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Certolizumab Pegol Efficacy in Patients With Non-Radiographic Axial Spondyloarthritis Stratified by Baseline MRI and C-Reactive Protein Status: An Analysis From the C-axSpAnd Study

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Objective. Tumor necrosis factor inhibitors (TNFi) are an effective treatment for non-radiographic axial spondyloarthritis (nr-axSpA). To be eligible, however, many authorities require patients with nr-axSpA to show active sacroiliitis on magnetic resonance imaging (MRI) and/or an elevated C-reactive protein (CRP) level, possibly resulting in a perception that patients with nr-axSpA without both factors have only low responses to TNFi treatment. We evaluated clinical responses to certolizumab pegol (CZP) in patients with nr-axSpA stratified by baseline MRI/CRP status.

Methods. C-axSpAnd was a phase 3, multicenter study on CZP in adult patients with active nr-axSpA and objective signs of inflammation. This analysis assessed efficacy of CZP over the 52-week randomized, double-blind, placebo-controlled period in patients stratified into subgroups based on the presence of active sacroiliitis on MRI and CRP level at baseline.

Results. CZP-treated patients across all MRI/CRP subgroups achieved clinical responses greater than placebo. Across outcome measures, CZP-treated MRI+/CRP+ patients demonstrated the greatest clinical responses, but substantial improvements were also observed in CZP-treated MRI+/CRP– and MRI–/CRP+ patients. Ankylosing Spondylitis Disease Activity Score Major Improvement response rates at week 52 among CZP-treated patients (75.6% MRI+/CRP+; 47.5% MRI–/CRP+; and 29.7% MRI+/CRP–) were higher than rates in placebo groups (range: 3.9%-12.5%). Assessment of SpondyloArthritis international Society 40% response, Bath Ankylosing Spondylitis Disease Activity Index, and Bath Ankylosing Spondyloarthritis Functional Index had similar response patterns, although differences between the CZP-treated MRI/CRP subgroups were smaller. Clinical responses among CZP-treated patients were also observed in additional subgroups, including those with low Spondyloarthritis Research Consortium of Canada MRI sacroiliac joint inflammation scores and those with normal baseline CRP levels.

Conclusion. Our findings indicate that CZP treatment benefits patients with nr-axSpA across MRI+/CRP+, MRI–/CRP+, and MRI+/CRP– subgroups.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that primarily affects the spine and sacroiliac (SI) joints (1). Non-radiographic axSpA (nr-axSpA) is one of the two subpopulations of axSpA. It is distinguished from radiographic axSpA (r-axSpA; also known as ankylosing spondylitis) by the absence or limited extent of damage to the SI joints on pelvic radiographs

[Correction added on 11 July 2022, after first online publication: The figure title and caption have been added in Figure S1.]

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Data from this manuscript may be requested by qualified researchers 6 months after product approval in the US and/or Europe, or global development is discontinued, and 18 months after trial completion. Investigators may request access to anonymized individual participant data (IPD) and redacted study documents, which may include: raw datasets, analysis-ready datasets, study protocol, blank case report form, annotated case report form, statistical analysis plan, dataset specifications, and clinical study report. Prior to use of the data, proposals need to be approved by an independent review panel at www.Vivli.org, and a signed data sharing agreement will need to be executed. All documents are available in English only,

(1). Both patients with nr-axSpA and r-axSpA have a significant and similar burden of disease (2,3). The main symptoms include chronic back pain, morning stiffness, fatigue, and increasing levels of disability contributing to worsening quality of life (2,4).

In nr-axSpA, diagnosis and therapeutic decision-making is complex because of the absence of definitive radiographic changes on SI joints found in r-axSpA, and the fact that most clinical measures of nr-axSpA are subjective and based on patient perceptions (2). The use of specific objective signs of inflammation represents a possible solution to this problem. These signs include active inflammation of the SI joints (active sacroiliitis) on magnetic resonance imaging (MRI; according to the Assessment of SpondyloArthritis international Society [ASAS] classification criteria) (5) and elevated levels of C-reactive protein (CRP) above the upper limit of normal (ULN). In both r-axSpA and nr-axSpA, these features have been shown to be correlated with disease progression and are strong predictors of response to tumor necrosis factor inhibitor (TNFi) therapy (6–12). Patients with nr-axSpA who either lack active sacroiliitis on MRI or lack elevated CRP, and especially those who lack both factors, have also been shown to be less likely to progress to the radiographic form of axSpA within a given time frame (12–14).

Many local, national, and regional regulatory authorities require patients diagnosed with nr-axSpA to show active sacroiliitis on MRI and/or an elevated CRP level in order to be eligible for TNFi treatment. As a result of these eligibility requirements and current evidence of the relationship between MRI/CRP status and treatment response, there is a perception that patients with nr-axSpA who are lacking one or both of these factors would only experience low or negligible responses to TNFi treatment. However, current understanding of clinical response to treatment in nr-axSpA, and especially of the impact that active sacroiliitis on MRI and CRP level has on clinical response, is limited by a paucity of evidence. This is reflected by the lack of consistency between countries in eligibility criteria for TNFi treatment.

Evaluating the impact of baseline MRI and CRP status on treatment response is crucial to ensure that TNFi therapy can be effectively targeted to patients who will benefit from therapy. Certolizumab pegol (CZP) is an Fc-free, PEGylated TNFi, which has previously demonstrated efficacy and safety in patients with axSpA, including both r-axSpA and nr-axSpA (15,16). This analysis from the C-axSpAnd phase 3 study aimed to evaluate the level of clinical response to CZP in patients with nr-axSpA stratified by their baseline MRI/CRP status, Spondyloarthritis Research Consortium of Canada (SPARCC) MRI SI joint inflammation score (17), and CRP level.

PATIENTS AND METHODS

The C-axSpAnd study protocol, amendments, and patient-informed consent were reviewed by a national, regional, or Independent Ethics Committee or Institutional Review Board. This study was conducted in accordance with the current version of the applicable regulatory and International Conference on Harmonisation–Good Clinical Practice requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws of the countries involved. Full details of the ethics committee involved are available upon request. All patients provided written informed consent to participate in the study.

Study design. C-axSpAnd (NCT02552212) was a phase 3, multicenter study that evaluated CZP 200 mg every 2 weeks in patients with active nr-axSpA who had active sacroiliitis on MRI and/or elevated CRP. The study included a 52-week randomized, double-blind, placebo-controlled period and a 2-year open-label safety follow-up extension. Patients were able to switch to open-label CZP treatment or any other biologic at any point during the trial if disease activity required escalation of treatment. Full details of the C-axSpAnd study design are reported elsewhere (15). We report an analysis of efficacy data to week 52 of the C-axSpAnd study for patients stratified by their MRI status at screening/CRP status at baseline.

Patients. Patients were enrolled at 80 sites across Australia, Europe, North America, and Taiwan. Eligible patients were 18 years of age or older, with confirmed adult-onset nr-axSpA (defined as i] physician-diagnosed axSpA, ii] not meeting the modified New York classification criteria as confirmed by SI joint x-rays, and iii] meeting the ASAS classification criteria for axSpA), symptom duration for 12 months or more, active disease (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] score ≥ 4 and spinal pain score ≥ 4), and previous inadequate response, intolerance, or contraindication to two or more nonsteroidal antiinflammatories (NSAIDs). For inclusion, patients were also required to have active sacroiliitis on MRI based on the ASAS definition of a positive MRI (5) (MRI+) at screening and/or a CRP level above the ULN (CRP+), measured in a central laboratory that used a threshold of 10.0 mg/L or more 3 to 5 days before baseline. All MRI and x-rays were assessed by two central readers and an adjudicator. Patients were excluded if they had exposure to more than one TNFi prior to baseline or primary failure to any TNFi therapy.

Study outcomes. Outcomes are reported to week 52 of C-axSpAnd for patients stratified into subgroups according to

for a prespecified time, typically 12 months, on a password-protected portal.

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their MRI status at screening and CRP status at baseline (MRI+/CRP−, MRI−/CRP+, and MRI+/CRP+; subgroups were prespecified), SPARCC MRI SI joint inflammation score at screening (SPARCC = 0, SPARCC >0 to <2, SPARCC ≥2 to <12, and SPARCC ≥12) (17), and CRP level at baseline (CRP <5 mg/L, CRP ≥5 to <10 mg/L, and CRP ≥10 mg/L). SPARCC score thresholds reflect the quartile values; CRP thresholds were selected to reflect different thresholds for ULN used in this and previous studies on patients with nr-axSpA (18,19).

The primary efficacy variable of the C-axSpAnd study was the proportion of patients achieving a Major Improvement in Ankylosing Spondylitis Disease Activity Score (ASDAS-MI; ≥2.0-point decrease from baseline or lowest possible score [0.6]) at week 52. These results have been reported previously (15). Here we report the following outcomes for all aforementioned subgroups: ASDAS-MI, ASAS 40% response (ASAS40), and BASDAI change from baseline (CfB). For MRI/CRP subgroups, we also report ASAS partial remission (ASAS PR), ASDAS disease activity states, ASDAS CfB, and Bath Ankylosing Spondyloarthritis Functional Index (BASFI) CfB. ASDAS-MI by MRI/CRP subgroup was the primary efficacy variable of this analysis; all other outcomes were secondary.

Statistical analysis. All patients randomized in C-axSpAnd (randomized set) were included in the MRI/CRP and CRP at baseline subgroup analyses. The SPARCC SI joint inflammation score subgroups included all patients from the randomized set with SI joint scores recorded from MRI scans at screening. Missing values, or values collected after switching to open-label CZP, were imputed using non-responder imputation for dichotomous variables or last observation carried forward for continuous variables. Outcomes were analyzed descriptively by randomized treatment and subgroup.

Table 1. Patient demographics and disease characteristics at baseline by MRI/CRP subgroup

	MRI+/CRP+		MRI+/CRP−		MRI−/CRP+	
	PBO (n = 42)	CZP (n = 45)	PBO (n = 76)	CZP (n = 74)	PBO (n = 40)	CZP (n = 40)
Age (y)						
Mean (SD)	36.1 (10.6)	35.0 (8.9)	38.2 (11.1)	38.8 (11.4)	37.1 (10.7)	36.9 (10.1)
Range	18-67	19-56	18-64	18-73	18-61	20-59
Female, n (%)	15 (35.7)	16 (35.6)	39 (51.3)	38 (51.4)	28 (70.0)	27 (67.5)
BMI (kg/m^2), mean (SD)	26.9 (6.5)	26.7 (5.4)	26.3 (5.1)	26.1 (4.5)	28.4 (7.1)	28.3 (6.2)[a]
HLA-B27 positive, n (%)	36 (85.7)	38 (84.4)	58 (76.3)	52 (70.3)	39 (97.5)[b]	38 (95.0)[b]
Symptom duration (y), mean (SD)	7.6 (8.1)	6.2 (6.5)	8.9 (7.8)	9.6 (8.6)	6.8 (6.3)	6.4 (6.5)
Time since diagnosis (y)						
Mean (SD)	3.5 (6.1)	2.8 (3.4)	4.4 (5.3)	4.7 (6.1)	3.9 (4.6)	2.4 (2.4)
Median	1.7	1.5	2.2	2.2	2.5	1.5
Range	0.1-38.2	0.1-15.1	0.1-24.9	0.1-29.2	0.0-20.6	0.1-9.2
SPARCC SI joint score						
Mean (SD)	13.6 (13.3)[a]	14.1 (13.3)	10.1 (12.5)	8.2 (10.4)[c]	0.3 (0.6)[d]	0.2 (0.7)[e]
Q1	3.0	4.0	1.5	1.5	0.0	0.0
Median	8.5	8.7	3.8	4.0	0.0	0.0
Q3	23.5	23.5	15.8	11.5	0.5	0.0
CRP (mg/L), mean (SD)	26.9 (17.7)	25.9 (15.2)	3.5 (2.5)	4.3 (7.6)	27.6 (18.8)	25.6 (21.1)
ASDAS, mean (SD)	4.5 (0.7)	4.3 (0.7)	3.2 (0.5)	3.3 (0.6)	4.3 (0.7)	4.4 (0.8)
BASDAI total score, mean (SD)	7.4 (1.2)	6.8 (1.4)	6.5 (1.1)	6.8 (1.3)	6.7 (1.5)	7.2 (1.6)
BASMI, mean (SD)	3.2 (1.7)	2.8 (1.3)	2.6 (1.3)[f]	3.0 (1.3)[c]	2.8 (1.1)	3.1 (1.4)[a]
BASFI, mean (SD)	6.4 (1.8)	5.2 (2.4)	4.8 (2.3)	5.3 (1.9)	5.6 (2.0)	5.9 (2.2)

Note: Randomized set (N = 317).
Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondyloarthritis Disease Activity Index; BASFI, Bath Ankylosing Spondyloarthritis Functional Index; BASMI, Bath Ankylosing Spondyloarthritis Metrology Index; BMI, body mass index; CRP, C-reactive protein; CZP, certolizumab pegol; HLA-B27, human leukocyte antigen B27; MRI, magnetic resonance imaging; PBO, placebo; Q1, first quartile; Q3, third quartile; SI, sacroiliac; SPARCC, Spondyloarthritis Research Consortium of Canada.
[a]n = 39.
[b]Three patients who were misrandomized and were MRI−/CRP− per data at baseline were analyzed as MRI−/CRP+ owing to having at least one CRP screening result >4 mg/L (the lower limit of quantification).
[c]n = 73.
[d]n = 38.
[e]n = 37.
[f]n = 74.

RESULTS

Patient disposition and baseline characteristics. In total, 317 patients were randomized to CZP (n = 159) or placebo (n = 158); at week 52, data were available for 121/159 patients randomized to CZP and 51/158 patients randomized to placebo. Patient characteristics at baseline were similar between treatment groups, as previously reported (15). Within the randomized patient population, 310 (CZP, n = 156; placebo, n = 154) patients had SPARCC SI joint inflammation scores recorded from MRI scans at screening; these patients comprised the analysis set for the SPARCC SI joint inflammation score subgroups. There were some key differences in baseline demographics between subgroups, including sex, symptom duration, and human leukocyte antigen-B27 positivity (Table 1). Baseline disease activity measures were generally comparable across all subgroups, although mean ASDAS was lower in the MRI+/CRP– subgroup (Table 1), as expected, given the weight of CRP in the ASDAS. [Correction added on 11 July 2022, after first online publication: The text "121/159 patients randomized to CZP and 51/158 patients randomized to placebo completed the visit at week 52 without switching to open-label CZP" was corrected to "at week 52, data were available for 121/159 patients randomized to CZP and 51/158 patients randomized to placebo" in this version.]

Treatment response by MRI/CRP subgroup. Across all MRI/CRP subgroups and outcomes, CZP-treated patients had numerically greater responses than patients on placebo (Table 2; Figures 1 and 2). For responses based on ASDAS, including ASDAS-MI and ASDAS-inactive disease (ID)/low disease activity (LDA) state, CZP-treated patients in the MRI+/CRP+ subgroup had the highest responses compared with the MRI–/CRP+ and MRI+/CRP– subgroups (Figures 1 and 2; Supplementary Figure 1C), as expected given the important weight of CRP in the calculation of ASDAS. At week 52, ASDAS-MI was achieved by 75.6% MRI+/CRP+ patients, 47.5% MRI–/CRP+ patients, and 29.7% MRI+/CRP– patients (Figures 1 and 2). CZP-treated patients in the MRI+/CRP+ subgroup also had the highest responses for ASAS40 and BASDAI improvement compared with the MRI–/CRP+ and MRI+/CRP– subgroups, although the responses were more comparable across all three subgroups (Figure 1). Similar patterns of responses were observed for ASAS PR and BASFI CfB (Supplementary Figure 1). Despite the higher responses in the MRI+/CRP+ subgroup, substantial clinical responses were observed among CZP-treated patients in both the MRI–/CRP+ and MRI+/CRP– subgroups (Figures 1 and 2; Supplementary Figure 1). For example, at week 52, ASAS40 was achieved by 42.5% of MRI–/CRP+ patients and 55.4% of MRI+/CRP– patients; the mean (SD) BASDAI CfB was –3.9 (2.7) for MRI–/CRP+ patients and –3.1 (2.6) for MRI+/CRP– patients (Figure 1).

Treatment response by SPARCC MRI SI joint inflammation score. Across all SPARCC score subgroups and outcomes, CZP-treated patients had numerically greater responses than patients on placebo (Figure 3). CZP-treated patients in the SPARCC 12 points or more subgroup had the highest response for ASDAS-MI, ASAS40, and BASDAI CfB (Figure 3). At week 52, ASDAS-MI was achieved by 75.8% of these patients; the mean (SD) BASDAI CfB was –4.7 (2.3). Substantial clinical responses were also observed among CZP-treated patients in the other SPARCC score subgroups (Figure 3). Among CZP-treated patients across the three subgroups with SPARCC scores of less than 12, week 52 ASDAS-MI and ASAS40 response rates ranged from 26.1% to 44.7% and from 39.1% to 62.9%, respectively, and mean BASDAI CfB ranged from –2.7 to –3.7.

Treatment response by CRP. Across all CRP subgroups and outcomes, CZP-treated patients had numerically greater responses than patients on placebo (Figure 4). CZP-treated patients in the subgroup with CRP 10 mg/L or more and the subgroup with CRP 5 mg/L or more to less than 10 mg/L had the highest responses for ASDAS-MI, ASAS40, and BASDAI CfB (Figure 4). Within the subgroup with CRP 10 mg/L or more at week 52, ASDAS-MI was achieved by 64.3% of CZP-treated patients; the mean (SD) BASDAI CfB was –4.2 (2.2). Within the subgroup with CRP 5 mg/L or more to less than 10 mg/L at week 52, ASDAS-MI was achieved by 52.6% of CZP-treated patients; the mean (SD) BASDAI CfB was –3.8 (3.1). At week 52, CZP-treated patients in the CRP less than 5 mg/L subgroup had a substantially lower ASDAS-MI response rate (19.6%) and mean (SD) BASDAI CfB (–2.7 [2.5]) than patients with CRP 5 mg/L or

Table 2. ASDAS-MI responder rates at week 52 stratified by baseline MRI/CRP status

	MRI+/CRP+		MRI+/CRP−		MRI−/CRP+	
	PBO (n = 42)	CZP (n = 45)	PBO (n = 76)	CZP (n = 74)	PBO (n = 40)	CZP (n = 40)
Responder, n (%)	3 (7.1)	34 (75.6)	3 (3.9)	22 (29.7)	5 (12.5)	19 (47.5)
Odds ratio vs. PBO (95% CI for odds ratio)	—	42.9 (10.9 to ≥100)	—	10.6 (3.0 to 37.6)	—	7.1 (2.3 to 22.4)

Note: Randomized set (N = 317). Missing values, or values collected after switching to open-label CZP, were imputed using NRI.
Abbreviations: ASDAS-MI, Ankylosing Spondylitis Disease Activity Score-Major Improvement; CI, confidence interval; CRP, C-reactive protein; CZP, certolizumab pegol; MRI, magnetic resonance imaging; NRI, non-responder imputation; PBO, placebo.

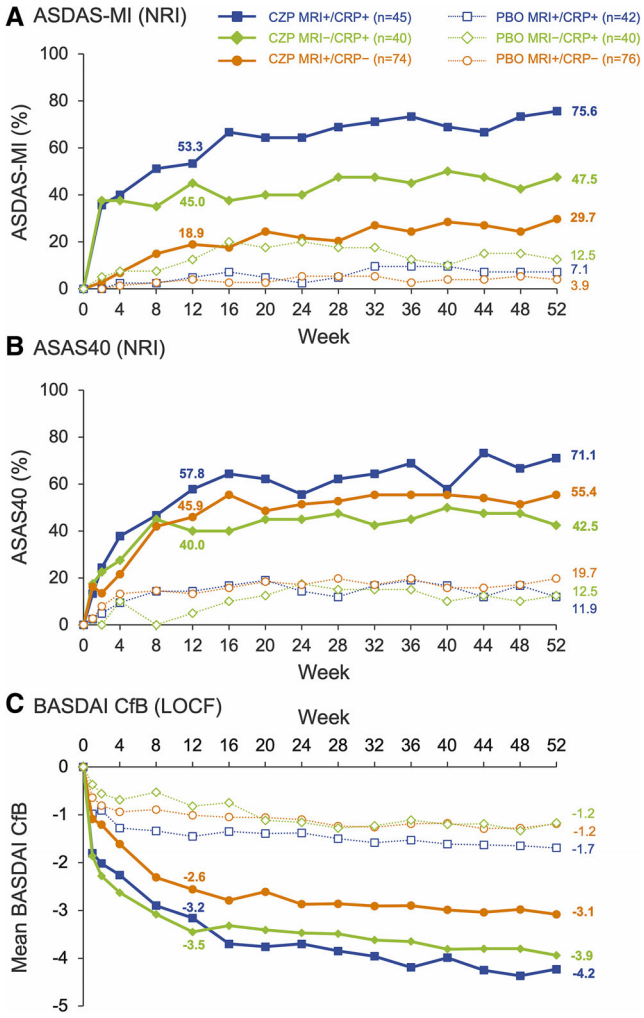

Figure 1. Clinical efficacy outcomes in patients stratified by baseline MRI/CRP status. Randomized set (N = 317). Missing values, or values collected after switching to open-label CZP, were imputed using NRI for dichotomous variables and LOCF for continuous variables: at week 52, data were available for 121/159 patients randomized to CZP and 51/158 patients randomized to PBO. ASDAS-MI, Ankylosing Spondylitis Disease Activity Score; CfB, change from baseline; CRP, C-reactive protein; CZP, certolizumab pegol; LOCF, last observation carried forward; MRI, magnetic resonance imaging; NRI, non-responser imputation; PBO, placebo.

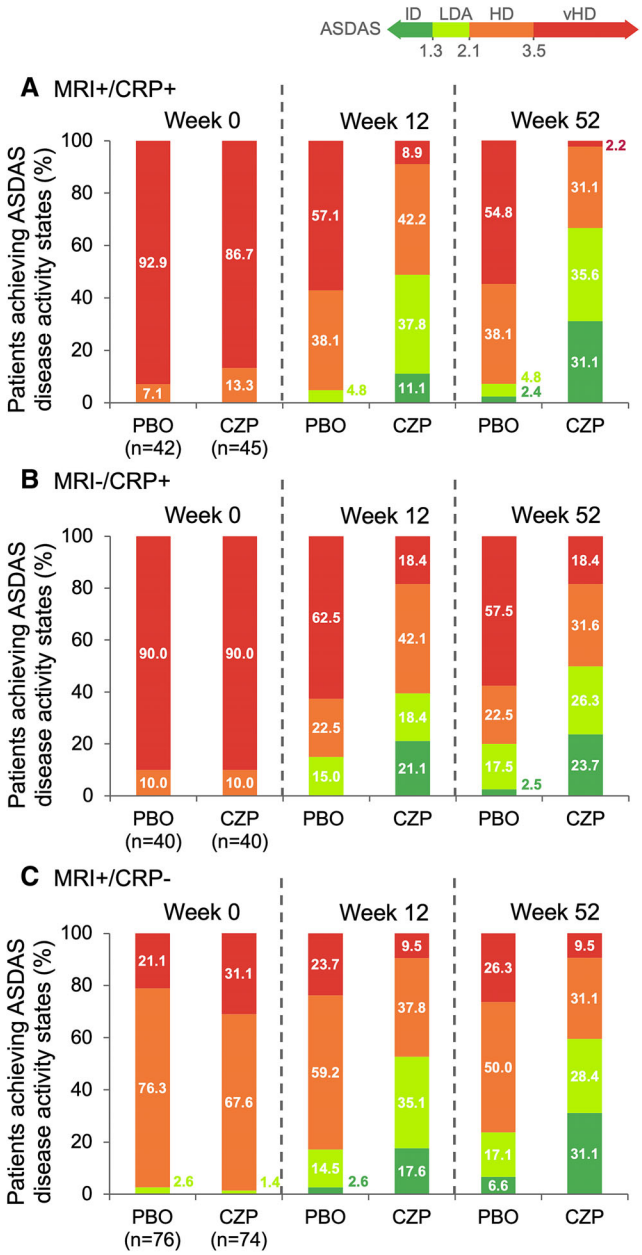

Figure 2. ASDAS states in patients stratified by baseline MRI/CRP status. Randomized set (N = 317); LOCF. ASDAS-HD: ASDAS ≥2.1 and ≤3.5; ASDAS-ID: ASDAS <1.3; ASDAS-LDA: ASDAS ≥1.3 and <2.1; ASDAS-vHD: ASDAS >3.5. ASDAS, Ankylosing Spondylitis Disease Activity Score; ASDAS-HD, Ankylosing Spondylitis Disease Activity Score high disease activity; ASDAS-ID, ASDAS-inactive disease; ASDAS-LDA, ASDAS-low disease activity; ASDAS-vHD, Ankylosing Spondylitis Disease Activity Score very high disease; CRP, C-reactive protein; CZP, certolizumab pegol; LOCF, last observation carried forward; MRI, magnetic resonance imaging; PBO, placebo.

more, but ASAS40 response rate (50.0%) was more comparable with the higher CRP subgroups (Figure 4).

DISCUSSION

This analysis of data from the C-axSpAnd study provides one of the most detailed evaluations to date of clinical responses to TNFi treatment across patients with nr-axSpA stratified according to their baseline MRI/CRP status. All MRI/CRP subgroups achieved notable responses over 52 weeks of treatment with CZP, with substantially greater responses among CZP-treated patients relative to patients on placebo across these subgroups. Across all outcome measures, MRI+/CRP+ CZP-treated patients demonstrated higher clinical responses, although the magnitude of the differences between MRI/CRP subgroups varied between outcomes. Importantly, substantial improvements

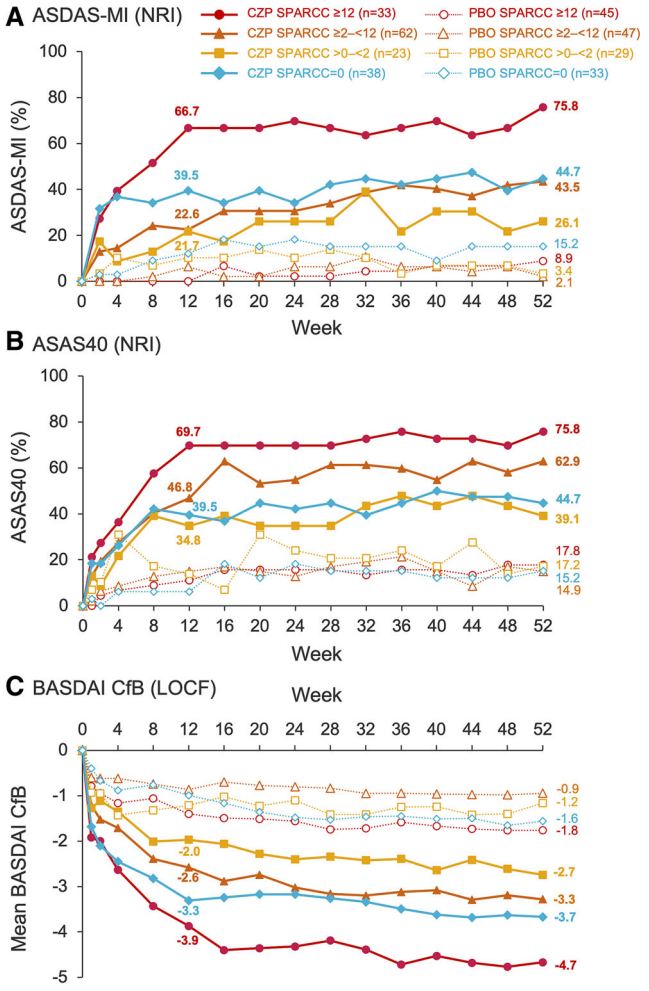

Figure 3. Clinical efficacy outcomes in patients stratified by baseline SPARCC MRI SI Joint Inflammation score. Analysis set comprised 310 patients from the randomized patient population who had SPARCC SI joint scores recorded from MRI scans at screening. Missing values, or values collected after switching to open-label CZP, were imputed using NRI for dichotomous variables and LOCF for continuous variables: at week 52, data from this analysis set were available for 110/156 patients randomized to CZP and 46/154 patients randomized to PBO. ASAS40, Assessment of SpondyloArthritis international Society 40% response; ASDAS-MI, Ankylosing Spondylitis Disease Activity Score-Major Improvement; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CfB, change from baseline; CZP, certolizumab pegol; LOCF, last observation carried forward; NRI, non-responser imputation; PBO, placebo; SPARCC, Spondyloarthritis Research Consortium of Canada.

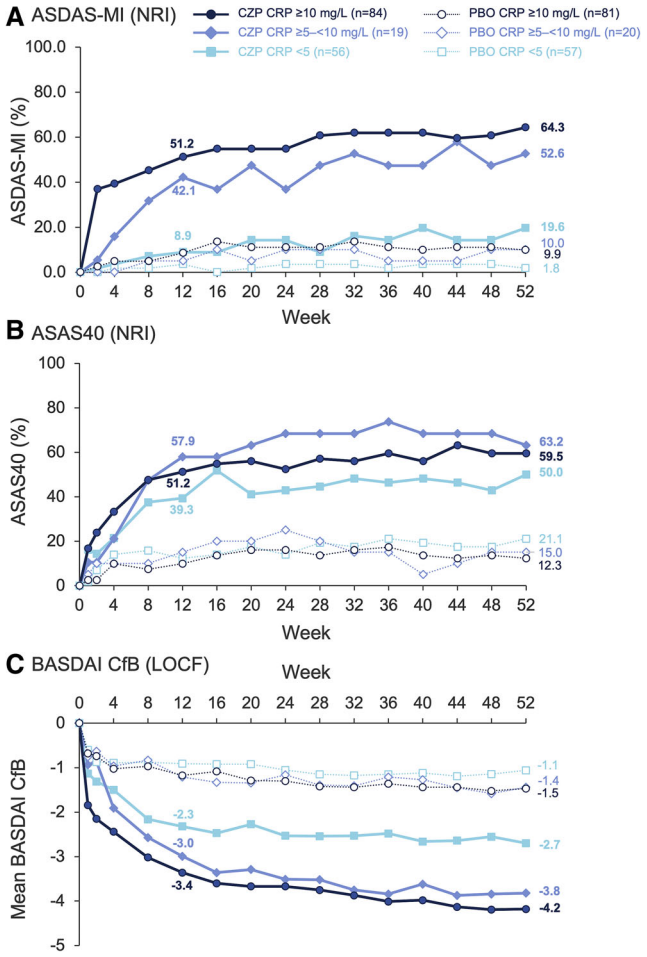

Figure 4. Clinical efficacy outcomes in patients stratified by baseline CRP. Randomized set (N = 317). Missing values, or values collected after switching to open-label CZP, were imputed using NRI for dichotomous variables and LOCF for continuous variables: at week 52, data were available for 121/159 patients randomized to CZP and 51/158 patients randomized to PBO. ASAS40, Assessment of SpondyloArthritis international Society 40% response; ASDAS-MI, Ankylosing Spondylitis Disease Activity Score-Major Improvement; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CfB, change from baseline; CRP, C-reactive protein; CZP, certolizumab pegol; LOCF, last observation carried forward; NRI, non-responser imputation; PBO, placebo.

were also observed in CZP-treated patients who had active sacroiliitis on MRI but had normal levels of CRP (MRI+/CRP–), and in those who did not have active sacroiliitis on MRI but had elevated CRP (MRI–/CRP+).

The ASDAS-MI response rate, the primary efficacy variable, was notably higher among CZP-treated patients in the MRI+/CRP+ and MRI–/CRP+ subgroups if compared with the MRI+/CRP– subgroup, although the latter subgroup still showed a numerically higher response rate compared with placebo. This was expected given that CRP level is one of the main factors that contributes to ASDAS (20). Patients with normal CRP at baseline consequently had lower baseline ASDAS and therefore less scope to improve through a reduction in CRP (21). For the secondary outcomes evaluated, including ASAS40 and BASDAI, which were not confounded by CRP, responses were greatest among CZP-treated patients in the MRI+/CRP+ subgroup, but differences between the MRI/CRP subgroups were smaller, with substantially greater responses among patients on CZP compared with those on placebo across all three subgroups.

The results presented here are corroborated by responses to TNFi treatment observed in earlier studies for patients with nr-axSpA stratified by baseline MRI/CRP status. In these studies, analyses of patients with normal CRP but active sacroiliitis on MRI, and of those without active sacroiliitis at baseline but elevated CRP, demonstrated greater clinical responses among TNFi-treated patients relative to placebo (7,8,22). Efficacy analyses on MRI/CRP subgroups from preliminary reports investigating interleukin-17A inhibitors in nr-axSpA have also demonstrated responses in MRI–/CRP+ and MRI+/CRP– subgroups over 16 weeks of active treatment compared with placebo (18,19). Previous studies have also shown higher ASDAS-MI response rates in patients with high CRP at baseline (7,8), which is perhaps unsurprising, because CRP is one of the key components in calculating ASDAS total score (23). More detailed comparisons between these previous studies and results presented here are constrained by differences in study design, CRP ULN threshold, and patient eligibility criteria; in particular, MRI–/CRP– patients were eligible to participate in the earlier TNFi studies (7,8,22).

In this analysis, responses to CZP were also evaluated on a more granular level across patients stratified by SPARCC MRI SI joint inflammation score and by baseline CRP. Patients with SPARCC scores of 12 or more demonstrated the greatest response across all outcomes, but notably all SPARCC score subgroups, including those with SPARCC scores less than 12, achieved substantially greater responses than placebo. Similarly, all CRP subgroups achieved greater responses than placebo. Responses were observed in patients with CRP below the ULN (CRP <5 mg/L and ≥5 to <10 mg/L), although patients with a CRP less than 5 mg/L showed less substantial responses compared with patients with higher levels of CRP, especially for ASDAS-MI in which patients with low baseline CRP had less potential for improvement via a reduction in CRP (21).

Strengths of this analysis include the fact that randomization of patients was stratified by presence of active sacroiliitis on MRI and elevated CRP to ensure balanced treatment allocation across MRI/CRP subgroups. The study was also placebo controlled over 52 weeks, allowing for comparisons between patients on placebo and CZP across the entire treatment period. Additionally, central assessment of screening radiographs by two experienced readers and an adjudicator ensured that patients with r-axSpA were not included in the C-axSpAnd study and that active sacroiliitis on MRI was correctly ascertained. Practical limitations of the MRI/CRP status in determining patient eligibility should be noted, including the variability in patients' CRP levels over time (24) and the complexity of interpreting MRI images (25–27). Further limitations include the differences in baseline demographics, notably the differences in proportion of females across the subgroups. These limitations highlight the need for caution when treatment decisions are made.

The findings of the present study on CZP, in combination with those from other TNFi treatments (7,8,22), have important implications for clinical practice in demonstrating the efficacy of TNFi treatment not only in patients with nr-axSpA who are MRI+/CRP+ but also in MRI+/CRP– patients who have normal CRP, and in MRI–/CRP+ patients who do not have active sacroiliitis on MRI. Although patients with nr-axSpA who are MRI–/CRP+ or MRI+/CRP– are less likely to progress to the radiographic form of axSpA within a given time frame, there is nonetheless a risk of radiographic progression among these patients (12–14). In addition, disease activity at baseline indicates that MRI–/CRP+ and MRI+/CRP– patients face a substantial burden of disease similar to patients who are MRI+/CRP+, with the burden remaining high after 52 weeks in the placebo groups; indeed, the burden of disease has also been shown to be comparable to r-axSpA (2,4). The findings of this study may have implications for regulatory decision making in some countries, given the substantial variation globally in current eligibility requirements for patients to receive biologics to treat nr-axSpA. As with most recent trials in nr-axSpA, patients who were MRI–/CRP– did not qualify for inclusion in the C-axSpAnd study; however, further research is warranted to investigate TNFi response in such patients.

The results of this analysis indicate that CZP treatment benefits patients with nr-axSpA across all the MRI/CRP subgroups studied. Responses were numerically higher in patients who were MRI+/CRP+, particularly for ASDAS-MI, but still substantial in MRI+/CRP– and MRI–/CRP+ patients. Despite having a potentially high burden of disease and the potential to respond to treatment with biologics, MRI+/CRP– and MRI–/CRP+ patients are currently deemed ineligible for such treatment by some regulatory authorities.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Robinson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Maksymowych, Gensler, Hall, Rudwaleit, Hoepken, Bauer, Kumke, Deodhar.

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