

SUPPLEMENTARY MATERIAL

Table S1. Summary of hierarchical testing procedure of primary and key secondary efficacy variables

Efficacy variables presented in order of hierarchical testing	p-value	Significant^a
Step 1: ASAS20 responder rate at Week 12 for CZP 200mg vs PBO	0.004 ^b	Yes
Step 2: ASAS20 responder rate at Week 12 for CZP 400mg vs PBO	<0.001 ^b	Yes
Step 3: ASAS20 responder rate at Week 24 for CZP 200mg vs PBO	<0.001 ^b	Yes
Step 4: ASAS20 responder rate at Week 24 for CZP 400mg vs PBO	<0.001 ^b	Yes
Step 5: Change from Baseline in BASFI at Week 12 for CZP 200mg+400mg vs PBO	<0.001 ^c	Yes
Step 6: Change from Baseline in BASDAI at Week 12 for CZP 200mg+400mg vs PBO	<0.001 ^c	Yes
Step 7: Change from Baseline in BASFI at Week 24 for CZP 200mg+400mg vs PBO	<0.001 ^c	Yes
Step 8: Change from Baseline in BASDAI at Week 24 for CZP 200mg+400mg vs PBO	<0.001 ^c	Yes
Step 9: Change from Baseline in BASMI at Week 12 for CZP 200mg+400mg vs PBO	<0.001 ^c	Yes
Step 10: Change from Baseline in BASMI at Week 24 for CZP 200mg+400mg vs PBO	<0.001 ^c	Yes

ASAS20: Assessment in Axial Spondyloarthritis International Society 20% response criteria; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI linear: Bath Ankylosing Spondylitis Metrology Index linear; a Statistical significance was assessed in the context of the hierarchical testing procedure. Each step was tested at 0.05 two-sided. If the result was not significant at any step, then all steps after that were considered not statistically significant. b p-value was estimated from standard 2-sided Wald asymptomatic test with a 5% alpha level. c p-value was estimated from the ANCOVA model with treatment, region, mNY criteria (Y/N), and prior TNF inhibitor exposure (Y/N) as factors, and baseline score as a covariate.

Table S2: Baseline characteristics of the AS and nr-axSpA subpopulations by treatment group

	AS			nr-axSpA		
	Placebo (n=57)	CZP 200mg Q2W (n=65)	CZP 400mg Q4W (n=56)	Placebo (n=50)	CZP 200mg Q2W (n=46)	CZP 400mg Q4W (n=51)
Demographic characteristics						
Age, mean yrs (SD)	41.6 (12.8)	41.0 (10.8)	41.9 (11.5)	38.0 (11.8)	36.6 (13.0)	37.5 (10.8)
Male, %	71.9	72.3	73.2	48.0	43.5	52.9
AxSpA characteristics						

Symptom duration, median, yrs (min, max)	10.2 (0.3, 50.9)	8.8 (0.3, 32.7)	8.8 (0.3, 44.8)	4.5 (0.5, 41.5)	4.8 (0.3, 34.2)	7.3 (0.3, 25.3)
Symptom duration < 5 years, n (%)	16 (28.1)	26 (40.0)	15 (26.8)	26 (52.0)	24 (52.2)	19 (37.3)
Definitive sacroiliitis on X-ray	57 (100.0)	65 (100.0)	56 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Positive for HLA-B27, n (%)	48 (84.2)	53 (81.5)	44 (78.6)	39 (78.0)	34 (73.9)	37 (72.5)
CRP mg/L						
Median, (min, max)	16.6 (1.4, 155.6)	14.0 (0.1, 174.8)	12.9 (0.7, 159.9)	13.5 (0.2, 156.2)	10.0 (2.0, 52.0)	12.1 (0.1, 120.0)
> ULN, n (%)	45 (78.9)	48 (73.8)	37 (66.1)	32 (64.0)	27 (58.7)	34 (66.7)
>15 mg/L, n (%)	31 (54.5)	27 (41.5)	22 (39.3)	22 (44.0)	15 (32.6)	16 (31.4)
BASDAI, [#] Mean (SD)	6.4 (1.9)	6.5 (1.7)	6.2 (1.3)	6.4 (1.5)	6.5 (1.4)	6.6 (1.6)
BASFI, [#] Mean (SD)	6.0 (2.0)	5.6 (2.3)	5.7 (2.3)	4.9 (2.2)	4.8 (2.2)	5.1 (2.4)
BASMI, [#] Mean (SD)	4.7 (1.6)	4.2 (1.6)	4.3 (1.8)	3.1 (1.6)	3.1 (1.4)	3.3 (1.5)
ASDAS, [#] Mean (SD)	4.1 (0.9)	4.0 (1.0)	3.8 (0.8)	3.8 (0.9)	3.7 (0.8)	3.8 (0.8)
Arthritis, [†] n (%)	30 (52.6)	39 (60.0)	27 (48.2)	31 (62.0)	23 (50.0)	26 (51.0)
Prior and concomitant medication						
Concomitant NSAIDs, n (%)	51 (89.5)	59 (90.8)	51 (91.1)	41 (82.0)	38 (82.6)	44 (86.3)
Concomitant DMARDs, n (%)	22 (38.6)	21 (32.3)	20 (35.8)	16 (32.0)	10 (21.7)	11 (21.6)
Prior anti-TNF α exposure, n (%)	16 (28.1)	11 (16.9)	9 (16.1)	10 (20.0)	4 (8.7)	2 (3.9)

Data refers to the overall patient population (RS). axSpA: axial spondyloarthritis; CZP: certolizumab pegol; Q2W: every 2 weeks; Q4W: every 4 weeks; SD: standard deviation, HLA-B27: human leukocyte antigen B27; CRP: C-reactive protein; ULN: upper limit of normal; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI linear: Bath Ankylosing Spondylitis Metrology Index linear; ASDAS: Ankylosing Spondylitis Disease Activity Score; NSAIDs: Non-steroidal anti-inflammatory drugs; DMARDs: Disease modifying anti-rheumatic drugs; TNF α : tumor necrosis factor alpha; AS: ankylosing spondylitis; nr-axSpA: non-radiographic axial spondyloarthritis. [#] in Full Analysis Set data set; [†] current and/or historical; CRP ULN = 7.9 mg/L.

Table S3. TEAEs by treatment group with an incidence of $\geq 5\%$ in either CZP group during the 24 week, placebo-controlled, double-blind phase

System Organ Class Preferred Term	Placebo* N=107 n (%)	CZP 200 mg Q2W N=111 n (%)	CZP 400 mg Q4W N=107 n (%)
Infections and infestations	14 (13.1)	19 (17.1)	16 (15.0)
Nasopharyngitis	7 (6.5)	11 (9.9)	11 (10.3)
Upper respiratory tract infections	3 (2.8)	6 (5.4)	4 (3.7)
Investigations	2 (1.9)	7 (6.3)	6 (5.6)
Blood creatine phosphokinase increased	2 (1.9)	7 (6.3)	6 (5.6)
Nervous system disorders	7 (6.5)	7 (6.3)	9 (8.4)
Headache	7 (6.5)	7 (6.3)	9 (8.4)

*Placebo escape at Week 16. Data not adjusted for exposure.

Table S4. Efficacy Outcomes to Week 24 of the RAPID-axSpA trial for the overall axSpA population and the AS and nr-axSpA subpopulations

	axSpA			AS			nr-axSpA		
Mean value (SD) or n (%) of patients	PBO (n=107)	CZP 200 mg Q2W (n=111)	CZP 400 mg Q4W (n=107)	PBO (n=57)	CZP 200 mg Q2W (n=65)	CZP 400 mg Q4W (n=56)	PBO (n=50)	CZP 200 mg Q2W (n=46)	CZP 400 mg Q4W (n=51)
Baseline									
ASDAS, mean (SD)	4.0 (0.9)	3.9 (0.9)	3.8 (0.8)	4.1 (0.9)	4.0 (1.0)	3.8 (0.8)	3.8 (0.9)	3.7 (0.8)	3.8 (0.8)
BASDAI, mean (SD)	6.5 (1.7)	6.5 (1.6)	6.4 (1.5)	6.4 (1.9)	6.5 (1.7)	6.2 (1.3)	6.5 (1.5)	6.5 (1.4)	6.6 (1.6)
BASFI, mean (SD)	5.5 (2.1)	5.3 (2.3)	5.4 (2.3)	6.0 (2.0)	5.6 (2.3)	5.7 (2.3)	4.9 (2.1)	4.8 (2.2)	5.1 (2.4)
BASMI linear, mean (SD)	4.0 (1.8)	3.7 (1.6)	3.8 (1.7)	4.7 (1.6)	4.2 (1.6)	4.3 (1.8)	3.2 (1.6)	3.1 (1.4)	3.3 (1.5)
Week 12									
ASAS20, n (%)	41 (38.3)	64 (57.7)	68 (63.6)	21 (36.8)	37 (56.9)	36 (64.3)	20 (40.0)	27 (58.7)	32 (62.7)
ASAS40, n (%)	19 (17.8)	48 (43.2)	52 (48.6)	11 (19.3)	26 (40.0)	28 (50.0)	8 (16.0)	22 (47.8)	24 (47.1)
ASAS PR, n (%)	4 (3.7)	26 (23.4)	26 (24.3)	1 (1.8)	13 (20.0)	11 (19.6)	3 (6.0)	13 (28.3)	15 (29.4)
ASAS 5/6, n (%)	9 (8.4)	50 (45.0)	44 (41.1)	5 (8.8)	31 (47.7)	20 (35.7)	4 (8.0)	19 (41.3)	24 (47.1)
ASDAS, mean (SD)	3.5 (1.1)	2.2 (1.1)	2.2 (1.0)	3.5 (1.0)	2.2 (1.1)	2.2 (1.0)	3.4 (1.1)	2.1 (1.1)	2.2 (1.1)
ASDAS, mean change from baseline (SD)	-0.5 (0.8)	-1.7 (1.2)	-1.6 (1.1)	-0.6 (0.8)	-1.8 (1.2)	-1.6 (1.1)	-0.5 (0.8)	-1.6 (1.2)	-1.6 (1.2)
ASDAS ID, n (%)	0	28 (25.2)	22 (20.6)	0	14 (21.5)	9 (16.1)	0	14 (30.4)	13 (25.5)
ASDAS MI, n (%)	1 (0.9)	46 (41.4)	37 (34.6)	1 (1.8)	29 (44.6)	18 (32.1)	0	17 (37.0)	19 (37.3)
BASDAI, mean (SD)	5.3 (2.2)	3.8 (2.4)	3.7 (2.3)	5.4 (2.2)	3.9 (2.4)	3.7 (2.1)	5.3 (2.3)	3.7 (2.3)	3.7 (2.5)
BASDAI, mean change from baseline (SD)	-1.1 (1.7)	-2.7 (2.3)	-2.7 (2.2)	-1.1 (1.7)	-2.6 (2.3)	-2.5 (2.1)	-1.1 (1.8)	-2.8 (2.3)	-2.9 (2.3)
BASDAI 50, n (%)	14 (13.2)	50 (45.0)	47 (43.9)	6 (10.5)	27 (41.5)	23 (41.1)	8 (16.3)	23 (50.0)	24 (47.1)
BASFI, mean (SD)	5.0 (2.4)	3.3 (2.7)	3.4 (2.6)	5.2 (2.4)	3.8 (2.8)	3.8 (2.6)	4.7 (2.5)	2.7 (2.6)	3.0 (2.6)
BASFI, mean change from	-0.5 (1.7)	-1.9 (2.3)	-2.0 (2.2)	-0.8 (1.6)	-1.8 (2.3)	-1.9 (2.3)	-0.3 (1.9)	-2.1 (2.4)	-2.1 (2.1)

baseline (SD)									
BASMI linear, mean (SD)	3.9 (1.7)	3.1 (1.6)	3.4 (1.8)	4.4 (1.7)	3.6 (1.7)	3.9 (1.8)	3.2 (1.5)	2.5 (1.3)	2.8 (1.6)
BASMI linear, mean change from baseline (SD)	-0.2 (0.9)	-0.6 (0.9)	-0.5 (0.8)	-0.3 (0.9)	-0.6 (1.0)	-0.4 (0.9)	0.1 (0.7)	-0.5 (0.9)	-0.5 (0.8)
Week 24									
ASAS20, n (%)	31 (29.0)	74 (66.7)	75 (70.1)	19 (33.3)	44 (67.7)	39 (69.6)	12 (24.0)	30 (65.2)	36 (70.6)
ASAS40, n (%)	16 (15.0)	57 (51.4)	56 (52.3)	9 (15.8)	31 (47.7)	33 (58.9)	7 (14.0)	26 (56.5)	23 (45.1)
ASAS PR, n (%)	9 (8.4)	34 (30.6)	32 (29.9)	4 (7.0)	20 (30.8)	14 (25.0)	5 (10.0)	14 (30.4)	18 (35.3)
ASAS 5/6, n (%)	5 (4.7)	41 (36.9)	51 (47.7)	3 (5.3)	22 (33.8)	26 (46.4)	2 (4.0)	19 (41.3)	25 (49.0)
ASDAS, mean (SD)	3.5 (1.1)	2.0 (1.0)	2.1 (1.1)	3.5 (1.0)	2.1 (1.0)	2.1 (1.1)	3.4 (1.2)	1.9 (1.1)	2.1 (1.1)
ASDAS, mean change from baseline (SD)	-0.5 (0.8)	-1.9 (1.2)	-1.7 (1.1)	-0.6 (0.8)	-1.9 (1.1)	-1.7 (1.2)	-0.4 (0.9)	-1.8 (1.3)	-1.7 (1.1)
ASDAS ID, n (%)	4 (3.7)	33 (29.7)	33 (30.8)	2 (3.5)	17 (26.2)	16 (28.6)	2 (4.0)	16 (34.8)	17 (33.3)
ASDAS MI, n (%)	1 (0.9)	51 (45.9)	42 (39.3)	1 (1.8)	30 (46.2)	22 (39.3)	0	21 (45.7)	20 (39.2)
BASDAI, mean (SD)	5.4 (2.5)	3.3 (2.3)	3.3 (2.3)	5.3 (2.3)	3.5 (2.1)	3.2 (2.2)	5.5 (2.6)	3.1 (2.4)	3.4 (2.5)
BASDAI, mean change from baseline (SD)	-1.1 (2.0)	-3.2 (2.3)	-3.1 (2.2)	-1.2 (1.9)	-3.1 (2.1)	-2.9 (2.2)	-1.0 (2.2)	-3.3 (2.5)	-3.2 (2.1)
BASDAI 50, n (%)	19 (17.9)	56 (50.5)	58 (54.2)	9 (15.8)	28 (43.1)	31 (55.4)	10 (20.4)	28 (60.9)	27 (52.9)
BASFI, mean (SD)	5.0 (2.7)	2.9 (2.5)	3.1 (2.6)	5.1 (2.5)	3.3 (2.5)	3.3 (2.7)	4.9 (3.0)	2.3 (2.3)	2.9 (2.5)
BASFI, mean change from baseline (SD)	-0.5 (2.1)	-2.4 (2.4)	-2.3 (2.3)	-0.9 (1.8)	-2.3 (2.4)	-2.3 (2.5)	-0.1 (2.3)	-2.5 (2.4)	-2.3 (2.2)
BASMI linear, mean (SD)	3.8 (1.7)	3.1 (1.7)	3.2 (1.7)	4.4 (1.6)	3.5 (1.7)	3.7 (1.6)	3.2 (1.5)	2.5 (1.4)	2.7 (1.6)
BASMI linear, mean change from baseline (SD)	-0.2 (0.9)	-0.6 (1.1)	-0.6 (0.8)	-0.4 (1.0)	-0.7 (1.0)	-0.6 (0.9)	0.1 (0.8)	-0.6 (1.1)	-0.5 (0.8)

Data shown are for the Randomized Set. Non-responder imputation was used for dichotomous outcomes and last observation carried forward was used for continuous outcomes; SD = Standard Deviation

Figure S1. Kinetics of BASFI, BASDAI, BASMI Linear and ASDAS response from Week 0 to Week 24 in axSpA population

Data refers to the full analysis set (FAS) population. **A**, BASFI; **B**, BASDAI; **C**, BASMI linear; and **D**, ASDAS absolute values in the three treatment groups from Week 0 to Week 24. * $p < 0.001$ for CZP vs. PBO.

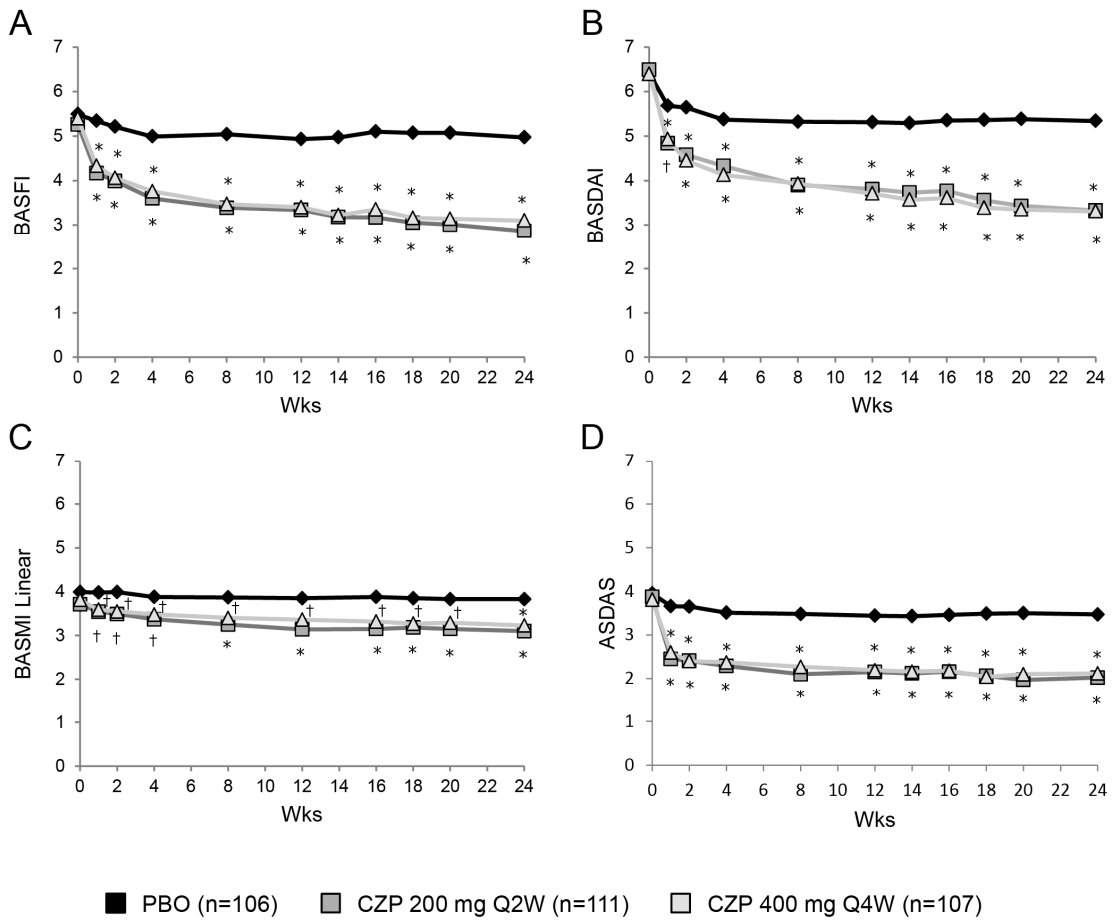
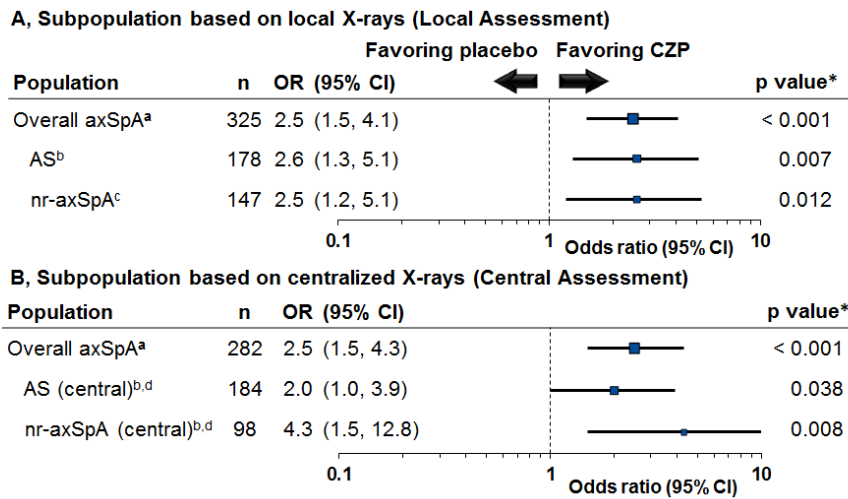


Figure S2. Logistic regression analysis of treatment interaction for AS and nr-axSpA subpopulations as defined by Local Assessment and Central Assessment X-rays.

Data refers to the full analysis set (FAS) population. Odds ratios (OR) and confidence intervals (CIs) for achieving ASAS20 response represent all CZP vs placebo groups, respectively. **A**, Subpopulation based on local X-rays (Local Assessment); **B**, Subpopulation based on centralized X-rays (Central Assessment)



^a With treatment, region, prior TNF exposure, and NY status as factors; ^b With treatment, region, and prior TNF exposure as factors; ^c With treatment and region as factors. ^d Based on central reading of baseline x-rays; * Nominal p value Randomized Set (NRI).

Figure S3. Kinetics of ASDAS, BASDAI, BASFI, and BASMI Linear response from Week 0 to Week 24 in the AS and nr-axSpA subpopulations

Data refers to the full analysis set (FAS) population. **A**, ASDAS; **B**, BASDAI; **C**, BASFI; and **D**, BASMI linear absolute values in the three treatment groups from Week 0 to Week 24. * $p < 0.001$; † $p < 0.05$ CZP vs. PBO.

■ PBO ■ CZP 200 mg Q2W □ CZP 400 mg Q4W

