SUPPLEMENTARY APPENDIX

Landewé RBM, *et al. Ann Rheum Dis* 2020; 79:920–928. doi: 10.1136/annrheumdis-2019-216839

Full patient selection criteria

Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent Form is signed and dated by the subject or by the parent(s) or legal representative.

2. Subject/legal representative is considered reliable and capable of adhering to the protocol (e.g., able to understand and complete diaries), visit schedule, or medication intake according to the judgment of the Investigator.

3. Subject is at least 18 years old and not older than 45 years at the start of Screening Visit.

4. Female subjects must be either postmenopausal for at least 1 year, surgically incapable of childbearing, or effectively practicing an acceptable method of contraception (including oral/parenteral/implantable hormonal contraceptives, intrauterine device, or barrier and spermicide). Abstinence only is not an acceptable method. Subjects must agree to use adequate contraception during the study; and after the last dose of study treatment for at least 10 weeks (or - for participating countries of the European Union - 5 months in accordance with the Summary of Product Characteristics [SmPC]) or longer, if required by local regulations after the last dose of study treatment. Male subjects must agree to ensure that also their female partner(s) use adequate contraception during the study and for at least 10 weeks (or - for participating countries of the European Union - 5 months in accordance with the SmPC) or longer, if required by local regulations after the subject receives their last dose of study treatment.

5. Subjects must have a documented diagnosis of adult-onset axSpA with at least 3 months' symptom duration and meet the ASAS classification criteria for axSpA (according to Appendix 18.1) and symptom duration of less than 5 years prior to the participation of this study.

6. Subjects must have active disease at Screening as defined by
    - ASDAS score ≥2.1
    - BASDAI score ≥4
    - Spinal pain ≥4 on a 0 to 10 NRS (from BASDAI Item 2)
    - for mNY-negative subjects only: CRP> upper limit of normal (ULN) and/or current evidence for sacroiliitis on the Screening MRI as defined by a ASAS/Outcome Measures in Rheumatology Clinical Trials (OMERACT) SI-MRI score ≥2 and confirmed by central reading

7. Subjects must have had an inadequate response to, have a contraindication to, or have been intolerant to at least 2 NSAIDs. Inadequate response to an NSAID is defined as lack of response to at least 14 days of continuous NSAID therapy at the highest tolerated dose of the administered NSAID.

Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria is met:

1. Subject has previously participated in this study or subject has previously been assigned to treatment in a study of the medication under investigation in this study.

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2. Subject has participated in another study of an investigational medicinal product (IMP) (or a medical device) within the previous 3 months (or five half-lives whichever is greater) or is currently participating in another study of an IMP (or a medical device).

3. Subject has history of chronic alcohol abuse or drug abuse within the last year.

4. Subject has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the subject's ability to participate in this study.

5. Subject has a known hypersensitivity to any components of the IMP or comparative drugs as stated in this protocol.

AxSpA disease-related exclusions

6. Subjects must not have fibromyalgia or total spinal ankylosis ("bamboo spine"), or any other inflammatory arthritis, eg, RA, systemic lupus erythematosus, sarcoidosis.

7. Subjects must not have a secondary, noninflammatory condition (eg, osteoarthritis) that in the Investigator's opinion is symptomatic enough to interfere with evaluation of the effect of study medication on the subject's primary diagnosis of axSpA.

Prior medications exclusions

8. Subjects must not have used the medications in the manner as detailed by the Exclusion Criteria in Table S1.

Previous clinical studies and previous biological therapy exclusions

9. Subjects must not have received any nonbiological therapy for axSpA not listed above within or outside a clinical study in the 3 months or within 5 half-lives prior to the Baseline Visit (whichever is longer).

10. Subjects must not have received any experimental biological agents (defined as those agents unlicensed for use in axSpA in Europe or the USA).

11. Subjects must not have received previous treatment with a polyethylene glycolylated (PEGylated) compound that resulted in a severe hypersensitivity reaction or an anaphylactic reaction.

12. Subjects may not have been exposed to more than 1 TNF antagonist prior to the Baseline Visit and may not be a primary failure to TNF antagonist therapy (defined as no response within the first 12 weeks of treatment with the TNF antagonist).

Medical History Exclusions

13. Female subjects who are breastfeeding, pregnant, or plan to become pregnant during the study or within 10 weeks (or – for participating countries of the EU – 5 months in accordance with the SmPC) following the last dose of the investigational product.

14. Subjects with a history of chronic or recurrent infections (more than 3 episodes requiring antibiotics or antivirals during the preceding year), recent serious or life-threatening infection within the 6 months prior to the Baseline Visit (including hospitalization for any infection in the last 6 months or any current sign or symptom that may indicate an infection).

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15. Subjects with a history of herpes zoster infection within 6 months prior to the Baseline Visit.

16. Subjects with known TB infection, at high risk of acquiring TB infection, or LTB infection are excluded.

    a. Known TB infection whether present or past is defined as:

        - Active TB infection or clinical signs and symptoms suggestive of TB (pulmonary or extra pulmonary)
        - History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection
        - Any evidence by radiography or other imaging modalities consistent with previously active TB infection that is not reported in the subject's medical history.

    b. High risk of acquiring TB infection is defined as:

        - Known exposure to another person with active TB infection within the 3 months prior to Screening
        - Time spent in a healthcare delivery setting or institution where individuals infected with TB are housed and where the risk of transmission of infection is high.

    c. Latent TB infection (unless appropriate prophylaxis is initiated prior to study treatment and continued to completion of prophylaxis). Please refer to Section 12.7.3 for further details and instructions.

17. Subjects with current acute or chronic viral hepatitis B or C or with human immunodeficiency virus (HIV) infection.

18. Subjects with current or a history of active infection with histoplasma, coccidiodes, paracoccidioides, pneumocystis, nontuberculous mycobacteria, blastomyces, or aspergillus.

19. Subjects must not have had a history of an infected joint prosthesis any time.

20. Subjects receiving any live (includes attenuated) vaccination within the 8 weeks prior to Baseline (eg, inactivated influenza and pneumococcal vaccines are allowed but nasal influenza vaccination is not allowed).

21. Subjects who, in the Investigator's opinion, have a high risk of infection (eg, subjects with leg ulcers, indwelling urinary catheter, persistent or recurrent chest infections, and subjects who are permanently bedridden or wheelchair bound).

22. Subjects with a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease.

23. Current malignancy or a history of malignancy, although subjects with less than 3 completely excised basal cell carcinomas or with cervical carcinoma in situ successfully surgically treated more than 5 years prior to Screening may be included.

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24. Subjects with Class III or IV congestive heart failure as per the New York Heart Association (NYHA) 1964 criteria.

25. Subjects with a history of or suspected demyelinating disease of the central nervous system (eg, multiple sclerosis or optic neuritis).
26. Subjects who have had major surgery (including joint surgery) within 8 weeks prior to Screening or have planned surgery within 6 months of the Screening Visit.

27. Subjects with current or history of severe, progressive, and/or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac, or neurological disease, as determined by the Investigator.

28. Subjects with significant laboratory abnormalities included but not limited to:

    - Liver function tests > 2.0 x ULN

    - Estimated Glomerular Filtration Rate (GFR) as measured by Chronic Kidney Disease Epidemiology Collaboration (Levey et al, 2009) < 60 mL/min/1.73m2

    - White blood cell (WBC) < 3.0x109/L

29. Subjects with any other condition that, in the Investigator's judgment, would make the subject unsuitable for inclusion in the study.

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Predictors of flare analysis

Logistic regression analysis modelling the probability of flare in patients randomised to either CZP or placebo was performed. Given the low number of flares in the CZP treatment groups, the CZP full and reduced maintenance dose groups were combined for this analysis. A stepwise regression model was used to identify any potential predictors that contribute significantly to the model. In the first step (forward selection), a cut-off of $p<0.05$ was used for variable entry into the predictive model; in the next step (backward elimination), a cut-off of $p>0.1$ was used to eliminate variables from the model (Chi square test).

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Table S1. Permitted concomitant medications

Drug class	Dose	Exclusion criteria	Study Visits
Analgesics (including, but not limited to acetaminophen, paracetamol, opiates, or combinations thereof)	Up to maximum approved dose	Any change in stable dose regimen is excluded in the 14 days prior to the Baseline Visit.	Ad hoc use of analgesics is not permitted within 24 hours prior to any post-screening visit. Stable dose of analgesics (including narcotics) are permitted throughout the study.
NSAIDs (including COX 2 inhibitors)	Up to maximum approved dose regimen	Any change in stable dose regimen is excluded in the 14 days prior to the Baseline Visit.	Ad hoc use of NSAIDs is not permitted within 24 hours prior to any post-screening visit. NSAID dose can be down-titrated at Investigator discretion, if clinically indicated, until Week 28, after which NSAID treatment should remain as stable as possible. NSAID dose should be stable until Week 96 (if subjects have to decrease or stop taking medication due to safety reasons, they may reduce their dose and continue in the study).
Oral corticosteroids	Maximum allowed ≤10 mg daily total prednisone equivalent	Any change in stable dose used for axSpA in the 28 days prior to the Baseline Visit.	A change in the dose is not allowed until Week 96. Oral corticosteroid tapers of less than 14 days used to treat other indications are allowed as long as the maximum daily dose is ≤20mg. The taper must end at least 1 week before study visit.
Intramuscular corticosteroids	Any dose	Use in the 28 days prior to the Baseline Visit.	Must not be used during the study.
Intra-articular corticosteroids	Up to maximum approved dose	Use in the 28 days prior to the Baseline Visit.	SIJ intra-articular corticosteroid injections are not allowed during the study. Peripheral joint injections are permitted.
Intravenous corticosteroids	Up to maximum approved dose	Use in the 28 days prior to the baseline Visit.	May be used for acute illnesses as long as the dose is not given within one week prior to Week 12, 24, 48 or 96 and the underlying disease does not present a contraindication to the subject remaining in the study.
Hyaluronic acid (intra-articular)	Any dose	Use in the 28 days prior to the Baseline Visit.	After Baseline, intra-articular injection may be used in the knee.
SAARDs: • SSZ • HCQ • MTX • AZA • LFN	Maximum allowed: • SSZ ≤3 g daily • HCQ ≤400 mg daily • MTX ≤25 mg weekly • AZA ≤150 mg/day • LFN ≤20 mg/day	SAARD use initiated and/or any change in the dose regimen in the 28 days prior to the Baseline Visit. No change is permitted in the route of administration for MTX in the 28 days prior to the Baseline Visit.	SAARDs should be stable until Week 96 (if a subject has to decrease or stop taking medications due to safety reasons, they may reduce their SAARDs and continue in the study).
SAARDs: • Cyclosporine • Cyclophosphamide • Mycophenolic acid • Apremilast	Up to maximum approved dose	Use within 28 days prior to the Baseline Visit.	Must not be started during the study.

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TNFi therapies: • IFX • ADA • ETN • GOL • CZP	Any dose	• IFX, ADA, GOL: any use within the 3 months prior to the Baseline Visit. • CZP: any exposure history. • ETN: use within the 28 days prior to the Baseline Visit. • Only 1 previous biologic is allowed.	Must not be started during the study.
Osteoporosis Medications: Risedronate, Alendronate, Ibandronate Denosumab, Cathepsin K inhibitor, Cinacalcet, Calcitonin	Up to maximum approved dose	All stable osteoporosis medications are permitted except for intravenous bisphosphonates.	Osteoporosis medications with the exception of intravenous bisphosphonates are allowed without restriction. Intravenous bisphosphonates are not permitted.

ADA: adalimumab; AZA: azathioprine; axSpA: axial spondyloarthritis; CD20: Cluster of Differentiation 20; COX 2: cyclooxygenase 2; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; HCQ: hydroxychloroquine; IFX: infliximab; LFN: leflunomide; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drug; RA: rheumatoid arthritis; SAARD: slow acting anti-rheumatic drug; SIJ: sacroiliac joint; SSZ: sulfasalazine.

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Table S2. Baseline demographics and disease characteristics for axSpA patients, including r-axSpA and nr-axSpA subpopulations

	Radiographic axSpA (n=407)	Non-radiographic axSpA (n=329)
Age, years		
Mean (SD)	33.7 (6.8)	32.1 (7.1)
Median (range)	34.0 (18–45)	32.0 (18–45)
Male, n (%)	319 (78.4)	195 (59.3)
BMI, kg/m^2, mean (SD)	25.6 (4.7)	25.8 (5.1)
Race, n (%)		
Caucasian	375 (92.1)	306 (93.0)
Asian	27 (6.6)	11 (3.3)
Other/mixed/missing	5 (1.2)	12 (3.6)
Geographic region, n (%)		
North America	13 (3.2)	20 (6.1)
Western Europe	30 (7.4)	61 (18.5)
Eastern Europe	320 (78.6)	217 (66.0)
Asia	44 (10.8)	31 (9.4)
mNY positive, n (%)	407 (100.0)	0
Symptom duration, years		
Mean (SD)	3.7 (2.5)	2.9 (1.7)
Median (range)	4.0 (0.2–23.5)	2.9 (0.2–10.1)
Time since diagnosis, years		
Mean (SD)	2.5 (1.8)	1.8 (1.6)
Median (range)	2.3 (0.2–12.1)	1.1 (0.2–5.3)
HLA-B27 positive, n (%)	363 (89.2)	254 (77.2)
CRP > ULN, n (%)	210 (51.6)	134 (40.7)
Prior TNFi therapy, n (%)	20 (4.9)	12 (3.6)
History of enthesitis (heel), n (%)	102 (25.1)	82 (24.9)
History of EAMs, n (%)		
Uveitis	63 (15.5)	48 (14.6)
Inflammatory bowel disease	9 (2.2)	8 (2.4)
Psoriasis	24 (5.9)	21 (6.4)
Disease characteristics, mean (SD)		
ASDAS	3.8 (0.8)	3.6 (0.8)
BASDAI	6.7 (1.4)	6.7 (1.4)
BASFI	5.4 (2.0)	5.1 (2.1)
BASMI	3.5 (1.6)	2.6 (1.3)
Tender joint count	1.9 (3.7)	3.4 (6.0)
Swollen joint count[a]	0.5 (1.4)	1.1 (2.7)
MASES	2.3 (2.8)	2.7 (3.1)
Imaging (MRI), mean (SD)		
SIJ SPARCC	8.2 (11.8)	7.9 (10.9)
ASspiMRI-a	4.6 (6.1)	1.4 (2.9)
Concomitant medication,[b] n (%)		
NSAIDs	352 (86.5)	266 (80.9)
DMARDs	97 (23.8)	69 (21.0)

[a] 44 joints; [b] Any intake during induction period (Weeks 0–48) or maintenance period (Weeks 48–96). 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; BASMI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CRP: C-reactive protein; DMARD: disease-

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modifying anti-rheumatic drug; mNY: modified New York; NSAID: non-steroidal anti-inflammatory drug; Q2W: every 2 weeks; Q4W: every 4 weeks; SD: standard deviation; TNF: tumor necrosis factor.

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Table S3. P values (Chi-square test) from a stepwise logistic regression model evaluating predictors of flare during the maintenance period of C-OPTIMISE

Variable	Baseline used	Continuous / categorical	All CZP		Placebo	
			OC	*NRI*	*OC*	*NRI*
Age group	Week 0	≤33 years vs >33 years	0.3547	0.6312	0.3719	0.7233
ASAS-NSAID score	Week 44–48	Continuous	0.0742	0.1046	0.0880	0.2528
ASDAS state	Week 0	HDA vs vHDA	0.6374	0.4068	0.7584	0.8041
BASDAI	Week 48	Continuous	0.0711	0.1281	0.2788	0.1201
BASFI	Week 48	Continuous	0.1702	0.0630	0.3215	0.6596
BASMI	Week 48	Continuous	0.9373	0.1393	0.0748	0.194
BMI	Week 0	<25, ≥25 and <30, ≥30	0.8306	0.2883	0.7137	0.4175
CRP level	Week 0	<10 mg/L vs ≥10 mg/L	0.8328	0.5733	0.7368	0.5145
Concomitant DMARD intake	Week 48	Yes vs no	0.2349	0.2238	0.2433	0.7016
Concomitant NSAID intake	Week 48	Yes vs no	0.3179	0.6087	0.7893	0.8134
Symptom duration	Week 0	≤3 years vs >3 years	0.4359	0.6218	0.5607	0.5757
Fatigue	Week 48	Continuous	0.3146	0.6330	0.7635	0.1659
HLA-B27	Week 0	Negative vs positive	**0.0154**	**0.0077**	0.3403	0.4762
mNY criteria	Week 0	Yes vs no	0.6748	0.5900	0.6663	0.6477
Morning stiffness	Week 48	Continuous	0.8822	0.8166	0.0798	0.0616
Pain	Week 48	Continuous	0.5356	0.3363	0.7932	0.1835
PGADA	Week 48	Continuous	0.1736	0.4042	0.1922	0.1916
Region	Week 0	Eastern Europe vs rest of world	0.9597	0.8061	0.8363	0.3845
Sex	Week 0	Male vs female	0.2192	0.2752	0.3842	0.3762
Smoker	Week 0	Current vs never + former	0.8250	0.6492	0.2563	0.4331
Deep remission[a]	Week 2–48	Yes vs no	0.6692	0.6806	0.0740	0.0933

CZP treatment groups (CZP 200 mg Q2W and CZP 200 mg Q4W) have been combined, given the low number of flares in these groups. [a] First timepoint of achieving and sustaining ASDAS-ID to Week 48. ASAS: Assessment of SpondyloArthritis international Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; 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; HDA: high disease activity; HLA-B27: human leukocyte antigen B27; ID: inactive disease; mNY: modified New York; NRI: non-responder imputation; NSAID: non-steroidal anti-inflammatory drug; OC: observed case; PGADA: Patient's Global Assessment of Disease Activity; vHDA: very high disease activity.

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Table S4. Post-flare efficacy outcomes for patients who escaped to CZP 200 mg Q2W

	CZP 200 mg Q2W (n=7)		CZP 200 mg Q4W (n=15)		Placebo (n=73)	
	Flare baseline[a]	Escape Week 12	Flare baseline[a]	Escape Week 12	Flare baseline[a]	Escape Week 12
ASDAS disease activity state, n (%)						
ID (<1.3)	0/7	1/6 (16.7)	1/15 (6.7)	9/15 (60.0)	1/73 (1.4)	45/71 (63.4)
LD (≥1.3 and <2.1)	4/7 (57.1)	3/6 (50.0)	6/15 (40.0)	3/15 (20.0)	6/73 (8.2)	19/71 (26.8)
HD (≥2.1 and ≤3.5)	1/7 (14.3)	2/6 (33.3)	7/15 (46.7)	3/15 (20.0)	32/73 (43.8)	6/71 (8.5)
vHD (>3.5)	2/7 (28.6)	0/6	1/15 (6.7)	0/15	34/73 (46.6)	1/71 (1.4)
ASDAS clinical improvement,[b] n (%)						
CII	—	1/6 (16.7)	—	7/15 (46.7)	—	60/71 (84.5)
MI	—	0/6	—	2/15 (13.3)	—	35/71 (49.3)
ASAS responder rates,[b] n (%)						
20	—	3/6 (50.0)	—	9/14 (64.3)	—	60/72 (83.3)
40	—	1/6 (16.7)	—	7/14 (50.0)	—	50/72 (69.4)
5/6	—	1/6 (16.7)	—	1/14 (7.1)	—	43/71 (60.6)
Partial remission	—	1/6 (16.7)	—	7/14 (50.0)	—	48/72 (66.7)
BASDAI50 response,[b] n (%)	—	1/6 (16.7)	—	10/15 (66.7)	—	54/72 (75.0)
Change from flare baseline, mean (SD; n)						
ASDAS	2.5 (1.1; 7)	-0.6 (0.6; 6)	2.3 (0.6; 15)	-0.8 (0.9; 15)	3.4 (1.0; 73)	-2.2 (1.1; 71)
BASDAI	4.5 (2.5; 7)	-1.6 (1.1; 6)	3.9 (1.9; 15)	-2.3 (2.4; 15)	5.3 (2.3; 73)	-3.8 (2.5; 72)
BASFI	2.7 (1.7; 7)	-0.7 (0.7; 6)	3.2 (2.3; 15)	-1.8 (2.4; 14)	3.7 (2.4; 73)	-2.5 (2.5; 72)
BASMI	2.7 (1.4; 7)	-0.3 (0.4; 6)	2.3 (1.4; 15)	-0.3 (0.3; 15)	2.7 (1.6; 71)	-0.4 (0.6; 67)
MRI outcomes, mean (SD; n)						
SIJ SPARCC score	0.4 (0.8; 4)	0.0 (0.0; 2)	2.0 (3.5; 12)	0.2 (3.1; 12)	9.4 (13.3; 64)	-9.3 (13.2; 48)
ASspiMRI-a	0.0 (0.0; 4)	0.0 (0.0; 2)	1.2 (2.5; 12)	-0.3 (1.0; 12)	2.3 (4.5; 64)	-2.3 (4.6; 48)

Observed case data. [a] Assessment immediately prior to starting escape treatment; [b] Improvement responses are calculated from flare baseline. ASDAS: Ankylosing Spondylitis Disease Activity Score; ASDAS-ID/LD/HD/vHD: ASDAS-inactive disease/low disease/high disease/very high disease; 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; PR: partial remission; MI: major improvement; Q2W: every 2 weeks; Q4W: every 4 weeks; SD: standard deviation; SIJ SPARCC: sacroiliac joint Spondyloarthritis Research Consortium of Canada.

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