

Original article

Efficacy and safety of switching from rituximab to biosimilar CT-P10 in rheumatoid arthritis: 72-week data from a randomized Phase 3 trial

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Abstract

Objective. To evaluate the efficacy and safety of CT-P10, a rituximab biosimilar after a single switch, during a multi-national, randomized, double-blind Phase 3 trial involving patients with RA.

Methods. Patients received 48 weeks' treatment with CT-P10 or United States- or European Union-sourced reference rituximab (US-RTX and EU-RTX, respectively). Patients entering the extension period (weeks 48–72) remained on CT-P10 (CT-P10/CT-P10; $n = 122$) or US-RTX (US-RTX/US-RTX; $n = 64$), or switched to CT-P10 from US-RTX (US-RTX/CT-P10; $n = 62$) or EU-RTX (EU-RTX/CT-P10; $n = 47$) for an additional course. Efficacy endpoints included Disease Activity Score using 28 joints (DAS28), American College of Rheumatology (ACR) response rates, and quality of life-related parameters. Pharmacodynamics, immunogenicity and safety were also assessed.

Results. At week 72, similar improvements were observed by disease activity parameters including DAS28 and ACR response rate in the four extension period treatment groups. Quality of life improvements at week 72 vs baseline were similarly shown during the extension period in all groups. Newly developed anti-drug antibodies were detected in two patients following study drug infusion in the extension period. Similar pharmacodynamic and safety profiles were observed across groups.

Conclusion. Long-term use of CT-P10 up to 72 weeks was effective and well tolerated. Furthermore, switching from reference rituximab to CT-P10 in RA was well tolerated and did not result in any clinically meaningful differences in terms of efficacy, pharmacodynamics, immunogenicity and safety.

Trail registration. ClinicalTrials.gov, <http://clinicaltrials.gov>, NCT02149121.

Key words: rituximab, CT-P10, rheumatoid arthritis, B cells, DMARDs (biologic), disease activity, anti-TNF, switch, biosimilar

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Rheumatology key messages

- Switching from reference rituximab to CT-P10 in RA patients was well tolerated.
- No detrimental outcomes were observed in efficacy, pharmacodynamics, immunogenicity and safety after switching to CT-P10.
- Long-term use of CT-P10 up to 72 weeks was effective and well tolerated in RA.

Introduction

B cells play a fundamental role in the pathogenesis of RA, through autoantibody-dependent and -independent mechanisms [1, 2]. Rituximab, a monoclonal antibody against the B-cell surface-antigen CD20, exerts its therapeutic effects via immune-mediated cytotoxicity, direct induction of apoptosis, and subsequent depletion of CD20-positive B cells [3]. Rituximab, in combination with MTX, can reduce clinical symptoms and signs of RA [4–6] and is approved for patients with moderate-to-severe RA who show an inadequate response or intolerance to anti-TNF agents [7, 8]. Available from the original manufacturer, Roche (Welwyn Garden City, UK) in Europe and Genentech, Inc. (South San Francisco, CA, USA) in the USA, rituximab is also approved in non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia, granulomatosis with polyangiitis and microscopic polyangiitis [7, 8]. CT-P10 (CELLTRION, Incheon, Republic of Korea) is a rituximab biosimilar approved in several regions or countries [9, 10]. To gain regulatory approval, a biosimilar must demonstrate that it exhibits no clinically meaningful differences from its reference product, in terms of quality, safety and efficacy [11, 12]. A comprehensive, stepwise approach is recommended, starting with analytical, *in vitro* and/or non-clinical *in vivo* studies, and concluding with clinical studies evaluating pharmacokinetics (PK), pharmacodynamics (PD), efficacy, immunogenicity and safety [13]. Comparisons with the reference product at each of these steps inform the type and extent of data required at the next step. Overall, it is the 'totality of evidence' that informs regulatory decisions, although approval usually requires proof of statistical equivalence of the biosimilar and reference product in terms of PK and efficacy, as well as a demonstration of comparable safety profiles [11, 12]. For CT-P10, a Phase 1 study in patients with active RA demonstrated equivalent PK to European-sourced rituximab (EU-RTX) with no substantial differences in efficacy, PD, immunogenicity or safety [14]. Two Phase 3 studies in patients with NHL also showed no clinically meaningful differences between CT-P10 and US-sourced rituximab (US-RTX) [15, 16].

Here, and in two previous reports [17, 18], we present the results of a multinational, double-blind, active-controlled Phase 3 study involving patients with active RA initially randomized to CT-P10, US-RTX, or EU-RTX (ClinicalTrials.gov identifier: NCT02149121). This study consisted of two periods: a main period of two treatment courses and an extension period of one additional course. For the first course of study treatment, PK and efficacy equivalence of CT-P10 and US-RTX or EU-RTX were demonstrated by achieving predefined endpoints at week 24 [17]. Follow-up of patients eligible for a second

course of their allocated study treatment (administered on weeks 24 and 26) until week 48 showed that CT-P10 and RTX were similar in terms of efficacy, PK, PD, immunogenicity and safety [18]. On completion of this main period, patients could enter an extension period from week 48 to week 72. Here we report results of the extension period, which evaluated the efficacy, PD, immunogenicity and safety of CT-P10 after a single switch from either US-RTX or EU-RTX, and in patients maintained on CT-P10 or US-RTX.

Methods

Patients

Full eligibility criteria are reported elsewhere [17, 18]. In brief, eligible patients were aged 18–75 years, had active RA, received MTX (7.5–25 mg/week orally or parenterally) for at least the past 12 weeks (with the final 4 weeks before screening at a stable dose), and had experienced an inadequate response or intolerance to TNF antagonists.

Eligibility criteria for the extension period included completion of the main period up to week 48 and that they met predefined safety criteria irrespective of clinical response (absolute neutrophil count $\geq 1.5 \times 10^9$ cells/L, platelet count $\geq 75 \times 10^9$ cells/L, aspartate aminotransferase or alanine aminotransferase ≤ 2.5 times upper limit of normal, and levels of immunoglobulin G ≥ 500 mg/dL at the last blood sample analysis; and the patient had not developed any condition that, in the investigator's opinion, precluded the patient receiving further courses of treatment).

Study design and treatment

Full details of the main period have been described previously [17, 18]. In the main period, patients received ≤ 2 treatment courses, each comprising two intravenous infusions of study drug (1000 mg CT-P10, US-RTX or EU-RTX) separated by a 2-week interval, co-administered with MTX (7.5–25 mg/week orally or parenterally) and folic acid (≥ 5 mg/week orally). After completing the main period, patients meeting the additional eligibility criteria could enter the extension period and receive a further treatment course comprising two intravenous infusions of CT-P10 or US-RTX at weeks 48 and 50. Patients who received CT-P10 or EU-RTX in the main period received CT-P10 in the extension period. Patients who received US-RTX in the main period were randomly assigned (1:1) to receive CT-P10 or US-RTX. Patients and investigators remained blinded to treatment until study completion. In the extension period, efficacy, PD, safety and immunogenicity were evaluated for 24 weeks until week 72.

The study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines [19, 20]. The study design was reviewed and approved by the relevant independent ethics committee at each site. All patients provided written informed consent for the main period and additional written informed consent for the extension period.

Study endpoints and assessments

Disease Activity Score using 28 joints (DAS28) and ACR 20%, 50%, and 70% improvement criteria (ACR20, ACR50 and ACR70, respectively) response rates were evaluated prior to the first infusion of study drug in the extension period (week 48) and then every 8 weeks until week 72. Other efficacy variables assessed during the extension period included hybrid ACR scores, European League Against Rheumatism (EULAR) response rates, 36-Item Short Form Health Survey (SF-36) subscale and component scores, Health Assessment Questionnaire Disability Index (HAQ-DI), joint damage score using the van der Heijde modification of the Sharp (SvdH) scoring system (0–448 scale) [21], and Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) scores. *Post hoc* analyses of remission rates by ACR-EULAR Boolean criteria and low disease activity (LDA; including remission) sustainability rates by DAS28 were also performed. PD, safety and immunogenicity assessments were evaluated during the extension period (detailed in Supplementary Table S1, available at *Rheumatology* online).

Statistical analysis

Continuous data were described using descriptive statistics (n , mean, s.d.), median, minimum and maximum) unless otherwise specified. Categorical data were reported using patient counts and percentages. Baseline was defined as last non-missing value on or before the first infusion of the first treatment course in the main period. The patient populations analysed are described in the Supplementary Methods, available at *Rheumatology* online. All analyses were conducted using Statistical Analysis System (SAS) software v9.1.3 (SAS Institute, Cary, NC, USA).

Results

Patients

The study was conducted between 6 August 2014 and 25 January 2017. As reported elsewhere [17, 18], 372 patients were randomized to CT-P10 ($n=161$), US-RTX ($n=151$), or EU-RTX ($n=60$) (Fig. 1). Of 331 patients who completed the main period, 36 did not enter the extension period (see Supplementary Table S2 for reasons, available at *Rheumatology* online). Overall, 295 patients initiated treatment in the extension period (CT-P10/CT-P10 group, $n=122$; US-RTX/US-RTX group, $n=64$; US-RTX/CT-P10 group, $n=62$; EU-RTX/CT-P10 group, $n=47$; Fig. 1). Of these, 292 (99.0%) completed this course; one patient from the CT-P10/CT-P10 group and two

patients from the US-RTX/CT-P10 group discontinued treatment due to consent withdrawal. Patient demographics and baseline disease characteristics were similar across treatment groups (Table 1).

Efficacy

Following improvements in disease activity during the main period [17, 18], mean DAS28-CRP and mean DAS28-ESR continued to decrease over time in the extension period (Fig. 2A and 2B, respectively). At week 72, mean (s.d.) change in DAS28-CRP from baseline was similar between the four extension period treatment groups: CT-P10/CT-P10, -3.0 (1.20); US-RTX/US-RTX, -3.0 (1.32); US-RTX/CT-P10, -2.9 (1.27); and EU-RTX/CT-P10, -3.0 (1.11). At week 72, mean decreases from baseline in DAS28-ESR were also similar among groups (Fig. 2B). Ten patients showed worsened disease activity at week 72 (defined as either an increase in DAS28-CRP of ≥ 1.2 from the start of the extension period, or an increase in DAS28-CRP of >0.6 but ≤ 1.2 from the start of the extension with DAS28-CRP >5.1 at week 72); five (4.2%), two (3.1%), two (3.3%) and one (2.1%) patients in the CT-P10/CT-P10, US-RTX/US-RTX, US-RTX/CT-P10 and EU-RTX/CT-P10 groups, respectively.

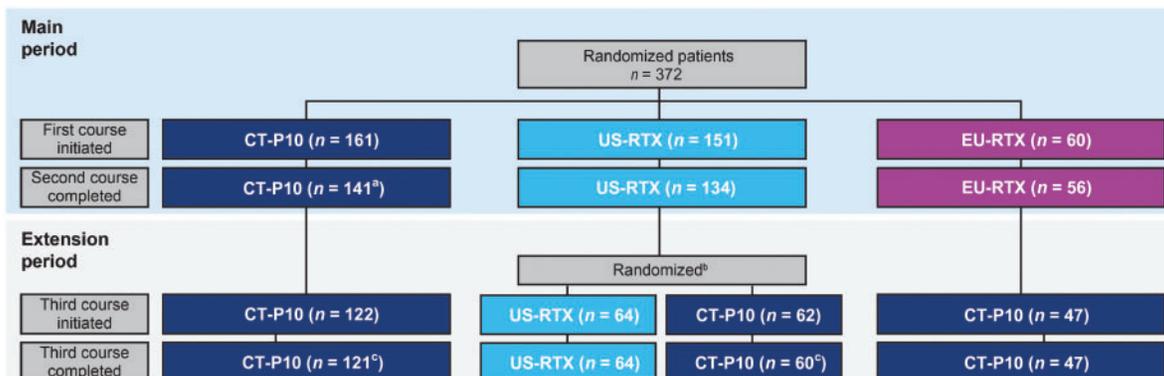
The proportion of patients achieving ACR20, ACR50 and ACR70 criteria rose during the extension period (Fig. 2C), with a similar proportion of patients in each treatment group showing ACR20, ACR50 and ACR70 responses at week 72 (Supplementary Fig. S1, available at *Rheumatology* online). Comparable improvements in mean hybrid ACR scores among treatment groups were also observed throughout the main period and extension period (Fig. 2D).

The proportion of patients with good or moderate EULAR-CRP responses increased to a similar degree over the extension period in all treatment groups (Fig. 2E). At week 72, the proportion of patients with good or moderate EULAR-CRP responses was 90.8%, 90.6%, 91.7% and 95.7%, in the CT-P10/CT-P10, US-RTX/US-RTX, US-RTX/CT-P10 and EU-RTX/CT-P10 groups, respectively.

The proportion of patients achieving remission by ACR-EULAR Boolean criteria [tender joint count (of 66 assessed), swollen joint count (of 68 assessed), CRP (mg/dL), patient global assessment (0–10 scale) all ≤ 1] increased through the extension period (Table 2). Rates of remission (i.e. DAS28 ≤ 2.6) and LDA (i.e. $2.6 < \text{DAS28} \leq 3.2$) increased through the extension period and were comparable between treatment groups (Table 2). Rates of sustained LDA (including remission) for ≥ 6 months according to DAS28-CRP or DAS28-ESR were also comparable across treatment groups (Table 2).

Reductions in mean CDAI and SDAI scores were observed throughout the main and extension periods; these were of similar magnitude across treatment groups (Supplementary Fig. S2A and S2B, available at *Rheumatology* online). Mean (s.d.) decreases from baseline in HAQ-DI scores were similar across the treatment groups during the main period (Table 1) and extension

Fig. 1 Patient flow



Reasons for drop-out in the main period have been published previously [18]. ^aIncludes one patient who did not receive the second treatment course (due to not satisfying safety criteria) and was monitored up to week 48. ^bRandomization in the extension period was stratified by the number of courses received in the main period and EULAR-CRP response status (responder vs non-responder) assessed at week 40. ^cThree patients were discontinued due to consent withdrawal (one in CT-P10/CT-P10, two in US-RTX/CT-P10). EU: European Union; RTX: rituximab; US: United States.

period, and at week 72 were -0.8 (0.60), -0.7 (0.67), -0.7 (0.52) and -0.8 (0.65) in the CT-P10/CT-P10, US-RTX/US-RTX, US-RTX/CT-P10 and EU-RTX/CT-P10 groups, respectively. Radiographic joint damage progression pattern was also similar across the treatment groups with mean (s.d.) increase from baseline of 1.2 (3.57), 1.5 (2.73), 0.9 (2.48) and 1.6 (2.35) at week 72, respectively. The overlapping cumulative probability distribution plot of SvdH scores is shown in Supplementary Fig. S2C, available at *Rheumatology* online. Increases in mean physical and mental component summary scores, and all SF-36 eight subscale scores, were observed at week 48 vs baseline (Table 1) and were maintained or increased during the extension period (Supplementary Fig. S3, available at *Rheumatology* online). No differences were observed between the four extension period treatment groups in these scores.

PD

Median B-cell counts decreased to below the lower limit of quantification (LLoQ; 20 cells/ μ L) immediately following the first infusion of study treatment in the main period and remained at this level to the end of the extension period in all treatment groups. Of patients with detectable baseline B-cell levels and depletion after treatment, the proportion with B-cell values above LLoQ at week 72 was 14/106 (13.2%), 4/59 (6.8%), 5/48 (10.4%) and 3/41 (7.3%) in the CT-P10/CT-P10, US-RTX/US-RTX, US-RTX/CT-P10 and EU-RTX/CT-P10 groups, respectively. Of note, there were no discernible differences in median B-cell counts among patients who switched to CT-P10 from the US- or EU-RTX groups, or among the CT-P10/CT-P10 and US-RTX/US-RTX maintenance groups. During the extension period, mean ESR and mean concentrations of CRP, anti-cyclic citrullinated peptide and rheumatoid factor maintained a

decreasing trend; mean decreases from baseline in these variables were similar in each treatment group.

Immunogenicity

Most patients tested negative for anti-drug antibodies (ADAs) throughout the main period [17, 18] and the extension period. At the beginning of the extension period, 47 patients were ADA-positive: 15 (12.3%), 9 (14.1%), 13 (21.0%) and 10 (21.3%) in the CT-P10/CT-P10, US-RTX/US-RTX, US-RTX/CT-P10 and EU-RTX/CT-P10 groups, respectively. At week 72, the numbers of ADA-positive patients were: five (4.1%), two (3.1%), eight (12.9%) and three (6.4%), respectively, with neutralizing antibodies (NAbs) detected in one (0.8%) patient (CT-P10/CT-P10 group). Of the 18 ADA-positive patients at week 72, 16 patients had at least one positive ADA test result up to the baseline of the extension period. The remaining two patients (one each in the US-RTX/US-RTX group and US-RTX/CT-P10 group) had new positive ADA test results after the first infusion of study drug in the extension period. Both patients tested negative for NAbs and achieved remission or LDA according to DAS28-CRP, CDAI and SDAI criteria at week 72; no adverse events were reported for either patient.

Safety

Safety results for the main period are discussed in detail elsewhere [17, 18]; treatment-emergent AEs (TEAEs) during the extension period, mostly grade 1 or 2 in severity, are shown in Table 3. The most common TEAEs across all treatment groups were upper respiratory tract infection, urinary tract infection, and infusion-related reactions (IRRs) (Supplementary Table S3, available at *Rheumatology* online). Infection TEAEs were grade 1 or 2 in severity, except for one case of grade 3 pneumonia in the US-RTX/CT-P10 group that resolved following

TABLE 1 Baseline demographics and clinical characteristics (all randomized population – extension period subset)

	CT-P10/CT-P10 (n = 122)	US-RTX/US-RTX (n = 64)	US-RTX/CT-P10 (n = 62)	EU-RTX/CT-P10 (n = 47)
Age, mean (s.d.), years	51.3 (12.00)	51.9 (10.25)	52.3 (11.24)	50.1 (10.71)
Female, n (%)	100 (82.0)	54 (84.4)	55 (88.7)	40 (85.1)
Race, n (%)				
White	68 (55.7)	41 (64.1)	40 (64.5)	30 (63.8)
Asian	6 (4.9)	4 (6.3)	1 (1.6)	4 (8.5)
Other ^a	48 (39.3)	19 (29.7)	21 (33.9)	13 (27.7)
BMI, mean (s.d.), kg/m ²	26.7 (5.6)	26.6 (4.4)	27.6 (6.0)	26.0 (5.2)
Time since RA diagnosis, median (range), years	7.9 (0.8–47.3)	7.1 (1.1–21.5)	6.7 (0.7–44.4)	8.1 (1.7–31.9)
Prior TNF-antagonist use, n (%)				
1	110 (90.2)	56 (87.5)	58 (93.5)	40 (85.1)
2	12 (9.8)	8 (12.5)	4 (6.5)	7 (14.9)
Prior anti-TNF status, n (%)				
Inadequate response	110 (90.2)	58 (90.6)	53 (85.5)	43 (91.5)
Intolerant case	12 (9.8)	6 (9.4)	9 (14.5)	4 (8.5)
Duration of prior TNF-antagonist use, mean (s.d.), months	15.0 (20.8)	16.1 (30.0)	16.9 (28.1)	13.6 (17.1)
Positive RF status, n (%)	97 (79.5)	53 (82.8)	53 (85.5)	38 (80.9)
Positive anti-CCP status, n (%)	100 (82.0)	53 (82.8)	51 (82.3)	42 (89.4)
CRP, mean (s.d.), mg/dL	2.2 (3.2)	2.1 (2.8)	2.4 (3.8)	3.7 (5.5)
ESR, mean (s.d.), mm/h	55.8 (29.0)	54.4 (25.5)	60.0 (31.3)	54.9 (21.1)
DAS28-CRP, mean (s.d.)				
Baseline	5.8 (0.9)	5.8 (0.9)	5.7 (1.0)	6.0 (0.9)
Week 48	3.2 (1.2)	3.3 (1.5)	3.1 (1.1)	3.6 (1.3)
DAS28-ESR, mean (s.d.)				
Baseline	6.7 (0.9)	6.7 (0.8)	6.7 (0.8)	6.8 (0.8)
Week 48	3.9 (1.3)	4.0 (1.6)	3.9 (1.2)	4.2 (1.4)
CDAI, mean (s.d.)				
Baseline	39.2 (12.0)	39.2 (12.0)	37.7 (11.1)	40.5 (12.6)
Week 48	11.4 (8.9)	12.8 (12.3)	10.5 (7.7)	15.0 (11.9)
SDAI, mean (s.d.)				
Baseline	41.4 (12.9)	41.4 (12.9)	40.1 (13.0)	44.2 (14.6)
Week 48	12.1 (9.3)	13.7 (13.1)	11.5 (8.3)	16.0 (12.5)
HAQ-DI, mean (s.d.)				
Baseline	1.7 (0.5)	1.6 (0.6)	1.7 (0.6)	1.7 (0.4)
Week 48	1.0 (0.7)	1.0 (0.7)	1.1 (0.7)	1.1 (0.7)

^aThe majority of patients included in the other category identified as Mestizo; the remainder identified as Hispanic or mixed. CDAI: Clinical Disease Activity Index; DAS28: Disease Activity Score using 28 joints; EU: European Union; HAQ-DI: Health Assessment Questionnaire Disability Index; RTX: rituximab; SDAI: Simplified Disease Activity Index; US: United States.

antibiotic treatment. The patient received a second infusion in the extension period and completed the study up to week 72.

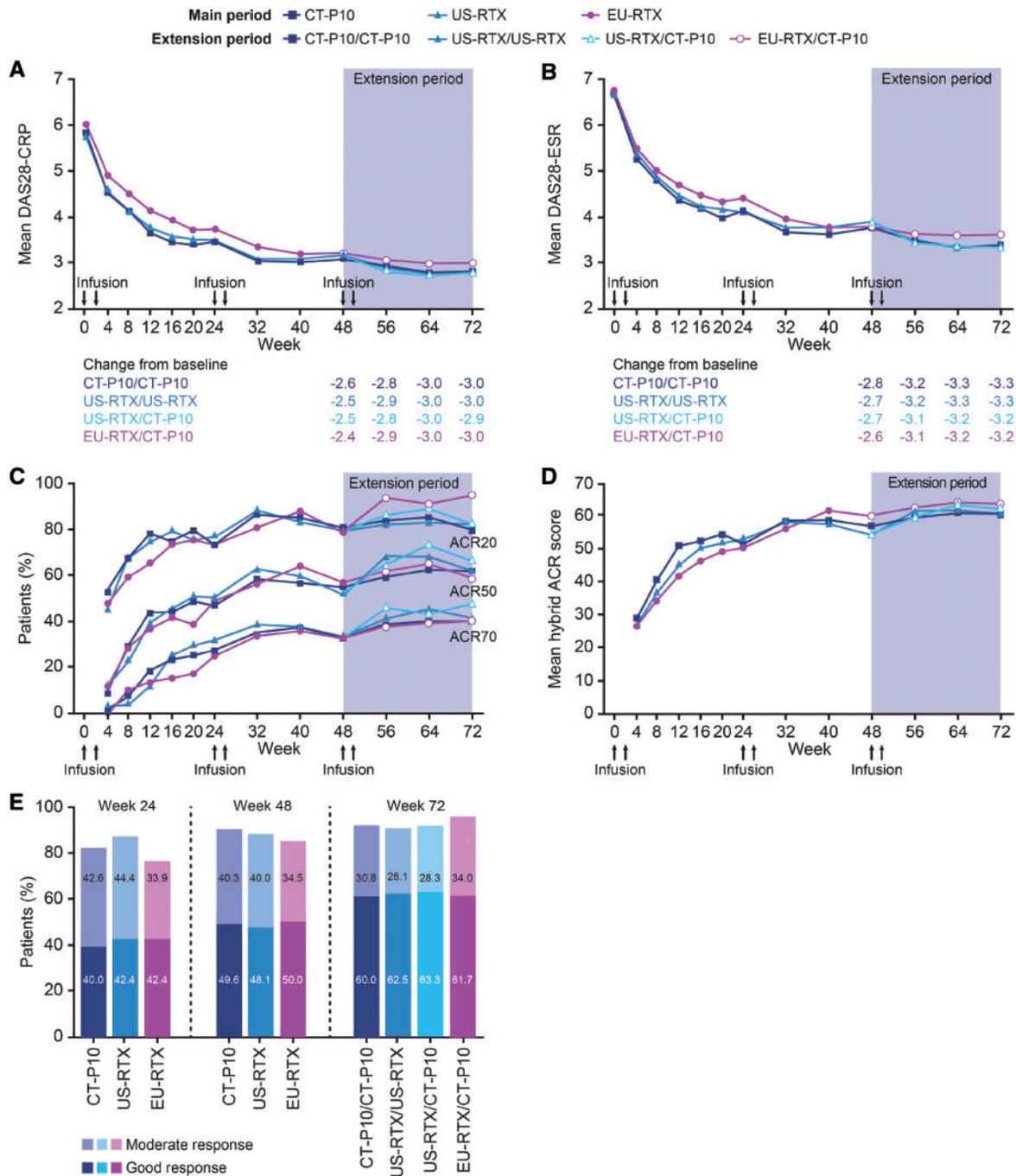
Seven serious TEAEs (TESAEs) were reported in five patients during the extension period (Supplementary Table S4, available at *Rheumatology* online). Only two patients experienced a TESAE that was considered to be related to study drug: one in the CT-P10/CT-P10 group (IRR) and one in the US-RTX/CT-P10 group (the pneumonia case described above). No previous IRRs had been reported for this patient and all signs and symptoms of the IRR event were resolved within 30 min of steroid therapy. CT-P10 was permanently discontinued and the patient completed the extension period with safety follow-up. No other TEAE or TESAE led to permanent discontinuation of study treatment. There were no cases of

progressive multifocal leukoencephalopathy and no reported malignancies or deaths during the extension period.

Discussion

The extension period of this randomized, active-controlled Phase 3 study demonstrated that after a single switch from either US-RTX or EU-RTX to CT-P10 at week 48, there were no discernible differences in efficacy, PD, immunogenicity or safety. These data provide evidence that switching from reference product to CT-P10 in RA is well tolerated, with no meaningful differences in efficacy and safety. These findings should offer valuable information for treatment decision making when considering a switch to CT-P10 in clinical practice. In addition, long-

Fig. 2 Efficacy outcomes



(A) Mean DAS28-CRP. (B) Mean DAS28-ESR. (C) Proportion of patients achieving clinical response according to ACR20, ACR50 and ACR70 criteria. (D) Mean hybrid ACR score. (E) Proportion of patients with good/moderate EULAR-CRP. Values for all data points in (A–D) are provided in Supplementary Tables S5–S8, available at *Rheumatology* online. Data are shown for the efficacy population [17] (including the second treatment course subset [18]) and the extension period subset beyond weeks 24 and 48, respectively. DAS28: Disease Activity Score using 28 joints; EU: European Union; RTX: rituximab; US: United States.

term evaluation of CT-P10 and reference rituximab (specifically, US-RTX) in the maintenance groups in the current study found these drugs to be similar in terms of all study

evaluations assessed for up to 72 weeks. These results confirm that CT-P10 provides an effective alternative for patients requiring rituximab therapy, supporting the recent

TABLE 2 Boolean-based remission^a, DAS28 disease activity^b and sustained LDA (including remission)^c (efficacy population – extension period subset)

	CT-P10/CT-P10 (n = 120)	US-RTX/US-RTX (n = 64)	US-RTX/CT-P10 (n = 60)	EU-RTX/CT-P10 (n = 47)
Boolean-based remission, n (%)				
Week 48	15 (12.5)	9 (14.1)	8 (13.3)	4 (8.5)
Week 56	18 (15.0)	15 (23.4)	7 (11.7)	6 (12.8)
Week 64	28 (23.3)	13 (20.3)	10 (16.7)	7 (14.9)
Week 72	25 (20.8)	15 (23.4)	9 (15.0)	8 (17.0)
DAS28-CRP, n (%)				
Week 48				
Remission	36 (30.0)	25 (39.1)	19 (31.7)	11 (23.4)
LDA	23 (19.2)	8 (12.5)	14 (23.3)	8 (17.0)
MDA	51 (42.5)	18 (28.1)	23 (38.3)	20 (42.6)
HDA	6 (5.0)	10 (15.6)	3 (5.0)	7 (14.9)
Week 72				
Remission	54 (45.0)	30 (46.9)	26 (43.3)	20 (42.6)
LDA	18 (15.0)	10 (15.6)	13 (21.7)	9 (19.1)
MDA	38 (31.7)	16 (25.0)	16 (26.7)	13 (27.7)
HDA	2 (1.7)	6 (9.4)	2 (3.3)	4 (8.5)
DAS28-ESR, n (%)				
Week 48				
Remission	19 (15.8)	14 (21.9)	11 (18.3)	5 (10.6)
LDA	17 (14.2)	8 (12.5)	6 (10.0)	8 (17.0)
MDA	62 (51.7)	24 (37.5)	34 (56.7)	23 (48.9)
HDA	18 (15.0)	16 (25.0)	8 (13.3)	10 (21.3)
Week 72				
Remission	33 (27.5)	19 (29.7)	19 (31.7)	6 (12.8)
LDA	20 (16.7)	12 (18.8)	11 (18.3)	15 (31.9)
MDA	47 (39.2)	21 (32.8)	23 (38.3)	21 (44.7)
HDA	13 (10.8)	10 (15.6)	5 (8.3)	4 (8.5)
Sustainability of LDA ^c				
DAS28-CRP, n (%)				
<6 months sustained LDA	59 (49.2)	27 (42.2)	29 (48.3)	17 (36.2)
≥6 months sustained LDA	42 (35.0)	24 (37.5)	22 (36.7)	20 (42.6)
DAS28-ESR, n (%)				
<6 months sustained LDA	63 (52.5)	29 (45.3)	26 (43.3)	29 (61.7)
≥6 months sustained LDA	24 (20.0)	14 (21.9)	15 (25.0)	8 (17.0)

Percentages were calculated using the all-randomized population – extension period subset as the denominator. ^aDefined according to ACR-EULAR Boolean criteria; i.e. tender joint count (of 66 assessed), swollen joint count (of 68 assessed), CRP (mg/dL), patient global assessment (0–10 scale) all ≤ 1. ^bRemission: DAS28 ≤ 2.6; LDA: 2.6 < DAS28 ≤ 3.2; MDA: 3.2 < DAS28 ≤ 5.1; HDA: DAS28 > 5.1. ^cLDA (including remission) was indexed as DAS28 ≤ 3.2. DAS28: Disease Activity Score using 28 joints; EU: European Union; HDA: high disease activity; LDA: low disease activity; MDA: moderate disease activity; RTX: rituximab; US: United States.

approval of CT-P10 in territories including Europe for the treatment of RA and other B-cell-related diseases.

Our analyses support the week 24 and week 48 findings of this study, which demonstrated the PK equivalence of CT-P10, US-RTX and EU-RTX; the efficacy equivalence of CT-P10 vs a pooled group of patients receiving US-RTX or EU-RTX; and comparable PD, immunogenicity and safety profiles between CT-P10 and its reference product [17, 18]. The data are also consistent with a previous Phase 1 study in patients with RA in which PK equivalence of single courses of CT-P10 and EU-RTX was demonstrated at week 24 [14], as well as with additional results of that study which showed that (i) the efficacy, PK, PD, immunogenicity and safety of up to two treatment courses of CT-

P10 and EU-RTX were comparable up to week 72 [22], and (ii) in a subsequent open-label extension of 56 weeks' duration, the efficacy and safety of continuous CT-P10 usage was comparable to that of switching from EU-RTX to CT-P10 [23].

A key strength of this Phase 3 study is that it assessed the similarity of CT-P10 and both the US and EU formulations of rituximab. However, a lack of a control group maintained on EU-RTX for the duration of the study including the extension period meant it was not possible to compare long-term results among CT-P10/CT-P10, US-RTX/US-RTX and EU-RTX/EU-RTX maintenance groups. Nevertheless, data from the main period and the extension period together provide evidence of a stable

TABLE 3 Adverse events in the extension period, up to week 72 (safety population – extension period subset)

	CT-P10/CT-P10 (n = 122)	US-RTX/US-RTX (n = 64)	US-RTX/CT-P10 (n = 62)	EU-RTX/CT-P10 (n = 47)
Total TEAEs, n	85	40	45	15
Patients with ≥1 TEAE, n (%)	48 (39.3)	21 (32.8)	26 (41.9)	10 (21.3)
Treatment-related, n (%)	24 (19.7)	13 (20.3)	14 (22.6)	4 (8.5)
TEAE grade ≥3, n (%)	5 (4.1)	1 (1.6)	2 (3.2)	0
Total TESAEs, n	6	0	1	0
Patients with ≥1 TESAE, n (%)	4 (3.3)	0	1 (1.6)	0
Treatment-related, n (%)	1 (0.8)	0	1 (1.6)	0
Discontinuation due to AEs, n (%)	1 (0.8)	0	0	0
TEAEs due to infection ^a , n (%)	21 (17.2)	14 (21.9)	14 (22.6)	3 (6.4)
URTI	10 (8.2)	10 (15.6)	8 (12.9)	0
UTI	8 (6.6)	2 (3.1)	2 (3.2)	1 (2.1)
LRTI	1 (0.8)	3 (4.7)	2 (3.2)	2 (4.3)
Gastroenteritis	0	0	2 (3.2)	0
Vaginitis	0	2 (3.1)	0	0
TEAEs due to IRRs, n (%)	5 (4.1)	3 (4.7)	2 (3.2)	2 (4.3)
Grade 1	2 (1.6)	1 (1.6)	1 (1.6)	2 (4.3)
Grade 2	3 (2.5)	2 (3.1)	1 (1.6)	0
Haematological TEAEs (grade ≥3), n (%)	5 (4.1)	2 (3.1)	3 (4.8)	1 (2.1)
Anaemia	0	1 (1.6)	1 (1.6)	0
Leukopenia	5 (4.1)	1 (1.6)	2 (3.2)	1 (2.1)

^aTEAEs reported for ≥3% patients in any group. AE: adverse event; EU: European Union; IRR: infusion-related reaction; LRTI: lower respiratory tract infection; RTX: rituximab; TEAE: treatment-emergent adverse event; TESAE: treatment-related serious adverse event; URTI: upper respiratory tract infection; US: United States; UTI: urinary tract infection.

therapeutic effect with CT-P10 over three treatment courses, as well as single switch data from the reference product.

Efficacy and safety of longer-term treatment with rituximab in patients with RA has been assessed in the 5-year follow-up REFLEX study [24]. In REFLEX, patients were given ≤5 courses of rituximab ‘as-needed’, with the results demonstrating that re-treatment was associated with maintained or improved efficacy. In addition, a pooled observed case analysis of >3000 patients, who received ≤17 courses of rituximab indicated that rituximab was associated with no increased safety risk up to 9.5 years [25]. Data on the comparability of other rituximab biosimilars to reference product are also available [26–30]. To our knowledge, this and past reports on CT-P10 [14, 15, 17, 18, 22, 23] provide the most extensive and rigorously analysed set of published data on the efficacy, safety and other clinical properties of a rituximab biosimilar.

Although rituximab is an established effective treatment option for RA patients with an inadequate response or intolerance to anti-TNF biologics [31], patient access can be highly restricted, particularly in lower income countries [32]. Effective biosimilar availability can ultimately result in considerably increased access to effective biological treatments. Recent EULAR and ACR consensus recommendations, largely based upon expert opinion, state that approved biosimilars should be preferred if they are appreciably cheaper than their reference products [33, 34], and the replacement of certain originator biologics with biosimilars has already begun apace. For example,

CT-P13, an infliximab biosimilar, has been utilized for RA and other immune-related inflammatory disorders, partly due to positive results of studies that have assessed the efficacy and safety of switching to CT-P13 from infliximab, including the large Phase 4 NOR-SWITCH trial [35–38]. However, more clinical trial data and real-world evidence are required to further strengthen the case for switching.

In conclusion, this Phase 3 extension study demonstrated that switching from US-RTX or EU-RTX after two treatment courses had no adverse effect on the efficacy, PD, immunogenicity and safety of a third treatment course with CT-P10, vs patients who remained on CT-P10 or US-RTX throughout the three treatment courses. CT-P10 appears efficacious and well tolerated up to week 72 in patients with RA.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

References

- Bugatti S, Vitolo B, Caporali R, Montecucco C, Manzo A. B cells in rheumatoid arthritis: from pathogenic players to disease biomarkers. *Biomed Res Int* 2014;2014:1.
- Marston B, Palanichamy A, Anolik JH. B cells in the pathogenesis and treatment of rheumatoid arthritis. *Curr Opin Rheumatol* 2010;22:307-15.
- Boross P, Leusen JH. Mechanisms of action of CD20 antibodies. *Am J Cancer Res* 2012;2:676-90.
- Edwards JC, Szczepanski L, Szechinski J. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;350:2572-81.
- Cohen SB, Emery P, Greenwald MW *et al*. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum* 2006;54:2793-806.
- Emery P, Fleischmann R, Filipowicz-Sosnowska A *et al*. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum* 2006;54:1390-400.
- European Medicines Agency. MabThera Summary of Product Characteristics; 2018. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf (14 May 2019, date last accessed).
- Genentech Inc. Rituxan Prescribing Information; 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103705s5453lbl.pdf (14 May 2019, date last accessed).
- Generics and Biosimilars Initiative. EC approval for first cancer biosimilar Truxima; 2017. <http://www.gabionline.net/Biosimilars/News/EC-approval-for-first-cancer-biosimilar-Truxima> (14 May 2019, date last accessed).
- European Medicines Agency. Truxima Summary of Product Characteristics; 2018. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004112/WC500222694.pdf (14 May 2019, date last accessed).
- European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf (14 May 2019, date last accessed).
- U.S. Food and Drug Administration. Scientific considerations in demonstrating biosimilarity to a reference product: Guidance for industry; 2015. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/scientific-considerations-demonstrating-biosimilarity-reference-product> (14 May 2019, date last accessed).
- Buske C, Ogura M, Kwon HC, Yoon SW. An introduction to biosimilar cancer therapeutics: definitions, rationale for development and regulatory requirements. *Future Oncol* 2017;13:5-16.
- Yoo DH, Suh CH, Shim SC *et al*. A multicentre randomised controlled trial to compare the pharmacokinetics, efficacy and safety of CT-P10 and innovator rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2017;76:566-70.
- Kim WS, Buske C, Ogura M *et al*. Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 compared with rituximab in patients with previously untreated advanced-stage follicular lymphoma: a randomised, double-blind, parallel-group, non-inferiority phase 3 trial. *Lancet Haematol* 2017;4:e362-73.
- Ogura M, Sancho JM, Cho SG *et al*. Efficacy, pharmacokinetics and safety of the biosimilar CT-P10 in comparison with rituximab in patients with previously untreated low tumour burden follicular lymphoma: a randomised, double-blind, parallel-group phase 3 trial. *Lancet Haematol* 2018;5:e543-53.
- Park W, Božić-Majstorović L, Milaković D *et al*. Comparison of biosimilar CT-P10 and innovator rituximab in patients with rheumatoid arthritis: a randomised controlled Phase III trial. *MAbs* 2018;10:934-43.
- Suh C-H, Yoo DH, Berrocal Kasay A *et al*. Long-term efficacy and safety of biosimilar CT-P10 versus innovator rituximab in rheumatoid arthritis: 48-week results from a randomized phase III trial. *BioDrugs* 2019;33:79-91.
- World Medical Association. WMA Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects; 2018. <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/> (14 May 2019, date last accessed).
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for

- Human Use. International Conference on Harmonisation Tripartite Guideline. Guidance for Good Clinical Practice E6(R1); 1996. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf (14 May 2019, date last accessed).
- 21 van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol* 2000;27:261-3.
 - 22 Yoo DH, Suh CH, Shim SC *et al.* Efficacy, safety and pharmacokinetics of up to two courses of the rituximab biosimilar CT-P10 versus innovator rituximab in patients with rheumatoid arthritis: results up to week 72 of a phase I randomized controlled trial. *BioDrugs* 2017;31:357-67.
 - 23 Park W, Suh CH, Shim SC *et al.* Efficacy and safety of switching from innovator rituximab to biosimilar CT-P10 compared with continued treatment with CT-P10: results of a 56-week open-label study in patients with rheumatoid arthritis. *BioDrugs* 2017;31:369-77.
 - 24 Keystone EC, Cohen SB, Emery P *et al.* Multiple courses of rituximab produce sustained clinical and radiographic efficacy and safety in patients with rheumatoid arthritis and an inadequate response to 1 or more tumor necrosis factor inhibitors: 5-year data from the REFLEX study. *J Rheumatol* 2012;39:2238-46.
 - 25 van Vollenhoven RF, Emery P, Bingham CO *et al.* Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. *Ann Rheum Dis* 2013;72:1496-502.
 - 26 Williams JH, Hutmacher MM, Zierhut ML *et al.* Comparative assessment of clinical response in patients with rheumatoid arthritis between PF-05280586, a proposed rituximab biosimilar, and rituximab. *Br J Clin Pharmacol* 2016;82:1568-79.
 - 27 Smolen JS, Cohen SB, Tony HP *et al.* A randomised, double-blind trial to demonstrate bioequivalence of GP2013 and reference rituximab combined with methotrexate in patients with active rheumatoid arthritis. *Ann Rheum Dis* 2017;76:1598-602.
 - 28 Jurczak W, Moreira I, Kanakasetty GB *et al.* Rituximab biosimilar and reference rituximab in patients with previously untreated advanced follicular lymphoma (ASSIST-FL): primary results from a confirmatory phase 3, double-blind, randomised, controlled study. *Lancet Haematol* 2017;4:e350-e61.
 - 29 Cohen SB, Burgos-Vargas R, Emery P *et al.* An extension study of PF-05280586, a potential rituximab biosimilar, versus rituximab in subjects with active rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2018;70:1598-606.
 - 30 Cohen S, Emery P, Greenwald M *et al.* A phase I pharmacokinetics trial comparing PF-05280586 (a potential biosimilar) and rituximab in patients with active rheumatoid arthritis. *Br J Clin Pharmacol* 2016;82:129-38.
 - 31 Singh JA, Saag KG, Bridges SL Jr *et al.* 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2016;68:1-25.
 - 32 Putrik P, Ramiro S, Kvien TK *et al.* Inequities in access to biologic and synthetic DMARDs across 46 European countries. *Ann Rheum Dis* 2014;73:198-206.
 - 33 Smolen JS, Landewé R, Bijlsma J *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017;76:960-77.
 - 34 Kay J, Schoels MM, Dörner T *et al.* Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. *Ann Rheum Dis* 2018;77:165-74.
 - 35 Glinborg B, Sørensen IJ, Loft AG *et al.* A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. *Ann Rheum Dis* 2017;76:1426-31.
 - 36 Jørgensen KK, Olsen IC, Goll GL *et al.* Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet* 2017;389:2304-16.
 - 37 Nikiphorou E, Kautiainen H, Hannonen P *et al.* Clinical effectiveness of CT-P13 (infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. *Expert Opin Biol Ther* 2015;15:1677-83.
 - 38 Vergara-Dangond C, Sáez Belló M, Climente Martí M, Llopis Salvia P, Alegre-Sancho JJ. Effectiveness and safety of switching from innovator infliximab to biosimilar CT-P13 in inflammatory rheumatic diseases: a real-world case study. *Drugs R D* 2017;17:481-5.