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Original article

Sustained efficacy, safety and patient-reported outcomes of certolizumab pegol in axial spondyloarthritis: 4-year outcomes from RAPID-axSpA

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Abstract

Objective. The aim was to assess the long-term safety and efficacy of certolizumab pegol over 4 years of continuous treatment in patients with axial spondyloarthritis (axSpA), including both AS and non-radiographic (nr-) axSpA.

Methods. RAPID-axSpA was a phase 3 randomized trial, double blind and placebo controlled to week 24, dose blind to week 48 and open label to week 204. Patients had a clinical diagnosis of axSpA, meeting Assessment of SpondyloArthritis international Society (ASAS) criteria, and had active disease. The assessed outcomes included ASAS20, ASAS40, AS DAS (ASDAS), BASDAI, BASFI and BASMI scores, along with selected measures of remission. Further patient-reported outcomes, peripheral arthritis, enthesitis, uveitis and quality-of-life measures are also reported.

Results. Two hundred and eighteen of 325 patients randomized (AS: 121; nr-axSpA: 97) received certolizumab pegol from week 0. Of these, 65% remained in the study at week 204 (AS: 67%; nr-axSpA: 63%). Across all outcomes, for AS and nr-axSpA, sustained improvements were observed to week 204 [week 204 overall axSpA: ASAS20: 54.1% (non-responder imputation); 83.7% (observed case, OC); ASAS40: 44.0% (non-responder imputation); 68.1% (OC); ASDAS inactive disease: 32.1% (last observation carried forward); 31.4% (OC)]. In the safety set (n = 315), there were 292.8 adverse events and 10.4 serious adverse events per 100 patient-years. No deaths were reported.

Conclusion. In the first study to evaluate the efficacy of an anti-TNF across both axSpA subpopulations, improvements in clinical and patient-reported outcomes at 24 and 96 weeks were sustained through 4 years of treatment, with no new safety signals.

Trial registration: ClinicalTrials.gov, http://clinicaltrials.gov, NCT01087762.

Key words: axial spondyloarthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, certolizumab pegol

CLINICAL SCIENCE

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Rheumatology key messages

- RAPID-axSpA is the first long-term study of an anti-TNF in axial SpA.
- Safety and efficacy of certolizumab pegol was maintained over 4 years in axial SpA patients.
- Responses to certolizumab pegol were maintained similarly in AS and non-radiographic axial SpA patients.

Introduction

Axial spondyloarthritis (axSpA) can be subclassified as AS or non-radiographic axSpA (nr-axSpA) according to the presence or absence of sacroiliac joint damage on X-ray; hence, whether the imaging criterion of the modified New York criteria is satisfied [1, 2]. This immune-mediated, inflammatory condition characteristically affects the spine and sacroiliac joints and can also involve peripheral joints and entheses, as well as extra-articular sites such as the eye (uveitis), gastrointestinal tract (IBD) and skin (psoriasis) [3, 4], of which eye involvement is the most common [4].

There is significant potential for axSpA to impact on patients' quality of life (QoL) [5]. Furthermore, it has been shown that neither QoL [6] nor the prevalence of extra-articular manifestations [3] differs between AS and nr-axSpA patients. It is therefore important that the effectiveness of different treatments be investigated across a range of disease phenotypes and in both AS and nr-axSpA patients.

A key change in the axSpA treatment pathway came about with the introduction of anti-TNF biologic agents. These have proved effective for treating AS and nr-axSpA in the short term [7–15]. However, while long-term data are available for patients with AS [16–20], only limited long-term data for nr-axSpA patients have been reported [21, 22].

The RAPID-axSpA trial of certolizumab pegol (CZP) in axSpA included patients with AS and nr-axSpA, allowing direct comparisons of treatment response between the two patient subpopulations [8]. Previous reports from the study have shown the efficacy of CZP compared with placebo for the treatment of patients with axSpA [8], and that this efficacy is sustained across both subpopulations over 96 weeks [23]. This publication forms the final report of efficacy and safety data over 4 years of CZP treatment, with further patient-reported outcomes also included.

Methods

Patients and study design

RAPID-axSpA (NCT01087762) was a 4-year, phase 3, randomized, double-blind, placebo-controlled, multicentre trial designed to investigate the efficacy and safety of CZP for the treatment of axSpA. Eighty-three sites enrolled patients in Central/Eastern and Western Europe, North America and Latin America. The trial was double blind and placebo controlled to week 24, dose blind to week 48 and open label (OL) to week 204. This study was approved by a national, regional or independent ethics committee or institutional review board at participating sites and was conducted in accordance with applicable regulatory and International Conference on Harmonization Good Clinical Practice requirements, based on the Declaration of Helsinki and local laws. All patients provided written informed consent prior to any protocol-specific procedures being performed.

To enter the study, patients were required to have a clinical diagnosis of axSpA, fulfilling Assessment of SpondyloArthritis international Society (ASAS) criteria, and have active disease. They must also have had an inadequate response to, or intolerance of, at least one NSAID. Detailed inclusion and exclusion criteria have been presented previously [8].

At week 0, patients were randomly assigned 1:1:1 to placebo, CZP 200 mg every 2 weeks (Q2W) or CZP 400 mg every 4 weeks (Q4W); method previously presented [8]. Patients assigned to CZP received a loading dose of 400 mg at weeks 0, 2 and 4 and remained on their assigned dose throughout the study. Patients assigned to placebo at week 0 were re-randomized 1:1 to CZP 200 mg Q2W or CZP 400 mg Q4W, at week 16, if they were non-responders according to the criteria for ASAS20 [24] at both weeks 14 and 16. Otherwise, re-randomization occurred at week 24, the end of the double-blind period.

Evaluations

The primary outcome of RAPID-axSpA (ASAS20 response at week 12) and safety, efficacy and patient-reported outcome data to week 96 have been reported previously [8, 23, 25]. Here, we report the long-term outcomes from the complete 4-year study period (to week 204).

Clinical efficacy was assessed using mean scores in the continuous disease activity measures AS disease activity score (ASDAS) and BASDAI, as well as the percentage of population meeting the composite response measures ASAS20, ASAS40, ASAS 5/6 and BASDAI 50 [24]. Remission data were reported using ASAS partial remission (ASAS-PR) criteria [26], ASDAS inactive disease (ASDAS-ID) and BASDAI <2 with normal CRP (CRP at or below the upper limit of normal) [27]. The numbers of patients achieving sustained remission (defined as a 6-month continuous period of ASDAS-ID at any point during the 4 years) and sustained partial remission (a 6-month continuous period of ASAS-PR) were analysed *post hoc*. Patient function and spinal mobility were assessed using the BASFI and BASMI-linear tools, respectively.

Further patient-reported outcomes included total back pain and nocturnal back pain, which were assessed using a numerical rating scale (NRS), with 0 corresponding to no pain and 10 to the most severe pain. Fatigue was assessed with question 1 of the BASDAI, and morning stiffness was evaluated by taking the mean of questions 5 and

6. All BASDAI questions use a 10-point NRS. Sleep problems were assessed using the Sleep Problems II Index of the Medical Outcomes Study (MOS) Sleep Scale, as previously described [25]. Health-related QoL was assessed using the disease-specific ASQoL tool [28] and the Short-Form 36-item (SF-36) physical and mental component summaries.

Inflammation of the peripheral joints was measured using counts of tender (TJC) and swollen (SJC) joints (44 joint count); enthesitis assessed using the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and by clinical inflammation of the proximal insertion of the Achilles tendons. Uveitis events were recorded on a case report form for extra-articular manifestations or on adverse event (AE) forms using the Medical Dictionary for Regulatory Activities version.14.1, preferred terms uveitis, iritis or iridocyclitis.

The safety of CZP over 4 years was investigated through analysis of AEs at every study visit. Most commonly occurring serious AEs are reported here. Only events occurring after the first dose of CZP are reported.

Statistical analyses

All efficacy data, including ASDAS, BASDAI, BASFI and BASMI-linear scores, as well as the composite disease activity responses and all other patient-reported outcomes, are reported for the randomized set, consisting of patients randomized into the study with an intention to treat. We specifically report results for those patients randomized to CZP (either 200 mg Q2W or 400 mg Q4W) at week 0; the CZP-randomized group.

Where data values were missing or patients had withdrawn, non-responder imputation (NRI) was used for the primary end point (ASAS20) and the secondary end points ASAS40, ASAS 5/6, ASAS-PR and BASDAI 50. Last observation carried forward (LOCF) was used for all other efficacy outcomes. Observed case (OC) data, where shown, are for patients with measurements recorded at the time point in question.

Articular outcomes are reported for patients with baseline joint involvement [for swollen (SJC >0) and tender (TJC >0) joint involvement, respectively]. Likewise, enthesitis data are reported for patients with baseline involvement (MASES >0 or $\geqslant 1$ inflamed proximal Achilles insertion).

Uveitis data are reported for CZP-randomized patients and for all patients who received at least one dose of CZP at any point in the study to week 204; the All CZP group.

Safety outcomes are reported for the safety set, which consisted of all patients treated with at least one dose of CZP at any point in the study to week 204. AE incidences are given as event rates per 100 patient-years.

Results

Patient disposition and baseline characteristics

At the beginning of the RAPID-axSpA study, a total of 325 patients were randomly assigned, 107 to placebo and 218 to CZP (111 to CZP 200 mg Q2W, 107 to CZP 400 mg Q4W; Fig. 1A). Of CZP-randomized patients, 121 had AS and 97 nr-axSpA. Overall, 315 patients received CZP at any time during the study, including those originally randomized to placebo and switched to CZP at week 16 or week 24 (All CZP group).

As has been reported previously, baseline disease activity was similar across treatment groups and between AS and nr-axSpA patients [8, 23]. The CZP-randomized patients had a mean age of 39.5 years, and 62% were male. For the All CZP group (n = 315), mean (S.D.) ASDAS score at baseline was 3.9 (0.9).

Sixty-three per cent (199/315) of the All CZP group remained in the study at week 204. Across the CZP-randomized patients, 93% completed the double-blind phase (to week 24), 88% the dose-blind phase (to week 48) and 65% the OL period (to week 204). Completion rates were similar between the two dose regimens (Fig. 1A) and between AS and nr-axSpA patient populations (Fig. 1B). The most common reasons for patients to discontinue the study were AEs or withdrawal of consent (each accounting for 13% of CZP-randomized patients). Eighteen patients (6%) overall withdrew because of a lack of efficacy, nine of whom were randomized to CZP at week 0 (Fig. 1A).

Efficacy

Clinical outcomes

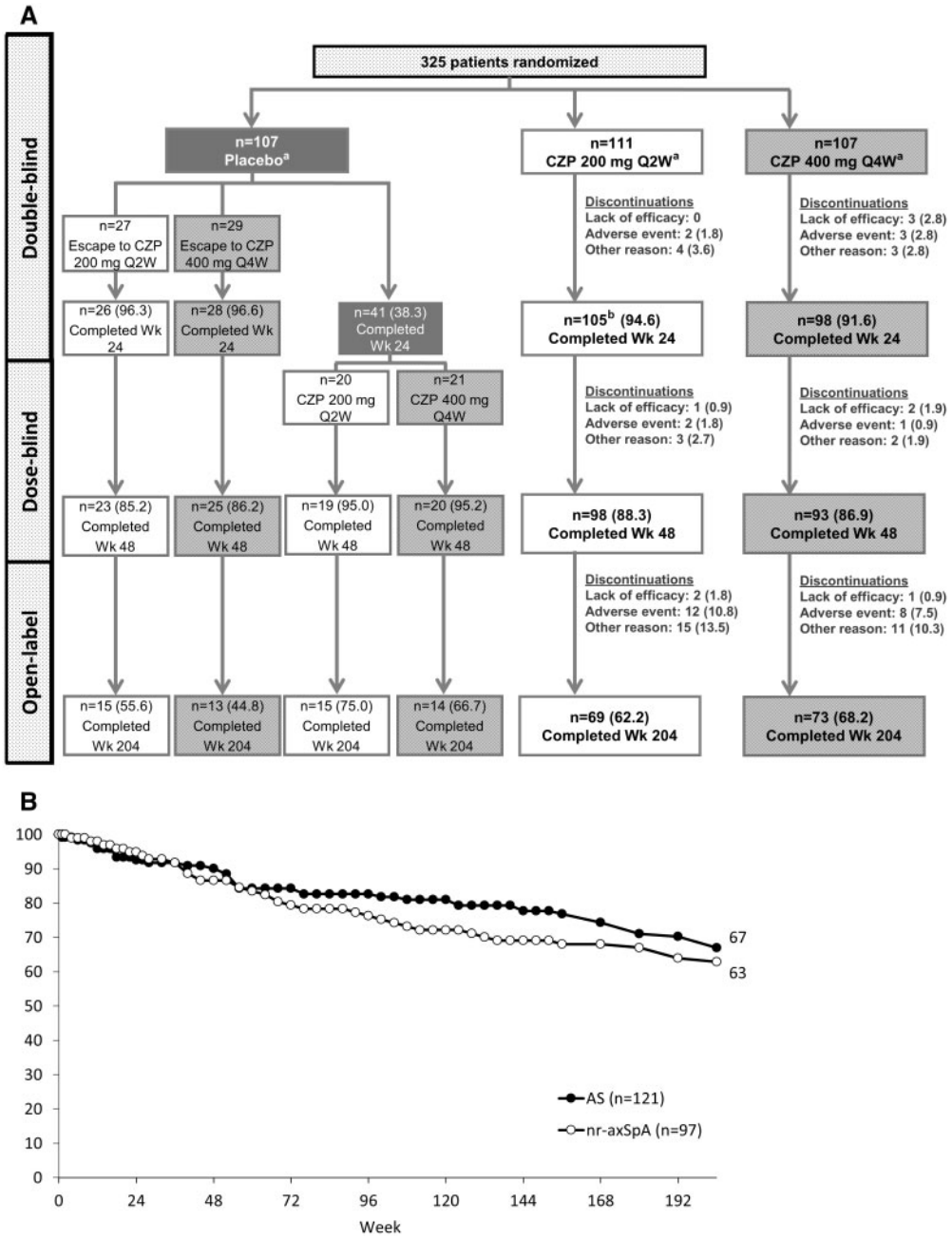
At week 204 (NRI), of CZP-randomized patients, ASAS20 and ASAS40 responses were achieved by 54.1 and 44.0% (NRI) and 83.7 and 68.1% (OC), respectively (Fig. 2), showing sustained efficacy from week 24. Responses were comparable between the AS and nr-axSpA subpopulations (Table 1).

Responses were maintained across the continuous disease activity outcomes BASDAI and ASDAS, and in measures of spinal mobility (BASMI-linear) and function (BASFI) (Table 1). Although AS patients tended to have higher BASFI scores than nr-axSpA patients at baseline (mean at baseline: AS: 5.6; nr-axSpA: 5.0) and week 204 [(LOCF); AS: 3.0; nr-axSpA: 2.2], the mean change from baseline was similar [week 204 (LOCF): AS: -2.6; nr-axSpA: -2.7].

Heat maps have been used to show the maintenance of efficacy through the dose-blind and OL periods (Fig. 3 and supplementary Fig. S1, available at *Rheumatology* Online). Individual patient ASDAS disease activity, as ASDAS-ID (ASDAS score <1.3; Fig. 3), ASDAS moderate disease [ASDAS-MD (ASDAS $\geqslant 1.3$ and <2.1)], high disease [ASDAS-HD-(ASDAS $\geqslant$ 2.1 and <3.5)] and very high disease [ASDAS-vHD (ASDAS $>$ 3.5)] (supplementary Fig. S1, available at *Rheumatology* Online), is shown at 12-weekly intervals, organized by disease activity at week 24. Thirteen patients with missing week 24 measurements are not shown. The heat maps illustrate that the disease activity achieved at week 24 is maintained with relative consistently to week 204, with many patients—particularly those with ASDAS-ID at week 24 (Fig. 3)—experiencing sustained remission.

Analyses of efficacy data by prespecified subgroups including age, gender, concomitant/prior DMARD use,

FIG. 1 Patient disposition and retention to week 204

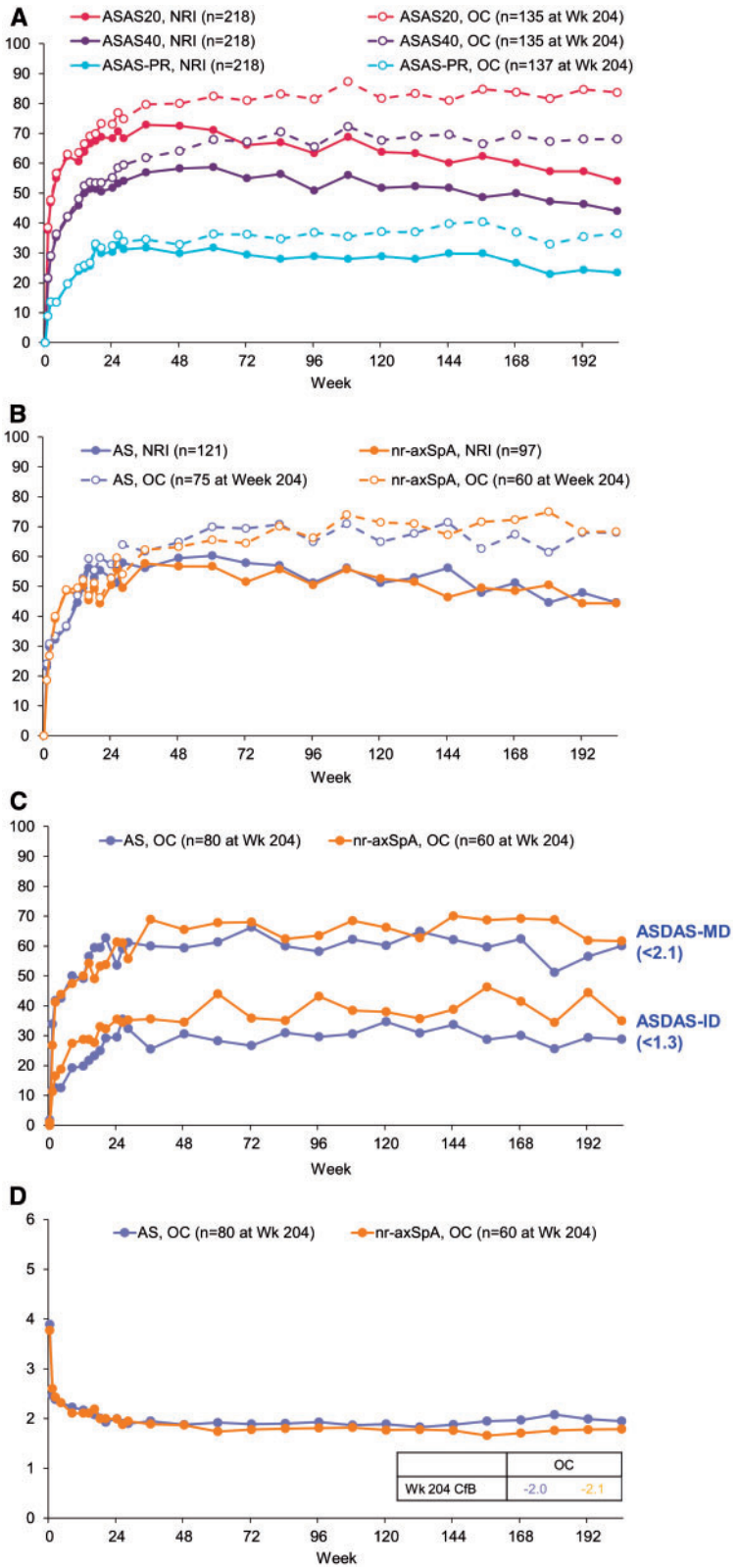


(**A**) Patient disposition to week 204 (percentages in brackets). [a]All patients received allocated treatment. [b]One patient did not enrol onto the dose-blind study period. (**B**) Patient retention to week 204 by subpopulations (CZP-randomized group, doses combined). CZP: certolizumab pegol.

symptom duration and prior anti-TNF exposure showed no substantial differences in outcome to week 204 between any of the subgroups where sample sizes were large enough to permit meaningful evaluation (data not shown).

Disease activity in CZP-randomized patients who withdrew from the study early for reasons besides lack of efficacy (n = 67) was comparable to those who completed the study (n = 142). Disease activity of patients who withdrew for reasons other than lack of efficacy, at the point of withdrawal, was as follows: ASDAS-ID: 38.8%; ASDAS-MD: 25.4%; ASDAS-HD: 22.4%; and ASDAS-vHD: 13.4%. Disease activity of patients who completed the study, at week 204, was as follows: ASDAS-ID: 31.0%;

FIG. 2 ASAS and ASDAS responses to week 204



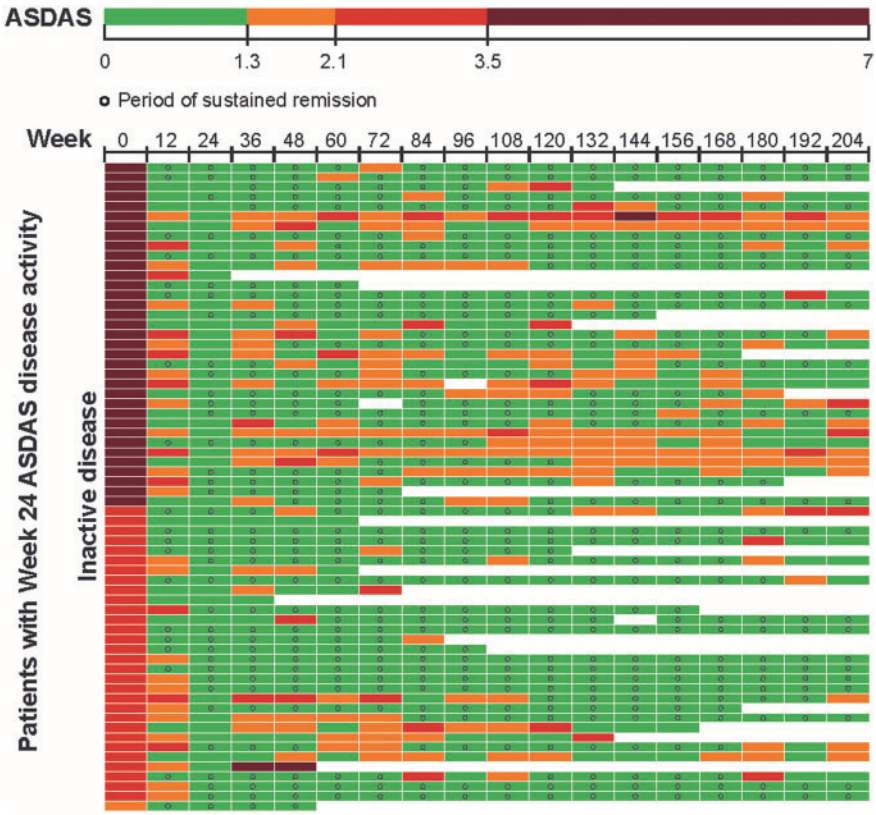
CZP-randomized group, doses combined. (**A**) ASAS responses to week 204 in axSpA population. (**B**) ASAS40 to week 204 by subpopulations. (**C**) ASDAS-ID and ASDAS-MD to week 204 by subpopulations. (**D**) ASDAS score to week 204 by subpopulations. ASDAS: AS DAS; ASDAS-ID: ASDAS inactive disease; ASDAS-MD: ASDAS moderate activity; CZP: certolizumab pegol.

Table 1 Efficacy in clinical and patient-reported outcomes (certolizumab pegol-randomized group, doses combined)

Outcome	All patients axSpA (n = 218)					AS (n = 121)					nr-axSpA(n = 97)				
		Week 24		Week 204			Week 24		Week 204			Week 24		Week 204	
	BL (n = 218)	OC (n = 205)	Imputed	OC (n = 140)	Imputed	BL (n = 121)	OC (n = 112)	Imputed	OC (n = 80)	Imputed	BL (n = 97)	OC (n = 93)	Imputed	OC (n = 60)	Imputed
Disease activity responses, n/N (%)															
ASDAS-ID[a]	-	66/205 (32.2)	66 (30.3)	44/140 (31.4)	70 (32.1)	-	33/112 (29.5)	33 (27.3)	23/80 (28.8)	39 (32.2)	-	33/93 (35.5)	33 (34.0)	21/60 (35.0)	31 (32.0)
ASDAS-MD[a]	3 (1.4)	51/205 (24.9)	54 (24.8)	41/140 (29.3)	59 (27.1)	2 (1.7)	27/112 (24/1)	29 (24.0)	25/80 (31.3)	33 (27.3)	1 (1.0)	24/93 (25.8)	25 (25.8)	16/60 (26.7)	26 (26.8)
ASAS20[b]	-	147/201 (73.1)	149 (68.3)	113/135 (83.7)	118 (54.1)	-	81/108 (75.0)	83 (68.6)	64/75 (85.3)	68 (56.2)	-	66/93 (71.0)	66 (68.0)	49/60 (81.7)	50 (51.5)
ASAS40[b]	-	111/201 (55.2)	113 (51.8)	92/135 (68.1)	96 (44.0)	-	62/108 (57.4)	64 (52.9)	51/75 (68.0)	54 (44.6)	-	49/93 (52.7)	49 (50.5)	41/60 (68.3)	42 (43.3)
ASAS 5/6[b]	-	90/199 (45.2)	92 (42.2)	72/134 (53.7)	75 (34.4)	-	48/108 (44.4)	48 (39.7)	40/75 (53.3)	41 (33.9)	-	42/91 (46.2)	44 (45.4)	32/59 (54.2)	34 (35.1)
ASAS-PR[b]	-	66/204 (32.4)	66 (30.3)	50/137 (36.5)	51 (23.4)	-	34/111 (30.6)	34 (28.1)	25/77 (32.5)	26 (21.5)	-	32/93 (34.4)	32 (33.0)	25/60 (41.7)	25 (25.8)
BASDAI <2 with CRP ⩽ULN[a]	-	66/205 (32.2)	66 (30.3)	46/142 (32.4)	72 (33.0)	-	33/112 (29.5)	33 (27.3)	23/81 (28.4)	38 (31.4)	-	33/93 (35.5)	33 (34.0)	23/61 (37.7)	34 (35.1)
BASDAI50[b]	-	114/205 (55.6)	114 (52.3)	89/140 (63.6)	89 (40.8)	-	59/112 (52.7)	59 (48.8)	51/80 (63.8)	51 (42.1)	-	55/93 (59.1)	55 (56.7)	38/60 (63.3)	38 (39.2)
Disease assessment scores, mean (S.D.)[a]															
ASDAS	3.8 (0.9)	2.0 (1.0)	2.1 (1.1)	1.9 (0.9)	2.0 (1.1)	3.9 (0.9)	2.0 (1.0)	2.0 (1.1)	2.0 (0.9)	2.1 (1.2)	3.8 (0.8)	2.0 (1.1)	2.0 (1.1)	1.8 (1.0)	1.9 (1.0)
BASDAI	6.4 (1.5)	3.2 (2.2)	3.3 (2.3)	2.7 (2.0)	3.0 (2.3)	6.4 (1.5)	3.2 (2.1)	3.4 (2.2)	2.8 (1.9)	3.0 (2.3)	6.6 (1.5)	3.2 (2.5)	3.3 (2.5)	2.6 (2.2)	2.9 (2.3)
BASFI	5.3 (2.3)	2.9 (2.5)	3.0 (2.5)	2.6 (2.2; 141)	2.7 (2.3)	5.6 (2.3)	3.2 (2.6)	3.3 (2.6)	2.9 (2.2)	3.0 (2.4)	5.0 (2.3)	2.6 (2.4)	2.6 (2.4)	2.3 (2.2; 61)	2.2 (2.2)
BASMI-linear	3.8 (1.7)	3.2 (1.7)	3.2 (1.7)	3.1 (1.7; 146)	3.1 (1.7)	4.2 (1.7)	3.6 (1.7)	3.6 (1.7)	3.6 (1.8; 83)	3.6 (1.8)	3.2 (1.5)	2.6 (1.5)	2.6 (1.5)	2.4 (1.2; 63)	2.5 (1.3)
Patient-reported outcomes, mean (S.D.)[a]															
Morning stiffness (NRS)	6.6 (1.9)	2.9 (2.4)	3.0 (2.5)	2.5 (2.0)	2.7 (2.4)	6.6 (1.9)	2.9 (2.1)	3.1 (2.2)	2.5 (1.9)	2.7 (2.3)	6.6 (1.9)	3.0 (2.8)	3.0 (2.8)	2.5 (2.2)	2.6 (2.5)
Fatigue (NRS)	6.8 (1.8)	3.9 (2.6)	4.1 (2.7)	3.2 (2.2)	3.6 (2.6)	6.7 (1.9)	3.9 (2.5)	4.1 (2.6)	3.3 (2.2)	3.6 (2.6)	6.9 (1.8)	3.9 (2.7)	4.0 (2.7)	3.1 (2.3)	3.6 (2.6)
Sleep (MOS Sleep Scale)[c]	49.0 (19.2)	35.3 (20.1)	36.2 (20.2)	32.4 (17.3; 145)	34.4 (18.6)	46.8 (19.9)	35.1 (19.3)	36.3 (19.5)	32.3 (15.9; 83)	34.1 (17.5)	51.7 (18.0)	35.4 (21.1)	36.1 (21.0)	32.5 (19.2; 62)	34.9 (20.0)
Nocturnal back pain (NRS)	6.9 (2.3)	3.1 (2.6)	3.3 (2.7)	2.7 (2.4; 141)	3.0 (2.7)	6.8 (2.3)	3.1 (2.4)	3.3 (2.6)	2.7 (2.3)	3.1 (2.6)	7.0 (2.4)	3.1 (2.9)	3.2 (2.9)	2.7 (2.6; 61)	2.9 (2.7)
Total back pain (NRS)	7.0 (1.9; 215)	3.5 (2.6; 204)	3.8 (2.7)	3.0 (2.4; 141)	3.3 (2.7)	7.0 (2.0; 118)	3.5 (2.3; 111)	3.8 (2.5)	3.1 (2.3)	3.4 (2.7)	7.0 (1.8)	3.6 (2.9)	3.8 (3.0)	2.8 (2.5; 61)	3.3 (2.7)
Health-related quality of life, mean (S.D.)[a]															
ASQoL	11.6 (4.4)	6.2 (5.5)	6.5 (5.6)	4.9 (5.0)	5.7 (5.4)	11.6 (4.4)	6.3 (5.3)	6.8 (5.6)	5.2 (4.9; 79)	5.9 (5.5)	11.6 (4.4)	6.1 (5.7; 91)	6.1 (5.7)	4.5 (5.1; 61)	5.3 (5.3)
SF-36 PCS	32.4 (7.5; 211)	42.1 (10.0; 204)	41.8 (9.9)	44.3 (9.4; 146)	43.5 (9.6)	31.7 (7.2; 117)	41.3 (9.6)	40.7 (9.6)	43.7 (9.5; 83)	42.8 (10.0)	33.2 (7.9; 94)	43.2 (10.4; 92)	43.1 (10.3)	45.1 (9.2; 63)	44.4 (9.0)
SF-36 MCS	41.0 (12.0; 211)	46.6 (11.6; 204)	46.0 (11.8)	46.8 (11.0; 146)	45.6 (11.5)	41.7 (11.5; 117)	46.8 (11.1)	45.8 (11.6)	45.8 (10.7; 83)	44.8 (11.3)	40.1 (12.6; 94)	46.5 (12.2; 92)	46.2 (12.1)	48.1 (11.4; 63)	46.6 (11.6)

n numbers indicate the number of patients reporting data for each outcome measure. Not all patients attending a visit reported data for every outcome. [a]Imputed values use last observation carried forward. [b]Imputed values use non-responder imputation. [c]Sleep Problems Index II. ASAS20: Assessment of Spondyloarthritis international Society 20% response criteria; ASAS40: Assessment of Spondyloarthritis international Society 40% response criteria; ASAS 5/6: Assessment of Spondyloarthritis international Society ⩾20% improvement in 5 of 6 domains; ASDAS: AS DAS; ASDS-ID: ASDAS inactive disease; ASDAS-MD: ASDAS moderate activity; ASQoL: AS quality of life; axSpA: axial spondyloarthritis; BASDAI50: ⩾50% improvement from baseline in BASDAI total score; BL: baseline; n/N: number of patients with the given response/number of observations at the visit; nr-axSpA: non-radiographic axial spondyloarthritis; NRS: numerical rating scale; OC: observed case; SF-36 MCS: short-form 36-item health survey mental component summary; SF-36 PCS: short-form 36-item health survey physical component summary; ULN: upper limit of normal.

Fig. 3 Heat map of ASDAS disease activity to week 204



Patients with ASDAS-ID at week 24, sorted by baseline ASDAS. CZP-randomized group. ASDAS: AS DAS; ASDAS-ID: AS DAS inactive disease; CZP: certolizumab pegol; sustained remission: remission according to ASDAS inactive disease for a continuous period of 6 months at any time during the study.

ASDAS-MD: 29.6%; ASDAS-HD: 34.5%; and ASDAS-vHD: 4.9%. In those patients who withdrew because of a stated lack of efficacy (n = 9), disease activity was high at the point they withdrew: seven had ASDAS-HD and two ASDAS-vHD.

Remission

The proportion of CZP-randomized patients in remission, as ASDAS-ID and BASDAI <2 with normal CRP (LOCF), was sustained from week 24 (30.3% for both measures) to week 204 (32.1 and 33.0%, respectively; Table 1).

Partial remission, as ASAS-PR, was achieved by 30.3% of CZP-randomized patients at week 24 and 23.4% at week 204 (NRI); 32.4 and 36.5%, respectively, using OCs (Table 1).

In all of these disease activity targets, similar improvements were seen in AS and nr-axSpA patients (Table 1 and supplementary Fig. S2, available at *Rheumatology* Online), and results were similar for both CZP dose regimens (supplementary Table S1, available at *Rheumatology* Online).

A total of 65 CZP-randomized patients (29.8%) achieved sustained remission as ASDAS-ID [AS: 28.9% (n = 35); nr-axSpA: 30.9% (*n* = 30)]. Sustained ASAS-PR was seen in 65 patients [29.8%; AS: 27.3% (n = 33); nr-axSpA: 33.0% (*n* = 32)].

Further patient-reported outcomes

Back pain, the quintessential symptom of axSpA, was previously shown to improve rapidly following treatment with CZP in RAPID-axSpA, with clinically relevant improvements observed in the overall axSpA population from day 2, compared with placebo [25]. Improvements of 3–4 points on the NRS, between baseline and week 24 (LOCF and OC), were sustained through to week 204 with CZP treatment (Table 1). Scores in patient-reported measures of fatigue, sleep (MOS Sleep Scale), health-related QoL outcomes both physical (SF-36 physical component summary) and mental (SF-36 mental component summary), and disease-specific (ASQoL) impact of CZP treatment on QoL all showed improvement by week 24 after the initiation of CZP, which were likewise sustained to week 204 (Table 1). Improvements in sleep by MOS Sleep Scale score were greater in nr-axSpA patients compared with AS, perhaps owing to the slightly higher mean baseline score in the nr-axSpA population (nr-axSpA: 51.7; AS: 46.8; Table 1).

Peripheral arthritis, enthesitis and uveitis

Improvements in SJC and TJC were observed at week 24 in both subpopulations and sustained or further improved to week 204 (Table 2).

Improvements in enthesitis (MASES) were seen in both the AS and nr-axSpA subpopulations by week 24, with further improvements to week 204 (Table 2). Despite the difference in baseline MASES (for those with baseline enthesitis: AS: 4.7; nr-axSpA: 5.6), mean change from baseline scores were similar in both AS and nr-axSpA patients [week 204, LOCF: AS: −3.4 (S.D. 3.7); nr-axSpA: −3.5 (S.D. 3.8). Substantial numbers of patients with baseline enthesitis, either as MASES >0 or involving the heel (a site often difficult to treat effectively), had achieved total resolution at week 24. Of all axSpA patients with baseline enthesitis by MASES (n = 148), 50.7% achieved a MASES score of 0 at week 24, and of those with heel enthesitis (n = 52), 61.5% had complete resolution at week 24 (LOCF). This effect was sustained to week 204; the proportion of patients with resolved enthesitis was 60.8% by MASES and 71.2% for heel enthesitis (LOCF).

The cumulative uveitis event rate seen to week 24 (3.0 per 100 person-years) remained low through week 96 [4.9/100 person-years; All CZP group (n = 315)] up to week 204 (4.5/100 person-years, All CZP group). The uveitis event rates for patients with (n = 63) or without (n = 252) current uveitis or a history of uveitis at baseline (All CZP group) were 15.2 and 1.8/100 person-years, respectively. The uveitis event rate at week 204 in CZP-randomized patients (n = 218) was 3.8/100 person-years (Table 2).

Safety

Patients in the safety set (n = 315) had a total CZP exposure of 981 person-years, with an AE rate per 100 person-years of 292.8 (Table 3). No new safety signals were identified from week 96 to 204, and no deaths were reported over 4 years.

Serious infections occurred at a rate of 2.3/100 person-years, serious cardiovascular events at a rate of 0.4/100 person-years, and malignancies at a rate of 0.5/100 person-years. Five patients were diagnosed with a malignancy during the study period (Table 3): one case each of breast cancer, cervical cancer, renal cell carcinoma, astrocytoma and basal cell carcinoma.

The most frequently occurring serious adverse events (SAEs; >0.5%) are shown in Table 3. There were three colitis SAEs by Medical Dictionary for Regulatory Activities preferred term (classed as serious owing to need for hospitalization), one of which was confirmed as IBD. The patient was assigned to CZP 400 mg Q4W at week 0, had no previous IBD history and was diagnosed with ulcerative colitis during the OL period, 708 days after the first injection. Later, the patient was diagnosed with Crohn's disease, after the end of week 204. A relationship to CZP was described as unlikely in both cases, and CZP was not interrupted.

Neither the other colitis nor the diarrhoea SAEs were confirmed as IBD, and none of the patients concerned had an IBD history. Two diarrhoea SAEs were reported (Table 3); one patient had suspected antibiotic-associated diarrhoea, and one patient reported diarrhoea with no significant findings on colonoscopy and upper gastrointestinal fibroscopy.

There was one additional SAE of biopsy-confirmed ulcerative colitis, captured under the preferred term of IBD. The episode occurred during the double-blind period, in a patient receiving placebo and with a ~15-year IBD history. The patient was re-randomized to CZP 200 mg Q2W at week 24 and completed the study, with no further IBD events recorded.

Abnormalities in liver function tests occurred with an event rate of 7.3/100 person-years, although only one event (a case of elevated γ-glutamyl transferase) was reported as an SAE, and none of them led to a permanent cessation of CZP treatment.

There was one case of active pulmonary tuberculosis during RAPID-axSpA (Table 3), in a patient from a high-risk geographical area. It occurred during the dose-blind period, while the patient was receiving CZP 200 mg Q2W, having been re-randomized from placebo at week 24. CZP was withdrawn. The event resolved slightly >6 months later.

Discussion

axSpA encompasses chronic conditions with the potential for considerable negative impact on physical function [5, 19], ability to work [29] and QoL [5, 19]. This underlines the need for evidence of the safety and efficacy of treatments used long term. Furthermore, the recognition that symptom burden and QoL impact are similar in patients with AS and nr-axSpA [3, 6] means that such evidence is needed for axSpA patients irrespective of subtype. RAPID-axSpA is the first international study to demonstrate the safety and efficacy of an anti-TNF over 4 years in both AS and nr-axSpA patients and the first study to report 4-year data in nr-axSpA patients.

With long-term CZP administration, improvements observed at early time points were sustained over 4 years of continuous treatment. Throughout the 4-year study period, similarly sustained responses were observed in both the AS and nr-axSpA patient populations, across all outcomes measured, including disease activity, function, spinal mobility, articular inflammation, enthesitis and uveitis. ASAS20 and ASAS40 responder rates in our cohort were generally similar to what has been shown in other studies of anti-TNF treatment in AS and nr-axSpA patients [19, 21, 30].

Patients with AS have reported stiffness, pain, fatigue and poor sleep as among their most prevalent concerns when it comes to QoL [31]. In a further study to assess the validity of patient-reported outcome instruments across the axSpA population, these were again identified as among the most important to patients [32]. As well as the improvements reported in physician-assessed and composite disease activity/assessment measures during the RAPID-axSpA study, sustained improvements were also seen in the stated patient-reported outcomes. Patients experienced reductions in back pain, fatigue

Table 2 Efficacy in peripheral joints, enthesitis and uveitis

	All patients axSpA (n = 218)					AS (n = 121)					nr-axSpA (n = 97)				
		Week 24		Week 204			Week 24		Week 204			Week 24		Week 204	
	BL	OC	LOCF	OC	LOCF	BL	OC	LOCF	OC	LOCF	BL	OC	LOCF	OC	LOCF
Articular manifestations, mean (S.D.)															
Swollen joint count[a]															
n	76	72	1.5	52	0.8	42	38	1.7	28	1.0	34	34	1.2	24	0.6
Mean (S.D.)	4.2 (5.6)	1.2 (2.7)	(3.2)	0.4 (1.1)	(2.4)	4.0 (4.6)	1.2 (1.9)	(3.1)	0.1 (0.4)	(3.0)	4.5 (6.8)	1.2 (3.4)	(3.4)	0.7 (1.5	(1.3)
Tender joint count[b]															
n	138	131	3.6	89	2.9	74	69	3.0	48	3.0	64	62	4.3	41	2.8
Mean (S.D.)	6.3 (7.1)	3.3 (6.4)	(6.5)	2.4 (5.0)	(5.5)	5.9 (6.5)	2.7 (4.7)	(4.8)	2.1 (5.0)	(5.7)	6.8 (7.7)	4.1 (7.8)	(8.0)	2.7 (5.1)	(5.3)
Enthesitis															
MASES[c]															
n	148	141	2.3	104	1.7	78	74	1.7	58	1.3	70	67	2.9	46	2.1
Mean (S.D.)	5.1 (3.5)	2.2	(3.5)	1.4 (2.5)	(3.0)	4.7 (3.4)	1.6 (2.7)	(2.7)	1.1 (2.2)	(2.5)	5.6 (3.6)	2.8 (4.0)	(4.1)	1.7 (2.9)	(3.4)
Complete resolution of enthesitis; MASES = 0, n/N (%)[c]	0	74/141 (52.5)	75 (50.7)	66/104 (63.5)	90 (60.8)	0	41/74 (55.4)	42 (53.8)	38/58 (65.5)	51 (65.4)	0	33/67 (49.3)	33 (47.1)	28/46 (60.9)	39 (55.7)
Heel enthesitis; complete resolution, n/N (%)[d]	0	32/49 (65.3)	32 (61.5)	26/35 (74.3)	37 (71.2)	0	13/23 (56.5)	13 (52.0)	12/17 (70.6)	17 (68.0)	0	19/26 (73.1)	19 (70.4)	14/18 (77.8)	20 (74.1)
Uveitis, event rate per 100 patient-years (n/N, %)[e]	All patients axSpA week 204					AS week 204					nr-axSpA week 204				
Week 0 CZP 200 + 400 mg (n = 218)	3.8 (19/218, 8.7)					3.5 (12/121, 9.9)					4.2 (7/97, 7.2)				

[a]For patients with baseline SJC > 0 (axSpA: 76; AS: 42; nr-axSpA: 34). [b]For patients with baseline TJC > 0 (axSpA: 138; AS: 74; nr-axSpA: 64). [c]For patients with baseline enthesitis [MASES > 0: axSpA: n = 148 (67.9% of CZP-randomized patients); AS: n = 78 (64.4% of CZP-randomized patients); nr-axSpA n = 70 (72.2% of CZP-randomized patients)]. [d]For patients with ⩾1 inflamed proximal Achilles tendon insertion at baseline [axSpA: n = 52 (23.9% of CZP-randomized patients); AS: n = 25 (20.7% of CZP-randomized patients); nr-axSpA: n = 27 (27.8% of CZP-randomized patients)]. [e]Data shown are cumulative from week 0. axSpA: axial spondyloarthritis; BL: baseline; CZP: certolizumab pegol; LOCF: last observation carried forward; MASES: Maastricht AS Enthesitis Score; n/N: number of patients with the given response/number of observations at the visit; nr-axSpA: non-radiographic axial spondyloarthritis; OC: observed case.

Table 3 Safety outcomes

Doses combined, 200 mg every 2 weeks + 400 mg every 4 weeks	All CZP (n = 315) n (%) [ER/100 patient-years]	AS (n = 174) n (%) [ER/100 PY]	nr-axSpA (n = 141) n (%) [ER/100 patient-years]
Patient exposure years	980.7	557.3	423.4
Any AE	303 (96.2) [292.8]	166 (95.4) [255.9]	137 (97.2)[341.5]
Serious AEs	69 (21.9) [10.4]	37 (21.3) [11.1]	32 (22.7) [9.4]
Serious infectious events	20 (6.3) [2.3]	11 (6.3) [2.5]	9 (6.4) [2.1]
Serious cardiovascular events	3 (0.3) [0.4]	0	3 (2.1) [0.9]
Malignancies	5 (1.6) [0.5]	2 (1.1) [0.4]	3 (2.1) [0.7]
Drug-related AEs[a]	170 (54.0) [67.4]	87 (50.0) [57.8]	83 (58.9) [80.1]
Deaths	0	0	0
AEs by intensity			
Mild	268 (85.1) [185.5]	143 (82.2) [152.2]	125 (88.7)[229.3]
Moderate	223 (70.8) [99.9]	123 (70.7) [96.7]	100 (70.9)[104.2]
Severe	49 (15.6) [7.4]	26 (14.9) [7.0]	23 (16.3) [8.0]
Most frequent SAEs by MedDRA preferred term (>0.5%)[b]			
Colitis[c]	3 (1.0) [0.3]	1 (0.6) [0.2]	2 (1.4) [0.5]
Diarrhoea[c]	2 (0.6) [0.2]	1 (0.6) [0.2]	1 (0.7) [0.2]
Chest pain	2 (0.6) [0.2]	1 (0.6) [0.2]	1 (0.7) [0.2]
Non-cardiac chest pain	2 (0.6) [0.2]	1 (0.6) [0.2]	1 (0.7) [0.2]
Cholelithiasis	2 (0.6) [0.2]	0	2 (1.4) [0.5]
Mycobacterial infection	2 (0.6) [0.2]	2 (1.1) [0.4]	0
Active tuberculosis	1 (0.3) [0.1]	1 (0.6) [0.2]	0
Pneumonia	3 (1.0) [0.5]	2 (1.1) [0.7]	1 (0.7) [0.2]
Back pain	2 (0.6) [0.2]	0	2 (1.4) [0.5]
Osteoarthritis	3 (1.0) [0.3]	2 (1.1) [0.4]	1 (0.7) [0.2]
Transient ischaemic attack	2 (0.6) [0.2]	2 (1.1) [0.4]	0
Major depression	2 (0.6) [0.3]	1 (0.6) [0.4]	1 (0.7) [0.2]

Safety set. [a]Drug-related AEs are those with a relationship of related, possibly related or those with missing responses. Non-drug-related AEs correspond to those with a relationship of Not related or Unlikely related. [b]In the All CZP group (n = 315). [c]Excluding infective. AE: adverse event; CZP: certolizumab pegol; ER: event rate; MedDRA: Medical Dictionary for Regulatory Activities; nr-axSpA: non-radiographic axial spondyloarthritis; SAE: serious adverse event.

and morning stiffness, and better sleep, and this was reflected in the overall QoL measures.

Treat-to-target guidelines for spondyloarthritides recommend remission as an appropriate treatment target, defined for axSpA as ASDAS-ID or BASDAI <2 with normal CRP [27]. The achievement of these treatment targets is particularly important overall, as although patients may have gained significant improvements from baseline, it is more important long term to look at achievement of a target disease activity state, either low disease activity or remission. The analyses reported here show that a considerable proportion of AS and nr-axSpA patients treated with CZP go on to achieve remission by ASDAS-ID or BASDAI <2 with normal CRP, and likewise with ASAS-PR (Table 1).

The maintenance of efficacy and remission using ASDAS disease activity scores is shown in a new way with the inclusion of heat maps, allowing the visualization of both cohort- and patient-level responses, to week 204 across the whole axSpA population (Fig. 3 and supplementary Fig. S1, available at *Rheumatology* Online). Some variation is shown in individual patients over time, but this is likely to represent the natural fluctuating course of the disease.

The retention rate in our study was comparable to that of other long-term extension studies of anti-TNF treatment in AS and nr-axSpA patients. Seventy-one per cent of patients in the All CZP group remained in the study after 3 years (156 weeks; AS: 74%; nr-axSpA: 67%), which was compared with other long-term extension studies reporting 3-year results (66% after 3 years in a study of nr-axSpA patients [21]; 82% in a study of AS patients [19]).

The number of CZP-randomized patients who withdrew from the study early because of a lack of efficacy was small, at nine patients, compared with the total number in this group who withdrew early for any reason (n = 76). The distribution of disease activity, at the point of withdrawal, in those patients who withdrew for reasons other than lack of efficacy, was comparable to disease activity at week 204 in patients who completed the study, which strengthens the conclusion that few patients withdrew because of lack of efficacy.

The limitations of this study include the lack of a placebo arm beyond week 24 and the bias inherent in having

dose-blind and OL periods, where patients know they are on active treatment, as do their physicians. Furthermore, subject withdrawals place a limitation on any clinical trial, as missing data introduce a risk of bias. In a long-term study, the cumulative impact of withdrawals is likely to be greater. Imputation helps to conserve the validity of intention-to-treat analyses but requires assumptions to be made about the measurements subjects would have given were they to have remained in the study. We have provided both observed and imputed data to minimize the risk of bias.

In conclusion, sustained efficacy was shown with continued CZP administration across a broad range of clinical, patient-reported and QoL outcomes over 4 years. The magnitude of the demonstrated improvements was similar for AS and nr-axSpA patients and sustained in both subpopulations. There were no new safety signals identified with the increased exposure to CZP, which was shown to have an acceptable long-term safety profile.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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