* (%)	9 (4.0)	5 (4.6)	3 (2.7)
Related	4 (1.8)	3 (2.8)	3 (2.7)
Unrelated	5 (2.2)	2 (1.8)	0
≥ 1 TEAE leading to death, *n* (%)	1 (0.4)	0	0
≥ 1 TEAESI, *n* (%)			
Infection	64 (28.4)	32 (29.4)	31 (28.2)
Hepatic event	44 (19.6)	21 (19.3)	25 (22.7)
Hypersensitivity, including anaphylaxis	1 (0.4)	0	0
Haemorrhage[a]	2 (0.9)	1 (0.9)	3 (2.7)
Gastrointestinal perforation	2 (0.9)[b]	0	0
Malignancy	0	0	0
Demyelinating disorder	0	0	0

r-TCZ reference tocilizumab, *TEAE* treatment-emergent adverse event, *TEAESI* treatment-emergent adverse event of special interest, *TESAE* treatment-emergent serious adverse event, *TP2* Treatment Period 2

[a]All events were considered as non-medically significant bleeding events, except for one Grade 3 TEAE of uterine haemorrhage reported in the CT-P47 switched group

[b]One patient died following peritonitis, which was classified as a TESAE, a TEAESI of infection and a TEAESI of gastrointestinal perforation, and was evaluated as unrelated to the study drug

to the study drug. The TEAESI analysis for gastrointestinal perforation included terms related to complications of diverticulitis (diverticular fistula, diverticular perforation and diverticulitis intestinal perforated), with no cases reported. No patients experienced either malignancy or demyelinating disorder TEAESIs.

Mean changes from baseline in soluble interleukin-6 receptor (sIL-6R) were comparable across treatment groups in TP2 (Table S3 of the ESM). Laboratory variables with the most severe Common Terminology Criteria for Adverse Events grading (≥ Grade 3) are summarised in Table S4 of the ESM, with a low proportion of patients affected across treatment groups.

Incidence of ADA conversion was consistently low across treatment groups in TP2 (Table S5 of the ESM). The proportions of patients who had positive conversion in ADAs were 2/209 (1.0%) in the CT-P47 maintenance group, 4/100 (4%) in the r-TCZ maintenance group and none (of 103 patients) in the CT-P47 switched group. The proportion of patients with positive conversion in neutralising antibodies was similar across treatment groups. Post hoc immunogenicity analyses showed that during TP2, a similar proportion of patients across treatment groups had one or more positive ADA results (CT-P47 maintenance: 10 [4.4%]; r-TCZ maintenance: 5 [4.6%]; CT-P47 switched: 4 [3.6%]) or one or more positive neutralising antibody results (CT-P47 maintenance: 4 [1.8%]; r-TCZ maintenance: 2 [1.8%]; CT-P47 switched: 2 [1.8%]). Serum tocilizumab concentrations in the CT-P47 maintenance, r-TCZ maintenance and CT-P47 switched study groups were

comparable during TP2 in ADA-negative patients (Fig. S2 of the ESM). In ADA-positive patients, serum tocilizumab concentrations in the r-TCZ maintenance group tended to be slightly lower than in the other groups (Fig. S2 of the ESM), but these results should be viewed with caution because of the small number of patients.

4 Discussion

The efficacy equivalence of CT-P47 and r-TCZ for treating patients with moderate-to-severe RA was demonstrated in a randomised, double-blind, multicentre, phase III trial with respect to the primary endpoint (DAS28-ESR mean change from baseline at week 12 and week 24) [15]. The week 52 results from this trial support the primary findings in terms of comparable efficacy, PK, safety and immunogenicity profile of CT-P47 and r-TCZ, and further establish the comparability of maintaining treatment with either CT-P47 or r-TCZ, or switching from r-TCZ to CT-P47.

In terms of disease activity, from the start of TP2 (week 24) until week 52, DAS28-ESR, DAS28-CRP, SDAI, CDAI, ACR20, ACR50 and ACR70 outcomes were comparable across the CT-P47 maintenance, r-TCZ maintenance and CT-P47 switched groups. Minimal joint damage progression observed across the CT-P47 maintenance, r-TCZ maintenance and CT-P47 switched groups indicates good control against joint damage with all treatments. Radiographic progression is closely associated with swollen joint counts [18–20] and as the reduction in swollen joint counts was similar across the treatment groups, any observed differences in radiographic changes are likely due to chance.

Comparable proportions of patients in all treatment groups achieved ACR-EULAR index-based remission (SDAI and CDAI) and LDA and ACR/EULAR Boolean-based remission (Boolean 2.0). Changes from baseline in DAS28-ESR, SDAI and CDAI scores during TP2 and the proportion of patients achieving ACR20, ACR50 and ACR70 during TP2 were highly similar between groups. Disease activity states are useful for setting, and measuring attainment of, treatment goals, but may mask improvements in actual disease activity that are an important part of the clinical assessment of therapeutic efficacy [21]. Indeed, in rheumatology, categorical analyses can have limitations and use of continuous variables may be preferable [22]. Therefore, it is important to consider both categorical and continuous analyses in rheumatology, as performed in this study. Specifically, highly comparable efficacy was demonstrated during TP2 when observing both categorical and continuous measures.

This study permitted the inclusion of patients who had received no more than one prior biologic treatment, provided it was not an IL-6 inhibitor. There was no difference in the DAS28-ESR score improvement between the CT-P47 maintenance, r-TCZ maintenance or CT-P47 switched groups relating to prior biologic use. This observation is important when considering the sequencing of treatment options in RA and supports the use of tocilizumab either before or after other biologics.

With respect to PK, serum tocilizumab concentrations were generally consistent across treatment groups between week 24 and week 52, confirming that switching did not adversely affect tocilizumab concentrations. Higher mean serum drug concentration in the CT-P47 switched group compared with the maintenance groups, at week 40, may have been due to high mean serum drug concentrations (> 70,000 ng/mL) in some individuals in the CT-P47 switched group at that timepoint. Safety findings were consistent with those previously reported in the earlier analysis of this study [15]. CT-P47 and r-TCZ were well tolerated up to week 52, with the frequency and nature of adverse events similar across treatment groups, and switching from r-TCZ to CT-P47 having no notable impact.

The most commonly reported TEAESIs were infections, consistent with previously reported data for CT-P47 [11, 15], and frequencies were similar across the three treatment groups. Upper respiratory tract infection was the most frequently reported infection, largely consistent with European Union and US prescribing information for r-TCZ [5, 6]. The second most frequently reported infection was latent tuberculosis, which was relatively high versus historical data [6]; this may have arisen because of the protocol-required interferon-gamma release assay testing performed at week 24 and week 52, with the majority of interferon-gamma release assay-positive conversion cases being reported as latent tuberculosis (defined as a positive interferon-gamma release assay with a negative chest X-ray result). No cases of active tuberculosis were reported, and no patients reported signs or symptoms of tuberculosis during the study period, despite the fact that patients with latent tuberculosis were permitted to enrol providing they had at least 3 weeks of prophylactic treatment.

From week 24, the mean change from baseline in sIL-6R levels showed a decreasing trend. This trend aligns with findings in the literature, which indicate that sIL-6R levels are associated with levels of free tocilizumab, as the formation of sIL-6R/tocilizumab immune complexes slows the elimination of sIL-6R [23]. From week 12 onwards, 70% of patients with drug concentrations below the limit of quantification had either dose modifications or skipped doses in previous visits, suggesting that these dose reductions could explain the observed decrease in sIL-6R levels. Elevations of hepatic transaminases are a known side effect of tocilizumab treatment, particularly when administered concomitantly with MTX [5]. In addition, decreases in

neutrophil and platelet counts have previously occurred following treatment with tocilizumab 8 mg/kg in combination with MTX [5]. Therefore, dose modification was included in the study protocol whereby laboratory value criteria were used to guide the need for a dose reduction (from 8 to 4 mg/kg), dose interruption or drug discontinuation. Regarding immunogenicity, the incidence of ADA formation was low in the r-TCZ and CT-P47 maintenance groups, in line with historical data from clinical studies and real-world data [6, 24, 25], and ADA-positive conversion did not occur in the CT-P47 switched group.

Study limitations have been discussed previously [15]. Briefly, all patients were white and all study centres located in Poland, limiting the generalisability of the results. The DAS28 instrument is subjective in nature, leading to potential inter-observer variability [26]; however, joint count assessments were performed independently by the same person at each study centre to mitigate this effect. DAS28-ESR may not be the most appropriate tool for assessing agents that target the IL-6 pathway [27, 28], given that these therapies can reduce ESR independently of clinical improvement; however, this is not a significant limitation as tocilizumab was used in all three treatment groups in this study. With respect to the study design limitations during TP2, the numbers of patients in the r-TCZ maintenance and CT-P47 switched groups were lower than in the CT-P47 maintenance group because of the second randomisation. TP2 of this study was not designed for statistical comparisons of equivalence between the CT-P47 and r-TCZ maintenance groups and the CT-P47 switched group; however, the results from TP2 in this study provide valuable data on switching from a reference product to a biosimilar.

5 Conclusions

The efficacy, PK, safety and immunogenicity results up to week 52 of this phase III study support the equivalence of efficacy and comparable PK, safety and immunogenicity between CT-P47 and r-TCZ in patients with moderate-to-severe RA demonstrated in the primary analysis, including after switching from r-TCZ to CT-P47.

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Declarations

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Conflict of Interest/Competing Interests Gerd Burmester has received honoraria for consulting and lectures from Celltrion, Inc., Chugai, Fresenius and Sanofi. Marek Krogulec has received support for meeting attendance from Accord, Egis, Medac and Sandoz. Sławomir Jeka has received consulting fees from AbbVie, Celltrion, Inc., Eli Lilly, Gilead, MSD, Novartis, Pfizer, Roche, Sanofi and UCB; and payments or honoraria from AbbVie, Celltrion, Inc., Eli Lilly, Gilead, MSD, Novartis, Pfizer, Roche, Sanofi and UCB. Rafał Wojciechowski has received speaker fees from Eli Lilly, Janssen, Novartis, SOBI and UCB; support for meeting attendance from AbbVie; and is involved in the leadership of the Polish Rheumatology Society. Magdalena Krajewska-Włodarczyk has received payments or honoraria from AbbVie, Boehringer Ingelheim, Eli Lilly, Janssen, Medac, MSD, Novartis, Pfizer, Sandoz, SOBI and UCB; and support for meeting attendance from AbbVie, Medac, Novartis, Pfizer and SOBI. Paweł Hrycaj has received research grants from Celltrion, Inc. SungHyun Kim is an employee of Celltrion, Inc. JeeHye Suh, GoEun Yang, YunAh Kim, YooBin Jung and GaHee Park are employees of Celltrion, Inc., and hold stocks in Celltrion, Inc. Josef S. Smolen has received payments to his institution from AbbVie, AstraZeneca, Eli Lilly, Novartis, Galapagos and Roche; personal fees from AbbVie, Amgen, Ananda, Astro, BMS, Celltrion, Inc., Chugai, Eli Lilly, Gilead, Immunovant, MSD, Novartis, Pfizer, Roche, R-Pharma, Samsung, Sanofi and UCB; payments or honoraria from Eli Lilly; and support for meeting attendance from Eli Lilly. Jakub Trefler, Artur Racewicz, Janusz Jaworski, Agnieszka Zielińska, Katarzyna Kolossa, Anna Dudek and Piotr Adrian Klimiuk have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval The study was conducted in accordance with the Declaration of Helsinki (and Good Clinical Practice Guideline). All national, state, and local laws or regulations were followed. Prior to study initiation, the study protocol, informed consent form, advertisements used for the recruitment of participants and any other written materials provided to participants were approved by the institutional review board. This study involves human participants and was approved by the Institutional Review Board, Komisja Bioetyczna przy OIL w Białymstoku, ul. Świętojańska 7, 15-082 Białystok, Poland, and the Ethics Committee at the Regional Medical Chamber with its seat in Białystok, 15-082 Białystok, ul. Świętojańska 7, Poland (reference number: 43/2022/VIII).

Consent to Participate Written informed consent was obtained from all patients prior to enrolment.

Consent for Publication Not applicable.

Availability of Data and Material All data relevant to the study are included in the article or uploaded as supplementary information.

Code Availability Not applicable.

Authors' Contributions GB, SHK, JHS, GEY, YAK, YBJ, GHP and JSS contributed to the study design. JT, AR, JJ, AZ, MK, SJ, RW,

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