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Assessment of effectiveness and safety of biosimilar infliximab (CT-P13) in a real-life setting for treatment of patients with active rheumatoid arthritis or ankylosing spondylitis

Cătălin Codreanu¹, Klára Šírová², Katerina Jarošová³, Anastas Batalov⁴

¹Center for Rheumatic Diseases, University of Medicine and Pharmacy, Bucharest, Romania

²Revmatologie, Revmatologie MU Dr. Klara Sirova, sro, Ostrava, Czech Republic

³Institute of Rheumatology, Prague, Czech Republic

⁴Rheumatology, Medical University of Plovdiv, UMHAT “Kaspela”, Plovdiv, Bulgaria

Corresponding author

Cătălin Codreanu

Postal address: 020389, Thomas Masaryk no. 5, Bucharest, Romania

Email: ccodreanu01@gmail.com

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Author contributions

All authors were involved in the conception and design of the study and interpretation of the data. CC was involved in drafting of the manuscript and final approval of the version to be published. All authors agreed to be accountable for all aspects of this paper.

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Abstract

Objective: To assess the effectiveness and safety of infliximab biosimilar, CT-P13, administered in a real-life setting to adult patients with active rheumatoid arthritis (RA) or ankylosing spondylitis (AS).

Methods: This multicentre, non-interventional, observational study was conducted in Bulgaria, Czech Republic and Romania. A total of 151 patients with severe active RA ($n = 81$) or AS ($n = 70$) were enrolled and treated with CT-P13 for 24 weeks, according to current medical recommendations. Effectiveness was assessed using the 4-item Disease Activity Score 28 with C-reactive protein (DAS28-CRP) for RA patients, and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for AS patients. Safety was assessed by withdrawals and adverse events (AEs).

Results: A total of 129 patients (RA: 67; AS: 62) were included in the effectiveness analysis. CT-P13 treatment significantly improved DAS28-CRP scores at 12 and 24 weeks ($p = 0.0001$ vs baseline for both timepoints) in patients with RA, and BASDAI scores at 12 and 24 weeks ($p = 0.0001$ vs baseline for both timepoints) in patients with AS. CRP levels were significantly reduced at 12 and 24 weeks ($p = 0.0001$ vs baseline for both timepoints). Among 713 infusions, 34 adverse events (AEs) were reported (4.8% of infusions), of which 11 were considered related to CT-P13 treatment. Two of seven serious AEs were considered possibly (hepatocellular injury) or definitely (dyspnoea due to allergic infusion reaction) treatment related. Eight patients discontinued CT-P13 due to AEs and four patients were withdrawn due to therapeutic failure.

Conclusions: CT-P13 was effective and safe in a real-life setting in patients with active RA or AS.

Key words: infliximab biosimilar, CT-P13, rheumatoid arthritis, ankylosing spondylitis

Introduction

Over the past decades, the introduction of biologics has significantly changed the management of several immune-mediated inflammatory diseases including rheumatoid arthritis (RA) and ankylosing spondylitis (AS)¹. However, the high cost of biologics imposes limits on their use, particularly in low-income countries²⁻⁴. A significant number of patients with arthritic conditions residing in European countries with lower GDP have limited access to biologic disease-modifying anti-rheumatic drugs (DMARDs)⁴.

The development and implementation of treatment protocols stipulating use of biosimilars can improve access to established biological therapies, whilst maintaining affordable healthcare budgets⁵. The estimated cost savings resulting from use of biosimilar drugs was predicted to be between €11.8 and 33.4 billion from 2007 to 2020 in the EU⁶, and \$44.2 billion from 2014 to 2024 in the United States (US)⁷. Cost savings generated by use of biosimilars may compensate for inequality of healthcare access in economically-disadvantaged countries⁸.

The infliximab biosimilar CT-P13 was the first monoclonal antibody biosimilar to be approved by the European Medicines Agency^{1,9}. CT-P13 has also received regulatory approval in other countries including Australia, Canada and Japan¹⁰, and recently by the US Food and Drug Administration⁹. Clinical trials designed to compare the efficacy and safety of CT-P13 with reference monoclonal antibody infliximab in patients with active RA or AS have consistently demonstrated therapeutic equivalence. In the PLANETRA phase III randomised clinical trial (RCT) of RA patients, CT-P13 and infliximab were comparable in terms of efficacy and safety at 30 weeks¹¹, 54 weeks¹² and in the two-year extension study¹³. Similarly, the efficacy and safety profiles of CT-P13 and infliximab were comparable in the PLANETAS phase III trial in AS patients at 30 weeks¹⁴, 54 weeks¹⁵ and two years¹⁶. In addition to demonstrating the efficacy and safety of a given intervention under the strict conditions of a RCT, it is also necessary to determine its effectiveness and tolerability under 'real-life' conditions; this can be achieved through observational studies conducted in everyday practice. The current study aimed to assess the effectiveness and safety of CT-P13 administered in a real-life setting to adult patients with active RA or AS from selected countries in Eastern and Central Europe.

Methods

Study design and inclusion criteria

This multicentre, non-interventional, observational study was conducted in Bulgaria, the Czech Republic and Romania involving patients with active progressive RA (and inadequate response to methotrexate or other conventional synthetic DMARDs) or active AS (and inadequate response to conventional therapy with non-steroidal anti-inflammatory drugs). Eligible patients were adults >18 years of age with RA, diagnosed according to 1987 American College of Rheumatology (ACR)¹⁷ or 2010 ACR/European League Against Rheumatism (EULAR)¹⁸ classification criteria and adult patients with severe active AS diagnosed according to Assessment of SpondyloArthritis international Society (ASAS) criteria¹⁹, who were candidates for biological therapy.

Patients received CT-P13 at baseline (visit 1), week 2 (visit 2), week 6 (visit 3), and between weeks 12 and 14 (visit 4) and were followed for 24 weeks. Study investigators determined specific doses/timing of infusions according to local product label and prescription and/or reimbursement guidelines.

Effectiveness was assessed at baseline and at visits 4 (week 12) and 5 (week 24) using the 4-item Disease Activity Score 28 with C-reactive protein (DAS28-CRP) for patients with RA²⁰, and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for patients with AS²¹.

The study was approved by the national ethics committees and written informed consent was obtained from all participants.

Endpoints

The primary endpoint was the percentage of patients with a response to CT-P13 at 24 weeks, where response was defined as: 1) an improvement of at least 1.2 points in the DAS28-CRP score if the

absolute score at week 24 was ≤ 3.2 , or an improvement of at least 0.6 points in the DAS28-CRP score if the absolute score at week 24 was > 3.2 and ≤ 5.1 , or an improvement of at least 1.2 points if the absolute score at week 24 was > 5.1 (good + moderate response as per EULAR criteria for patients with RA)²²; 2) an improvement of at least 50% in the BASDAI score or an absolute change of 2 units (on a 0–10 scale) relative to baseline (for patients with AS).

The number of patients in remission or low disease activity at 24 weeks was also evaluated using established criteria. In RA, remission is defined as a DAS28 score of < 2.6 points and low disease activity is defined as a DAS28 score < 3.2 points^{23,24}. In AS, low disease activity is defined as a BASDAI score of ≤ 3 points²⁵. As the Bath Ankylosing Spondylitis Functional Index was not applied in this study, response/remission as per ASAS was not available and, instead, remission criteria based on the Ankylosing Spondylitis Disease Activity Score (ASDAS) were applied: $0.12 \times \text{Back Pain} + 0.06 \times \text{Duration of Morning Stiffness} + 0.11 \times \text{Patient Global} + 0.07 \times \text{Peripheral Pain/Swelling} + 0.58 \times \ln(\text{CRP}+1)$ ^{26–28}. Remission was defined as an ASDAS score of < 1.3 points^{25,29}.

Secondary endpoints were: change in DAS28-CRP score (for patients with RA) and change in BASDAI score (for patients with AS) from baseline to weeks 12 and 24; change in CRP levels from baseline to weeks 12 and 24 (in both patient groups).

Safety was assessed based on numbers of treatment discontinuations and adverse events (AEs) reported. AEs were assessed with respect to type, seriousness, severity, causal relationship with study medication, date of onset, date of resolution, actions taken, and outcome.

Statistical analyses

As the study was observational, no hypothesis testing was performed in the primary analyses. Descriptive statistics were used. Continuous parameters were described as mean $\pm$ standard deviation (SD). Qualitative data were described by absolute and relative (%) frequency distributions. For assessments over time, the observed case method was used without imputations for missing data. In the secondary analyses, paired t tests were applied to compare week 12 and week 24 measurements to baseline. A p value of < 0.5 was considered as significant.

Results

Patient characteristics

Study enrolment began in December 2014. By October 2016, 151 subjects (47% male, 53% female) with a mean age of 49.1 ± 13.6 years had been enrolled (Table 1). The population consisted of 81 patients with RA and 70 patients with AS. Consistent with the age and gender distribution observed in clinical practice, the RA group had a higher mean age (55.8 ± 11.4 years) and a higher proportion of females (55 vs 26 males), whereas the AS group had a lower mean age (41.4 ± 13.6 years) and a higher proportion of males (45 vs 25 females). The majority of enrolled patients (RA: 66.7%; AS: 80.0%) had no previous exposure to anti-TNF α therapy.

Median follow-up was 167 days. At week 24 (visit 5), mean doses of CT-P13 were 247 ± 61 mg (3.3 ± 0.6 mg/kg) for patients with RA and 384 ± 86 mg (4.9 ± 0.5 mg/kg) for patients with AS.

Patient disposition

Of the 151 enrolled patients, 19 terminated the study prematurely and three patients with missing efficacy measurements were excluded from the effectiveness analyses. Thus, a total of 129 patients (RA: 67; AS: 62) had baseline and follow-up primary efficacy measurements at visit 5 (week 24) and were evaluated for effectiveness of study treatment. Two subjects reached the 24-week efficacy measurement time point (end of study) and were included in the effectiveness analyses, but had to discontinue CT-P13 due to adverse events (AEs). All patients (n=151) were included in the safety analysis.

Seven patients discontinued CT-P13 during the course of the study due to AEs, which included four definitely-related and one possibly-related allergic infusion reactions; one possibly-related hepatocellular injury; and one unrelated ischemic stroke. Other withdrawals from CT-P13 treatment

included five patients due to therapeutic failure, two patients due to non-compliance, two patients at their own request (reasons not specified), and one patient at the request of the sponsor (ambiguous tuberculosis test result). Three patients were lost to follow-up.

Effectiveness

After 24 weeks of CT-P13 treatment, 71.6% of patients with RA and 80% of patients with AS were classified as responders, yielding a response rate of 75.5% in the overall effectiveness population (Table 2). Patients who had discontinued CT-P13 treatment and those with missing values were considered to be non-responders.

Among patients with RA, 36 (44%) achieved remission and 45 (56%) achieved low disease activity at week 24. Among patients with AS, 22 (31%) achieved remission and 45 (64%) achieved low disease activity at week 24.

Disease activity indices showed rapid and significant improvement within the first 12 weeks of CT-P13 treatment, followed by more gradual but continuous improvement up to week 24. In evaluable patients with RA, mean DAS28-CRP scores improved from 5.8 ± 1.0 at baseline to 3.4 ± 1.4 at week 12 ($p = 0.0001$), and to 3.2 ± 1.4 at week 24 ($p = 0.0001$) (Figure 1). In evaluable patients with AS, mean BASDAI scores improved from 6.8 ± 1.7 at baseline to 3.3 ± 2.2 at week 12 ($p = 0.0001$ vs baseline), and to 2.6 ± 1.8 at week 24 ($p = 0.0001$ vs baseline) (Figure 2).

There was a significant decrease in CRP levels after 12 and 24 weeks of CT-P13 treatment. In patients with RA, mean CRP levels decreased from 26.1 ± 26.0 mg/L at baseline to 10.2 ± 18.8 mg/L at week 12 ($p = 0.0001$ vs baseline), and to 7.7 ± 11.5 mg/L at week 24 ($p = 0.0001$ vs baseline). In patients with AS, mean CRP levels decreased from 28.8 ± 23.5 mg/L to 6.8 ± 11.0 mg/L at week 12 ($p = 0.0001$ vs baseline), then increased slightly to 7.6 ± 15.5 mg/L at week 24, but remained significantly lower than the baseline value ($p = 0.0001$). Figure 3 shows changes from baseline in CRP levels in the overall effectiveness population ($n = 128$).

Safety

A total of 713 infusions of CT-P13 were administered over the course of the study and 34 AEs (4.8% of infusions) were recorded of which 23 events (3.2%) were considered unrelated to CT-P13 treatment. Among 11 related AEs (six infusion reactions, five hepatocellular injury), five events (0.7% of infusions) were considered definitely related, one event (0.1%) was probably related, and five events (0.7%) were possibly related to CT-P13 treatment. The majority of treatment-related AEs were mild to moderate in severity (Table 3). Seven serious AEs were reported: spontaneous pneumothorax ($n = 2$), worsening of arthritis ($n = 1$), upper respiratory tract infection ($n = 1$), and ischemic stroke ($n = 1$) were unrelated to CT-P13; hepatocellular injury ($n = 1$, resolved without sequelae) was possibly related to CT-P13; and dyspnoea due to allergic infusion reaction ($n = 1$) was definitely related to CT-P13. Among 34 total AEs, 15 occurred in RA patients and 19 occurred in AS patients. Among 11 related AEs, there were three in RA patients and eight in AS patients.

Discussion

The current study showed that the infliximab biosimilar, CT-P13, administered to patients with active RA or AS in a real world setting was effective and safe during 24 weeks' observation. To our knowledge this is the first study of CT-P13 in patients with RA and AS treated in daily clinical practice in countries from Eastern and Central Europe.

In terms of efficacy, 71.6% of patients with RA and 80% of patients with AS were responders to CT-P13 after 24 weeks of treatment according to DAS28-CRP and BASDAI criteria, respectively. Rapid and marked improvement in disease activity was observed from the start of CT-P13 treatment. A statistically significant reduction in DAS28-CRP and BASDAI scores relative to baseline was observed at 12 weeks and was maintained through to 24 weeks. CRP levels showed a similar pattern, with a marked decrease from baseline to 12 weeks followed by further improvement or maintenance at 24

weeks. At week 24, 44% and 56% of patients with RA, and 31% and 64% of patients with AS, were in remission or had achieved low disease activity.

With regard to safety, of 34 AEs (4.8% of total CT-P13 infusions) reported over the 24-week observation period, 11 events (1.5% of total infusions) were deemed to have a definite, probable or possible causal relationship with CT-P13 treatment, and the majority (91%) of events were mild to moderate in severity. Among seven serious AEs reported, two events had a definite (dyspnoea due to allergic infusion reaction) or possible (hepatocellular injury) relationship with CT-P13. During 24 weeks of treatment, eight patients discontinued CT-P13 due to AEs, of which six events (five allergic infusion reactions, one hepatocellular injury) had a definite or possible causal relationship.

The effectiveness and safety of CT-P13 observed in the current study aligns well with that reported in RCTs of CT-P13 in patients with inflammatory arthritides. The PLANETRA and PLANETAS trials provided initial long-term randomized evidence of the equivalence of CT-P13 and reference product infliximab in patients with RA and AS, respectively, with respect to efficacy, immunogenicity, pharmacokinetics/pharmacodynamics and safety¹¹⁻¹⁶. The pattern of change in disease activity indices reported in these trials was similar to that observed in the patient population included in the present study. In PLANETRA, the DAS28-CRP decreased from 5.9 at baseline to 3.8 at week 14, to 3.7 at week 30, and was maintained at 3.6 at week 54¹². In PLANETAS, the BASDAI decreased from 6.7 at baseline to 3.9 at week 14, to 3.7 at week 30, and was maintained at 3.8 at week 54¹⁵. Respective extension studies confirmed that switching from reference infliximab to CT-P13 had no negative effects on efficacy and safety in either patient population over an additional year of treatment^{13,16}. These studies were instrumental to CT-P13 gaining regulatory approval in Europe and elsewhere for the treatment of patients with RA and AS.

Further long-term randomized evidence is available from Japan where CT-P13 and reference infliximab were shown to be pharmacokinetically equivalent and comparable in terms of their therapeutic effectiveness and tolerability over 54 weeks in patients with RA³⁰. In the subsequent extension phase, CT-P13 was well tolerated with persistent efficacy for up to two additional years in patients who maintained treatment and in those who switched to CT-P13 from reference infliximab³¹.

Several prospective observational studies have reported the clinical experience of patients with rheumatic diseases switching from reference infliximab to biosimilar CT-P13³²⁻³⁶. With the exception of one group reporting a 30% disease relapse rate (7 of 23 patients) within 1-2 months of switching³³, the other real-life switching experiences showed no differences in the efficacy, safety, and immunogenicity profiles of patients who switched from reference infliximab to biosimilar CT-P13 and those treated with CT-P13 only for up to one year^{32,34-36}. Our population differed in that the majority of patients (RA: 66.7%; AS: 80.0%) had no previous exposure to anti-TNF α therapy. Although no obvious differences were apparent between patients who had or had not previously been treated with anti-TNF α therapy, we acknowledge that the patient numbers in the present study were smaller and that the observation period was shorter compared with the switching studies, especially those from Norway³⁵ and Denmark³⁶.

Although the study may be limited to some extent by its observational design which can introduce selection bias and provides a lower evidence level compared with RCTs, and by the relatively modest sample size, the similarities between the effectiveness and safety results presented here and those reported in CT-P13 registration studies strengthen the findings. Moreover, data derived from usual clinical practice provide valuable insight into the real-world management of patients. Indeed, our results correlate well with clinical response rates of approximately 70% for biosimilar and reference infliximab, and with the pattern and numerical value of change in disease activity indices from baseline to evaluation timepoints, reported in RCTs in patient with RA or AS^{12,15,23}. This level of efficacy, combined with good tolerability over 2 years of treatment^{13,16,24} suggests an important role for CT-P13 in the treatment of patients with inflammatory rheumatic conditions.

Conclusions

Overall, the results presented in the current study corroborate previous research findings from CT-P13 RCTs of up to 2 years' duration and suggest that biosimilar CT-P13 is an effective and safe alternative to originator infliximab in a real-world setting in patients with active RA or AS. CT-P13 has the potential to provide equivalent disease control and tolerability as reference infliximab in a greater number of patients with RA and AS, in a more cost-effective manner.

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Figure legends

Figure 1: Change from baseline in the Disease Activity Score 28 with C-reactive protein (DAS28-CRP) score in patients with rheumatoid arthritis at week 12 (n = 66) and week 24 (n = 67).

Figure 2: Change from baseline in the Bath Ankylosing Spondylitis Activity Index (BASDAI) score in patients with ankylosing spondylitis at week 12 (n = 64) and week 24 (n = 62).

Figure 3: Change from baseline in C-reactive protein (CRP) at week 12 (n = 124) and week 24 (n = 128) in patients with rheumatoid arthritis or ankylosing spondylitis.

Figure 1

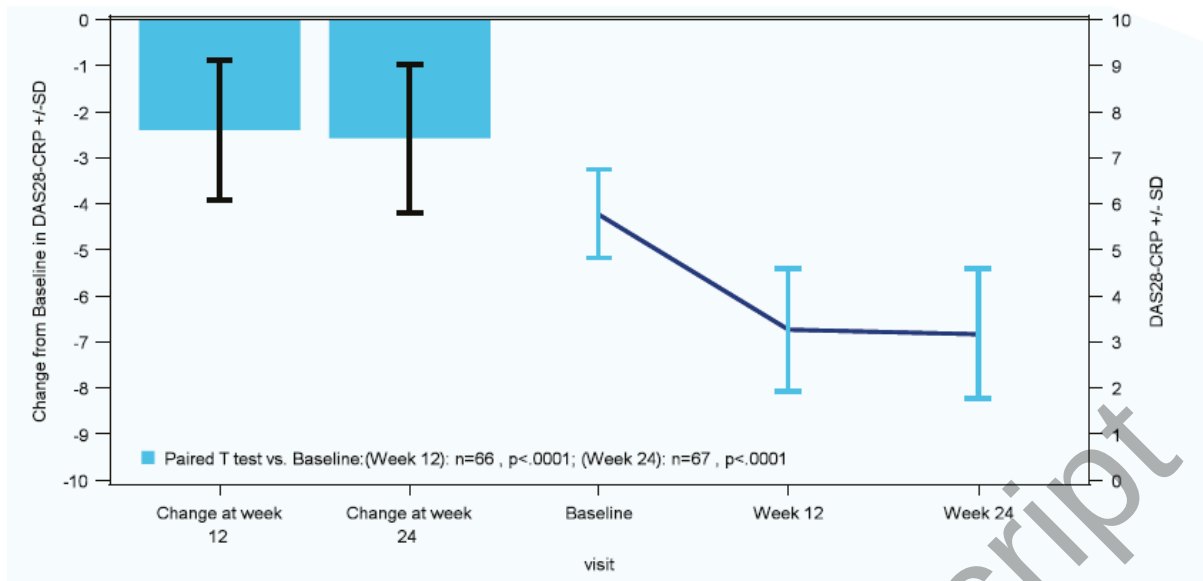


Figure 2

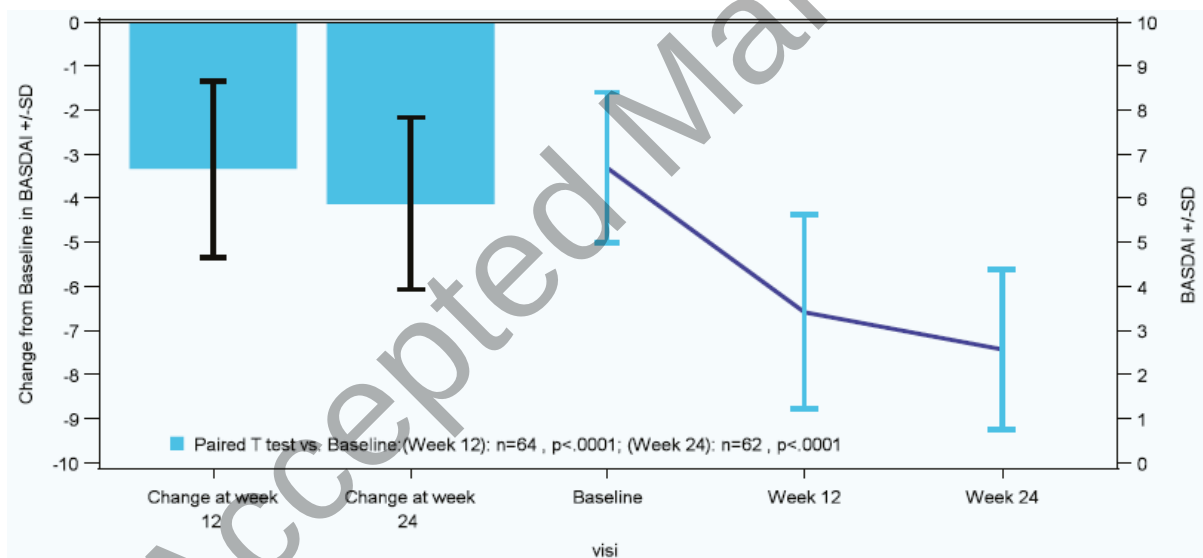


Figure 3

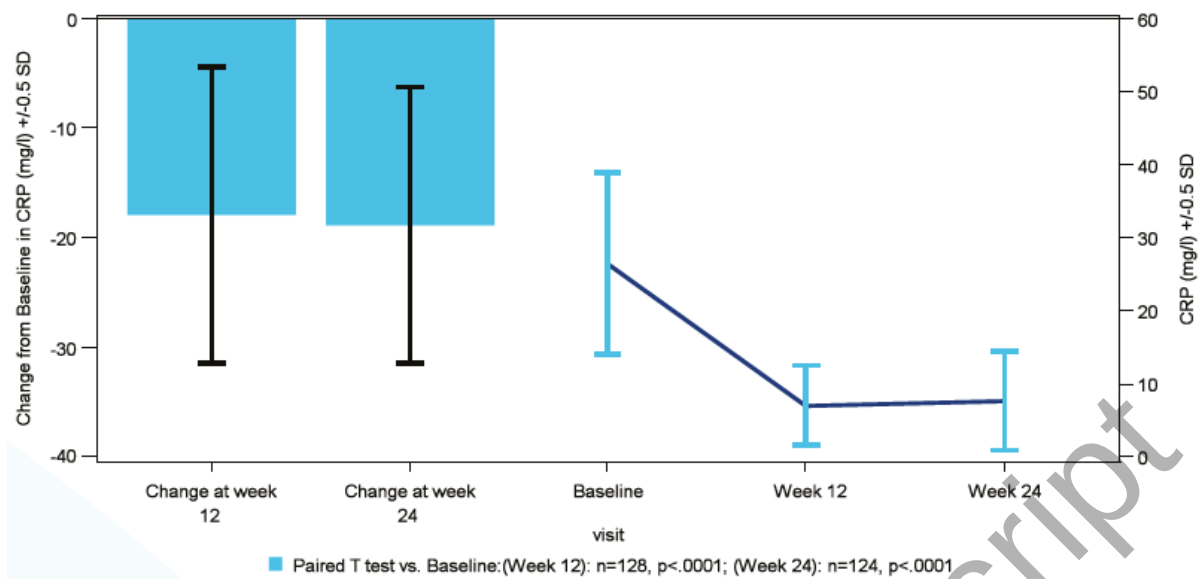


Table 1. Patients' baseline demographic and treatment characteristics.

	Rheumatoid arthritis (n=81)	Ankylosing spondylitis (n=70)	All (n=151)
Gender (M : F)	26 : 55	45 : 25	71 : 80
Age (years), mean $\pm$ SD	55.8 $\pm$ 11.4	41.4 $\pm$ 11.7	49.1 $\pm$ 13.6
DAS28-CRP, mean $\pm$ SD	5.8 $\pm$ 1.0	NA	NA
BASDAI, mean $\pm$ SD	NA	6.8 $\pm$ 1.7	NA
CRP (mg/L), mean $\pm$ SD	26.1 $\pm$ 26.0	28.8 $\pm$ 23.5	NA
<i>De novo</i> anti-TNF α treatment, n (%)	54 (66.7%)	56 (80.0%)	110 (72.8%)
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-Reactive Protein; DAS28-CRP, 28-joint Disease Activity Score with CRP; NA, not applicable; TNF α , Tumor Necrosis Factor alpha.			

Table 2. Response rates to CT-P13 in patients with severe active rheumatoid arthritis (RA) and ankylosing spondylitis (AS) at week 24. Study dropouts and patients with missing values at study end were considered to be non-responders.

RA ^a (n = 81)	AS ^b (n = 70)	All
71.6%	80.0%	75.5%
^a For patients with RA, a response was defined as an improvement of > 0.6 in the DAS28-CRP score if the absolute score was ≤ 5.1, or an improvement of ≥ 1.2 if the absolute score was > 5.1. ^b For patients with AS, a response was defined as an absolute change (decrease) of at least 2 units (on a 0 to 10 scale) or a ≥ 50% decrease in the BASDAI score relative to baseline.		

DAS28-CRP: Disease Activity Score 28 with C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

Table 3. Treatment-related adverse events.

	Mild	Moderate	Severe
Total	6 (0.9%)	4 (0.6%)	1 (0.1%)
Infusion reaction	2 (0.3%)	3 (0.4%)	1 (0.1%)
Hepatocellular injury	4 (0.6%)	1 (0.1%)	0