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ORIGINAL RESEARCH

Induction of Sustained Clinical Remission in Early Axial Spondyloarthritis Following Certolizumab Pegol Treatment: 48-Week Outcomes from C-OPTIMISE

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ABSTRACT

Introduction: Achievement of remission is a key treatment goal for patients with axial spondyloarthritis (axSpA). C-OPTIMISE assessed achievement of sustained clinical remission in patients with axSpA, including radiographic (r) and non-radiographic (nr) axSpA, during certolizumab pegol (CZP) treatment, and subsequent maintenance of remission following CZP dose continuation, dose reduction or withdrawal. Here, we report outcomes from the first 48 weeks (induction period) of C-OPTIMISE, during which patients received open-label CZP.

Methods: C-OPTIMISE (NCT02505542) was a two-part, multicenter, phase 3b study in adult patients with early axSpA (r-/nr-axSpA), including a 48-week open-label induction period followed by a 48-week maintenance period. Patients with active adult-onset

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axSpA, < 5 years' symptom duration, and fulfilling Assessment of SpondyloArthritis international Society classification criteria, were included. During the induction period, patients received a loading dose of CZP 400 mg at weeks 0, 2, and 4, followed by CZP 200 mg every 2 weeks (Q2W) up to week 48. The main outcome of the 48-week induction period was the achievement of sustained clinical remission (defined as an Ankylosing Spondylitis Disease Activity Score [ASDAS] < 1.3 at week 32 and < 2.1 at week 36 [or vice versa], and < 1.3 at week 48).

Results: In total, 736 patients (407 with r-axSpA, 329 with nr-axSpA) were enrolled into the study. At week 48, 43.9% (323/736) of patients achieved sustained remission, including 42.8% (174/407) of patients with r-axSpA and 45.3% (149/329) with nr-axSpA. Patients also demonstrated substantial improvements in axSpA symptoms, MRI outcomes and quality of life measures. Adverse events occurred in 67.9% (500/736) of patients, of which 6.0% (44/736) were serious.

Conclusions: Over 40% of patients with early axSpA achieved sustained remission during 48 weeks of open-label CZP treatment. Additionally, patients across the axSpA spectrum demonstrated substantial improvements in imaging outcomes and quality of life following treatment. No new safety signals were identified.

Trial Registration: NCT02505542.

Keywords: Axial spondyloarthritis; Clinical remission; Early disease; TNF inhibitor

Key Summary Points

Why carry out this study?

Achievement of remission is a key treatment goal for patients with axial spondyloarthritis (axSpA), a chronic inflammatory disease characterized by chronic lower back pain and stiffness with a subsequent loss of function that imposes a substantial burden on patients' quality of life.

The induction period of C-OPTIMISE assessed achievement of sustained clinical remission in patients with early active axSpA, including radiographic and non-radiographic axSpA, during open-label treatment with the TNF inhibitor certolizumab pegol (CZP).

What was learned from the study?

After 48 weeks of CZP treatment, 43.9% (323/736) of patients achieved sustained remission, including 42.8% (174/407) of patients with radiographic axSpA and 45.3% (149/329) with non-radiographic axSpA. There were also substantial improvements in axSpA signs and symptoms, physical function, quality of life, and MRI outcomes.

These results confirm that CZP is a suitable treatment option for patients across the broad axSpA spectrum, and provide further support for the concept of axSpA as a single disease, encompassing both radiographic and non-radiographic axSpA.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that affects the axial skeleton and is characterized by chronic lower back pain. Peripheral manifestations include arthritis, enthesitis, and dactylitis, while extra-musculoskeletal manifestations of the disease extend to acute anterior uveitis, psoriasis, and inflammatory bowel disease, amongst others [1, 2]. The two sub-types of axSpA, radiographic axSpA (r-axSpA; also known as ankylosing spondylitis) and non-radiographic axSpA (nr-axSpA), are differentiated by the degree of structural damage of the sacroiliac joints observed using pelvic radiography (as part of the modified New York classification criteria) [2–4]. Despite this difference, the burden of disease for patients in terms of clinical presentation, quality of life, and extra-musculoskeletal

manifestations is comparable between r-axSpA and nr-axSpA [5, 6].

Symptom onset in axSpA often occurs in the second to fourth decade of a patient's life, necessitating early and effective treatment to limit the impact of the disease on physical function, work and social productivity, and overall quality of life [7]. In addition to this, diagnosis is typically delayed for several years after the onset of symptoms, although the extent of this delay shows geographic variation [8–12]. Efforts to reduce the diagnostic delay have had limited success, with recent studies still reporting delays of up to 14 years in some regions [10, 12].

Current treatment options for patients with axSpA include non-steroidal anti-inflammatory drugs (NSAIDs) in combination with physical exercise and physical therapy as a first-line treatment, followed by tumor necrosis factor inhibitors (TNFi) and interleukin (IL)-17A inhibitors as second-line treatments [13]. Clinical remission is now recommended as a major treatment target in the Assessment of SpondyloArthritis international Society (ASAS)/European League Against Rheumatism (EULAR) recommendations for axSpA and treat-to-target recommendations for spondyloarthritis [14]. Once remission has been achieved, strategies for the maintenance of remission are necessary to prevent future deterioration in disease status. Given the high cost of TNFi and patients wanting to limit their long-term exposure to biologic therapy, dose reduction and treatment withdrawal of TNFi have been explored as options for maintaining remission [15–17]. However, results from previous studies suggest that complete treatment withdrawal in axSpA often leads to relapse [18, 19]. In addition, there are few controlled studies evaluating the maintenance of remission following dose reduction and/or withdrawal, and none that evaluate this in both the r- and nr-axSpA subpopulations.

The PEGylated, Fc-free TNFi certolizumab pegol (CZP) is an effective and well-tolerated treatment for patients with axSpA, and is approved for the treatment of both r-axSpA and nr-axSpA [14, 20, 21]. The phase 3b C-OPTIMISE trial investigated the use of CZP for the induction and maintenance of remission in patients with early axSpA, including those with r-axSpA and nr-axSpA. Here we report outcomes from the first 48 weeks of C-OPTIMISE, during which patients were treated with open-label CZP to induce sustained remission. Results from the maintenance period of C-OPTIMISE are reported elsewhere [22].

METHODS

Study Design

C-OPTIMISE (ClinicalTrials.gov number NCT02505542) was a two-part, multicenter phase 3b study in adult patients with axSpA (including r-axSpA and nr-axSpA) comprising a 48-week open-label induction period, followed by a 48-week maintenance period [22]. The study aimed to evaluate the induction of sustained remission and the effect of CZP maintenance dose continuation, reduction, or withdrawal on flares in patients who had achieved sustained remission (Fig. 1a).

During the induction period (baseline to week 48), patients received a loading dose of CZP 400 mg at weeks 0, 2 and 4, followed by open-label CZP 200 mg every 2 weeks (Q2W) until week 48. Patients achieving sustained remission during this 48-week induction period were eligible to proceed to the maintenance phase of the C-OPTIMISE study. Sustained remission was recorded as achieved when a subject had an Ankylosing Spondylitis Disease Activity Score (ASDAS) [23, 24] < 1.3 at week 32 or 36 (if ASDAS was < 1.3 at week 32, it must have been < 2.1 at week 36, or vice versa) and at week 48.

The maintenance period (weeks 48–96) was a randomized, double-blind period which investigated the efficacy and safety of CZP treatment in patients who had achieved sustained remission during the induction period. These patients were randomized to CZP 200 mg Q2W (full maintenance dose), CZP 200 mg Q4W (reduced maintenance dose) or placebo (withdrawal) [22].

The C-OPTIMISE study was approved by institutional review boards and independent ethics committees at participating sites

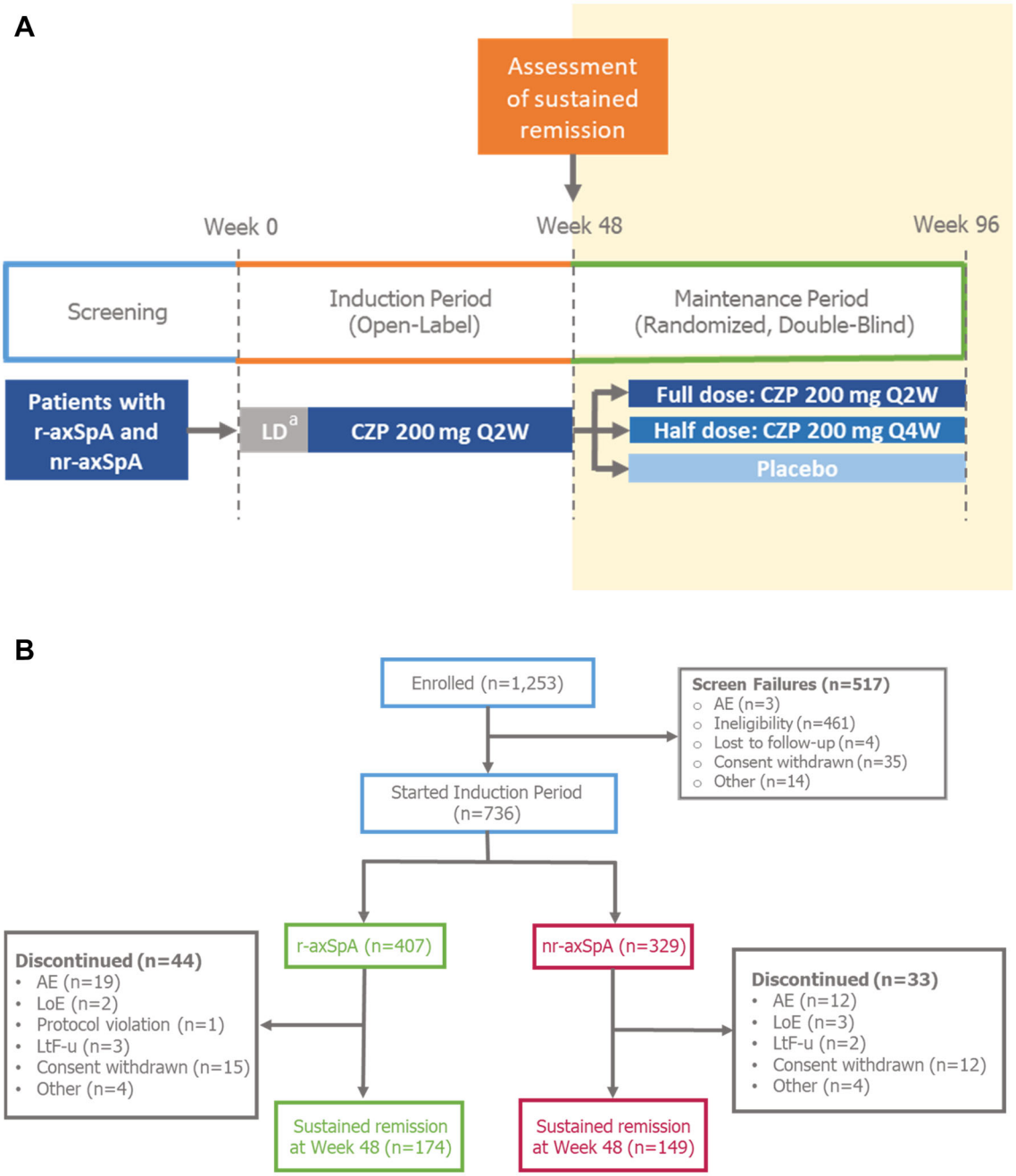


Fig. 1 C-OPTIMISE study design (**a**) and patient disposition (**b**). [a]The LD consisted of CZP 400 mg at weeks 0, 2 and 4. *LD* loading dose, *r-axSpA* radiographic axial spondyloarthritis, *nr-axSpA* non-radiographic axial spondyloarthritis, *CZP* certolizumab pegol, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *AE* adverse event, *LoE* lack of efficacy, *LtF-u* lost to follow-up

(Supplementary Material) and was conducted in accordance with local regulations and the International Conference on Harmonization Good Clinical Practice requirements, based on the Declaration of Helsinki. All patients provided informed consent to participate.

Patients

Eligible patients were between the ages of 18 and 45 years, and had a documented diagnosis of adult-onset axSpA which met ASAS classification criteria [25], a symptom duration of $\geq$ 3 months but < 5 years, and active disease (defined as ASDAS $\geq$ 2.1, Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] $\geq$ 4, and spinal pain $\geq$ 4 on a 0–10 numerical rating scale [BASDAI item 2]). In addition, all patients must have had inadequate response, contraindication, or intolerance to $\geq$ 2 NSAIDs.

Both subpopulations of axSpA (r-axSpA and nr-axSpA) were included in the study. Central reading by two independent readers (plus adjudicator, if necessary) was applied to all radiographs. Patients fulfilling the ASAS classification criteria and the imaging criterion of the modified New York classification criteria [26] were classified as having r-axSpA. Those fulfilling the ASAS classification criteria but not the modified New York classification criteria, and with objective signs of inflammation (C-reactive protein level above the upper limit of normal [10 mg/l], and/or evidence of active sacroiliitis on magnetic resonance imaging) were classified as having nr-axSpA.

Study Procedures

Patients visited their respective study sites for administration of study drug and study assessments at weeks 0, 2, 4, 12, 24, 32, 36, and week 48, plus an additional visit 3–5 days prior to the week 48 visit. Patients were taught to self-administer their study medication at weeks 2 and 4, and then self-administered at each of the remaining time points.

Outcomes

The primary outcome of C-OPTIMISE was the proportion of patients not experiencing a flare (ASDAS $\geq$ 2.1 [high disease activity] at two consecutive visits or ASDAS > 3.5 [very high disease activity] at any visit) during the maintenance period (weeks 48–96). These outcomes are reported elsewhere [22].

The main secondary outcome (reported herein) was the percentage of patients achieving sustained remission at week 48, the end of the open-label induction phase. Additional secondary outcomes included assessment of ASDAS status (ASDAS inactive disease [ID], low disease [LD] activity, high disease activity and very high disease activity) [18] and change from baseline in ASDAS major improvement (MI; ASDAS reduction from baseline of $\geq$ 2) and clinically important improvement (CII; ASDAS reduction from baseline of $\geq$ 1.1) [18].

Other outcomes included change from baseline in ASAS response rates (ASAS20, ASAS40 and ASAS5/6), ASAS partial remission (PR) [19, 20], BASDAI50, mean ASDAS, BASDAI [21], Bath Ankylosing Spondylitis Functional Index (BASFI) [22] and Bath Ankylosing Spondylitis Metrology Index (BASMI; linear definition) [23, 24], Ankylosing Spondylitis Quality of Life (ASQoL) and 36-Item Short Form Survey (SF-36) [27, 28], and MRI outcomes, including sacroiliac joint Spondyloarthritis Research Consortium of Canada (SIJ SPARCC) score [29] and the Berlin modification of the Ankylosing Spondylitis spine MRI score for activity (ASspiMRI-a) [22]. Mean Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and tender and swollen joint counts (44 joints evaluation) were also evaluated at week 48.

Safety Data

Safety analyses included all patients who received $\geq$ 1 dose of study medication during the induction period. Treatment-emergent adverse events (TEAEs) are reported as the number of patients experiencing each event and were classified according to the Medical

Dictionary for Regulatory Activities (MedDRA) version 19.0. Serious TEAEs were defined as medical occurrences that were life-threatening or led to death, hospitalization, congenital anomalies or birth defects, persistent or significant disability, or were considered medically important by the study investigator (regardless of severity). Event rates (ER) per 100 patient-years (PY) were calculated for all TEAEs and serious TEAEs (to include repeat events in the same patients).

Statistical Analysis

It was assumed that approximately 28% of patients would achieve sustained remission at the end of the open-label induction period. Hence, 750 patients were planned for enrolment into the study in order to provide sufficient power to detect differences (at a two-sided significance level of 0.05) between the CZP 200 mg Q2W and CZP 200 Q4W treatment groups vs. placebo during the 48-week maintenance period of the study.

The percentage of patients achieving sustained remission is summarized using descriptive statistics (counts and percentages). Continuous data are summarized using mean and standard deviation (SD). Missing data for secondary outcomes were imputed using non-responder imputation (NRI) for binary response measures, and last observation carried forward (LOCF) for continuous measures. For additional outcomes (not primary or secondary), observed data are reported.

Statistical analyses were performed using SAS Version 9.3.

RESULTS

Patient Disposition and Baseline Characteristics

Out of 1253 screened patients, 736 were enrolled in the open-label induction period, including 407 patients with r-axSpA and 329 patients with nr-axSpA (Fig. 1b). The majority of screen failures ($n = 461$) were due to patients not meeting study eligibility criteria. Baseline characteristics were generally comparable for patients with r-axSpA and nr-axSpA (Table 1). However, as expected, a higher proportion of patients with r-axSpA were male (78.4%) compared to nr-axSpA (59.3%). Patients with r-axSpA also had a longer average symptom duration at baseline than those with nr-axSpA (3.7 vs. 2.9 years).

Overall, 89.5% (659/736) axSpA patients completed the open-label induction period, including 89.2% (363/407) patients with r-axSpA and 90.0% (296/329) patients with nr-axSpA.

Of the 77 patients who discontinued during the induction period after starting open-label treatment, reasons for discontinuation included adverse events, lack of efficacy, protocol violation, lost to follow-up, consent withdrawal and 'other' (Fig. 1b).

Achievement of Sustained Remission

After 48 weeks of open-label CZP treatment, 43.9% (323/736) patients had achieved sustained remission according to the study definition (Fig. 2a), including 42.8% (174/407) r-axSpA and 45.3% (149/329) nr-axSpA patients. Over the 48-week open-label treatment period, there was a gradual increase in the percentage of patients who achieved and then maintained ASDAS-ID (used in the definition of sustained remission) up to week 48, with over a third (35.6%) achieving and maintaining sustained remission from week 12 onwards, and approximately half (52.0%) from week 24 onwards (Fig. 2b).

Clinical and Quality of Life Outcomes

Clinical improvements were observed as early as week 2 in the overall axSpA population, with 37.1% of patients reaching ASDAS < 2.1 (including 25.9 and 11.2% with ASDAS-LD and ASDAS-ID, respectively; Fig. 3a). By week 4, half of all patients (50.2%) had ASDAS < 2.1.

At week 48, 75.2% of all patients had ASDAS < 2.1 (22.8% with ASDAS-LD and 52.5% with ASDAS-ID), with comparable responses

Table 1 Baseline demographics and disease characteristics for patients enrolled in the C-OPTIMISE study

	All axSpA (*n* = 736)	r-axSpA (*n* = 407)	nr-axSpA (*n* = 329)
Age, years			
Mean (SD)	32.9 (7.0)	33.7 (6.8)	32.1 (7.1)
Median (range)	33.0 (18–45)	34.0 (18–45)	32.0 (18–45)
Male, *n* (%)	514 (69.8)	319 (78.4)	195 (59.3)
BMI, kg/m^2, mean (SD)	25.7 (4.9)	25.6 (4.7)	25.8 (5.1)
Race, *n* (%)			
Caucasian	681 (92.5)	375 (92.1)	306 (93.0)
Asian	38 (5.2)	27 (6.6)	11 (3.3)
Other/mixed/missing	17 (2.3)	5 (1.2)	12 (3.6)
Geographic region, *n* (%)			
North America	33 (4.5)	13 (3.2)	20 (6.1)
Western Europe	91 (12.4)	30 (7.4)	61 (18.5)
Eastern Europe	537 (73.0)	320 (78.6)	217 (66.0)
Asia	75 (10.2)	44 (10.8)	31 (9.4)
mNY positive, *n* (%)	407 (55.3)	407 (100.0)	0
Symptom duration, years			
Mean (SD)	3.3 (2.2)	3.7 (2.5)	2.9 (1.7)
Median	3.5	4.0	2.9
Time since diagnosis, years			
Mean (SD)	2.2 (1.7)	2.5 (1.8)	1.8 (1.6)
Median	1.6	2.3	1.1
HLA-B27 positive, *n* (%)	617 (83.8)	363 (89.2)	254 (77.2)
CRP > ULN, *n* (%)	344 (46.7)	210 (51.6)	134 (40.7)
Prior TNFi therapy, *n* (%)	32 (4.3)	20 (4.9)	12 (3.6)
History of enthesitis (heel), *n* (%)	184 (25.0)	102 (25.1)	82 (24.9)
MASES > 0, *n* (%)	447 (60.7)	241 (59.2)	206 (62.6)
Peripheral arthritis,[a] *n* (%)	4 (0.5)	2 (0.5)	2 (0.6)
History of EMMs, *n* (%)			
Uveitis	111 (15.1)	63 (15.5)	48 (14.6)
Inflammatory bowel disease	17 (2.3)	9 (2.2)	8 (2.4)
Psoriasis	45 (6.1)	24 (5.9)	21 (6.4)
Disease characteristics, mean (SD)			
ASDAS	3.7 (0.8)	3.9 (0.8)	3.6 (0.8)

Table 1 continued

	All axSpA (n = 736)	r-axSpA (n = 407)	nr-axSpA (n = 329)
BASDAI	6.7 (1.4)	6.7 (1.4)	6.7 (1.4)
BASFI	5.3 (2.1)	5.4 (2.0)	5.2 (2.1)
BASMI	3.1 (1.5)	3.5 (1.6)	2.6 (1.3)
Tender joint count	2.6 (5.0)	1.9 (3.8)	3.4 (6.0)
Swollen joint count[b]	0.7 (2.1)	0.5 (1.4)	1.1 (2.7)
MASES, mean (SD)	2.5 (3.0)	2.3 (2.8)	2.7 (3.1)
Imaging (MRI), mean (SD)			
SIJ SPARCC	8.0 (11.4)	8.2 (11.8)	7.9 (10.9)
ASspiMRI-a	3.1 (5.2)	4.6 (6.1)	1.4 (2.9)
Concomitant medication,[c] n (%)			
NSAIDs	618 (84.0)	352 (86.5)	266 (80.9)
DMARDs	166 (22.6)	97 (23.8)	69 (21.0)

Induction period baseline characteristics are reported

ASDAS Ankylosing Spondylitis Disease Activity Score, *ASspiMRI-a* Ankylosing Spondylitis spine MRI score for activity, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BASMI* Bath Ankylosing Spondylitis Metrology Index, *BMI* body mass index, *CRP* C-reactive protein, *CZP* certolizumab pegol, *DMARD* disease-modifying anti-rheumatic drug, *EMM* extra-musculoskeletal manifestation, *HLA-B27* human leukocyte antigen B27, *MASES* Maastricht Ankylosing Spondylitis Enthesitis Score, *mNY* modified New York, *MRI* magnetic resonance imaging, *NSAID* non-steroidal anti-inflammatory drug, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *SD* standard deviation, *SIJ SPARCC* sacroiliac joint Spondyloarthritis Research Consortium of Canada, *TNF* tumor necrosis factor, *ULN* upper limit of normal

[a] Reported as previous history or ongoing at baseline

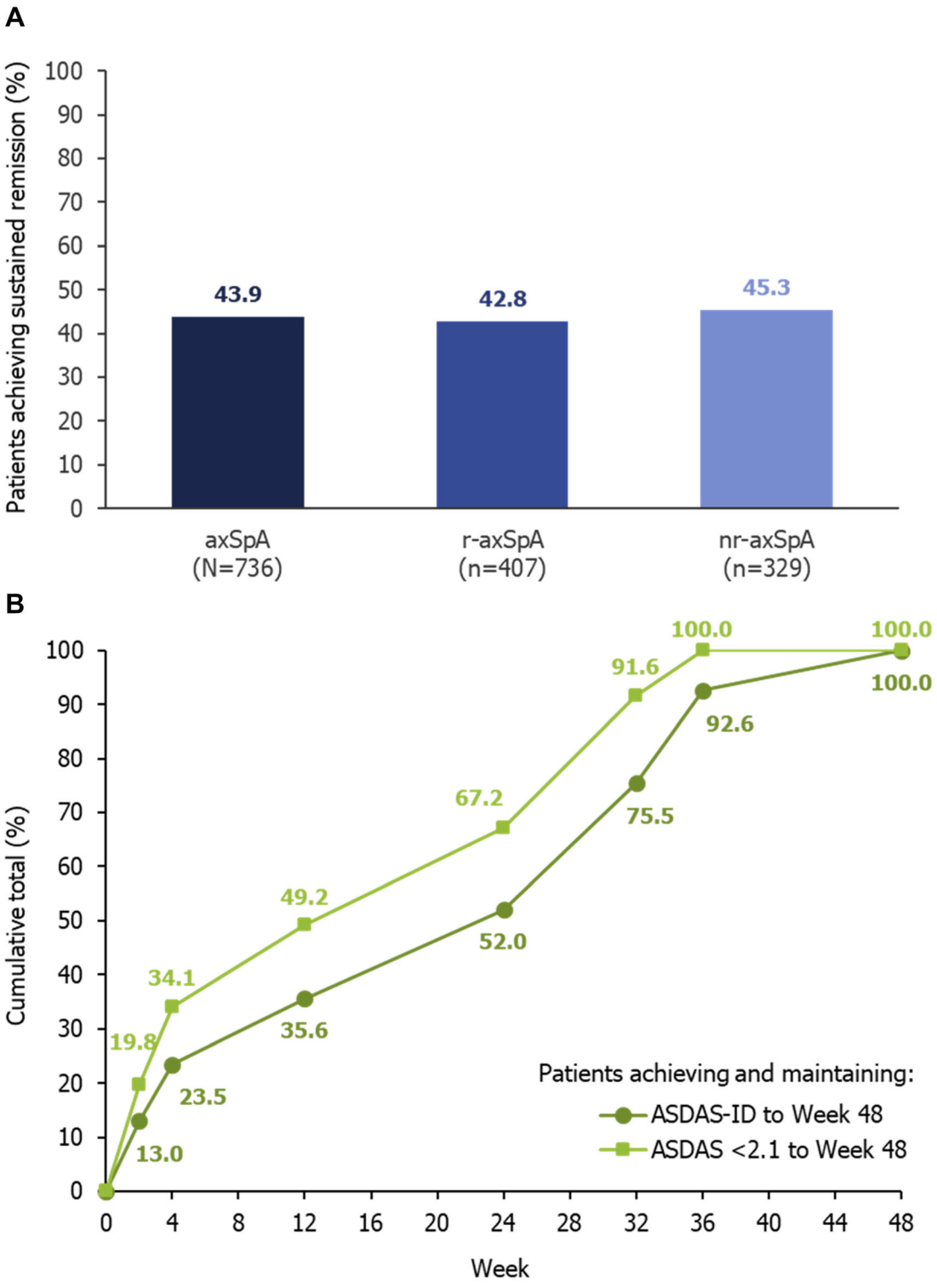
[b] 44 joints

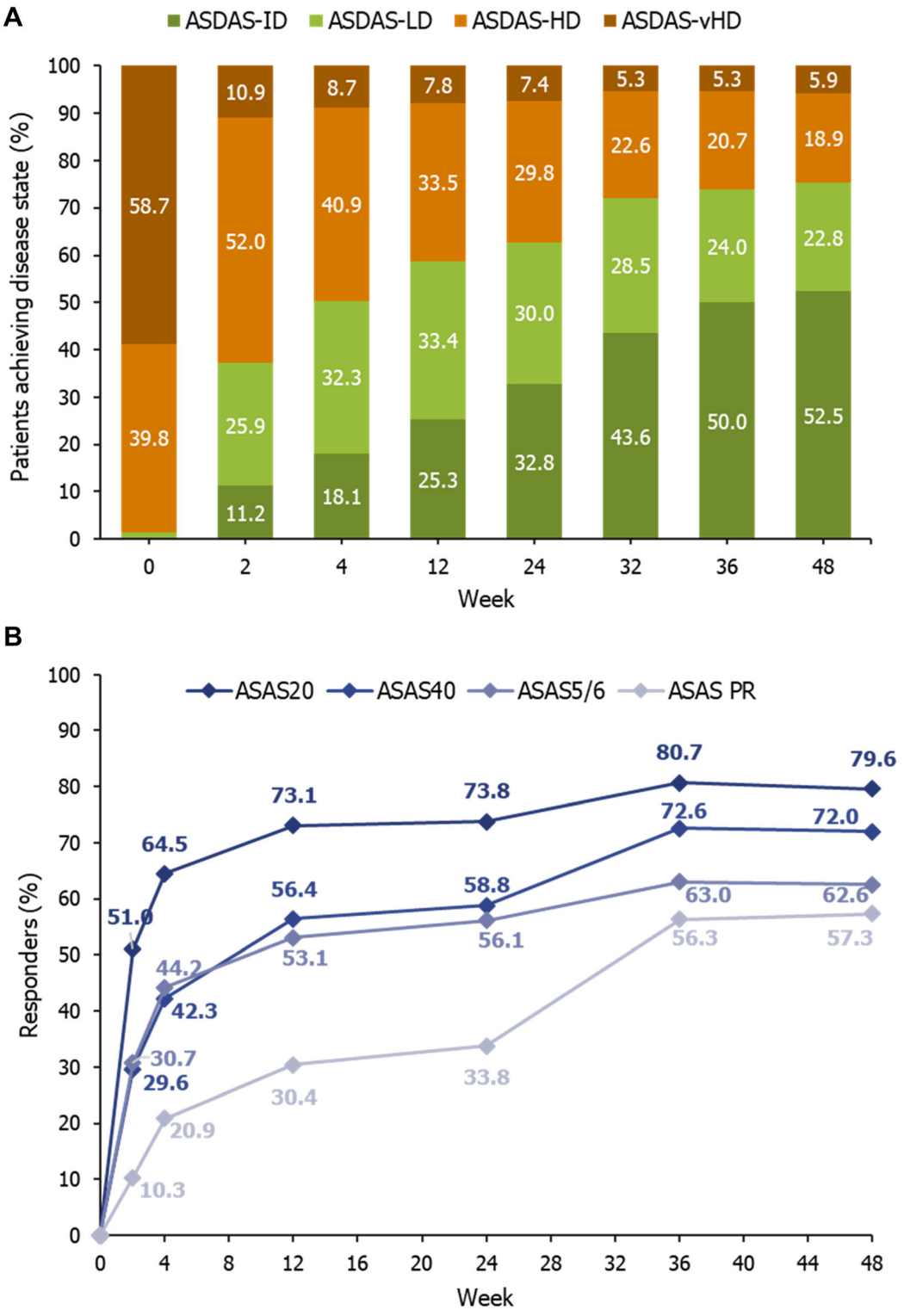
[c] Any intake during induction period (weeks 0–48).

amongst r-axSpA and nr-axSpA patients (74.2 and 76.5%, respectively; Table 2). This is compared to just 1.5% who had ASDAS < 2.1 at study baseline. The percentage of patients reaching ASAS PR at week 48 (57.3%) was similar to the percentage achieving ASDAS-ID (52.5%). Similar trends were observed in ASAS20 and ASAS40 response rates, with 73.1 and 56.4% of patients achieving an ASAS20 and ASAS40 response, respectively, by week 12, and 79.6 and 72.0% by week 48 (Fig. 3b).

Other outcome measures also demonstrated improvements at week 48, including those assessing disease activity (ASDAS and BASDAI), physical function (BASFI), mobility (BASMI) and quality of life (SF-36, ASQoL). All responses were comparable between r-axSpA and nr-axSpA subpopulations (Table 2).

Fig. 2 **a** Proportion of patients achieving sustained remission following 48 weeks' open-label CZP. **b** Kinetics of ASDAS-ID and ASDAS < 2.1 achievement to week 48 in the 323 patients who achieved sustained remission. Non-responder imputation. *ASDAS-ID* Ankylosing Spondylitis Disease Activity Score inactive disease, *axSpA* axial spondyloarthritis, *r-axSpA* radiographic axial spondyloarthritis, *nr-axSpA* non-radiographic spondyloarthritis


A
Patients achieving sustained remission (%)
100
90
80
70
60
50
40
30
20
10
0
43.9
42.8
45.3
axSpA
(N=736)
r-axSpA
(n=407)
nr-axSpA
(n=329)
B
Cumulative total (%)
100.0
100.0
91.6
100.0
92.6
67.2
75.5
49.2
52.0
34.1
35.6
19.8
23.5
13.0
Patients achieving and maintaining:
ASDAS-ID to Week 48
ASDAS <2.1 to Week 48
0 4 8 12 16 20 24 28 32 36 40 44 48
Week


A
ASDAS-ID
ASDAS-LD
ASDAS-HD
ASDAS-vHD
Patients achieving disease state (%)
100
90
80
70
60
50
40
30
20
10
0
58.7
39.8
10.9
52.0
25.9
11.2
8.7
40.9
32.3
18.1
7.8
33.5
33.4
25.3
7.4
29.8
30.0
32.8
5.3
22.6
28.5
43.6
5.3
20.7
24.0
50.0
5.9
18.9
22.8
52.5
0
2
4
12
24
32
36
48
Week
B
ASAS20
ASAS40
ASAS5/6
ASAS PR
Responders (%)
100
90
80
70
60
50
40
30
20
10
0
51.0
64.5
73.1
73.8
80.7
79.6
44.2
42.3
56.4
58.8
72.6
72.0
30.7
29.6
53.1
56.1
63.0
62.6
20.9
10.3
30.4
33.8
56.3
57.3
0
4
8
12
16
20
24
28
32
36
40
44
48
Week

◀**Fig. 3** **a** ASDAS disease states and **b** ASAS responses during the 48-week induction period for the overall axSpA population ($N = 736$). ASDAS disease states: last observation carried forward; ASAS response: non-responder imputation, *ASDAS-ID/LD/HD/vHD* Ankylosing Spondylitis Disease Activity Score inactive disease/low disease/high disease/very high disease, *ASAS* Assessment of Spondyloarthritis international Society, *axSpA* axial spondyloarthritis

MRI Outcomes

Improvements were also reported for MRI outcomes assessing active inflammation in the SIJ and spine at week 48 across both axSpA subpopulations (Table 2). At baseline, mean SIJ SPARCC scores were comparable in patients with r-axSpA and nr-axSpA (8.2 and 7.9, respectively), and demonstrated similar reductions over the 48 weeks to 1.4 and 1.5, respectively. ASspiMRI-a scores were higher at baseline in patients with r-axSpA compared to nr-axSpA (4.6 and 1.4, respectively), but following 48 weeks' treatment had reduced substantially in both groups to 1.2 and 0.5, respectively.

Peripheral and Extra-Musculoskeletal Manifestations

Despite higher baseline tender and swollen joint counts in patients with nr-axSpA (3.4 and 1.1, respectively) compared with r-axSpA (1.9 and 0.5, respectively), at week 48 mean scores had improved in both subpopulations (Table 2). Improvements in enthesitis (MASES) were also reported at week 48 across all subpopulations (Table 2). In patients who had enthesitis at baseline, by week 48, 72.6% (291/401) of all patients had achieved full enthesitis resolution (including 75.1% [160/213] r-axSpA patients and 69.7% [131/188] nr-axSpA patients).

At baseline, 15.1% (111/736) patients had a history of anterior acute uveitis (11 patients had uveitis at screening). During the 48-week induction period, 7.2% (8/111) of these patients experienced a total of ten uveitis flares. In the total population, including patients without any history of uveitis, 1.4% (10/736) patients experienced 13 uveitis flares.

At baseline, 17 of 736 (2.3%) patients had a history of inflammatory bowel disease (nine with r-axSpA and eight with nr-axSpA). Of these 17 patients, 3 (17.6%) had an exacerbation of their inflammatory bowel disease during the treatment period, all of whom had nr-axSpA. There were four de novo cases of inflammatory bowel disease, all in patients with r-axSpA.

Safety

During the 48-week open-label induction period, TEAEs were reported for 67.9% of axSpA patients (67.3% of patients with r-axSpA and 68.7% of patients with nr-axSpA; Table 3). Serious TEAEs were reported for 6.0% of axSpA patients (ER = 6.74/100 PY). The rates of serious TEAEs were similar for patients with r-axSpA (6.1%, ER = 7.02/100 PY) and nr-axSpA patients (5.8%, ER = 6.40/100 PY).

There were two reported cases of opportunistic infection, both serious and in patients with r-axSpA; this included one case of pulmonary tuberculosis (resolving at the time of preliminary drop-out) and one of tuberculous pleurisy (resolved). Patients were tested for the signs and symptoms of latent or active TB infection before CZP treatment; both of these cases had an onset after the start of treatment, were considered to be treatment-related, and occurred in patients based in Romania. There were 13 reported cases of oral herpes, and ten of these were in patients with r-axSpA (2.5% of r-axSpA patients); five of the 13 cases were considered to be related to the study drug. A single case of demyelinating disorder (optic neuritis) was reported in a patient with nr-axSpA and judged to be related to the study drug by the investigator. There were no reported cases of oral candidiasis, malignancy, serious cardiovascular or bleeding events. No deaths were reported.

DISCUSSION

The induction period of the C-OPTIMISE trial evaluated the achievement of sustained

Table 2 Efficacy outcomes following 48 weeks' of open-label CZP 200 mg Q2W

	Imputation	All axSpA (N = 736)		r-axSpA (n = 407)		nr-axSpA (n = 329)	
		BL	Week 48	BL	Week 48	BL	Week 48
ASDAS disease states, n (%)							
ASDAS-ID	LOCF	0/736 (0.0)	385/734 (52.5)	0/407 (0.0)	213/407 (52.3)	0/329 (0.0)	172/327 (52.6)
ASDAS-LD	LOCF	11/736 (1.5)	167/734 (22.8)	6/407 (1.5)	89/407 (21.9)	5/329 (1.5)	78/327 (23.9)
ASDAS-HD	LOCF	293/736 (39.8)	139/734 (18.9)	136/407 (33.4)	79/407 (19.4)	157/329 (47.7)	60/327 (18.3)
ASDAS-vHD	LOCF	432/736 (58.7)	43/734 (5.9)	265/407 (65.1)	26/407 (6.4)	167/329 (50.8)	17/327 (5.2)
ASDAS clinical improvement, n (%)							
ASDAS-CII	NRI	–	564 (76.6)	–	321 (78.9)	–	243 (73.9)
ASDAS-MI	NRI	–	413 (56.1)	–	238 (58.5)	–	175 (53.2)
ASAS responder rates, n (%)							
ASAS20	NRI	–	586 (79.6)	–	325 (79.9)	–	261 (79.3)
ASAS40	NRI	–	530 (72.0)	–	290 (71.3)	–	240 (72.9)
ASAS5/6	NRI	–	461 (62.6)	–	281 (69.0)	–	180 (54.7)
ASAS PR	NRI	–	422 (57.3)	–	227 (55.8)	–	195 (59.3)
BASDAI50 response, n (%)	NRI	–	528 (71.7)	–	290 (71.3)	–	238 (72.3)
ASDAS, mean (SD)	LOCF	3.7 (0.8)	1.6 (1.0)	3.9 (0.8)	1.6 (1.0)	3.6 (0.8)	1.5 (1.0)
BASDAI, mean (SD)	LOCF	6.7 (1.4)	2.1 (2.4)	6.7 (1.4)	2.1 (2.3)	6.7 (1.4)	2.2 (2.4)
BASFI, mean (SD)	LOCF	5.3 (2.1)	1.7 (2.1)	5.4 (2.0)	1.7 (2.1)	5.2 (2.1)	1.6 (2.1)
BASMI, mean (SD)	LOCF	3.1 (1.5)	2.3 (1.3)	3.5 (1.6)	2.6 (1.4)	2.6 (1.3)	1.9 (1.1)
ASQoL, mean (SD; n)	OC	11.1 (4.4; 735)	2.7 (4.3; 667)	11.1 (4.4; 407)	2.7 (4.2; 365)	11.2 (4.5; 328)	2.8 (4.5; 302)

Table 2 continued

	Imputation	All axSpA (N = 736)		r-axSpA (n = 407)		nr-axSpA (n = 329)	
		BL	Week 48	BL	Week 48	BL	Week 48
SF-36 PCS, mean (SD; n)	OC	34.5 (7.6; 734)	50.4 (8.0; 667)	34.8 (7.4; 406)	50.5 (7.7; 365)	34.2 (7.7; 328)	50.3 (8.3; 302)
SF-36 MCS, mean (SD; n)	OC	43.4 (10.7; 734)	52.6 (9.6; 667)	43.3 (10.7; 406)	52.6 (9.4; 365)	43.6 (10.8; 328)	52.6 (9.8; 302)
MRI outcomes							
SIJ SPARCC, mean (SD; n)	OC	8.0 (11.4; 657)	1.4 (4.5; 620)	8.2 (11.8; 358)	1.4 (4.2; 341)	7.9 (10.9; 299)	1.5 (4.8; 279)
ASspiMRI-a, mean (SD; n)	OC	3.1 (5.2; 655)	0.9 (2.1; 620)	4.6 (6.1; 357)	1.2 (2.5; 341)	1.4 (2.9; 298)	0.5 (1.3; 279)
MASES, mean (SD; n)	OC	2.5 (3.0; 736)	0.6 (1.6; 668)	2.3 (2.8; 407)	0.5 (1.5; 366)	2.7 (3.1; 329)	0.6 (1.7; 302)
Tender joint count, mean (SD; n)	OC	2.6 (5.0; 736)	0.5 (2.3; 669)	1.9 (3.8; 407)	0.3 (1.3; 367)	3.4 (6.0; 329)	0.7 (3.0; 302)
Swollen joint count, mean (SD; n)	OC	0.7 (2.1; 736)	0.1 (0.7; 669)	0.5 (1.4; 407)	0.1 (0.4; 367)	1.1 (2.7; 329)	0.1 (0.9; 302)

ASAS Assessment of Spondyloarthritis international Society, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *ASspiMRI-a* Ankylosing Spondylitis spine MRI score for activity, *BASDAI50* Bath Ankylosing Spondylitis Disease Activity Index 50% improvement, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BASMI* Bath Ankylosing Spondylitis Metrology Index, *CII* clinically important improvement, *CZP* certolizumab pegol, *LS* least squares, *MASES* Maastricht Ankylosing Spondylitis Enthesitis Score, *MI* major improvement; *MMRM* mixed effect model for repeated measures, *MRI* magnetic resonance imaging, *NRI* non-responder imputation, *OC* observed case, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *SD* standard deviation, *SE* standard error, *SIJ SPARCC* sacroiliac joint Spondyloarthritis Research Consortium of Canada

Table 3 Safety outcomes for r-axSpA and nr-axSpA subpopulations at the end of the induction period (week 48)

n **(%), unless otherwise specified**	**All axSpA (*n* = 736)**	**r-axSpA (*n* = 407)**	**nr-axSpA (*n* = 329)**
CZP exposure duration (days)			
Mean (SD)	317.1 (64.0)	315.4 (66.6)	319.3 (60.7)
Median (range)	336.0 (14–384)	336.0 (14–384)	336.0 (14–369)
Patient-years at risk	697.1	384.4	312.7
Any TEAE	500 (67.9)	274 (67.3)	226 (68.7)
Event rate per 100 PY	225.0	211.0	242.1
Serious TEAEs	44 (6.0)	25 (6.1)	19 (5.8)
Event rate per 100 PY	6.7	7.0	6.4
Discontinuation due to TEAEs	31 (4.2)	18 (4.4)	13 (4.0)
Drug-related TEAEs	194 (26.4)	105 (25.8)	89 (27.1)
TEAEs of interest			
Opportunistic infections	2 (0.3)	2 (0.5)	0
Pulmonary tuberculosis	1 (0.1)	1 (0.2)	0
Tuberculous pleurisy	1 (0.1)	1 (0.2)	0
Oral candidiasis	0	0	0
Malignant or unspecified tumors	0	0	0
Serious cardiovascular events	0	0	0
Serious hematopoietic cytopenia	0	0	0
Serious bleeding events	0	0	0
Hepatic events	46 (6.3)	26 (6.4)	20 (6.1)
Liver function analyses	32 (4.3)	19 (4.7)	13 (4.0)
Hypersensitivity and anaphylactic reactions	3 (0.4)	0	3 (0.9)
Demyelinating disorders[a]	1 (0.1)	0	1 (0.3)
Deaths	0	0	0

axSpA axial spondyloarthritis, *CZP* certolizumab pegol, *PY* patient-years, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *TEAE* treatment-emergent adverse event

[a] The singular case of demyelinating disorder was optic neuritis, judged to be related to the study drug by the investigator. Safety events are reported for the safety set ($N = 736$) according to the Medical Dictionary for Regulatory Activities version 19.0

remission in patients with early axSpA, including both r- and nr-axSpA, during 48 weeks' open-label CZP treatment. The definition of remission in C-OPTIMISE was based on achievement of ASDAS-ID (< 1.3), a disease activity measure in axSpA that is considered in the ASAS/EULAR recommendations to reflect a state of clinical remission [30, 31]. The definition of 'sustained' remission also corresponds to that used in the ABILITY-3 study, by requiring

patients to have ASDAS-ID at consecutive timepoints over at least 12 weeks, although the overall induction period in C-OPTIMISE was longer (48 vs. 28 weeks) [18]. Since there is no widely established definition for clinical remission in axSpA, definitions used in previous, mostly observational, studies have been heterogeneous [19].

Using the study definition for sustained remission, over 40% of patients had reached sustained remission by week 48. All of these patients were in sustained remission for at least 12 weeks, but 23.5% achieved and maintained ASDAS-ID from week 4 onwards, and 52.0% from week 24 onwards. This means that almost a quarter of patients were in a state of deep sustained remission for nearly a year (44 weeks), and approximately half were in sustained remission for 6 months.

The response to CZP was similar for r-axSpA and nr-axSpA patients, with 42.8 and 45.3%, respectively, achieving sustained remission. Given that the burden of disease is similar amongst the two axSpA subpopulations [6], the finding that similar proportions of patients can achieve clinical remission after CZP treatment further supports the concept of axSpA as a single disease, encompassing both r- and nr-axSpA.

Across other measures, responses showed similar rapid and sustained improvements over the 48-week treatment period. Over half of all patients had reached ASAS PR, another measure of remission, by the end of the induction period, with a fifth of patients achieving ASAS PR at week 4. Improvements in patient mobility and physical function were also observed, as assessed by the BASMI and BASFI, respectively. As the physical limitations of axSpA can impact on many areas of a patient's life, including employment, social relationships and mood, improvements in these outcomes are crucial to patients' quality of life [32, 33]. Indeed, there were also improvements in the ASQoL and SF-36 quality of life measures. Finally, patients also demonstrated improvements in extra-musculoskeletal and peripheral manifestations of disease, including enthesitis, uveitis, inflammatory bowel disease and peripheral arthritis. For all measures, responses were similar across r-axSpA and nr-axSpA subpopulations, further validating the unified axSpA concept, and supporting results from a recent meta-analysis which suggested that the treatment effect is comparable in both subpopulations [6].

Structural progression of disease is a risk in axSpA, both in r-axSpA and nr-axSpA, and has an impact on the degree of disability experienced by patients [34]. Active inflammation is known to be a predictor of structural disease progression, and is reflected in MRI outcomes including ASspiMRI-a and SIJ SPARCC [35]. In C-OPTIMISE, substantial improvements were shown in ASspiMRI-a and SIJ SPARCC outcomes in both subpopulations after 48 weeks of CZP treatment.

The results from this study are also comparable with previous studies assessing the efficacy and tolerability of CZP in patients with axSpA [14, 21]. RAPID-axSpA, a phase 3 randomized controlled trial (NCT01087762), investigated the effect of CZP on a broad axSpA population, and was double-blind and placebo-controlled to week 24, dose-blind to week 48 and open-label to week 204 [14]. The study investigated improvements in clinical and patient-reported outcomes in a controlled setting, providing a valuable comparison for the secondary outcomes of this open-label trial across the same time period [14]. After 48 weeks of treatment, approximately 70 and 60% of patients in RAPID-axSpA achieved ASAS20 and ASAS40, respectively, compared to 79.6 and 72.0% in this study [14]. It is possible that the increase in the percentages of patients achieving ASAS20/40 in C-OPTIMISE is attributable to the open-label nature of this study period, as patients in RAPID-axSpA were blinded up to week 48 [14]. However, the increase may also be affected by the younger patient population in C-OPTIMISE (mean patient age 32.9 years vs. 39.5 years in RAPID-axSpA) or the shorter symptom duration in C-OPTIMISE (median 3.5 years vs. 7.7 years in RAPID-axSpA) [36].

Despite the overall lower ASAS40 response rates in RAPID-axSpA, it is important to note that similar percentages of patients with r-axSpA and nr-axSpA achieved ASAS40 (approximately 59 and 57%, respectively), which was also observed in C-OPTIMISE (71.3 and 72.9%, respectively) [14]. This indicates that

r-axSpA and nr-axSpA patient populations achieve similar ASAS40 outcomes, regardless of open-label or blinded treatment, highlighting that TNFi treatment is equally effective in both patient groups.

Improvements in axSpA symptoms and quality of life for patients during the induction period of C-OPTIMISE were also comparable to those observed in the C-axSpAnd trial (NCT02552212), a double-blind, placebo-controlled trial which focused on patients with nr-axSpA [21]. In C-axSpAnd, 47.2% of patients with nr-axSpA achieved ASDAS-MI (52-week data), compared to 53.2% of patients with nr-axSpA in C-OPTIMISE at 48 weeks [21].

Safety data reported for the induction period of C-OPTIMISE were comparable to previous reports for CZP in axSpA and no new safety signals were identified [14, 21].

A potential limitation of the induction period of C-OPTIMISE is the fact that it was open-label with no placebo comparator arm, which may introduce an element of bias to the observed improvements, particularly as many of the outcomes are patient-reported. Indeed, clinical responses during the induction period such as ASAS20/40 were higher than in previous double-blinded studies of CZP in axSpA, indicating that perception bias may have impacted the outcomes [14, 21]. However, it is also important to note that there were large improvements in objective measures such as MRI outcomes.

In summary, the induction period of C-OPTIMISE evaluated the achievement of sustained remission in patients across the axSpA spectrum in a controlled setting. Sustained remission was achieved in over 40% of patients during 48 weeks of open-label treatment with CZP, demonstrating the benefits of early treatment in patients with axSpA. Improvements in disease activity and other outcome measures were comparable across r-axSpA and nr-axSpA patient groups, supporting the findings of previous studies in this area, with no new safety signals identified.

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Data Availability. Underlying 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 patient-level data and redacted trial documents which may include: analysis-ready datasets, study protocol, 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 https://www.Vivli.org and a signed data sharing agreement will need to be executed. All documents are available in English only, for a prespecified time, typically 12 months, on a password protected portal.

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