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Effect of Certolizumab Pegol over 96 Weeks in Patients with Axial Spondyloarthritis: Results from a Phase 3 Randomized Trial

Short title: RAPID-axSpA 96-week Safety and Efficacy

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Abstract

Objective: Previous reports of RAPID-axSpA (NCT01087762) demonstrated efficacy and safety of certolizumab pegol (CZP) over 24 weeks (wks) in patients with axial spondyloarthritis (axSpA), including ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA). We herein report efficacy and safety data from a 96-wk interim data cut of RAPID-axSpA.

Methods: RAPID-axSpA is double-blind and placebo-controlled to Wk24, dose-blind to Wk48 and open-label to Wk204. Outcome variables assessed included ASAS20/40 and ASAS-partial remission responses (analyzed by non-responder imputation [NRI]), and ASDAS, ASDAS Inactive Disease , ASDAS Major Improvement, BASDAI, BASFI and BASMI-linear (analyzed by last observation carried forward [LOCF]). Safety data are shown for patients treated with ≥1 dose of CZP.

Results: 325 patients were randomized, of whom 218 received CZP from Wk0. Of these, 93% completed Wk24, 88% Wk48 and 80% Wk96. Improvements in ASAS responses were maintained to Wk96 (ASAS20: 67.4%, 72.0%, 62.8% at Wks 24, 48, 96, respectively), as well as improvements in ASDAS, BASDAI (mean score: 3.3, 3.1, 3.0 at Wks 24, 48, 96, respectively), BASFI and BASMI-linear. Comparable improvements were observed with both dosing regimens (200mg Q2W/400mg Q4W) and in AS and nr-axSpA patients. In the Safety Set, adverse events occurred in 279 patients (88.6%) and serious adverse events in 41 (13.0%). No deaths or malignancies were reported.

Conclusion: Clinical improvements to Wk24 in both CZP dosing regimens were sustained to Wk96. Similar sustained improvements were observed in AS and nr-axSpA subpopulations. The safety profile was in-line with previous reports from RAPID-axSpA, with no new safety signals observed with longer exposure duration.

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease primarily characterized by inflammation of the sacroiliac (SI) joints and spine. AxSpA encompasses a spectrum of disease, including ankylosing spondylitis (AS)(1) and axSpA without radiographic evidence of AS (non-radiographic axSpA [nr-axSpA]).(2) There are often long delays between symptom onset and diagnosis, since back pain from axSpA can be difficult to distinguish from more common causes of back pain. Historically, diagnosis has been challenging in patients with nr-axSpA because of the lack of definitive structural changes on SI X-rays. Nevertheless, the burden of disease is similar across the axSpA spectrum,(3) and patients with AS and nr-axSpA often suffer for many years before a diagnosis is made.

Due to the chronic nature of axSpA, treatments must be tolerable and efficacious in controlling the signs and symptoms of disease over the long-term. Current pharmacological treatments are limited to either non-steroidal anti-inflammatory drugs (NSAIDs) or a limited number of anti-tumor necrosis factor (TNF) drugs,(4) hence there is a substantial need for additional treatment options in this disease area. Furthermore, treatment options are especially limited for nr-axSpA patients with only two anti-TNFs licensed in the European Union for the treatment of nr-axSpA.(5, 6) The long-term safety and efficacy data available for axSpA treatment predominantly focuses on the AS subpopulation(7-10) with limited data available in the broader axSpA population.

RAPID-axSpA is the first trial to present data on the efficacy of an anti-TNF across the broad spectrum of patients with active axSpA as defined by the Assessment of SpondyloArthritis international Society (ASAS) criteria, including both AS and nr-axSpA patients. In this trial it was shown that certolizumab pegol (CZP), a PEGylated Fc-free anti-TNF, rapidly reduced the signs and symptoms of axSpA disease in the broad axSpA patient population over 24 weeks of treatment.(11, 12)

Here we present the first long-term data directly comparing outcomes in AS and nr-axSpA patients, and we report long-term efficacy and safety of two CZP dosing regimens (CZP 200 mg every two weeks [Q2W] and CZP 400 mg every four weeks [Q4W]) from the dose-blind (Week 24 to Week 48) and early open-label treatment period (Week 48 to Week 96) of the RAPID-axSpA trial.

Patients and Methods

Patients

Detailed inclusion and exclusion criteria for the RAPID-axSpA trial have been reported previously.(11) Eligible patients had active disease (Bath AS Disease Activity Index [BASDAI] and spinal pain ≥4), an inadequate response to ≥1 NSAID, and fulfilled ASAS criteria of adult-onset axSpA and included patients with AS (>50% of patients) and nr-axSpA (no definitive sacroiliitis on X-ray), as defined by the modified New York [mNY] criteria.

Further exclusion criteria are reported in the primary manuscript.(11)

Trial Design

Treatment Procedures

The RAPID-axSpA trial (NCT01087762) is a Phase 3, multicenter trial in axSpA, which is double-blind and placebo-controlled to Week 24, dose-blind to Week 48 and an open-label extension (OLE) to Week 204. Here we report the outcomes of the dose-blind (to Week 48) and early OLE (to Week 96) treatment periods. Patients were randomized 1:1:1 to placebo, or CZP 400 mg at Weeks 0, 2 and 4 (loading dose) followed by either CZP 200 mg Q2W or CZP 400 mg Q4W. Patients originally randomized to CZP in the double-blind phase continued on their assigned dose in the dose-blind phase and OLE. Placebo patients who were non-responders according to ASAS20 response criteria (ASAS20) at both Weeks 14 and 16, or placebo patients who completed the 24-week double-blind phase, entered the dose-blind phase and were re-randomized 1:1 to CZP 200 mg Q2W or CZP 400 mg Q4W following CZP loading dose (Figure 1A).

At all study sites, all investigators and other health care professionals involved with safety or efficacy assessments were completely blind to the study medications. Due to differences in the presentation and viscosity of CZP and placebo, all study treatments (CZP and placebo) were administered by dedicated, unblinded, trained study center personnel with no other involvement in the study, to maintain study blinding.

Evaluations

The primary endpoint of RAPID-axSpA (ASAS20 response at Week 12) has been reported previously.(11) Efficacy outcomes reported here include self-reported assessments for back pain and disease activity (0 – 10 numeric rating scales), as well as health-related quality of life, assessed using short-form 36-item health survey mental and physical component summaries (SF-36 MCS and PCS). Serum C-reactive protein (CRP) levels were assessed as an objective measure of inflammation. Spinal mobility and functionality were assessed using the Bath AS Metrology Index linear (BASMI-linear) and Bath AS Functional Index (BASFI), respectively.

Efficacy results to Week 96 are presented using composite endpoints validated for use by the Assessment of SpondyloArthritis international Society:(13) ASAS20, ASAS40 response criteria (ASAS40), ASAS Partial Remission (ASAS-PR) and ASAS 5 out of 6 (ASAS5/6). The BASDAI and Ankylosing Spondylitis Disease Activity Score (ASDAS) were utilized to assess disease activity.(14) In addition to absolute scores , we report the proportion of patients achieving BASDAI 50 (a BASDAI improvement from baseline of ≥50%), ASDAS Major Improvement (ASDAS MI) and ASDAS Inactive Disease (ASDAS ID) criteria, defined as ASDAS reduction from baseline ≥2 and ASDAS <1.3, respectively.

The long-term safety of CZP was investigated through analysis of adverse events (AEs) at every study visit to Week 96. For laboratory analyses of plasma concentrations of anti-CZP antibodies, levels >2.4 units/mL on at least 1 study visit were considered positive.(15)

In an attempt to identify a potential increase in the risk of tuberculosis infection with CZP-treatment, the sponsor required that all patients have a systematic Purified Protein Derivative (PPD) test (and/or Interferon Gamma Release Assay [IGRA]) at Weeks 48 and 96, regardless of risk of tuberculosis (signs, symptoms or close contact with tuberculosis patient). All cases of PPD ≥5mm or suspected tuberculosis were reviewed post hoc by independent experts. Active tuberculosis was confirmed according to World Health Organization criteria for tuberculosis.

Statistical Analysis

The majority of efficacy outcomes are presented for all patients randomized to either CZP 200 mg Q2W or CZP 400 mg Q4W arms at baseline (randomized set, RS), although selected data are also shown for patients who were re-randomized from placebo to either CZP dose regimen at Week 16 or 24. Response rates (%) are calculated using non-responder imputation (NRI) and quantitative assessments are shown as arithmetic means and use last observation carried forward imputation (LOCF). Observed data are also shown for patients completing Week 96. Analyses are presented in the overall axSpA population and for the AS and nr-axSpA subpopulations. Data are shown with no inferential statistics.

Safety data are presented for all patients treated with ≥1 dose of CZP at any stage of the 96-week trial period (Safety Set), placebo patients re-randomized to CZP were included from the date of their first CZP injection. Geometric

means for CZP plasma concentrations were analyzed for all subjects from the Safety Set who had valid pharmacokinetic assessments.

Results

Patient Disposition and Baseline Characteristics

A total of 325 patients were randomized, of whom 218 received CZP (200 mg Q2W or 400 mg Q4W) from Week 0 (RS). Of these patients, 203 (93%) completed to Week 24, 191 (88%) to Week 48 and 174 (80%) to Week 96 (Figure 1B). Between Week 24 and Week 48, 3 of these patients (1.4%) withdrew due to an AE, 3 (1.4%) due to lack of efficacy and 5 (2.3%) due to other reasons. Between Week 48 and Week 96, 11 (5.0%) patients withdrew due to an AE, 2 (0.9%) due to lack of efficacy and 4 (1.8%) due to other reasons. The number of patients withdrawing from the study were similar in both the AS and nr-axSpA subpopulations.

Of the 35 (11.1%) patients who suffered an AE leading to withdrawal of study drug, 6 patients (1.9%) withdrew due to infection (the most frequent cause). Of note, 14 (4.4%) patients were withdrawn by the sponsor due to their having a PPD tuberculin skin test >5mm (and one positive IGRA test) – according to study protocol, the PPD test was performed in all patients, including those who were asymptomatic or without additional risk factors for tuberculosis.

Of the 107 patients originally randomized to placebo, 56 (52.3%) escaped early (according to study protocol) and were re-randomized in a double-blind fashion at Week 16 to CZP 200 mg Q2W (n=27) or CZP 400 mg Q4W (n=29) following CZP loading dose (Figure 1B). At Week 24, 41 placebo completers were re-randomized to CZP 200 mg Q2W (n=20) or CZP 400 mg Q4W (n=21) following CZP loading dose (Figure 1B).. The proportion of placebo completers were similar between the two subpopulations: Of the 41, 18 (43.9%) were nr-axSpA patients and 23 (56.1%) were AS patients.

Disease characteristics were similar between all populations for those patients randomized to CZP at baseline (Table 1). It was noted that placebo patients who demonstrated a clinical response at Week 14 or 16 and continued on placebo to Week 24, had less severe disease activity at baseline compared to placebo patients who did not respond clinically (and who therefore withdrew from the placebo arm at Week 16) (Supplemental Table 1).

Efficacy Outcomes

Improvements from baseline to Week 24 in disease activity (ASDAS, BASDAI), spinal mobility (BASMI), and function (BASFI) were maintained throughout the dose-blind trial period to Week 48 and the OLE to Week 96 (Figure 2A–C, Figure 3A–C, Supplemental Figure 2 and Supplemental Table 2). Improvements in BASDAI50 were maintained from Week 24 (50.5%, 54.2%) to Week 96 (46.8%, 48.6%) in CZP 200 mg Q2W and CZP 400 mg Q4W patients respectively. For some outcomes, such as ASDAS MI and ASDAS ID,

a small improvement was seen between Week 24 and Week 96 (Supplemental Table 2).

Similarly, improvements in ASAS20, ASAS40 and ASAS-PR responses, seen for both CZP 200 mg Q2W and CZP 400 mg Q4W in the 24-week double-blind phase were maintained through the dose-blind phase to Week 48 and to Week 96 in the OLE (Figure 4A). Improvements were maintained across both the AS and nr-axSpA subpopulations (Figure 4B). A comparison of imputed and observed ASAS response rates in this study demonstrated the more conservative nature of NRI (Figure 4 [table]), with 82.0% of patients completing to Week 96 achieving an ASAS20 response compared with 62.8% when data were imputed using NRI. Improvements in ASAS5/6 response seen in the double-blind study period were maintained in the dose-blind and open-label periods (41.3% [Week 24], 41.7% [Week 48] and 42.2%, [Week 96] respectively, for the overall axSpA population [NRI]) (Supplemental Table 2). Improvements in nocturnal back pain and health-related quality of life (ASQoL, SF-36 MCS, SF-36 PCS) were maintained through to Week 96 of CZP treatment (Supplemental Table 3).

Similar efficacy responses were seen in patients with (n=26) and without (n=192) prior anti-TNF exposure; improvements were maintained to Week 96 in both response measures and continuous outcomes: at Week 96, ASAS40 responses were 50.0% (with prior anti-TNF exposure) and 50.5% (without prior anti-TNF exposure) and BASDAI change from baseline scores were -3.5 (with prior anti-TNF exposure) and -3.4 (without prior anti-TNF exposure).

However, these results should be interpreted with caution given the low patient numbers in these analyses.

Patients originally randomized to placebo that either escaped early at Week 16, or completed the double-blind phase to Week 24 and were subsequently re-randomized to CZP treatment (CZP 200 mg Q2W or CZP 400 mg Q4W), saw improvements in both ASAS20 response and ASDAS score following their switch to CZP treatment, which were maintained through to Week 96 of the study (Supplemental Figure 1).

We also looked at baseline MRI SI joint score (SPARCC) and CRP as potential predictors of response to certolizumab pegol. These data indicate a possible association between higher baseline CRP or higher baseline SPARCC scores and a greater chance of achieving ASDAS MI or an ASAS40 response, a benefit that is maintained to Week 96 (data not shown).

Safety

The Safety Set consisted of 315 patients who received ≥1 dose of CZP at any stage of the 96-week trial period. The total exposure to CZP was 486 PY. AEs occurred in 279 patients (88.6%; ER/100 PY = 360.3) and were predominantly mild (74.9%) or moderate (59.4%) in nature. Serious AEs occurred in 41 patients (13.0%; ER/100 PY = 10.9). Serious infections occurred in 12 patients (3.8%; ER/100 PY = 2.7). 1 case of active tuberculosis infection was identified (0.3%; ER/100 PY = 0.2). No new safety

signals were observed, and no deaths, malignancies or cases of demyelinating disease were reported during the 96-week trial period.

Of the patients treated with CZP, 215 were tested for the presence of anti-CZP antibodies at Week 96. Of these patients, 9 (4.2%) were observed to have developed anti-CZP antibodies. The proportion of patients developing anti-CZP antibodies was roughly similar in both CZP dosing regimens, with 2.7% and 5.8% of patients testing positive for anti-CZP antibodies at Week 96 in the CZP 200 mg Q2W and CZP 400 mg Q4W treatment groups, respectively. The plasma concentration of CZP was lower in those patients with anti-CZP antibodies than in those without (geometric means: 2.5 units/mL and 19.7 units/mL, respectively). Since the number of patients developing anti-CZP antibodies was relatively low, an investigation into efficacy in this subgroup of patients was not carried out.

Discussion

The rapid improvements observed over the first 24 weeks of the RAPID-axSpA trial in clinical measures of efficacy and patient-reported outcomes were maintained in both CZP dosing regimens and in both AS and nr-axSpA patients throughout the dose-blind (patients blinded to CZP dosing regimen to Week 48) and OLE (Week 48 to Week 96) treatment periods. Indeed, for some outcome measures, slight improvements were observed between Week 24 and Week 96.

RAPID-axSpA is the first study to investigate the efficacy of an anti-TNF in the broad axSpA population, including both AS and nr-axSpA patients. Baseline disease activity, as measured by BASDAI and ASDAS, was similar in the AS and nr-axSpA subpopulations. The similarities between these subpopulations in terms of disease characteristics and burden,(19, 20) underline the need for more treatment options to be available across the broader axSpA population. The similarity in improvements observed across both AS and nr-axSpA patients indicates that CZP is efficacious for the treatment of axSpA patients with objective signs of inflammation, independent of whether the patient has sufficient structural damage in the SI joints to meet the mNY classification criteria for AS.

RAPID-axSpA is also the first study to report long-term efficacy data for axSpA patients, who were required to be either CRP-positive or MRI-positive for inclusion in the trial; these characteristics have been associated with a good response to anti-TNF treatment. The maintenance of response seen with continued CZP treatment to Week 96 confirms its long-term efficacy in axSpA patients with objective signs of inflammation. Additionally, the similar long-term reduction in disease activity for both CZP 200 mg Q2W and CZP 400 mg Q4W is important, as this may offer the treating physician more freedom to switch between the dosing regimens.

The ASAS20 scores observed over the first 96 weeks of the RAPID-axSpA trial were comparable to those observed over a similar time period with adalimumab treatment of nr-axSpA patients,(21) and etanercept,(9)

adalimumab,(10) infliximab(7) and golimumab(8) treatment of AS patients. However, care must be taken when interpreting inter-trial comparisons, since different studies use different patient populations, trial designs and data analysis methods. Here we reported ASAS20 response rates conservatively using NRI as well as observed data, according to recommendations for reporting long-term results.(22)

In line with previous reports of CZP in axSpA,(11) AEs were predominantly mild to moderate in nature, with 9.8% of AEs considered to be severe and a Serious AE ER of 10.9/100 PY. There were no malignancies or deaths observed over the 96-week trial period and no new safety signals identified compared with previous reports of CZP.

The presence of anti-CZP antibodies was low in this trial, with only 9 of 215 patients testing positive at Week 96 (4.2%). Due to the low numbers of anti-CZP positive patients, an investigation into the impact of antibody levels on treatment efficacy was not carried out.

This report has a number of limitations, including the lack of a placebo arm beyond Week 24, and limitations inherent to the unblinded nature of the open-label study period. Furthermore, no radiographic data are presented here, precluding any analysis of disease progression from nr-axSpA to AS.

In this publication, the rapid improvements in clinical outcomes observed in axSpA patients treated with CZP over 24 weeks, were maintained through the dose-blind phase to Week 48 and the OLE to Week 96 in both the AS and nr-

axSpA subpopulations. This maintenance of efficacy was observed when CZP was administered as either 200 mg Q2W or 400 mg Q4W. The safety profile of CZP in patients with axSpA over a period of 96 weeks was comparable with that reported over shorter time periods and in other indications, with no new previously unreported safety signals occurring over the 96-week trial period.

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Tables

Table 1: Disease characteristics for patients randomized to CZP at baseline

	All patients axSpA (N=218)	AS (n=121)	nr-axSpA (n=97)
Except where indicated otherwise, values are n (%) at baseline			
Age, yrs, mean (SD)	39.5 (11.6)	41.4 (11.1)	37.1 (11.8)
Gender, Male	135 (61.9)	88 (72.7)	47 (48.5)
Symptom duration, Median, yrs (min, max)	7.8 (0.3, 44.8)	8.8 (0.3, 44.8)	5.9 (0.3, 34.2)
Symptom duration < 5 years	84 (38.5)	41 (33.9)	43 (44.3)
CRP mg/L Median	12.5	14.0	11.0
>ULN (7.9 mg/L)	146 (67.0)	85 (70.2)	61 (62.9)
≥ 15 mg/L	80 (36.7)	49 (40.5)	31 (32.0)
BASDAI	6.4 (1.5)	6.4 (1.5)	6.6 (1.5)
BASFI	5.3 (2.3)	5.6 (2.3)	5.0 (2.3)
BASMI	3.8 (1.7)	4.2 (1.7)	3.2 (1.5)
ASDAS	3.8 (0.9)	3.9 (0.9)	3.8 (0.8)
Peripheral arthritis,[†] n (%)	76 (34.9)	42 (34.7)	34 (35.1)
Enthesitis, n (%)[#]	148 (67.9)	78 (64.5)	70 (72.2)
Extra-Spinal Features of axSpA (either patient history or current diagnosis) Defined by the ASAS Classification Criteria screening assessment			
Heel Enthesitis, n (%)	72 (33.0)	41 (33.9)	31 (32.0)
Uveitis, n (%)	38 (17.4)	20 (16.5)	18 (18.6)
Psoriasis, n (%)	13 (6.0)	5 (4.1)	8 (8.2)
Crohn's Disease/ Ulcerative Colitis, n (%)	10 (4.6)	6 (5.0)	4 (4.1)

[†]Defined as at least 1 swollen joint in 44-joint assessment. [#]Defined as a MASES score greater than 0. Results shown for the randomized set. ASDAS: Ankylosing spondylitis disability assessment score; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; BASMI: Bath ankylosing spondylitis metrology index; CRP: C-Reactive Protein; CZP: Certolizumab pegol; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; ULN: Upper Limit of Normal

Table 2: Adverse Events to Week 96 of the RAPID-axSpA study

	CZP 200 mg Q2W (n=111)		CZP 400 mg Q4W (n=107)		All CZP (n=315)	
	n (%)	**ER/100 PY**	**n (%)**	**ER/100 PY**	**n (%)**	**ER/100 PY**
Any AE	104 (93.7)	376.5	92 (86.0)	352.5	279 (88.6)	360.3
Serious AEs	13 (11.7)	8.2	14 (13.1)	9.1	41 (13.0)	10.9
Most Frequent Serious AEs (>1% of the safety population) by SOC						
Gastrointestinal disorders	0		3 (2.8)	1.7	4 (1.3)	0.8
Infections and infestations	4 (3.6)	2.7	2 (1.9)	1.1	12 (3.8)	2.7
Injury, poisoning and procedural complications	1 (0.9)	0.5	1 (0.9)	0.6	4 (1.3)	1.0
Musculoskeletal and connective tissue disorders	1 (0.9)	0.5	1 (0.9)	0.6	4 (1.3)	0.8
AEs by intensity	**n (%)**		**n (%)**		**n (%)**	
Mild	89 (80.2)		78 (72.9)		236 (74.9)	
Moderate	69 (62.2)		62 (57.9)		187 (59.4)	
Severe	8 (7.2)		9 (8.4)		31 (9.8)	
Drug-related AEs	56 (50.5)		52 (48.6)		148 (47.0)	
Deaths	0		0		0	

Results reported for the Safety Set. AE: Adverse Event; CZP: certolizumab pegol; ER/100 PY: Event rate per 100 patient years; Q2W: Every 2 weeks; Q4W: Every 4 weeks

Figure Legends

Figure 1: A) Trial design of RAPID-axSpA; B) Patient disposition in RAPID-axSpA to Week 96

*All patients received allocated treatment. ‡One patient did not enrol onto the dose-blind trial period. Data shown in 1B are n (%). CZP: Certolizumab pegol; Wk: Week

Figure 2: ASDAS Improvements to Week 96 [LOCF] in the axSpA, AS and nr-axSpA populations: (A) ASDAS Score, (B) ASDAS Major Improvement, (C) ASDAS Inactive Disease

*Observed case (OC) data for Week 96: axSpA, n=171; AS, n=97; nr-axSpA, n=74. Figures show LOCF data. Results reported for the Randomized Set. ASDAS: Ankylosing Spondylitis Disease Activity Score; CZP: Certolizumab pegol; LOCF: Last Observation Carried Forward

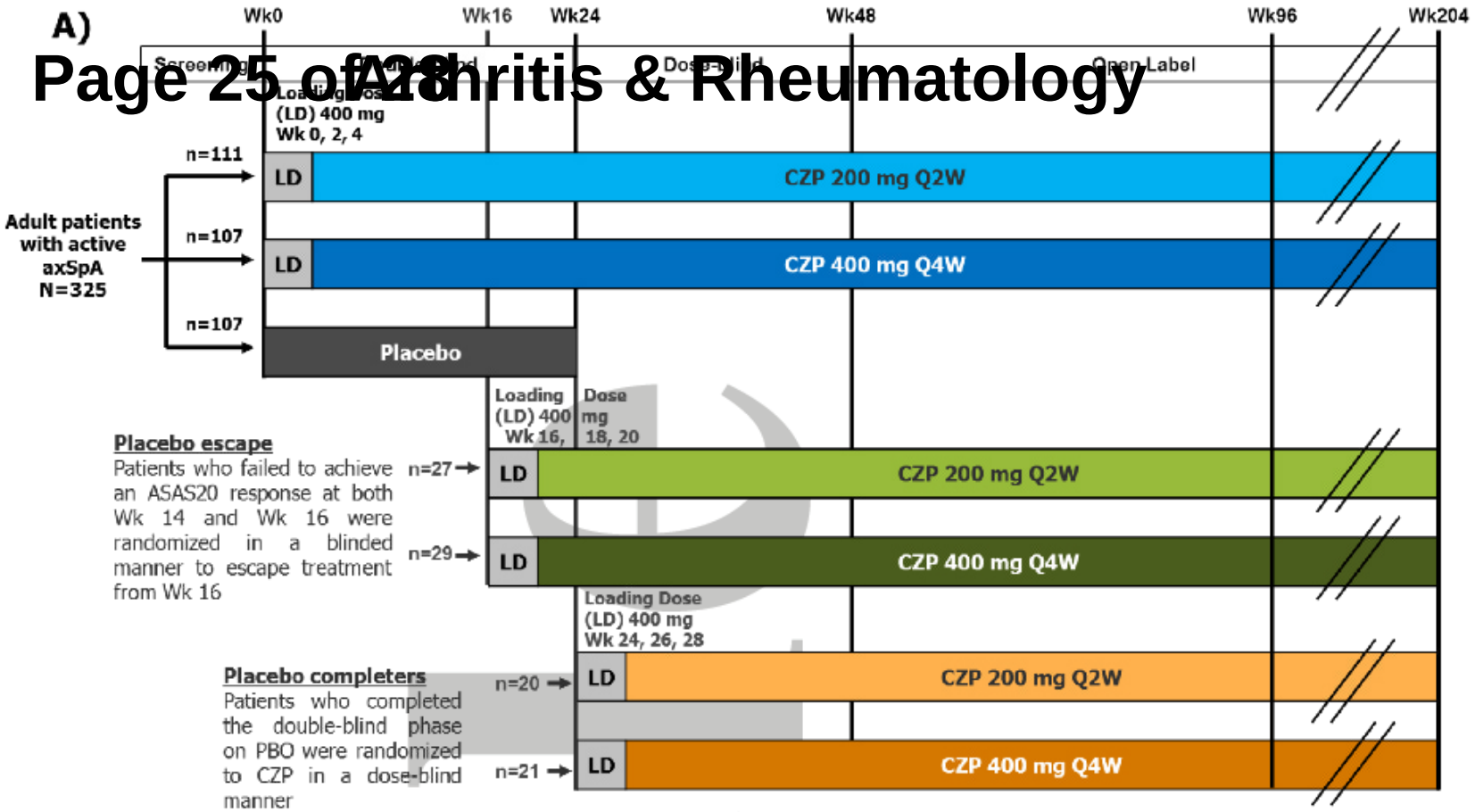
Figure 3: Improvements to Week 96 [LOCF] in the axSpA, AS and nr-axSpA populations in: (A) BASMI-linear Score, (B) BASDAI Score and (C) BASFI Score

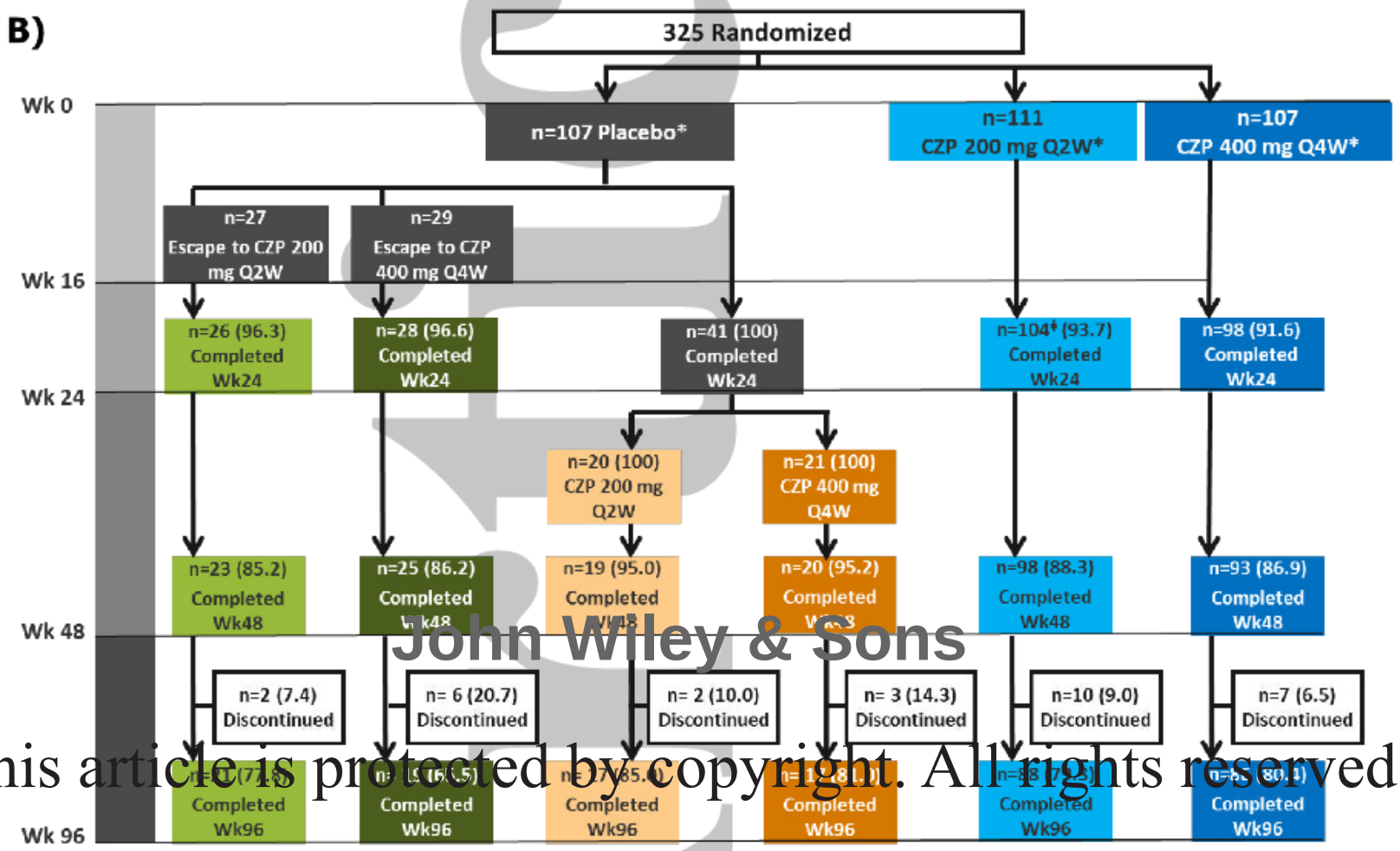
*Observed case (OC) data for Week 96: axSpA, n=171; AS, n=97; nr-axSpA, n=74. Figures show LOCF data. Results reported for the Randomized Set. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis

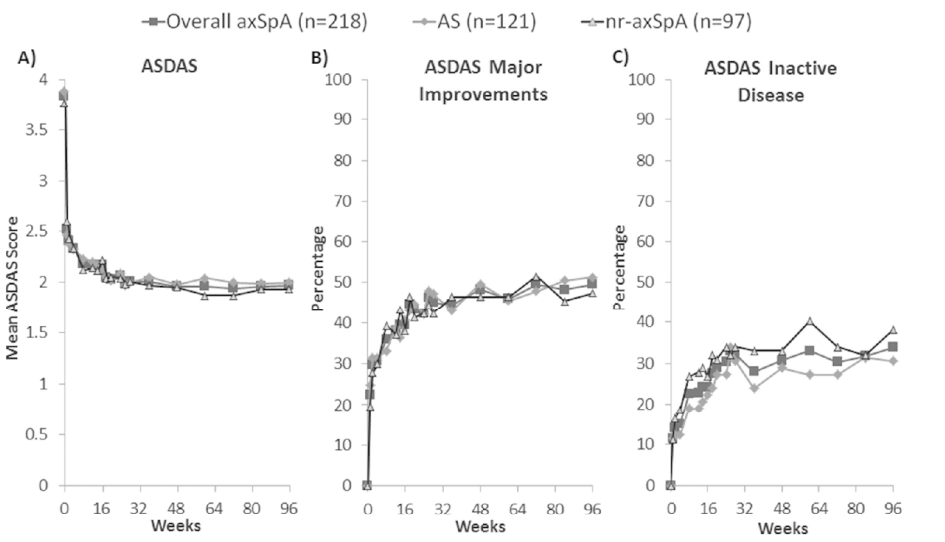
Metrology Index; CZP: Certolizumab pegol; LOCF: Last Observation Carried Forward

Figure 4: Percentage of patients achieving an ASAS20, ASAS40 and ASAS-PR response to Week 96 in; A) The overall axSpA population separated by dose [NRI]; B) The overall axSpA, AS and nr-axSpA populations, dose combined [NRI]

Results reported for the Randomized Set. ASAS20: assessment of Axial SpondyloArthritis international Society 20% response criteria; ASAS40: assessment of Axial SpondyloArthritis international Society 40% response criteria; ASAS-PR: ASAS Partial Remission; CZP: Certolizumab pegol; NRI: non-responder imputation; OC: observed case; Q2W: Every 2 weeks; Q4W: Every 4 weeks







Week	ASDAS Mean Score					ASDAS Major Improvements (%)					ASDAS Inactive Disease (%)				
	12 (LOCF)	24 (LOCF)	48 (LOCF)	96 (LOCF)	96 (OC)*	12 (LOCF)	24 (LOCF)	48 (LOCF)	96 (LOCF)	96 (OC)*	12 (LOCF)	24 (LOCF)	48 (LOCF)	96 (LOCF)	96 (OC)*
axSpA	2.2	2.1	2.0	2.0	1.9	38.1	42.2	48.2	49.5	54.4	22.9	30.3	30.7	33.9	35.1
AS	2.2	2.1	2.0	2.0	1.9	38.8	42.1	49.6	51.2	54.6	19.0	27.3	28.9	30.6	29.9
nr-axSpA	2.1	2.0	2.0	1.9	1.8	37.1	42.3	46.4	47.4	54.1	27.8	34.0	33.0	38.1	41.9

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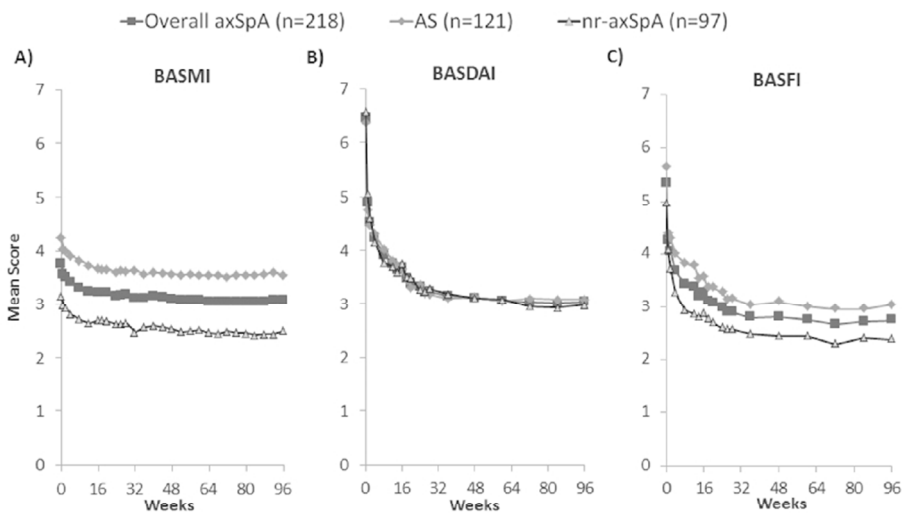

Week	BASMI Mean Score					BASDAI Mean Score					BASFI Mean Score				
	12 (LOCF)	24 (LOCF)	48 (LOCF)	96 (LOCF)	96 (OC)*	12 (LOCF)	24 (LOCF)	48 (LOCF)	96 (LOCF)	96 (OC)*	12 (LOCF)	24 (LOCF)	48 (LOCF)	96 (LOCF)	96 (OC)*
axSpA	3.3	3.2	3.1	3.1	3.0	3.8	3.3	3.1	3.0	2.8	3.4	3.0	2.8	2.7	2.6
AS	3.7	3.6	3.6	3.6	3.5	3.8	3.4	3.1	3.1	2.8	3.8	3.3	3.1	3.0	2.8
nr-axSpA	2.6	2.6	2.5	2.5	2.4	3.7	3.3	3.1	3.0	2.7	2.9	2.6	2.4	2.4	2.3

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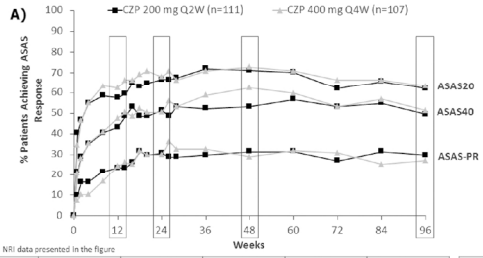

NRI data presented in the figure

Week	12 (NRI)		24 (NRI)		48 (NRI)		96 (NRI)		96 (OC)	
	CZP 200 mg Q2W	CZP 400 mg Q4W	CZP 200 mg Q2W	CZP 400 mg Q4W	CZP 200 mg Q2W	CZP 400 mg Q4W	CZP 200 mg Q2W	CZP 400 mg Q4W	CZP 200 mg Q2W (n=84)	CZP 400 mg Q4W (n=83)
ASAS20	57.7	62.6	66.7	68.2	71.2	72.9	62.2	63.6	82.1	81.9
ASAS40	43.2	47.7	51.4	50.5	53.2	62.6	49.5	51.4	65.5	66.3
ASAS-PR	23.4	24.3	30.6	29.9	31.5	29.0	29.7	27.1	39.3	34.9

NRI data presented in the figure

Week	12 (NRI)			24 (NRI)			48 (NRI)			96 (NRI)			96 (OC)		
	axSpA	AS	nr-axSpA	axSpA	AS	nr-axSpA	axSpA	AS	nr-axSpA	axSpA	AS	nr-axSpA	axSpA (n=167)	AS (n=93)	nr-axSpA (n=74)
ASAS20	60.1	59.5	60.8	67.4	66.9	68.0	72.0	73.6	70.1	62.8	64.5	60.8	82.0	83.9	79.7
ASAS40	45.4	43.8	47.4	50.9	51.2	50.5	57.8	57.9	57.7	50.5	50.4	50.5	65.9	65.6	66.2
ASAS-PR	23.9	19.8	28.9	30.3	28.1	33.0	30.3	29.8	30.9	28.4	24.8	33.0	37.1	32.3	43.2

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