# Common Drug Review
## *Clinical Review Report*

**September 2017**

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|---|---|
| **Drug** | certolizumab pegol (Cimzia) (subcutaneous injection) |
| **Indication** | Reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) who have had an inadequate response to conventional therapy |
| **Listing request** | As per indication |
| **Manufacturer** | UCB Canada Inc. |

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in rheumatology who provided input on the conduct of the review and the interpretation of findings.

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# ABBREVIATIONS

| | |
|---|---|
| **ACE** | Arthritis Consumer Experts |
| **AE** | adverse event |
| **AS** | ankylosing spondylitis |
| **ASAS** | Assessment in Ankylosing Spondylitis |
| **ASQoL** | Ankylosing Spondylitis Quality of Life |
| **axSpA** | axial spondyloarthritis |
| **BASDAI** | Bath Ankylosing Spondylitis Disease Activity Index |
| **BASFI** | Bath Ankylosing Spondylitis Functional Index |
| **BASMI** | Bath Ankylosing Spondylitis Metrology Index |
| **CI** | confidence interval |
| **CRP** | C-reactive protein |
| **CZP** | certolizumab pegol |
| **DB** | double-blind |
| **DMARD** | disease-modifying antirheumatic drugs |
| **ESR** | erythrocyte sedimentation rate |
| **EQ-5D** | EuroQol 5-Dimensions Questionnaire |
| **FAS** | full analysis set |
| **HRQoL** | health-related quality of life |
| **ITT** | intention to treat |
| **LOCF** | last observation carried forward |
| **MCID** | minimally clinically important difference |
| **MCS** | mental component summary |
| **MRI** | magnetic resonance imaging |
| **MRIS** | Magnetic Resonance Imaging Set |
| **mSASSS** | modified Stokes Ankylosing Spondylitis Spinal Score |
| **MTX** | methotrexate |
| **n** | number of patients with event |
| **N** | number of patients |
| **NRS** | numerical rating scale |
| **NSAID** | nonsteroidal anti-inflammatory drug |
| **nr-axSpA** | non-radiographic-axSpA |
| **NSAID** | numerical rating scale |
| **PL** | placebo |
| **PCS** | physical component summary |
| **PPS** | per-protocol set |
| **Q2W** | every two weeks |
| **Q4W** | every four weeks |
| **RCT** | randomized controlled trial |
| **RS** | Randomized Set |

| | |
|---|---|
| **SAE** | serious adverse event |
| **SC** | subcutaneous |
| **SD** | standard deviation |
| **SF-36** | Short-form 36-item Health Survey |
| **TNF** | tumour necrosis factor |
| **VAS** | visual analogue scale |
| **WDAE** | withdrawal due to adverse event |
| **WPS** | Work Productivity Survey |

# EXECUTIVE SUMMARY

## Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that involves the sacroiliac joints, axial skeleton, and entheses (i.e., the sites where tendons and ligaments attach to bones, and, in some cases, peripheral joints). According to the Arthritis Society, about 150,000 to 300,000 Canadians (prevalence of 0.42% to 0.84% in 2014) are affected by AS.[1] A separate report by the Arthritis Community Research & Evaluation Unit of the Ministry of Health and Long-term Care estimated the prevalence to be up to one per cent among Canadian adults.[2]

Certolizumab pegol (CZP) is a pegylated Fc-free anti-tumour necrosis factor (TNF) for the treatment of AS, and its structure represents a novel approach to TNF inhibition.[3] The Health Canada Notice of Compliance is for reducing signs and symptoms in adult patients with active AS who have had an inadequate response to conventional therapy. CZP is also approved for use in adult patients with moderately to severely active rheumatoid arthritis (RA) and in adult patients with moderately to severely active psoriatic arthritis (PsA).[3] The Health Canada recommended dose for adult patients is 400 mg (given as two subcutaneous injections of 200 mg each) initially (week 0) and at weeks 2 and 4. After the loading dose, the recommended maintenance dose of CZP for adult patients with AS is 200 mg every two weeks or 400 mg every four weeks.[3]

The objective of this review is to perform a systematic review of the beneficial and harmful effects of CZP for the treatment of active AS in adults who have had an inadequate response to conventional therapy.

## Results and interpretation

### Included studies

AS-001, a phase 3, multi-centre, randomized, double-blind, placebo-controlled study met the inclusion criteria for this systematic review. The study population included adult patients with active axial spondyloarthritis (axSpA), including the AS subpopulation (modified New York criteria = yes) and non-radiographic-axSpA (nr-axSpA) subpopulation (modified New York criteria = no). For the purpose of this review and consistent with the approved Health Canada indication, only results for the AS subpopulation are discussed. AS-001 (N = 178), a three-group superiority study, evaluated the efficacy and safety of CZP 200 mg subcutaneously (SC) every two weeks (Q2W) or CZP 400 mg SC every four weeks (Q4W) compared with placebo SC injection compared with a double-blind duration of 24 weeks. Both CZP groups received a loading dose of 400 mg SC at baseline, week 2 and week 4. Placebo patients who did not achieve at least a minimal response (defined as patients who did not achieve Assessment of SpondyloArthritis International Society [ASAS] 20) at both weeks 14 and 16 were allocated to escape treatment (randomized in a 1:1 ratio to receive CZP 200 mg SC Q2W or CZP 400 mg SC Q4W) from week 16 onwards. Unblinded trained site personnel administered study treatments. During the dose-blind period (week 24 to week 48), patients originally randomized to placebo were re-randomized in a 1:1 ratio to receive three loading doses of CZP SC 400 mg at weeks 24, 26, and 28 followed by either CZP 200 mg Q2W from week 30 onward or CZP 400 mg Q4W from week 32 onward. At weeks 26 and 28, patients were trained to self-administer one injection at home Q4W from week 30. AS-001 includes an ongoing open-label extension from week 48 to week 204 where patients will continue to receive the same dose regimen of CZP during the dose-blind period. A safety follow-up will also be performed for all patients, including those withdrawn from study treatment, 10 weeks after their last dose of study treatment.

The early escape design, while common in AS trials based on ethical considerations, potentially limits the interpretation and clinical relevance of the trial data. In particular, there is uncertainty regarding the internal validity of results at week 24 as the early escape study design was only applied to placebo patients at week 16. With the use of non-responder imputation and with more than half of patients in the placebo group changing their assigned treatment at week 16 after meeting criteria for early escape, results for the patient-reported outcomes are potentially biased in favour of the CZP treatment groups. Furthermore, a hierarchical testing procedure was used for select efficacy outcomes (ASAS at week 24, Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and Bath Ankylosing Spondylitis Metrology Index (BASMI) end points at weeks 12 and 24). Thus, all other outcomes, as well as subgroup analyses, were not adjusted for multiplicity and should be interpreted with caution.

**Efficacy**

For clinical response outcomes, both CZP regimens were statistically significantly superior to placebo for improvements in ASAS 20 response with a mean absolute difference of 20.1% (95% confidence interval [CI], 2.7% to 37.5%) and 27.4% (95% CI, 9.7% to 45.2%) at week 12 and 34.4% (95% CI, 17.7% to 51.1%) and 36.3% (95% CI, 19.1% to 53.5%) at week 24 for the CZP 200 mg 2QW and CZP 400 mg 4QW groups respectively. For ASAS 40 response, both CZP regimens were statistically significantly superior to placebo with a mean absolute difference of 20.7% (95% CI, 5.0% to 36.4%) and 30.7% (95% CI, 14.1% to 47.3%) at week 12 and 31.9% (95% CI, 16.5% to 47.3%) and 43.1% (95% CI, 27.2% to 59.1%) at week 24 for the CZP 200 mg 2QW and CZP 400 mg 4QW groups respectively.

Health-related quality of life (HRQoL) was evaluated using the Ankylosing Spondylitis Quality of Life (ASQoL); Short-form 36-item Health Survey (SF-36) mental component summary (MCS), physical component summary (PCS), and physical functioning; and EuroQol 5-Dimensions Questionnaire (EQ-5D) instruments at week 12 and week 24. Both CZP treatment groups demonstrated greater numeric improvement in HRQoL (ASQoL and SF-36) at week 12. Patients receiving CZP reported improvements in mobility, self-care, and usual activities (EQ-5D) at week 12. Results were analyzed descriptively. Post-hoc between-group analyses were performed for the ASQoL and SF-36 outcomes (results not shown).

Disease activity was measured using the BASDAI instrument. Both CZP treatment groups were statistically significantly superior to placebo with a mean absolute difference of –1.49 units (95% CI, –2.20 to –0.78) and –1.40 units (95% CI, –2.15 to –0.66) at week 12 and –1.87 units (95% CI, –2.57 to –1.16) and –1.85 units (95% CI, –2.59 to –1.11) at week 24 for the CZP 200 mg 2QW and CZP 400 mg 4QW groups respectively.

Function and disability outcomes were measured using the BASFI and BASMI linear instruments. Both CZP treatment groups were statistically significantly superior to placebo for improvements in BASFI score with a mean absolute difference of –1.15 (95% CI, –1.88 to –0.42) and –1.13 units (95% CI, –1.89 to –0.36) at week 12 and –1.62 units (95% CI, –2.38 to –0.86) and –1.55 units (95% CI, –2.34 to –0.75) at week 24 for the CZP 200 mg 2QW and CZP 400 mg 4QW groups respectively. The BASMI linear end point did not reach statistical significance for any treatment group at week 12; hence, according to the hierarchical testing procedure, the analysis should have stopped.

Overall, improvements in work productivity were demonstrated, as there was a statistically significant difference for one of eight questions of the Work Productivity Survey (WPS) among the CZP 200 mg Q2W group, and five of eight questions for the CZP 400 mg 4QW group when compared with placebo at week 12. There was a statistically significant difference for three of eight questions among the CZP

200 mg Q2W group, and four of eight questions for the CZP 400 mg 4QW group when compared with placebo at week 24.

Radiographic change was evaluated using the modified Stokes Ankylosing Spondylitis Spinal Score (mSASSS). The results revealed an improvement among the CZP 400 mg Q4W at week 12. Results were analyzed descriptively with no between-group comparisons.

Subgroup analyses for prior TNF-alpha exposure and baseline C-reactive protein (CRP) levels did not provide any meaningful conclusion given the small sample size.

**Harms**

There were no reported deaths in the study. Over 24 weeks, the overall frequency of serious adverse events (SAEs) was 3.1%, 3.6%, and 5.3% in the CZP 200 mg 2QW, CZP 400 mg 4QW, and placebo groups respectively. The overall frequency of withdrawals due to adverse events (WDAEs) was 3.1%, 5.4%, and 1.8% in the CZP 200 mg 2QW, CZP 400 mg 4QW, and placebo groups respectively. The overall frequency of treatment-emergent adverse events (TEAEs) was 69.2%, 69.6%, and 61.4% in the CZP 200 mg 2QW, CZP 400 mg 4QW, and placebo groups respectively (Table 15). The most common reason for AEs reported for all three groups was nasopharyngitis (7.7%, 12.5%, and 7.0% in the CZP 200 mg 2QW, CZP 400 mg 4QW, and placebo groups respectively). One patient in the CZP 200 mg Q2W group experienced a serious infection. There were no events of spinal fractures, cardiac disorder, lupus, or injection reactions during the entire treatment period.

## Conclusions

Based on one double-blind randomized controlled trial in patients with active AS, treatment with CZP either 200 mg Q2W or 400 mg Q4W resulted in statistically significant and clinically meaningful improvements in clinical response (ASAS 20, ASAS 40), disease activity (BASDAI), and function (BASFI) at week 12 and week 24 when compared with placebo. A non-statistically significant improvement in disability (BASMI linear) was seen at week 12 among both CZP treatment groups compared with placebo; however, because of the hierarchical step-down analysis procedure, statistical significance at week 24 could not be assessed. Statistically significant improvements in work productivity were also demonstrated, though the clinical meaningfulness of these results remains uncertain. Without between-group comparisons, there is uncertainty regarding differences in HRQoL and radiographic change between CZP treatment groups and placebo. Subgroup analyses for prior TNF-alpha exposure and baseline CRP levels did not provide any meaningful conclusions. Overall, the incidence of treatment-emergent AEs was similar to placebo with both CZP groups, although the study was not designed to identify between-group differences in safety. Moreover, AS is a chronic condition that will be treated over a lifetime; therefore, a 24-week controlled trial is a short duration to evaluate harms.

The early escape study design, though typically used in recent AS studies for ethical reasons, potentially weakens the internal validity of results observed at week 24. In particular, because early escape criteria only applied to placebo patients and use of non-responder imputation for assessments at week 24, results for the patient-reported outcomes at week 24 are potentially biased in favour of the CZP treatment groups and should be interpreted with caution.

**TABLE 1: SUMMARY OF RESULTS**

| Outcome | AS-001 | | |
|---|---|---|---|
| | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| **ASAS 20 at week 12** (RS with imputation[a]) | | | |
| Responders (%) | 56.9 | 64.3 | 36.8 |
| 95% CI | 44.9 to 69.0 | 51.7 to 76.8 | (24.3 to 49.4) |
| Difference to PL (%)[b] | 20.1 | 27.4 | — |
| 95% CI | 2.7 to 37.5 | 9.7 to 45.2 | — |
| *P* value | 0.026 | 0.003 | — |
| **ASAS 20 at week 24** (RS with imputation[a]) | | | |
| Responders (%) | 67.7 | 69.6 | 33.3 |
| 95% CI | 56.3 to 79.1 | 57.6 to 81.7 | (21.1 to 45.6) |
| Difference to PL (%)[b] | 34.4 | 36.3 | — |
| 95% CI | 17.7 to 51.1 | 19.1 to 53.5 | — |
| *P* value | < 0.001 | < 0.001 | — |
| **ASAS 40 at week 12** (FAS with imputation[a]) | | | |
| Responders (%) | 40.0 | 50.0 | 19.3 |
| 95% CI | NR | NR | NR |
| Difference to PL (%)[b] | 20.7 | 30.7 | — |
| 95% CI | 5.0 to 36.4 | 14.1 to 47.3 | — |
| *P* value | 0.011 | < 0.001 | — |
| **ASAS 40 at week 24** (FAS with imputation[a]) | | | |
| Responders (%) | 47.7 | 58.9 | 15.8 |
| 95% CI | NR | NR | NR |
| Difference to PL (%)[b] | 31.9 | 43.1 | — |
| 95% CI | 16.5 to 47.3 | 27.2 to 59.1 | — |
| *P* value | < 0.001 | < 0.001 | — |
| **BASDAI at week 12** (RS with imputation[c]) | | | |
| Mean at baseline | 6.52 (1.67) | 6.18 (1.29) | 6.44 (1.85) |
| LS mean change from baseline (SE)[d] | –2.51 (0.31) | –2.43 (0.33) | –1.02 (0.30) |
| LS mean difference to PL (SE)[d] | –1.49 (0.36) | –1.40 (0.36) | — |
| 95% CI | –2.20 to –0.78 | –2.15 to –0.66 | — |
| *P* value | < 0.001 | < 0.001 | — |
| **BASDAI at week 24** (RS with imputation[c]) | | | |
| Mean at baseline | 6.52 (1.67) | 6.18 (1.29) | 6.44 (1.85) |
| LS mean change from baseline (SE)[d] | –3.00 (0.30) | –2.98 (0.33) | –1.13 (0.30) |
| LS mean difference to PL (SE)[d] | –1.87 (0.36) | –1.85 (0.37) | — |
| 95% CI | –2.57 to –1.16 | –2.59 to –1.11 | — |

| Outcome | AS-001 | | |
|---|---|---|---|
| | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| *P* value | < 0.001 | < 0.001 | — |
| **BASFI at week 12** (RS with imputation[c]) | | | |
| Mean at baseline | 5.61 (2.28) | 5.65 (2.25) | 5.98 (2.01) |
| LS mean change from baseline (SE)[d] | –1.73 (0.31) | –1.71 (0.34) | –0.58 (0.31) |
| LS mean difference to PL (SE)[d] | –1.15 (0.37) | –1.13 (0.39) | — |
| 95% CI | –1.88 to –0.42 | –1.89 to –0.36 | — |
| *P* value | 0.002 | 0.004 | — |
| **BASFI at week 24** (RS with imputation[c]) | | | |
| Mean at baseline | 5.61 (2.28) | 5.65 (2.25) | 5.98 (2.01) |
| LS mean change from baseline (SE)[d] | –2.36 (0.33) | –2.29 (0.35) | –0.74 (0.32) |
| LS mean difference to PL (SE)[d] | –1.62 (0.38) | –1.55 (0.40) | — |
| 95% CI | –2.38 to –0.86 | –2.34 to –0.75 | — |
| *P* value | < 0.001 | < 0.001 | — |
| **BASMI linear at week 12** (RS with imputation[c]) | | | |
| Mean at baseline | 4.18 (1.55) | 4.31 (1.77) | 4.74 (1.62) |
| LS mean change from baseline (SE)[d] | –0.57 (0.14) | –0.34 (0.15) | –0.24 (0.14) |
| LS mean difference to PL (SE)[d] | –0.32 (0.17) | –0.10 (0.17) | — |
| 95% CI | –0.65 to 0.01 | –0.44 to 0.25 | — |
| *P* value | 0.058 | 0.578 | — |
| **BASMI linear at week 24** (RS with imputation[c]) | | | |
| Mean at baseline | 4.18 (1.55) | 4.31 (1.77) | 4.74 (1.62) |
| LS mean change from baseline (SE)[d] | –0.62 (0.15) | –0.56 (0.16) | –0.27 (0.14) |
| LS mean difference to PL (SE)[d] | –0.35 (0.17) | –0.29 (0.18) | — |
| 95% CI | –0.69 to –0.01 | –0.64 to 0.07 | — |
| *P* value | NA[e] | NA[e] | — |
| **ASQoL at week 12** (FAS with imputation[c]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] | [redacted] |
| **ASQoL at week 24** (FAS with imputation[c]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] | [redacted] |
| **SF-36 MCS at week 12** (FAS with imputation[c]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] | [redacted] |
| **SF-36 MCS at week 24** (FAS with imputation[c]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] | [redacted] |
| **SF-36 PCS at week 12** (FAS with imputation[c]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |

| Outcome | AS-001 | | |
|---|---|---|---|
| | CZP 200 mg Q2W (n = 65) | CZP 400 mg Q4W (n = 56) | PL (n = 57) |
| Mean change from baseline (SD) | [redacted] | [redacted] | [redacted] |
| **SF-36 PCS at week 24** (FAS with imputation[c]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] | [redacted] |
| **SF-36 Physical Functioning at week 12** (FAS with imputation[c]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] | [redacted] |
| **SF-36 Physical Functioning at week 24** (FAS with imputation[c]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] | [redacted] |

ASAS = Assessment in Ankylosing Spondylitis; ASQoL = Ankylosing Spondylitis Quality of Life assessment; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; CI = confidence interval; CZP = certolizumab pegol; FAS = full analysis set; LS = least square; MCS = mental component summary; n = number of patients with event; NR = not reported; *P* = probability; PL = placebo; PCS = physical component summary; Q2W = every two weeks; Q4W = every four weeks; RS = randomized set; SD = standard deviation; SE = standard error; SF-36 = Short-form 36-item Health Survey.

[a] Non-responder Imputation (NRI) was used: patients who withdrew for any reason or PL patients who used escape medication were considered non-responders from the time that they dropped out or when escape therapy was initiated. Patients who had missing data at a visit were counted as a non-responder for the respective visit.

[b] Treatment difference: CZP 200 mg minus PL, CZP 400 mg minus PL, and CZP 200 mg plus 400 mg minus PL (and corresponding 95% CI and *P* value) were estimated using a standard two-sided Wald asymptotic test with a five per cent alpha level.

[c] Last observation carried forward (LOCF) was used: for patients who withdrew for any reason or patients with a missing week 12/24 measurement, last observation before the early withdrawal or week 12/24 was carried forward to week 12/24.

[d] Analysis of covariance (ANCOVA) model with treatment, region, and prior anti-TNF-alpha exposure (yes/no) as factors, and baseline score as a covariate.

[e] Based on the described hierarchical testing procedure in the statistical analysis plan, statistical significance at week 24 could not be assessed.

Note: EQ-5D data can be found in Table 11.

# 1. INTRODUCTION

## 1.1 Disease prevalence/incidence

Ankylosing spondylitis (AS) is a chronic inflammatory disease that involves the sacroiliac joints, axial skeleton, and entheses (i.e., the sites where tendons and ligaments attach to bones, and, in some cases, peripheral joints). Chronic inflammation results in back pain and stiffness, and potentially leads to new bone formation and joint fixation (i.e., ankyloses). The relationship between inflammation and bone formation is not as clearly established in AS as it has been with rheumatoid arthritis (RA). While chronic inflammation leads to bone erosion, pathways to bone formation are not as well elucidated and may include both inflammatory and non-inflammatory pathways. According to the Arthritis Society, about 150,000 to 300,000 Canadians (prevalence of 0.42% to 0.84% in 2014) are affected by AS.[1] A separate report by the Arthritis Community Research & Evaluation Unit of the Ministry of Health and Long-term Care estimated the prevalence to be up to one per cent among Canadian adults.[2]

## 1.2 Standards of therapy

In Canada, nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line therapy for AS patients with pain and stiffness.[4] For patients with no therapeutic advantage who have increased gastrointestinal risk, selective cyclooxygenase-2 **(**COX-2) inhibitor therapy is suggested.[4] Corticosteroid injection directed to the local site of inflammation may be considered. There is limited evidence for the efficacy of disease-modifying antirheumatic drugs (DMARD) for the treatment of axial disease.[5] Anti-tumour necrosis factor (TNF) treatment is recommended for patients with persistently high disease activity despite conventional treatments.[4] Non-pharmacological treatments include patient education and regular exercise.[4]

## 1.2 Drug

Certolizumab pegol (CZP) is a pegylated Fc-free anti-TNF for the treatment of AS, and its structure represents a novel approach to TNF inhibition.[3] In Canada, CZP is indicated for: 1) reducing signs and symptoms in adult patients with active AS who have had an inadequate response to conventional therapy; 2) in combination with methotrexate (MTX) for reducing signs and symptoms, inducing major clinical response, and reducing the progression of joint damage as assessed by X-ray, in adult patients with moderately to severely active rheumatoid arthritis (RA) and as monotherapy for reducing signs and symptoms in adult patients with moderately to severely active RA who do not tolerate MTX; and 3) as monotherapy or in combination with MTX for reducing signs and symptoms and inhibiting the progression of structural damage as assessed by X-ray, in adult patients with moderately to severely active psoriatic arthritis (PsA) who have failed one or more DMARDs.[3] The Health Canada recommended dose for adult patients is 400 mg (given as two subcutaneous injections of 200 mg each) initially (week 0) and at weeks 2 and 4. After the loading dose, the recommended maintenance dose of Cimzia for adult patients with AS is 200 mg every two weeks (Q2W) or 400 mg every four weeks (Q4W).[3] In addition to CZP, four other anti-TNF-alpha drugs — infliximab, etanercept, adalimumab, and golimumab — are currently approved in Canada for the treatment of AS patients who have inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs) (Table 2).

| Indication under review |
|---|
| Reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) who have had an inadequate response to conventional therapy. |
| **Listing criteria requested by sponsor** |
| As per indication. |

**TABLE 2: KEY CHARACTERISTICS OF ADALIMUMAB, CERTOLIZUMAB, ETANERCEPT, GOLIMUMAB, AND INFLIXIMAB**

| | Adalimumab (Humira) | Certolizumab Pegol (Cimzia) | Etanercept (Enbrel) | Golimumab (Simponi) | Infliximab (Remicade, Inflectra) |
|---|---|---|---|---|---|
| **Mechanism of Action** | A recombinant human IgG1 monoclonal antibody that inhibits binding of TNF to TNF receptors | A recombinant, humanized antibody Fab fragment inhibits binding of TNF to TNF receptors | A dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p.75) TNF receptor linked to the Fc portion of human IgG1. Etanercept inhibits binding of TNF to TNF receptors | A human IgG1 monoclonal antibody inhibits binding of TNF to TNF receptors | A chimeric IgG1 monoclonal antibody that inhibits binding of TNF to TNF receptors |
| **Indication**[a] | Reducing signs and symptoms in patients with active AS who have had an inadequate response to conventional therapy | Reducing signs and symptoms in adult patients with active AS who have had an inadequate response to conventional therapies | Reducing signs and symptoms of active AS | Reducing signs and symptoms in adult patients with active AS who have had an inadequate response to conventional therapies | Reducing signs and symptoms and improvement in physical function in patients with active AS who have responded inadequately, or are intolerant to, conventional therapies |
| **Route of Administration** | SC | | | | IV |
| **Recommended Dose** | 40 mg administered every other week as a single-dose through SC injection | Loading dose of 400 mg (given as 2 SC injections of 200 mg each) initially (week 0) and at weeks 2 and 4 followed by a maintenance dose of 200 mg Q2W or 400 mg Q4W | 50 mg per week in one SC injection or as two 25 mg SC injections on the same day once weekly or 3 or 4 days apart | 50 mg SC once a month on same date each month | 5 mg/kg given as an IV infusion followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks thereafter |
| **Serious Side Effects / Safety Issues** | Infections, particularly opportunistic ones and TB<br>Malignancies<br>Allergic reactions<br>Injection or infusion site reactions | | | | |

AS = ankylosing spondylitis; IgG1 = immunoglobin G1; IV = intravenous; Q2W = every two weeks; Q4W = every four weeks; SC = subcutaneous; TB = tuberculosis; TNF = tumour necrosis factor.
[a] Health Canada indication.
Source: Health Canada product monographs.[3,6-9]

# 2. OBJECTIVES AND METHODS

## 2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of CZP (Cimzia) for the treatment of active AS in adults who have had an inadequate response to conventional therapy.

## 2.2 Methods

Studies selected for inclusion in the systematic review included the pivotal studies supporting the Health Canada indication provided in the manufacturer's submission to CADTH Common Drug Review (CDR), as well as those meeting the selection criteria presented in Table 3.

**TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW**

| | |
|---|---|
| **Patient Population** | Adults (≥ 18 years of age) with active AS with inadequate response to conventional therapies<br>Subgroups:<br>• Prior TNF-alpha inhibitor use<br>• Baseline body weight<br>• Baseline CRP<br>• Baseline ESR |
| **Intervention** | CZP at Health Canada-approved dose |
| **Comparators** | Biologic response modifiers (e.g., infliximab, etanercept, adalimumab, golimumab) |
| **Outcomes** | **Efficacy outcomes:**<br>• Clinical response (e.g., ASAS 20, ASAS 40, ASAS 5/6 response)<br>• HRQoL<br>• Disease activity (e.g., BASDAI)<br>• Functional and disability outcomes (e.g., BASFI, BASMI)<br>• Work productivity<br>• Radiographic changes<br>**Harms outcomes:**<br>• Mortality, SAEs, WDAEs, AEs<br>• AEs of interest: spinal fractures, serious infections, heart failure malignancies, lupus, injection reactions |
| **Study Design** | Published and unpublished phase 3 RCTs |

AE = adverse event; AS = ankylosing spondylitis; ASAS = Assessment in Ankylosing Spondylitis; 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; ESR = erythrocyte sedimentation rate; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse event; TNF-alpha = tumour necrosis factor inhibitor; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Patient Headings), and keywords. The main search concepts were certolizumab (Cimzia) and AS.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on October 30, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on March 18, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/grey-matters): Health Technology Assessments, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, databases, and an Internet search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4.

# 3. RESULTS

## 3.1 Findings from the literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 2 and described in Section 3.2. None of the identified studies were excluded from the review (Appendix 3).

**FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES**

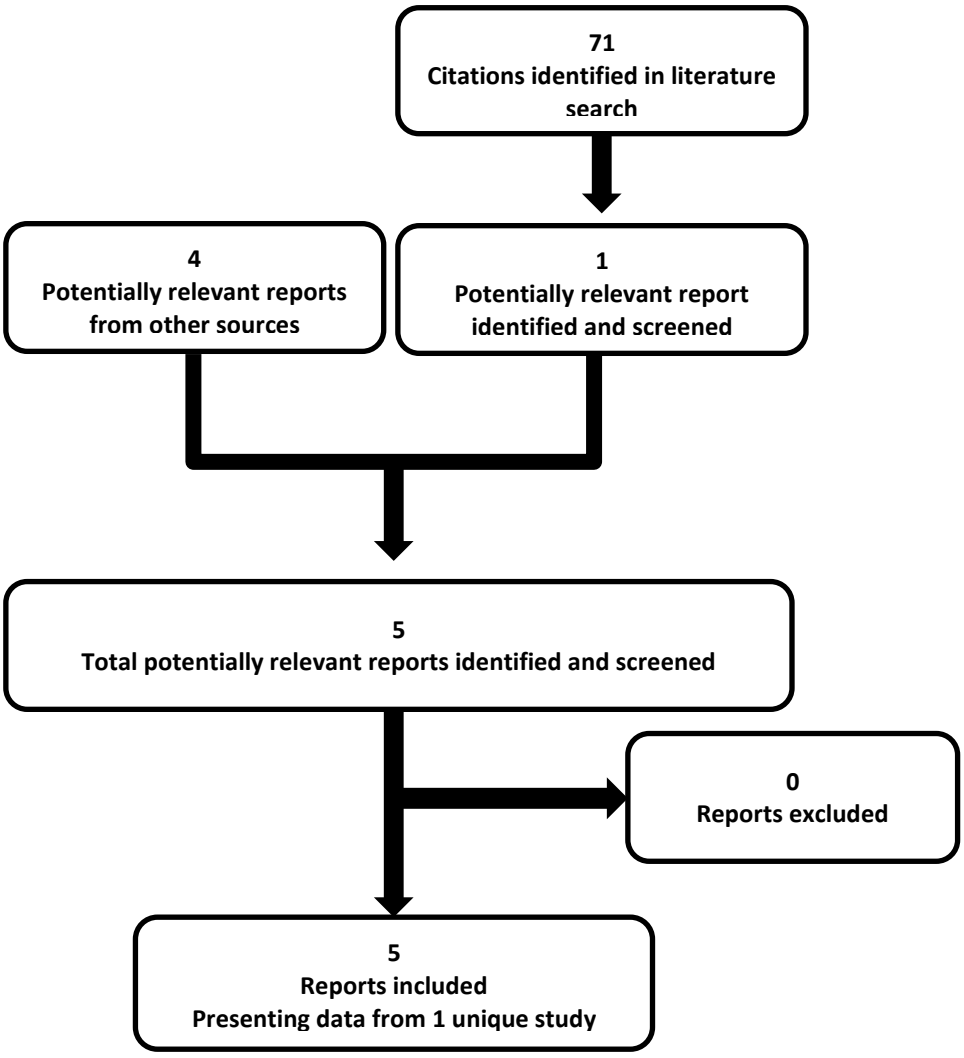


**TABLE 4: DETAILS OF INCLUDED STUDIES[A]**

| | | AS-001 |
|---|---|---|
| DESIGNS & POPULATIONS | **Study Design** | DB RCT |
| | **Locations** | Canada, US, W. Europe, E. Europe, Mexico, Brazil, and Argentina |
| | **Randomized (N)** | 325 (entire axSpa population) / 178 (AS subpopulation) |
| | **Inclusion Criteria** | • 18 years old at screening<br>• Female patients had to be either postmenopausal for at least 1 year, surgically incapable of childbearing, or effectively practising an acceptable method of contraception<br>• A documented diagnosis of adult-onset axSpA of at least 3 months symptom duration as defined by the specified ASAS criteria<br>• Active disease as defined by each of the following:<br>  ○ BASDAI score ≥ 4<br>  ○ Spinal pain ≥ 4 on a 0 to 10 NRS (from BASDAI item 2)<br>  ○ CRP > ULN and/or current evidence (i.e., within the last 3 months from Screening) for sacroiliitis on MRI as defined by ASAS criteria<br>• Had to have been intolerant to or have had an inadequate response to at least 1 NSAID. Inadequate response to an NSAID was defined as lack of response to at least 30 days of continuous NSAID therapy at the highest tolerated dose of the administered NSAID or the lack of response to treatment with at least 2 NSAIDs at the maximum tolerated dose for 2 weeks each |
| | **Exclusion Criteria** | • History of chronic or recurrent infections, serious or life-threatening infection (< 6 months before baseline, including herpes zoster)<br>• Active/high risk of TB, hepatitis B/C, or HIV<br>• Had been previously exposed to CZP or > 2 other biological drugs (> 1 TNF inhibitor)<br>• Experienced primary failure of a prior TNF inhibitor<br>• Diagnosis of total spinal ankylosis (“bamboo spine”) |
| DRUGS | **Intervention** | CZP 400 mg SC loading dose at baseline, week 2 and week 4 followed by either:<br>• CZP 200 mg Q2W SC<br>• CZP 400 mg Q4W SC |
| | **Comparator(s)** | Placebo prefilled syringe |
| DURATION | **Phase:** | |
| | Run-in | NA |
| | Double-blind | 24 weeks (week 0 to week 24) |
| | Dose-blind | 24 weeks (week 24 to week 48) |
| | Open-label extension | 110 weeks (week 48 to week 158) (ongoing) |
| | Follow-up | 10 weeks (week 158 to week 166) (safety follow-up) |
| OUTCOMES | **Primary End Point** | ASAS 20 response at week 12 |
| | **Other End Points** | • ASAS 20 response at week 24<br>• ASAS 40 response at week 12<br>• ASAS 40 response at week 24<br>• Change from baseline in BASFI to weeks 12 and 24 |

| | | AS-001 |
|---|---|---|
| | | • Change from baseline in BASDAI to weeks 12 and 24<br>• Change from baseline in mSASSS at week 12<br>• Change from baseline in ASQoL to weeks 12 and 24<br>• Change from baseline in the SF-36 PCS to weeks 12 and 24<br>• Change from baseline in the SF-36 Physical Functioning domain to weeks 12 and 24<br>• Change from baseline in the EQ-5D domains and VAS to weeks 12 and 24<br>• WPS responses at weeks 12 and 24 |
| NOTES | **Publications** | Landewé et al. 2003[10] |

AS = ankylosing spondylitis; ASAS = Assessment of SpondyloArthritis International Society; ASQoL = Ankylosing Spondylitis Quality of Life assessment; axSpA = axial spondyloarthritis; 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; DB = double-blind; E. = Eastern; EQ-5D = EuroQol 5-Dimensions Questionnaire; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; mSASSS = modified Stokes Ankylosing Spondylitis Spinal Score; N = number of patients; NA = not applicable; NRS = numerical rating scale; NSAID = nonsteroidal anti-inflammatory drug; PCS = physical component summary; Q2W = every two weeks; Q4W = every four weeks; RCT = randomized controlled trial; SC = subcutaneous; SF-36 = Short-form 36-item Health Survey; TB = tuberculosis; TNF = tumour necrosis factor; ULN = upper limit of normal; US = United States; VAS = visual analogue scale; W. = Western; WPS = Work Productivity Survey.

[a] Four additional reports were: Interim Clinical Study Report, week 24: AS001[11]; Interim Clinical Study Report, week 48[12]; CDR submission[13]; Health Canada reviewer's report.[14]

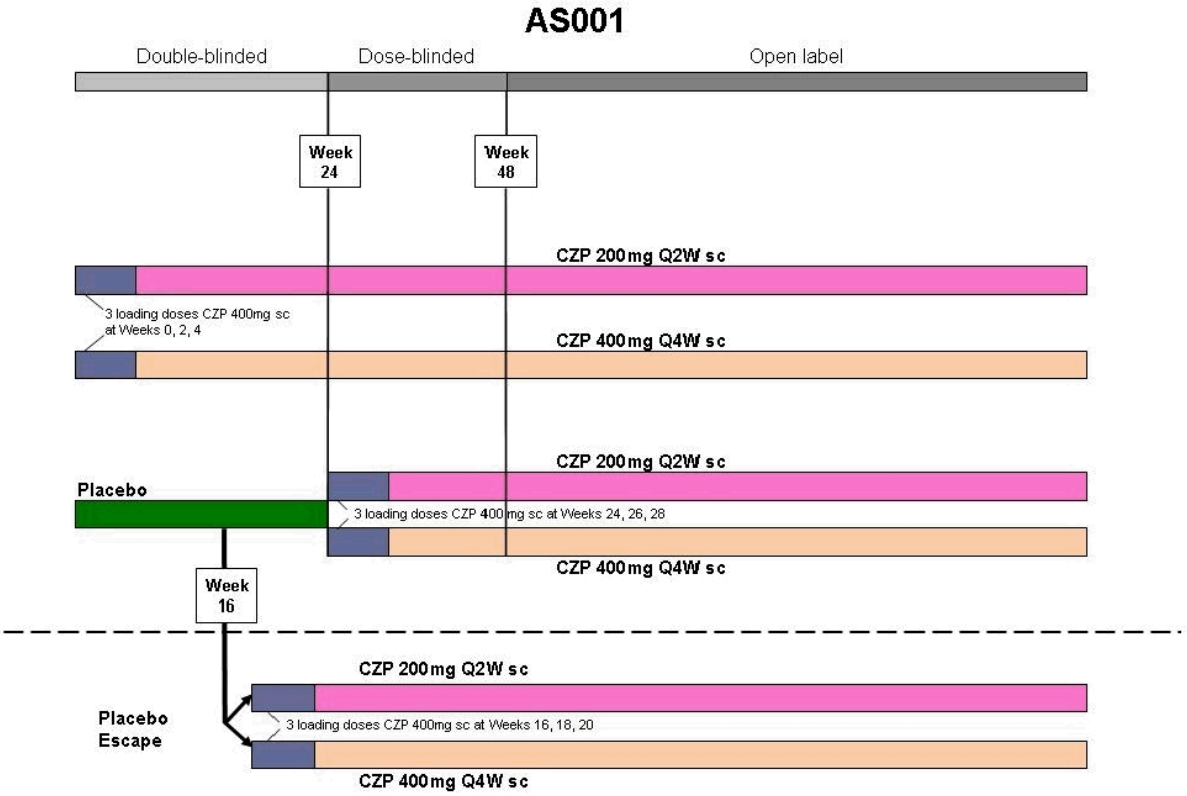
## 3.2 Included studies

### 3.2.1 Description of studies

AS-001, a phase 3, multi-centre, randomized, double-blind, placebo-controlled study met the inclusion criteria for this systematic review. The study population included adult patients with active axial spondyloarthritis (axSpA), including the AS subpopulation (modified New York [NY] criteria = yes) and non-radiographic-axSpA (nr-axSpA) subpopulation (modified NY criteria = no). During recruitment, it was specified that 50% of patients had to comply with meeting the definite AS diagnosis according to the modified NY criteria in order to recruit a broadly balanced population between the two subpopulations. For the purpose of this review and consistent with the approved Health Canada indication, only results for the AS subpopulation are discussed. AS-001 (N = 178), a three-group superiority study, evaluated the efficacy and safety of CZP 200 mg SC Q2W or CZP 400 mg SC Q4W compared with placebo SC injection compared with a double-blinded duration of 24 weeks. Both CZP groups received a loading dose of 400 mg SC at baseline, week 2 and week 4. Placebo patients who did not achieve at least a minimal response (defined as patients who did not achieve an ASAS 20) at both weeks 14 and 16 were allocated to early escape treatment (randomized in a 1:1 ratio to receive CZP 200 mg SC Q2W or CZP 400 mg SC Q4W) from week 16 onwards. Study treatments were administered by unblinded trained site personnel. Randomization was stratified by site, fulfillment of modified NY criteria, and prior anti-TNF-alpha exposure.

During the dose-blind period (weeks 24 to 48), patients originally randomized to placebo were re-randomized in a 1:1 ratio to receive three loading doses of CZP SC 400 mg at weeks 24, 26, and 28 followed by either CZP 200 mg Q2W from week 30 onward or CZP 400 mg Q4W from week 32 onward. At weeks 26 and 28, patients were trained on self-administration and self-administered one injection at home Q4W from week 30. AS-001 includes an ongoing open-label extension from week 48 to week 204 where patients continued to receive the same dose regimen of CZP during the dose-blind period. A safety follow-up will also be performed for all patients, including those withdrawn from study treatment, 10 weeks after their last dose of study treatment. A schematic design of AS-001 can be found below (Figure 2)

**FIGURE 2: AS-001 SCHEMATIC DESIGN**




AS: ankylosing spondylitis; CZP = certolizumab pegol; Q2W = every two weeks; Q4W = every four weeks; SC = subcutaneously.
Source: Clinical Study Report AS-001 week 48.[12]

### 3.2.2 Populations

#### a) Inclusion and exclusion criteria

The inclusion criteria in AS-001 were patients 18 years of age or older with a documented diagnosis of adult-onset axSpA of at least three months symptom duration as defined by the specified ASAS criteria. Patients had to have active disease as defined by each of the following: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score greater than or equal to four; spinal pain greater than or equal to four on a 0 to 10 numerical rating scale (NRS) (from BASDAI item 2); and C-reactive protein (CRP) greater than upper limit of normal (ULN) and/or current evidence (i.e., within the last three months from screening) for sacroiliitis on magnetic resonance imaging (MRI) as defined by ASAS criteria.

To include a balance between the two axSpA subpopulations (AS and nr-axSpA), 50% of the study population who met the ASAS criteria should not have fulfilled the modified NY criteria for definite diagnosis of AS, but at least 50% had to meet the new ASAS imaging criteria. The remainder could be enrolled based on meeting the specified ASAS clinical criteria only. Patients had to have been intolerant to or have had an inadequate response to at least one NSAID, defined as lack of response to at least 30 days of continuous NSAID therapy at the highest tolerated dose of the administered NSAID or the lack of response to treatment with at least two NSAIDs at the maximum tolerated dose for two weeks each. Female patients had to be either postmenopausal for at least one year, surgically incapable of childbearing, or effectively practising an acceptable method of contraception. Patients were excluded if they had a history of chronic or recurrent infections, serious or life-threatening infection (fewer than six

months before baseline, including herpes zoster), or active/high risk of tuberculosis (TB), hepatitis B/C, or HIV. Patients previously exposed to CZP or more than two other biological drugs (greater than one TNF inhibitor), experienced primary failure of a prior TNF inhibitor, with total spinal ankylosis ("bamboo spine"), diagnosis of any other inflammatory arthritis (e.g., RA, systemic lupus erythematosus, sarcoidosis) or a known diagnosis of fibromyalgia were excluded.

**b) Baseline characteristics**

There were differences in baseline characteristics as there was a greater proportion of prior TNF-alpha exposure in the placebo group (28.1% ) compared with the CZP 200 mg Q2W (16.9%) and 400 mg Q4W (16.1%) groups at baseline (Table 5). [redacted]

**TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS OF ANKYLOSING SPONDYLITIS SUBPOPULATION**

| Characteristics | AS-001 | | |
|---|---|---|---|
| | CZP 200 mg Q2W N = 65 | CZP 400 mg Q4W N = 56 | PL N = 57 |
| **Sex, n (%)** | | | |
| Male | 47 (72.3) | 41 (73.2) | 41 (71.9) |
| Female | 18 (27.7) | 15 (26.8) | 16 (28.1) |
| **Age (years)** | | | |
| Mean (SD) | 41.0 (10.8) | 41.9 (11.5) | 41.6 (12.8) |
| Range | 24 to 64 | 19 to 66 | 21 to 68 |
| **Weight (kg)** | | | |
| Mean (SD) | [redacted] | [redacted] | [redacted] |
| Range | [redacted] | [redacted] | [redacted] |
| **BMI (kg/m$^2$)** | | | |
| Mean (SD) | [redacted] | [redacted] | [redacted] |
| Range | [redacted] | [redacted] | [redacted] |
| **Race n (%)** | | | |
| Caucasian | [redacted] | [redacted] | [redacted] |
| Black or African American | [redacted] | [redacted] | [redacted] |
| Asian | [redacted] | [redacted] | [redacted] |
| Other | [redacted] | [redacted] | [redacted] |
| **Prior TNF-alpha use** | | | |
| Yes | [redacted] | [redacted] | [redacted] |
| No | [redacted] | [redacted] | [redacted] |
| **Screening CRP, n (%)** | | | |
| ≤ 15 mg/L | [redacted] | [redacted] | [redacted] |
| > 15 mg/L | [redacted] | [redacted] | [redacted] |
| **HLA-B27 positive, n (%)** | [redacted] | [redacted] | [redacted] |
| **Screening ESR, mean (SD)** | [redacted] | [redacted] | [redacted] |

| Characteristics | AS-001 | | |
|---|---|---|---|
| | **CZP 200 mg Q2W N = 65** | **CZP 400 mg Q4W N = 56** | **PL N = 57** |
| **(mm/hour)** | | | |
| **Prior joint surgery/procedure, n (%)** | [redacted] | [redacted] | [redacted] |
| **Time since diagnosis of AS, mean (SD) yrs** | [redacted] | [redacted] | [redacted] |
| **Duration of inflammatory back pain, mean (SD) yrs** | [redacted] | [redacted] | [redacted] |
| **Patients with extraspinal features of AS at baseline, n (%)** | | | |
| Uveitis | [redacted] | [redacted] | [redacted] |
| Psoriasis | [redacted] | [redacted] | [redacted] |
| Dactylitis | [redacted] | [redacted] | [redacted] |
| Enthesitis | [redacted] | [redacted] | [redacted] |
| Peripheral | [redacted] | [redacted] | [redacted] |
| **Baseline BASDAI scores, mean (SD)** | [redacted] | [redacted] | [redacted] |
| **Baseline BASMI linear scores, mean (SD)** | [redacted] | [redacted] | [redacted] |
| **Baseline BASFI scores, mean (SD)** | 5.61 (2.28) | 5.65 (2.25) | 5.98 (2.01) |

AS = ankylosing spondylitis; 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; ESR = erythrocyte sedimentation rate; HLA = human leukocyte antigen; n = number of patients with event; N = number of patients; PL = placebo; Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation; TNF-alpha = tumour necrosis factor inhibitor; yrs = years.

### 3.2.3 Outcomes

#### a) Clinical response

**Assessment of SpondyloArthritis International Society (ASAS 20)**

The core sets of outcomes were selected by the ASAS working group in order to create uniformity, allow standardization of measures, and allow direct comparison and the pooling of results from clinical trials. The ASAS 20 response is defined as an improvement of at least 20% and absolute improvement of at least one unit on a 0 to 10 NRS in at least three of the four following domains[15]: 1) Patient's Global Assessment of Disease Activity (PtGADA); 2) Pain assessment (the total spinal pain NRS score; 3) Function (represented by BASFI); or 4) Inflammation (the mean of the BASDAI questions 5 and 6 concerning the intensity and duration of morning stiffness).

**Assessment of SpondyloArthritis International Society (ASAS 40)**

The ASAS criteria for 40% improvement is defined as relative improvement of at least 40% and absolute improvement of at least two units on a 0 to 10 NRS in at least three of the four domains and no worsening at all in the remaining domain.

**Assessment of SpondyloArthritis International Society (ASAS Partial Remission Response)**
The ASAS partial remission (ASAS-PR) response is defined as a score of greater than two units on a 0 to 10-unit scale in all four domains.

**Assessment of SpondyloArthritis International Society (ASAS 5/6 Response)**
The ASAS 5/6 response is defined as at least 20% improvement in five of six domains, including spinal mobility (i.e., lateral spinal flexion, BASMI, and CRP as more objective measures).[16]

### b) Health-related quality of life

**Ankylosing Spondylitis Quality of Life assessment**
The Ankylosing Spondylitis Quality of Life assessment (ASQoL) is an 18-item disease-specific questionnaire for measuring health-related quality of life (HRQoL) in patients with AS.[17] Items assess the impact of disease on sleep, mood, motivation, coping, activities of daily living, independence, relationships, and social life. The ASQoL score ranges from 0 to 18 with higher scores indicating worse HRQoL. The minimal clinically important difference (MCID) of the ASQoL remains unknown.

**Short-form 36-item Health Survey**
The Short-form 36-item Health Survey (SF-36) is a 36-item generic HRQoL instrument that uses a recall period of four weeks. Items are grouped into eight domains as follows: Physical Functioning (10 items), Role Physical (four items), Bodily Pain (two items), General Health (five items), Vitality (four items), Social Functioning (two items), Role Emotional (three items), Mental Health (five items), and one item for perceived stability or change in health (Health Transition) during the last year. The concepts represented by these domains contribute to physical, mental, and social aspects of HRQoL. In addition to domain scores, the physical component summary (PCS) and mental component summary (MCS) scores are calculated from the eight domains (excluding the Health Transition item). Each of the eight domain scores and the component summary scores range from 0 to 100, with a higher score indicating a better health status. The domains and the two component summary scores are standardized with a mean of 50 and a standard deviation (SD) of 10 in the general US population. Among the general population, changes between 2.5 to 5.0 points in the PCS and MCS of the SF-36 are considered to be clinically relevant, as are changes of 5 to 10 points in the domain scores.[18] The SF-36 has been used and has shown to be responsive in axSpA,[19] though the MCID among the specific AS population remains unknown.

**EuroQol 5-Dimensions questionnaire**
The European Quality of Life Scale is a generic HRQoL instrument that may be applied to a wide range of health conditions and treatments.[20,21] The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing “no problems,” “some problems,” and “extreme problems,” respectively. The second part is a 20 cm visual analogue scale (VAS) that has end points labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state.” Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their health on that day. The MCID for the EQ-5D scores and VAS among the specific AS population remains unknown.

### c) Disease activity

**Bath Ankylosing Spondylitis Disease Activity Index**
The BASDAI is a self-reported instrument that consists of six 10-unit horizontal NRS (or 10 cm VAS) to measure severity of fatigue, spinal and peripheral joint pain and swelling, enthesitis, and morning

stiffness (both severity and duration, respectively) during the last week. The NRS version was used for the answering options of each item. To give each symptom equal weighting, the average of the two scores relating to morning stiffness is taken. The resulting 0 to 50 sum score is divided by five to give a final BASDAI score ranging from 0 to 10, with lower scores indicating lower disease activity. The MCID used to interpret scores is 10 mm on a VAS or 22.5% of the baseline score.[22-24]

### d) Functional and disability outcomes

**Bath Ankylosing Spondylitis Functional Index**

The BASFI is a disease-specific instrument for assessing physical function.[25,26] The BASFI comprises 10 items relating to the past week. The NRS version was used for the answering options of each item on a scale of 0 ("Easy") to 10 ("Impossible"). The first eight questions evaluate activities related to functional anatomical limitations due to the course of this inflammatory disease. The final two questions evaluate the patients' ability to cope with everyday life. An NRS ranging from 0 to 10 is used to answer the questions on the test. The BASFI is the mean of the 10 scores such that the total score ranges from 0 to 10, with lower scores indicating better physical function. The MCID used to interpret scores is 7 mm on a 0 mm to 100 mm VAS or 17.5% of the baseline score [24,26]

**Bath Ankylosing Spondylitis Metrology Index**

The BASMI linear characterizes the spinal mobility of patients with AS. The BASMI linear is a clinical measure consisting of five clinical measures to reflect subject axial status: cervical rotation; tragus-to-wall distance; lumbar flexion (modified Schober test); intermalleolar distance; and lateral spinal flexion. Each of the five movements is scored according to the BASMI linear definition (Table 6). The mean of the five scores provides the BASMI linear score. The higher the BASMI linear score, the more severe the patient's limitation of movement due to their axSpA. For cervical rotation, tragus-to-wall distance, and lumbar flexion, the mean of the left and right measurements was used, if both were available. Otherwise, the available measurement was used. The MCID is currently unknown.

**TABLE 6: BATH ANKYLOSING SPONDYLITIS METROLOGY INDEX LINEAR DEFINITION**

| | |
|---|---|
| S = (21.1 cm – A) / 2.1 cm | For the lateral spinal flexion (mean right/left) |
| S = (A – 8 cm) / 3 cm | For the tragus-to-wall distance (mean right/left) |
| S = (7.4 cm – A) / 0.7 cm | For the lumbar flexion (modified Schober) |
| S = (124.5 cm – A) / 10 cm | For the maximal intermalleolar distance |
| S = (89.3° – A) / 8.5° | For the cervical rotation (mean right/left) |
| Always with the additional condition 0 ≤ S ≤ 10 | |

A = assessment; S = score.
Source: Clinical Study Report AS-001 week 48.[12]

### e) Work productivity

**Work Productivity Survey**

The WPS is a nine-question instrument used to assess the impact of arthritis on productivity within and outside the home during the preceding four weeks. One of the WPS questions concerns employment status, three relate to work productivity outside the home, and five ask about household work and daily activities. Patients employed outside the home were asked questions about the number of work days missed due to arthritis, the number of days with productivity at work reduced by half or more due to arthritis, and the interference of arthritis on work productivity on a 0 to 10 scale (0 = no interference; 10 = complete interference). In addition, all patients — regardless of their employment status — were asked questions about the number of household work days missed due to arthritis; the number of days

with productivity in household work reduced by half or more; the number of family, social, or leisure activities days missed due to arthritis; the number of days with outside help hired due to arthritis; and the interference of arthritis on household work productivity on a 0 to 10 scale (0 = no interference; 10 = complete interference). The eight items addressed in the questionnaire are analyzed separately. The MCID is currently unknown.

**f) Radiographic changes**

**Modified Stokes Ankylosing Spondylitis Spine Score**

The modified Stokes Ankylosing Spondylitis Spinal Score (mSASSS) is a radiographic assessment of structural spinal changes that assesses the anterior vertebral edges of the cervical and lumbar spine by grading the presence of chronic changes using a score between 0 and 3.[27] The total range of the score is 0 to 72 points. Damage at baseline was defined as a score of greater than or equal to one (sclerosis or erosion), and definite radiographic damage was defined as a score of greater than or equal to two (appearance of at least one syndesmophyte) in at least one vertebral edge. Radiographic progression was assessed by evaluating the change of the mSASSS between time points. Any radiographic change was defined as worsening or improvement of greater than or equal to one mSASSS units, and definite radiographic change as the change from mSASSS scorings of 0 (no damage) or 1 (sclerosis or erosion) to 2 (syndesmophyte) or 3 (bridging syndesmophyte/ankylosis) between time points.[27] All images were scored by two independent readers blinded to both the order of the scans and to the treatment group. The mSASSS was performed on radiographs obtained at baseline, week 12, and early withdrawal (if patient withdrew before week 96) at selected sites only.

**g) Adverse events**

An adverse event (AE) was any untoward medical occurrence in a patient administered a pharmaceutical product that did not necessarily have a causal relationship with this treatment. An AE could therefore have been any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

### 3.2.4 Statistical analysis

**a) Efficacy criteria**

**Double-blind period (up to week 24)**

- The analysis for the primary end point (ASAS 20 response at week 12) was performed using the randomized set (RS) population. Treatment comparisons with placebo for the two CZP treatment groups were performed using a standard two-sided Wald asymptotic test with a five per cent alpha level along with 95% asymptotic Wald confidence limits. Calculations were performed without continuity corrections. For the primary analysis, patients who withdrew for any reason before week 12 or who had missing data for all of the ASAS components at week 12 were considered as non-responders.
- Sensitivity analyses for the primary end point using the full analysis set (FAS) and per-protocol set (PPS) populations were performed.
- Key secondary end points included ASAS 20 response at week 24, and change from baseline to weeks 12 and 24 in BASFI, BASDAI, and BASMI using the RS population. ASAS 20 at week 24 was analyzed using the same approach for week 12. The changes from baseline in the BASDAI, BASFI, and BASMI at weeks 12 and 24 were compared between treatment groups using an analysis of covariance (ANCOVA). The model included baseline score, treatment group, region, modified NY criteria (yes/no) and prior anti-TNF-alpha exposure (yes/no). For missing post-baseline values, the

last observation carried forward (LOCF) approach was applied, and for placebo patients who escaped early, their last observation before escape was also carried forward to week 24.

- The primary and key secondary efficacy analyses were performed in the hierarchical testing procedure:
  - ASAS 20 response at week 12 for CZP 200 mg Q2W
  - ASAS 20 response at week 12 for CZP 400 mg Q4W
  - ASAS 20 response at week 24 for CZP 200 mg Q2W
  - ASAS 20 response at week 24 for CZP 400 mg Q4W
  - Change from baseline in BASFI at week 12 for CZP 200 mg Q2W and CZP 400 mg Q4W combined
  - Change from baseline in BASDAI at week 12 for CZP 200 mg Q2W and CZP 400 mg Q4W combined
  - Change from baseline in BASFI at week 24 for CZP 200 mg Q2W and CZP 400 mg Q4W combined
  - Change from baseline in BASDAI at week 24 for CZP 200 mg Q2W and CZP 400 mg Q4W combined
  - Change from baseline in BASMI at week 12 for CZP 200 mg Q2W and CZP 400 mg Q4W combined
  - Change from baseline in BASMI at week 24 for CZP 200 mg Q2W and CZP 400 mg Q4W combined.

Other secondary end points included:

1. Using RS population and analyzed similar to the primary end point
- ASAS 40 at weeks 12 and 24
- ASAS-PR responder at weeks 12 and 24
- ASAS 5/6 response at weeks 12 and 24.

2. Using the FAS population and analyzed using the nonparametric bootstrap-t-method (with bootstrap CIs and *P* values) and LOCF for missing post-baseline values:
- WPS responses at weeks 12 and 24.

3. Using the FAS population (descriptive analysis only; LOCF for missing post-baseline values):
- SF-36 PCS change from baseline to weeks 12 and 24
- SF-36 MCS change from baseline to weeks 12 and 24
- SF-36 Physical Functioning domain change from baseline to weeks 12 and 24
- EQ-5D and VAS from baseline to weeks 12 and 24
- ASQoL change from baseline to weeks 12 and 24.

4. Using the magnetic resonance imaging set (MRIS) population (descriptive analysis only; LOCF for missing post-baseline values):
- Change in mSASSS from baseline at week 12.
- Baseline was defined as the last valid measurement before the first study medication administration.
- The sample size was determined for both the entire axSpA population as well as the AS subpopulation based on anticipated differences between the CZP groups and placebo in percentage of patients with ASAS 20 response at week 12.
- For the entire axSpA population, 105 participants for each treatment group (1:1:1 randomization) was expected to be sufficient to achieve 99% power for the group comparison with a 30% difference in ASAS 20 between the active and placebo groups. The 30% difference in

ASAS 20 is a conservative assumption as published data with other anti-TNF-alpha for the AS subpopulation comparting placebo with active treatment groups in ASAS 20 were greater than 38%.[28]

- For the AS subpopulation, the significance level of five per cent for ASAS 20 response at week 12 was not further adjusted, as testing for the modified AS subpopulation was conditional on the statistical test for the ASAS 20 response at week 12 being significant for a group comparison in the entire axSpA population. Given the modified AS subpopulation included patients with prior anti-TNF-alpha exposure, the difference was assumed to be smaller (33%). Thus, by ensuring half the patients were in the AS subgroup, the determined sample size was also sufficient to detect a statistically significant difference between the active treatment groups and placebo with 90% power.
- The study was powered for the primary variable, and other variables from the hierarchical test procedure were not utilized in the estimation of study power.
- Subgroup analyses for prior TNF-alpha exposure and baseline CRP levels, identified a priori, were performed for the AS population.

**Dose-blind period (Up to week 48)**

- For the dose-blind analysis, no formal statistical analyses were performed for the primary and secondary efficacy variables and only descriptive statistics were provided through week 48.

**b) Analysis populations**

The RS consisted of all patients randomized into the study with an intention to treat (ITT).

The safety set (SS) consisted of all patients in the RS who received at least one dose of study medication.

The FAS consisted of all patients in the RS who received at least one dose of study medication, had a valid baseline, and had a valid post-baseline efficacy measurement for the ASAS 20. The ASAS measurement had to be obtained through to week 12 (i.e., at least one post-baseline ASAS measurement had to be available).

The PPS consisted of patients in the FAS who had completed a minimal exposure of 12 weeks in the treatment regimen without any major protocol deviations that could have influenced the validity of the data for the primary efficacy variables. Post-baseline deviations did not necessarily lead to exclusion of a patient from PPS analyses, but could have led to exclusion of ASAS 20 data.

The MRIS consisted of all patients that had valid MRI assessments at baseline and at week 12.

## 3.3 Patient disposition

Patient disposition is summarized in Table 7. In the double-blind phase (up to week 24), a total of 178 patients were randomized. [redacted]

[redacted].

**TABLE 7: PATIENT DISPOSITION IN AS-001 – ANKYLOSING SPONDYLITIS SUBPOPULATION**

| AS-001 | | | |
|---|---|---|---|
| **Double-blind Phase (Up to week 24)** | | | |
| | **CZP 200 mg Q2W N = 65** | **CZP 400 mg Q4W N = 56** | **PL N = 57** |
| **Screened[a], N** | 591 | | |
| **Randomized, N (%)** | [redacted] | [redacted] | [redacted] |
| **Discontinued before week 24 (end of Double-blind), N (%)** | [redacted] | [redacted] | [redacted] |
| AE | [redacted] | [redacted] | [redacted] |
| Lack of efficacy | [redacted] | [redacted] | [redacted] |
| Protocol violation | [redacted] | [redacted] | [redacted] |
| Withdrew consent | [redacted] | [redacted] | [redacted] |
| Lost to follow-up | [redacted] | [redacted] | [redacted] |
| **Escape to CZP 200 mg Q2W at week 16** | [redacted] | [redacted] | [redacted] |
| **Escape to CZP 400 mg Q4W at week 16** | [redacted] | [redacted] | [redacted] |
| **Completed, week 24** | [redacted] | [redacted] | [redacted] |
| **RS, N** | [redacted] | [redacted] | [redacted] |
| **FAS, N** | [redacted] | [redacted] | [redacted] |
| **PP, N** | [redacted] | [redacted] | [redacted] |
| **Safety, N** | [redacted] | [redacted] | [redacted] |
| **MRI, N** | [redacted] | [redacted] | [redacted] |
| **Dose-blind Phase (Up to week 48)** | | | |
| | **CZP 200 mg Q2W N = 91** | **CZP 400 mg Q4W N = 83** | |
| **Total entering Dose-blind, N (%)** | [redacted] | [redacted] | |
| From PL Escape (week 16) | [redacted] | [redacted] | |
| From PL Completion | [redacted] | [redacted] | |
| From original CZP regimen Completion | [redacted] | [redacted] | |
| **Discontinued before week 48 (end of Dose-blind), N (%)** | [redacted] | [redacted] | |
| AE | [redacted] | [redacted] | |
| Lack of efficacy | [redacted] | [redacted] | |
| Withdrew consent | [redacted] | [redacted] | |
| Completed, week 48 | [redacted] | [redacted] | |
| RS, N | [redacted] | [redacted] | |
| FAS, N | [redacted] | [redacted] | |

| AS-001 | | |
|---|---|---|
| PPS, N | [redacted] | [redacted] |
| Safety, N | [redacted] | [redacted] |

AE = adverse event; AS = ankylosing spondylitis; CZP = certolizumab pegol; FAS = full analysis set; MRI = magnetic resonance imaging; N = number of patients; PL = placebo; PPS = per-protocol set; Q2W = every two weeks; Q4W = every four weeks; RS = randomized set.
[a] Screened for axSpA.

**FIGURE 3: PATIENT DISPOSITION IN AS-001 UP TO END OF DOSE-BLIND PHASE IN ANKYLOSING SPONDYLITIS SUBPOPULATION (WEEK 48)**

***Figure 3 contained confidential information and was removed at the request of the manufacturer.***

Source: AS-001 Clinical Study Report week 48.[12]

## 3.4 Exposure to study treatments

At week 24, the median (SD) number of doses received was [redacted].

**TABLE 8: EXTENT OF EXPOSURE AT 24 WEEKS (END OF DOUBLE-BLIND) IN AS-001 – ANKYLOSING SPONDYLITIS SUBPOPULATION (SAFETY SET)**

| AS-001 | | | |
|---|---|---|---|
| | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| **Number of Doses Received[a]** | | | |
| Mean (SD) | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Min, max | [redacted] | [redacted] | [redacted] |
| **Duration of Exposure in Narrow Sense[b] (Weeks)** | | | |
| Mean (SD) | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Min, max | [redacted] | [redacted] | [redacted] |
| **Duration of Exposure in Broader Sense[c] (Weeks)** | | | |
| Mean (SD) | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Min, max | [redacted] | [redacted] | [redacted] |

AS = ankylosing spondylitis; CZP = certolizumab pegol; max = maximum; min = minimum; n = number of patients with event; PL = placebo; Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation.
[a] Number of doses received = dose days (PL injection days for the 400 mg Q4W group were not counted).
[b] Exposure in the narrow sense = last injection date minus first injection date plus 14 (28) days.
[c] Exposure in the broader sense = last injection date minus first injection date plus 70 days.

**TABLE 9: CONCOMITANT MEDICATION USE IN DOUBLE-BLIND PERIOD (WEEK 24)**

| AS-001 | | | |
|---|---|---|---|
| **N (%)** | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| **NSAID** | [redacted] | [redacted] | [redacted] |
| **Analgesics** | [redacted] | [redacted] | [redacted] |
| **Corticosteroid for systemic use, plain** | [redacted] | [redacted] | [redacted] |
| **DMARDs** | [redacted] | [redacted] | [redacted] |
| sulfasalazine | [redacted] | [redacted] | [redacted] |
| hydroxychloroquine | [redacted] | [redacted] | [redacted] |
| methotrexate | [redacted] | [redacted] | [redacted] |

CZP = certolizumab pegol; DMARDs = disease-modifying antirheumatic drugs; n = number of patients with event; N = number of patients; NSAID = nonsteroidal anti-inflammatory drug; PL = placebo; Q2W = every two weeks; Q4W = every four weeks.

At week 48, the median number of doses received was [redacted].

## 3.5 Critical appraisal

### 3.5.1 Internal validity

**a) Selection, allocation and disposition of patients**

- AS-001 was randomized and double-blinded up to week 24, and dose-blinded up to week 48. Randomization was stratified by site, fulfillment of criteria (yes/no), and prior anti-TNF-alpha exposure (yes/no). The investigators and patients remained blinded to their allocated CZP dose regimen until the patient reached his/her week 48 visit. Dedicated unblinded trained site personnel administered study treatments. Pharmacokinetic, antibody, and CRP data were to be provided only once the study was unblinded.
- [redacted]

[redacted]

- At baseline, there was a greater proportion of prior TNF-alpha exposure in the placebo group (28.1%) compared with the CZP 200 mg Q2W (16.9%) and 400 mg Q4W (16.1%) groups at baseline. The placebo group also had a greater mean duration of AS (9.86 years) compared with the CZP
  200 mg Q2W (8.75 years) and 400 mg Q4W (10.05 years) groups at baseline. The proportion of patients with CRP levels > 15 mg/L was lower in the CZP 200 mg Q2W group (33.8%) compared with the CZP 400 mg Q4W (55.4%) and placebo (47.4%) groups. According to the expert consulted on this review, imbalances in baseline characteristics likely did not affect the clinical outcomes. Discontinuation was relatively low and similar in all groups (ranging from 7.0% to 7.7%).

**b) Statistical analyses and study design**

- The original study design included the general axSpA population. Subgroup analyses were performed for the specific AS population of interest. Analyses for the primary outcome (ASAS 20 at week 12) for the AS subpopulation were adequately powered.
- To adjust for multiplicity, a hierarchical testing procedure was used for the study's key secondary variables (ASAS at week 24; BASFI, BASDAI, and BASMI end points at weeks 12 and 24).
- The following outcomes were not part of the hierarchical testing procedure, thus were not adjusted for multiplicity: ASAS 40, ASAS-PR responder, ASAS 5/6 response, WPS responses at weeks 12 and 24, change from baseline to weeks 12 and 24 for SF-36 PCS, SF-36 MCS, SF-36 Physical Functioning domain, EQ-5D and VAS, ASQoL, and change in mSASSS from baseline at week 12.
- More than half of patients in the placebo group changed their assigned treatment at week 16 after meeting criteria for early escape. This limits the ability to make assertions about the results beyond the week 16-time point. Data for these patients were carried forward from week 16 to the end of the placebo-controlled phase at week 24. The early escape study design is commonly used in rheumatologic drug treatment trials, including in AS, for ethical considerations. Nevertheless, because only those in the placebo group were evaluated for early escape at week 16 and use of non-responder imputation (NRI) after this point, early escape potentially biased results in favour of the CZP treatment groups as the number of remaining patients in the placebo group (non-escapers) was considerably reduced after week 16.
- Results for the dose-blind phase at week 48 should be interpreted with caution as all patient self-reported outcomes may have been biased when patients were unblinded to treatment allocation.

**c) Intervention and comparator**

- The study compared both Health Canada-approved CZP doses (i.e., 200 mg Q2W and 400 mg Q4W).
- To adjust for missing data for the ASAS end points, patients who withdrew for any reason or placebo patients who used escape medication were considered non-responders from the time that they dropped out or when escape therapy was initiated. For all other end points, the LOCF approach was used to impute missing data, assuming patient's scores at the time of dropout would be the same at the end of study. Concern regarding the

appropriateness of this approach for outcomes measured at 12 weeks is mitigated given the low proportion of dropouts (approximately seven per cent) before week 16. Health-related quality of life (ASQoL, SF-36, EQ-5D) and radiographic change end points were analyzed descriptively and in an exploratory manner. Post-hoc between-group analyses were performed for the ASQoL and SF-36 outcomes. Given the limitations associated with such analyses, differences between treatment groups remain difficult to interpret.

- Subgroup analyses for prior TNF-alpha exposure and baseline CRP levels, identified a priori, were performed for the AS population. Results should be interpreted with caution as they are likely not adequately powered given the small sample sizes and were not adjusted for multiplicity.

### 3.5.2 External validity

#### a) Patient characteristics

- The results of AS-001 appear to be generalizable to Canadian AS patients as — according to the clinical expert involved in the review — patient characteristics were generally similar to what is seen in clinical practice.
- The inclusion and exclusion criteria appear to be reflective of Canadian AS patients.
- Outcomes were measured at 12, 24, and 48 weeks, which (according to the clinical expert involved in the review) is a sufficient amount of time to see a clinically meaningful difference. However, AS is a chronic disease, and it is expected that patients will be on treatment for many years. Although longer-term harms data were reported when patients had switched to the active drug after week 24, the controlled data that exist for CZP from only 24 weeks. Of the 24-week placebo-controlled data, only 12 to 16 weeks are not potentially affected by early escape.

## 3.5 Efficacy

Only those efficacy outcomes identified in the review protocol are reported hereafter (see Section 2.2, Table 3). *See* APPENDIX 4: DETAILED OUTCOME DATA *for detailed efficacy data at 48 weeks.*

### 3.5.1 Clinical response

#### a) ASAS 20

Results for the absolute difference in percentage of ASAS 20 responders for CZP 200 mg 2QW and CZP 400 mg 4QW compared with placebo at week 12 and 24 are presented in Figure 4. [redacted]

**FIGURE 4: ABSOLUTE DIFFERENCE (%) OF ASAS 20 RESPONDERS AT 12 AND 24 WEEKS IN AS-001 — ANKYLOSING SPONDYLITIS SUBPOPULATION (RANDOMIZED SET)**

***Figure 4 contained confidential information and has been removed at the request of the manufacturer.***

**b) ASAS 40**

Results for the absolute difference in percentage of ASAS 40 responders for CZP 200 mg 2QW and CZP 400 mg 4QW compared with placebo at weeks 12 and 24 are presented in Figure 5.

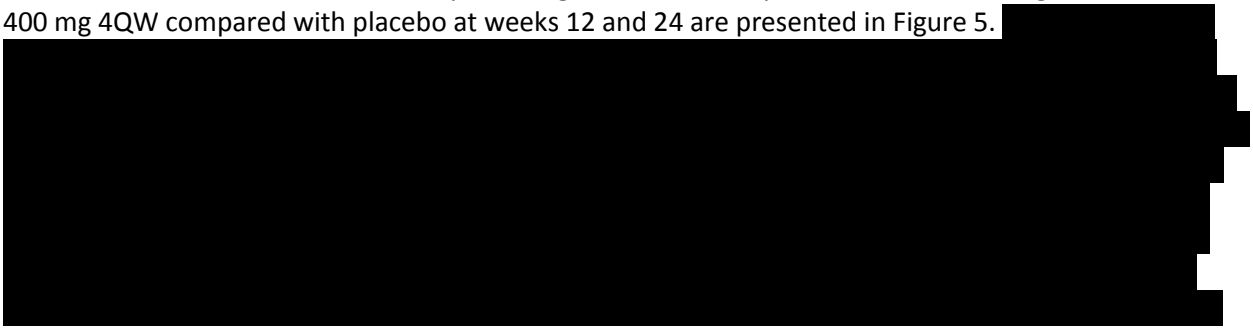


**FIGURE 5: ABSOLUTE DIFFERENCE (%) OF ASAS 40 RESPONDERS AT 12 AND 24 WEEKS IN AS-001 — ANKYLOSING SPONDILITIS SUBPOPULATION (RANDOMIZED SET)**

***Figure 5 contained confidential information has been removed at the request of the manufacturer.***

### 3.5.2 ASAS 5/6 response

Results for the absolute difference in percentage of patients with at least 20% improvement in five of six domains (ASAS 5/6) for CZP 200 mg 2QW and CZP 400 mg 4QW compared with placebo at weeks 12 and 24 are presented in Table 10.

### 3.5.3 ASAS Partial remission

Results for the absolute difference in percentage of ASAS partial remission responders for CZP 200 mg 2QW and CZP 400 mg 4QW compared with placebo at weeks 12 and 24 are presented in Table 10.

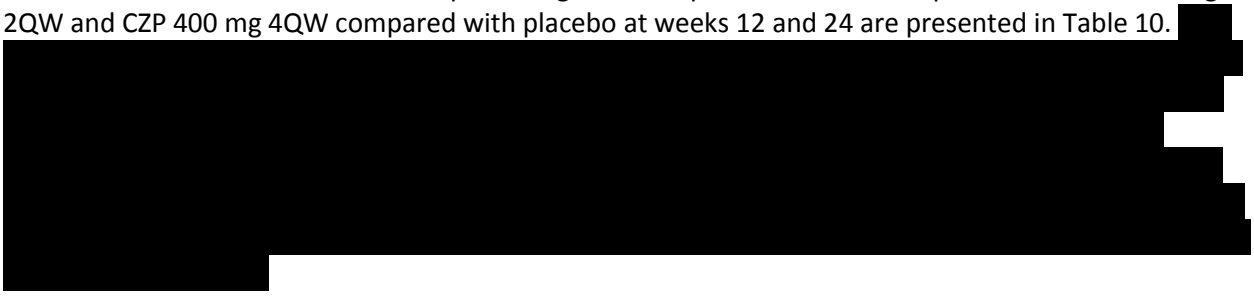


**TABLE 10: CLINICAL RESPONSE IN AS-001 – ANKYLOSING SPONDYLITIS SUBPOPULATION**

| AS-001 | | | |
|---|---|---|---|
| | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| **ASAS 20 at week 12** (RS with imputation[a]) | | | |
| Responders (%) | 56.9 | 64.3 | 36.8 |
| 95% CI | [redacted] | [redacted] | [redacted] |

| AS-001 | | | |
|---|---|---|---|
| | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| Difference to PL (%)[b] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **ASAS 20 at week 24** (RS with imputation[a]) | | | |
| Responders (%) | 67.7 | 69.6 | 33.3 |
| 95% CI | [redacted] | [redacted] | [redacted] |
| Difference to PL (%)[b] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **ASAS 40 at week 12** (FAS with imputation[a]) | | | |
| Responders (%) | 40.0 | 50.0 | 19.3 |
| 95% CI | [redacted] | [redacted] | [redacted] |
| Difference to PL (%)[b] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **ASAS 40 at week 24** (FAS with imputation[a]) | | | |
| Responders (%) | 47.7 | 58.9 | 15.8 |
| 95% CI | [redacted] | [redacted] | [redacted] |
| Difference to PL (%)[b] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **ASAS 5/6 at week 12** (FAS with imputation[a]) | | | |
| Responders (%) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| Difference to PL (%)[b] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **ASAS 5/6 at week 24** (FAS with imputation[a]) | | | |
| Responders (%) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| Difference to PL (%)[b] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **ASAS partial remission at week 12** (FAS with imputation[a]) | | | |
| Responders (%) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| Difference to PL (%)[b] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **ASAS partial remission at week 24** (FAS with imputation[a]) | | | |
| Responders (%) | [redacted] | [redacted] | [redacted] |

| AS-001 | | | |
|---|---|---|---|
| | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| 95% CI | [redacted] | [redacted] | [redacted] |
| Difference to PL (%)[b] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |

AS = ankylosing spondylitis; ASAS = Assessment in Axial SpondyloArthritis International Society; CI = confidence interval; CZP = certolizumab pegol; FAS = full analysis set;; n = number of patients with event; PL = placebo; Q2W = every two weeks; Q4W = every four weeks.

[a] Non-responder Imputation (NRI) was used: patients who withdrew for any reason or PL patients who used escape medication were considered non-responders from the time that they dropped out or when escape therapy was initiated. Patients who had missing data at a visit were counted as a non-responder for the respective visit.

[b] Treatment difference: CZP 200 mg minus PL, CZP 400 mg minus PL, and CZP 200 mg plus 400 mg minus PL (and corresponding 95% CI and *P* value) were estimated using a standard two-sided Wald asymptotic test with a five per cent alpha level.

### 3.5.4 Health-related quality of life

#### a) Ankylosing Spondylitis Quality of Life assessment

Results for the mean change from baseline in ASQoL at weeks 12 and 24 are presented in Table 11. [redacted]

#### b) Short-form 36-item health survey

Results for the mean change from baseline in SF-36 MCS, PCS and physical functioning at weeks 12 and 24 are presented in Table 11. [redacted]

#### c) EuroQol 5-Dimensions questionnaire

Results for the mean change from baseline in EQ-5D VAS and mobility, self-care, usual activities, pain/discomfort, and anxiety/depression domains at week 12 and week 24 are presented in Table 11

**TABLE 11: HEALTH-RELATED QUALITY OF LIFE IN AS-001 – ANKYLOSING SPONDYLITIS SUBPOPULATION (FULL ANALYSIS SET WITH IMPUTATION)[A]**

| | AS-001 | | |
|---|---|---|---|
| | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| **ASQoL at week 12** (FAS with imputation[c]) | | | |
| Mean at baseline | | | |
| Mean change from baseline (SD) | | | |
| **ASQoL at week 24** (FAS with imputation[c]) | | | |
| Mean at baseline | | | |
| Mean change from baseline (SD) | | | |
| **SF-36 MCS at week 12** (FAS with imputation[c]) | | | |
| Mean at baseline | | | |
| Mean change from baseline (SD) | | | |
| **SF-36 MCS at week 24** (FAS with imputation[c]) | | | |
| Mean at baseline | | | |
| Mean change from baseline (SD) | | | |
| **SF-36 PCS at week 12** (FAS with imputation[c]) | | | |
| Mean at baseline | | | |
| Mean change from baseline (SD) | | | |
| **SF-36 PCS at week 24** (FAS with imputation[c]) | | | |
| Mean at baseline | | | |
| Mean change from baseline (SD) | | | |
| **SF-36 Physical Functioning at week 12** (FAS with imputation[c]) | | | |
| Mean at baseline | | | |
| Mean change from baseline (SD) | | | |

| AS-001 | | | |
|---|---|---|---|
| | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| **SF-36 Physical Functioning at week 24** (FAS with imputation[c]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] | [redacted] |
| **EQ-5D VAS at week 12** (FAS with imputation[c]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] | [redacted] |
| **EQ-5D VAS at week 24** (FAS with imputation[c]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] | [redacted] |
| **EQ-5D Mobility domain baseline** (FAS with imputation[c]), N (%) | | | |
| No problem in walking about | [redacted] | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] | [redacted] |
| **EQ-5D Mobility domain at week 12** (FAS with imputation[c]), N (%) | | | |
| No problem in walking about | [redacted] | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] | [redacted] |
| **EQ-5D Mobility domain at week 24** (FAS with imputation[c]), N (%) | | | |
| No problem in walking about | [redacted] | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] | [redacted] |
| **EQ-5D Self-care domain baseline** (FAS with imputation[c]), N (%) | | | |
| No problem in walking about | [redacted] | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] | [redacted] |
| **EQ-5D Self-care domain at week 12** (FAS with imputation[c]), N (%) | | | |
| No problem in walking about | 44 (67.7) | 42 (75.0) | 25 (43.9) |
| Some problem in walking about | [redacted] | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] | [redacted] |
| **EQ-5D Self-care domain at week 24** (FAS with imputation[c]), N (%) | | | |
| No problem in walking about | [redacted] | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] | [redacted] |
| **EQ-5D Usual Activities domain baseline** (FAS with imputation[c]), N (%) | | | |
| No problem in walking about | [redacted] | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] | [redacted] |
| **EQ-5D Usual Activities domain at week 12** (FAS with imputation[c]), N (%) | | | |
| No problem in walking about | [redacted] | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] | [redacted] |
| **EQ-5D Usual Activities domain at week 24** (FAS with imputation[c]), N (%) | | | |
| No problem in walking about | [redacted] | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] | [redacted] |

| AS-001 | | | |
|---|---|---|---|
| | **CZP 200 mg** | **CZP 400 mg** | **PL** |
| **EQ-5D Pain/Discomfort domain baseline** (FAS with imputation[c]), N (%) | | | |
| No problem in walking about | [redacted] | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] | [redacted] |
| **EQ-5D Pain/Discomfort domain at week 12** (FAS with imputation[c]), N (%) | | | |
| No problem in walking about | [redacted] | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] | [redacted] |
| **EQ-5D Pain/Discomfort domain at week 24** (FAS with imputation[c]), N (%) | | | |
| No problem in walking about | [redacted] | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] | [redacted] |
| **EQ-5D Anxiety/Depression domain baseline** (FAS with imputation[c]), N (%) | | | |
| No problem in walking about | [redacted] | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] | [redacted] |
| **EQ-5D Anxiety/Depression domain at week 12** (FAS with imputation[c]), N (%) | | | |
| No problem in walking about | [redacted] | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] | [redacted] |
| **EQ-5D Anxiety/Depression domain at week 24** (FAS with imputation[c]), N (%) | | | |
| No problem in walking about | [redacted] | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] | [redacted] |

AS = ankylosing spondylitis; ASQoL = Ankylosing Spondylitis Quality of Life assessment; CZP = certolizumab pegol; EQ-5D = EuroQol 5-Dimensions Questionnaire; FAS = full analysis set; MCS = mental component summary; n = number of patients with event; N = number of patients; PCS = physical component summary; PL = placebo; Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation; SF-36 = Short-form 36-item Health Survey; VAS = visual analogue scale.
[a] Last observation carried forward (LOCF) was used: for patients who withdrew for any reason or patients with a missing week 12/24 measurement, last observation before the early withdrawal or week 12/24 was carried forward to week 12/24.

### 3.5.5 Disease activity

#### a) Bath Ankylosing Spondylitis Disease Activity Index

Results for the absolute difference in mean difference in BASDAI score for CZP 200 mg 2QW and CZP 400 mg 4QW compared with placebo at weeks 12 and 24 are presented in Table 12. [redacted]

#### b) Bath Ankylosing Spondylitis Functional Index

Results for the absolute difference in mean difference in BASFI score for CZP 200 mg 2QW and CZP 400 mg 4QW compared with placebo at weeks 12 and 24 are presented in Table 12. [redacted]

[redacted]

### c) Bath Ankylosing Spondylitis Metrology Index Linear

Results for the absolute difference in mean difference in BASMI linear score for CZP 200 mg 2QW and CZP 400 mg 4QW compared with placebo at weeks 12 and 24 are presented in Table 12. [redacted]

**TABLE 12: FUNCTIONAL AND DISABILITY OUTCOMES IN AS-001 – AS SUBPOPULATION**

| | AS-001 | | |
|---|---|---|---|
| | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| **BASDAI at week 12** (RS with imputation[a]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE)[b] | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE)[b] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASDAI at week 24** (RS with imputation[a]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE)[b] | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE)[b] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASFI at week 12** (RS with imputation[a]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE)[b] | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE)[b] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASFI at week 24** (RS with imputation[a]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE)[b] | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE)[b] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASMI linear at week 12** (RS with imputation[a]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE)[b] | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE)[b] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |

| AS-001 | | | |
|---|---|---|---|
| | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| **BASMI linear at week 24** (RS with imputation[a]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE)[b] | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE)[b] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |

AS = ankylosing spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; CI = confidence interval; CZP = certolizumab pegol; LS = least square; n = number of patients with event; PL = placebo; Q2W = every two weeks; Q4W = every four weeks; RS = randomized set; SE = standard error.

[a] Last observation carried forward (LOCF) was used: for patients who withdrew for any reason or patients with a missing week 12/24 measurement, last observation before the early withdrawal or week 12/24 was carried forward to week 12/24.

[b] Analysis of covariance (ANCOVA) model with treatment, region, and prior anti-TNF-alpha exposure (yes/no) as factors, and baseline score as a covariate.

[c] Based on the described hierarchical testing procedure in the statistical analysis plan, statistical significance at week 24 could not be assessed.

### 3.5.6 Work productivity

#### a) Work productivity survey

Results for work productivity scores for the individual questions (questions 2 to 9) at baseline, weeks 12 and 24 are presented in Table 13. [redacted]

[redacted]

**TABLE 13: WORK PRODUCTIVITY IN AS-001 — ANKYLOSING SPONDYLITIS SUBPOPULATION (FULL ANALYSIS SET WITH IMPUTATION[A])**

| AS-001 | | | |
|---|---|---|---|
| **Mean Score (SD)** | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| **Q2. Work days missed due to arthritis in the last month[b]** | | | |
| **Baseline** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |

| AS-001 | | | |
|---|---|---|---|
| **Mean Score (SD)** | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| N = | [redacted] | [redacted] | [redacted] |
| **Week 12** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Week 24** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Q3. Work days with productivity reduced by at least half due to arthritis in the last month[b]** | | | |
| **Baseline** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Week 12** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Week 24** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Q4. Level of arthritis interference on work productivity in the last month[b,c]** | | | |
| **Baseline** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Week 12** | | | |

| AS-001 | | | |
|---|---|---|---|
| **Mean Score (SD)** | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Week 24** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Q5. Household work days missed due to arthritis in the last month** | | | |
| **Baseline** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Week 12** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Week 24** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Q6. Household work days with productivity reduced by at least half due to arthritis in the last month** | | | |
| **Baseline** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Week 12** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |

| AS-001 | | | |
|---|---|---|---|
| **Mean Score (SD)** | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Week 24** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Q7. Days with family, social, or leisure activities days missed due to arthritis in the last month** | | | |
| **Baseline** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Week 12** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Week 24** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Q8. Outside help hired due to arthritis in the last month** | | | |
| **Baseline** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Week 12** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |

| AS-001 | | | |
|---|---|---|---|
| **Mean Score (SD)** | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| N = | [redacted] | [redacted] | [redacted] |
| **Week 24** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Q.9 Level of arthritis interference on household work productivity in the last month[c]** | | | |
| **Baseline** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Week 12** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |
| **Week 24** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N = | [redacted] | [redacted] | [redacted] |

AS = ankylosing spondylitis; CI = confidence interval; CZP = certolizumab pegol; FAS = full analysis set; n = number of patients with event; N = number of patients; PL = placebo; Q. = question; Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation.

[a] Last observation carried forward (LOCF) was used: for patients who withdrew for any reason, patients with a missing measurement, or placebo patients who used escape medication, last observation before the early withdrawal or the missing measurement or before receiving CZP was carried forward. For the entire placebo group, last observation before escape was carried forward for patients escaping to CZP.

[b] Relate to work outside the home and assessed only in patients employed outside the home.

[c] Score was based on a scale of 0 (no interference) to 10 (complete interference).

### 3.5.7 Radiographic changes

#### a) Modified Stokes Ankylosing Spondylitis Spine Score

Results for the mSASSS at week 12 can be found in Table 14. [redacted]

**TABLE 14: RADIOGRAPHIC CHANGES IN AS-001 — ANKYLOSING SPONDYLITIS SUBPOPULATION (MAGNETIC RESONANCE IMAGING SET)**

| AS-001 | | | |
|---|---|---|---|
| | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| **mSASSS at week 12** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] | [redacted] |

AS = ankylosing spondylitis; CZP = certolizumab pegol; n = number of patients with event; MRIS = magnetic resonance imaging set; mSASSS = modified Stokes Ankylosing Spondylitis Spine Score; PL = placebo; Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation.

### 3.5.8 Subgroup analyses

Subgroup analyses for prior TNF-alpha exposure and baseline CRP levels were performed for efficacy outcomes ASAS 20, BASDAI, BASFI and BASMI at weeks 12 and 24 and are presented in Table 22. No subgroup analyses for baseline body weight and erythrocyte sedimentation rate (ESR) levels were performed.

## 3.6 Harms

Only those harms identified in the review protocol are reported hereafter (see 2.2.1, Protocol). Safety results from week 48 and beyond included the originally randomized CZP patients and the CZP data from patients switching from placebo to CZP.

**Mortality**

No deaths occurred during the double-blind and dose-blind phases of the study.

### 3.6.1 Serious adverse events

[redacted]

### 3.6.2 Withdrawals due to adverse events

[redacted]

### 3.6.3 Adverse events

[redacted]

### 3.6.4 Notable harms

[redacted]

**TABLE 15: HARMS AT WEEK 24 (END OF DOUBLE-BLIND) IN AS-001 – ANKYLOSING SPONDYLITIS SUBPOPULATION (SAFETY SET)**

| | AS-001 | | |
|---|---|---|---|
| | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| **DEATHS** | [redacted] | [redacted] | [redacted] |
| **SAEs[a], N (%)** | [redacted] | [redacted] | [redacted] |
| **WDAEs, N (%)** | [redacted] | [redacted] | [redacted] |
| **Patients with > 0 AEs[a], N (%)** | [redacted] | [redacted] | [redacted] |
| **Notable harms** | | | |
| Spinal fractures | [redacted] | [redacted] | [redacted] |
| Serious infections | [redacted] | [redacted] | [redacted] |
| Heart failure (cardiac disorders) | [redacted] | [redacted] | [redacted] |
| Lupus | [redacted] | [redacted] | [redacted] |
| Injection reactions (rash) | [redacted] | [redacted] | [redacted] |

AE = adverse event; AS = ankylosing spondylitis; CZP = certilizumab pegol; n = number of patients with event; N = number of patients; NR = not reported; PL = placebo; Q2W = every two weeks; Q4W = every four weeks; SAEs = serious adverse events; WDAEs = withdrawals due to adverse events.

[a] Frequency greater than five patients.

# 4. DISCUSSION

## 4.1 Summary of available evidence

One published, manufacturer-sponsored, double-blind RCT was included in this systematic review: AS-001.[10] In AS-001, the AS subpopulation (N = 178) received active treatment with SC injections of CZP or placebo prefilled syringes. Patients receiving CZP treatment received an initial 400 mg loading dose at baseline, week 2 and week 4 followed by either CZP 200 mg every two weeks or, 400 mg every four weeks. [redacted]

## 4.2 Interpretation of results

### 4.2.1 Efficacy

[redacted] (APPENDIX 6: SUMMARY OF THE EXTENDED PHASE OF STUDY AS-001). [redacted]

[redacted] (APPENDIX 1: PATIENT INPUT SUMMARY). [redacted] The MCID for the SF-36 PCS and MCS has been reported to range between 2.5 and 5 points for the general population[29,30], [redacted]

[redacted]

[redacted]

[redacted]

The reported MCID for the BASDAI instrument is 10 mm on the VAS or a 22.5% improvement from the baseline score;[22-24] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] (APPENDIX 7: SUMMARY OF MANUFACTURER-SUBMITTED MIXED TREATMENT COMPARISON). [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

### 4.2.2 Harms

[redacted]

[redacted] (APPENDIX 7: SUMMARY OF MANUFACTURER-SUBMITTED MIXED TREATMENT COMPARISON).

# 5. CONCLUSIONS

Based on one double-blind RCT in patients with active AS, treatment with CZP either 200 mg Q2W or 400 mg Q4W resulted in statistically significant and clinically meaningful improvements in clinical response (ASAS 20, ASAS 40), disease activity (BASDAI), and function (BASFI) at week 12 and week 24 when compared with placebo. A non-statistically significant improvement in disability (BASMI linear) was seen at week 12 among both CZP treatment groups compared with placebo; however, because of the hierarchical step-down analysis procedure, statistical significance at week 24 could not be assessed. Statistically significant improvements in work productivity were also demonstrated, though the clinical meaningfulness of these results remains uncertain. Without between-group comparisons, there is uncertainty regarding differences in HRQoL and radiographic change between CZP treatment groups and placebo. Subgroup analyses for prior TNF-alpha exposure and baseline CRP levels did not provide any meaningful conclusions. Overall, the incidence of TEAEs was similar to placebo with both CZP groups, although the study was not designed to identify between-group differences in safety. Moreover, AS is a chronic condition that will be treated over a lifetime, and therefore a 24-week controlled trial is a short duration to evaluate harms.

The early escape study design, though typically used in recent AS studies for ethical reasons, potentially weakens the internal validity of results observed at week 24. In particular, because early escape criteria only applied to placebo patients and use of NRI for assessments at week 24, results for the patient-reported outcomes at week 24 are potentially biased in favour of the CZP treatment groups and should be interpreted with caution.

# APPENDIX 1: PATIENT INPUT SUMMARY

### 1. Brief description of patient group(s) supplying input

The Canadian Spondylitis Association (CSA) is a volunteer-run patient support and advocacy association for those living with spondyloarthritis (SpA) (including ankylosing spondylitis [AS] and psoriatic arthritis [PsA]). The majority of members have AS, but some may have other forms of SpA or are family members. The CSA receives funding from AbbVie (unrestricted and restricted grants), Janssen (restricted educational grants), and UCB (restricted travel grants). The CSA declared no conflicts of interest in compiling their submission.

The Canadian Arthritis Patient Alliance (CAPA) is national education and advocacy organization that aims to improve the quality of life of individuals with arthritis. Sources of grants and support received by CAPA in the last year include: AbbVie, Amgen Canada, Arthritis Alliance of Canada, The Arthritis Society, Canadian Rheumatology Association, Janssen, Novartis, Ontario Rheumatology Association, and UCB Pharma. Additionally, CAPA has also received grants and donations in the past from: Canadian Institutes for Health Research (CIHR), Hoffmann-La Roche, Pfizer Canada, Rx&D, Schering Canada, Scleroderma Society, and STA Communications. The Canadian Arthritis Patient Alliance declared no conflicts on interest in compiling their submission.

The Arthritis Consumer Experts (ACE) is a national organization working to educate and empower individuals with arthritis to take control of their disease and improve their quality of life; to make evidence-based information more accessible to and interpretable by the general public, government, and media; and to train individuals with arthritis to be able to contribute meaningfully to research initiatives and governmental decision-making. The Arthritis Consumer Experts receives unrestricted grants-in-aid from public and private sector organizations including AbbVie, Amgen, Arthritis Research Centre of Canada, BIOTECanada, Bristol-Myers Squibb, Canadian Rheumatology Research Consortium, Canadian Institutes of Health Research, Celgene, GlaxoSmithKline, Hoffmann-La Roche, Janssen, Pfizer Canada, Purdue Pharma, Takeda, the University of British Columbia, as well as unsolicited funding from individual donors. The Arthritis Consumer Experts declared no conflicts of interest in compiling their submission.

### 2. Condition and current therapy-related information

Information was gathered through interactions with the memberships (patient forums, newsletters, website, Facebook page), from personal experience of members living with AS and through telephone or email correspondence.

The onset of AS is early in life, in the teenage years or early 20s, and there is no cure. Different levels of severity exists, but the symptoms are pain in the sacroiliac joints, the hips, the lower back spreading up to the neck; morning stiffness; fatigue; and depression. Progression of the disease causes fusion in the vertebra and spinal deformity that limit movements and activities. A patient reported that “she has difficulty looking up or down, left or right, without turning her whole body or leaning at precarious and slightly odd angles.” Other joints such as knees, ankles and wrists can become involved as well as the eye (iritis, uveitis). The chronic pain, fatigue, and depression associated with AS reduce the quality of life for patients. Normal activities become limited, while working, studying, or practising impact sports become difficult or impossible. Activities to be done in one day may have to be planned ahead. It is devastating for young people to be diagnosed with AS, as they end up losing the capacity to receive an education and to do extra-curricular activities that are critical for their development. Patients also suffer

because of the lack of understanding of AS. Ankylosing spondylitis can result in long-term disability and is a major burden to the health care system.

Therapies include nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, disease-modifying antirheumatic drugs (DMARDs), biologics, and exercise. Nonsteroidal anti-inflammatory drugs combined with exercise are effective for milder disease. DMARDs are effective only for peripheral disease and are not effective for all patients. Biologics, often used after failure of conventional therapies, have proved to be effective in many cases of severe AS. However, they are not always effective and every patient's response is different. Also, the efficacy of the biologics may wear off. A switch to another biologic is then needed. The choice of biologics effective for AS is limited, and they are costly. Some contraindications, like infections, may also limit their use. Since refractive AS is debilitating and has a disastrous effect on a patient's life, patients feel they need as many options as possible. Patients note early treatment with controlled inflammation is associated with better outcomes and are, thus, concerned with the long time to get a diagnosis. Sometimes, biologics are not prescribed until radiographic evidence of AS, which may be many years after onset. Patients feel that axial SpA (axSpA) should be considered a precursor to AS and should be treated with biologics from the time of diagnosis so patients can continue to be productive members of society.

Ankylosing spondylitis is insidious, and caregivers may find it difficult to understand — especially before diagnosis—what is happening when faced with someone who looks healthy but has unexplained health issues, who can be normal and active one day, and sleep all day the next. The disabling nature of the disease causes a physical and mental burden on parents and caregivers.

**3. Related information about the drug being reviewed**

None of the submissions included patients with AS who had been treated with certolizumab pegol (CZP). Patients see biologics as effective therapies and as drugs that increase patient productivity. Patients hope that CZP will lessen their pain, improve their functionality, and provide a therapeutic option, although some expressed concern about needing to see a rheumatologist to receive the drug as they thought it needed to be administered intravenously. Patients are willing to trade side effects from biologics for a better quality of life. They believe they should have access to all treatment options that have been demonstrated to be safe and effective as patients' responses to drugs are different. Patients noted that the preferred treatment is one that is covered by insurance plans, has fewer adverse effects, eliminates pain, is easy to self-administer, and is non-invasive.

# APPENDIX 2: LITERATURE SEARCH STRATEGY

*This section was summarized by CADTH staff based on the input provided by patient groups.*

| **OVERVIEW** | |
|---|---|
| Interface: | Ovid |
| Databases: | Embase 1974 to present<br>MEDLINE Daily and MEDLINE 1946 to present<br>MEDLINE In-Process & Other Non-Indexed Citations<br>**Note:** Patient headings have been customized for each database. Duplicates between databases were removed in Ovid. |
| Date of Search: | October 30, 2014 |
| Alerts: | Biweekly (twice monthly) search updates until March 18, 2015. |
| Study Types: | No search filters were applied |
| Limits: | No date or language limits were used<br>Human filter was applied<br>Conference abstracts were excluded |
| **SYNTAX GUIDE** | |
| / | At the end of a phrase, searches the phrase as a patient heading |
| .sh | At the end of a phrase, searches the phrase as a patient heading |
| MeSH | Medical Patient Heading |
| fs | Floating subheading |
| exp | Explode a patient heading |
| * | Before a word, indicates that the marked patient heading is a primary topic;<br>or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings |
| # | Truncation symbol for one character |
| ? | Truncation symbol for one or no characters only |
| adj | Requires words are adjacent to each other (in any order) |
| adj# | Adjacency within # number of words (in any order) |
| .ti | Title |
| .ab | Abstract |
| .ot | Original title |
| .hw | Heading word; usually includes patient headings and controlled vocabulary |
| .pt | Publication type |
| .po | Population group [PsycInfo only] |
| .rn | CAS registry number |
| .nm | Name of substance word |
| pmez | Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present |
| oemezd | Ovid database code; Embase 1974 to present, updated daily |

| MULTI-DATABASE STRATEGY | |
|---|---|
| **#** | **Searches** |
| | **MEDLINE search** |
| 1 | (Cimzia* or certolizumab* or CDP870 or CDP-870 or PHA-738144 or PHA738144).ti,ab,ot,sh,rn,hw,nm. |
| 2 | (428863-50-7 or UMD07X179E).rn,nm. |
| 3 | 1 or 2 |
| 4 | 3 use pmez |
| | **Embase search** |
| 5 | *certolizumab pegol/ |
| 6 | (Cimzia* or certolizumab* or CDP870 or CDP-870 or PHA-738144 or PHA738144).ti,ab. |
| 7 | 5 or 6 |
| 8 | 7 use oemezd |
| 9 | 8 not conference abstract.pt. |
| | **Combine MEDLINE and Embase searches** |
| 10 | 4 or 9 |
| | **Combine with ankylosing spondylitis search terms** |
| 11 | Spondylitis, Ankylosing/ |
| 12 | *ankylosing spondylitis/ |
| 13 | (ankylo* adj3 spondyl*).ti,ab. |
| 14 | rheumatoid spondylitis.ti,ab. |
| 15 | ((Bechterew* or Marie-Strumpell*) adj (disease or syndrome)).ti,ab. |
| 16 | (axial spondyloarthr* or axial SpA or axSpA).ti,ab. |
| 17 | or/11-16 |
| 18 | 10 and 17 |
| | **Remove non-human studies and duplicates** |
| 19 | exp animals/ |
| 20 | exp animal experimentation/ or exp animal experiment/ |
| 21 | exp models animal/ |
| 22 | nonhuman/ |
| 23 | exp vertebrate/ or exp vertebrates/ |
| 24 | animal.po. |
| 25 | or/19-24 |
| 26 | exp humans/ |
| 27 | exp human experimentation/ or exp human experiment/ |
| 28 | human.po. |
| 29 | or/26-28 |
| 30 | 25 not 29 |
| 31 | 18 not 30 |
| 32 | remove duplicates from 31 |

# APPENDIX 3: EXCLUDED STUDIES

There were no excluded studies.

# APPENDIX 4: DETAILED OUTCOME DATA

**TABLE 16: EXTENT OF EXPOSURE AT 48 WEEKS (END OF DOSE-BLIND) IN AS-001 – ANKYLOSING SPONDYLITIS SUBPOPULATION (SAFETY SET)**

| AS-001 | | |
|---|---|---|
| | **CZP 200 mg Q2W (n = 91)** | **CZP 400 mg Q4W (n = 83)** |
| **Number of doses received**[a] | | |
| Mean (SD) | [redacted] | [redacted] |
| Median | [redacted] | [redacted] |
| Min, max | [redacted] | [redacted] |
| **Duration of exposure in narrow sense**[b] **(weeks)** | | |
| Mean (SD) | [redacted] | [redacted] |
| Median | [redacted] | [redacted] |
| Min, max | [redacted] | [redacted] |
| **Duration of exposure in broader sense**[c] **(weeks)** | | |
| Mean (SD) | [redacted] | [redacted] |
| Median | [redacted] | [redacted] |
| Min, max | [redacted] | [redacted] |

AS = ankylosing spondylitis; CZP = certolizumab pegol; max = maximum; min = minimum; n = number of patients with event; Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation.

**TABLE 17: CONCOMITANT MEDICATION USE IN DOSE-BLIND PERIOD (WEEK 48)**

| AS-001 | | |
|---|---|---|
| **N (%)** | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** |
| **NSAID** | [redacted] | [redacted] |
| **Analgesics** | [redacted] | [redacted] |
| **Corticosteriod for systemic use, plain** | [redacted] | [redacted] |
| **DMARDs** | [redacted] | [redacted] |
| sulfasalazine | [redacted] | [redacted] |
| hydroxychloroquine | [redacted] | [redacted] |

n = number of patients with event; N = number of patients; NSAID = nonsteroidal anti-inflammatory drug; Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation.

### TABLE 18: CLINICAL RESPONSE FOR PATIENTS ESCAPING IN PLACEBO GROUP IN AS-001 – ANKYLOSING SPONDYLITIS SUBPOPULATION

| | AS-001 | | |
|---|---|---|---|
| | **PL Escape to CZP 200 mg Q2W (n = 16)** | **PL Escape to CZP 400 mg Q4W (n = 14)** | **PL Non-escape (n = 27)** |
| **ASAS 20 at week 24** (FAS) | | | |
| Responders (%) | [redacted] | [redacted] | [redacted] |
| **ASAS 40 at week 24** (FAS) | | | |
| Responders (%) | [redacted] | [redacted] | [redacted] |

AS = ankylosing spondylitis; ASAS = Assessment in Ankylosing Spondylitis; CZP = certolizumab pegol; FAS = full analysis set; n = number of patients with event; PL = placebo; Q2W = every two weeks; Q4W = every four weeks.

### TABLE 19: EFFICACY RESULTS AT END OF DOSE-BLIND PHASE (WEEK 48) IN AS-001 – ANKYLOSING SPONDYLITIS SUBPOPULATION

| | AS-001 | |
|---|---|---|
| | **CZP 200 mg Q2W (n = 91)** | **CZP 400 mg Q4W (n = 83)** |
| **ASAS 20 at week 48** (FAS with imputation[a]) | | |
| Responders (%) | [redacted] | [redacted] |
| **ASAS 40 at week 48** (FAS with imputation[a]) | | |
| Responders (%) | [redacted] | [redacted] |
| **ASAS 5/6 at week 48** (FAS with imputation[a]) | | |
| Responders (%) | [redacted] | [redacted] |
| **ASAS partial remission at week 48** (FAS with imputation[a]) | | |
| Responders (%) | [redacted] | [redacted] |
| **BASDAI at week 48** (FAS with imputation[b]) | | |
| Mean at baseline | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] |
| **BASFI at week 48** (FAS with imputation[b]) | | |
| Mean at baseline | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] |
| **BASMI linear at week 48** (FAS with imputation[b]) | | |
| Mean at baseline | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] |

AS = ankylosing spondylitis; ASAS = Assessment in Ankylosing Spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; CZP = certolizumab pegol; FAS = full analysis set; n = number of patients with event; PL = placebo; Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation.

[a] Non-responder imputation (NRI) was used: patients who withdrew for any reason or PL patients who used escape medication were considered non-responders from the time that they dropped out or when escape therapy was initiated. Patients who had missing data at a visit were counted as a non-responder for the respective visit.

[b] Last observation carried forward (LOCF) was used: for patients who withdrew for any reason, or patients with a missing measurement, last observation before the early withdrawal or the missing measurement was carried forward.

**TABLE 20: EFFICACY RESULTS AT END OF DOSE-BLIND PHASE (WEEK 48) IN AS-001 – ANKYLOSING SPONDYLITIS SUBPOPULATION (ORIGINAL CERTOLIZUMAB PEGOL GROUPS AT BASELINE)**

| | AS-001 | |
|---|---|---|
| | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** |
| **ASAS 20 at week 48** (FAS with imputation) | | |
| Responders (%) | [redacted] | [redacted] |
| **ASAS 40 at week 48** (FAS with imputation) | | |
| Responders (%) | [redacted] | [redacted] |
| **ASAS 5/6 at week 48** (FAS with imputation) | | |
| Responders (%) | [redacted] | [redacted] |
| **ASAS partial remission at week 48** (FAS with imputation) | | |
| Responders (%) | [redacted] | [redacted] |
| **ASQoL at week 48** | | |
| Mean at baseline | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] |
| **SF-36 MCS at week 48** | | |
| Mean at baseline | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] |
| **SF-36 PCS at week 48** | | |
| Mean at baseline | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] |
| **SF-36 Physical Functioning at week 48** | | |
| Mean at baseline | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] |
| **EQ-5D Mobility domain Baseline** (FAS with imputation), N (%) | | |
| No problem in walking about | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] |
| **EQ-5D Mobility domain at week 48** (FAS with imputation), N (%) | | |
| No problem in walking about | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] |
| **EQ-5D Self-Care domain baseline** (FAS with imputation), N (%) | | |
| No problem in walking about | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] |
| **EQ-5D Self-Care domain at week 48** (FAS with imputation), N (%) | | |
| No problem in walking about | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] |
| **EQ-5D Usual Activities domain baseline** (FAS with imputation), N (%) | | |
| No problem in walking about | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] |

| | AS-001 | |
|---|---|---|
| | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** |
| Confined to bed | [redacted] | [redacted] |
| **EQ-5D Usual Activities domain at week 48** (FAS with imputation), N (%) | | |
| No problem in walking about | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] |
| **EQ-5D Pain/Discomfort domain baseline** (FAS with imputation), N (%) | | |
| No problem in walking about | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] |
| **EQ-5D Pain/Discomfort domain at week** 48 (FAS with imputation), N (%) | | |
| No problem in walking about | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] |
| **EQ-5D Anxiety/Depression domain Baseline** (FAS with imputation), N (%) | | |
| No problem in walking about | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] |
| **EQ-5D Anxiety/Depression domain at week 48** (FAS with imputation), N (%) | | |
| No problem in walking about | [redacted] | [redacted] |
| Some problem in walking about | [redacted] | [redacted] |
| Confined to bed | [redacted] | [redacted] |
| **BASDAI at week 48** | | |
| Mean at baseline | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] |
| **BASFI at week 48** | | |
| Mean at baseline | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] |
| **BASMI linear at week 48** | | |
| Mean at baseline | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] |

AS = ankylosing spondylitis; ASAS = Assessment in Ankylosing Spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; CZP = certolizumab pegol; EQ=5D = EuroQol 5-Dimensions Questionnaire; FAS = full analysis set; MCS = mental component summary; n = number of patients with event; N = number of patients; PCS = physical component summary; Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation; SF-36 = Short-form 36-item Health Survey.

**TABLE 21: WORK PRODUCTIVITY IN AS-001 — ANKYLOSING SPONDYLITIS SUBPOPULATION (FULL ANALYSIS SET WITH IMPUTATION[A]) AT END OF DOSE-BLIND PHASE**

| AS-001 | | | |
|---|---|---|---|
| **Mean Score (SD)** | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| **Q2. Work days missed due to arthritis in the last month[b]** | | | |
| **Baseline** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| **week 48** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | |
| N | [redacted] | [redacted] | [redacted] |
| **Q3. Work days with productivity reduced by at least half due to arthritis in the last month[b]** | | | |
| **Baseline** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| **week 48** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N | [redacted] | [redacted] | [redacted] |
| **Q4. Level of arthritis interference on work productivity in the last month[b,c]** | | | |
| **Baseline** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| **week 48** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N | [redacted] | [redacted] | [redacted] |
| **Q5. Household work days missed due to arthritis in the last month** | | | |
| **Baseline** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| **week 48** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |

| AS-001 | | | |
|---|---|---|---|
| **Mean Score (SD)** | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N | [redacted] | [redacted] | [redacted] |
| **Q6. Household work days with productivity reduced by at least half due to arthritis in the last month** | | | |
| **Baseline** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| **week 48** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N | [redacted] | [redacted] | [redacted] |
| **Q7. Days with family, social, or leisure activities days missed due to arthritis in the last month** | | | |
| **Baseline** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| **week 48** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N | [redacted] | [redacted] | [redacted] |
| **Q8. Outside help hired due to arthritis in the last month** | | | |
| **Baseline** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| **week 48** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N | [redacted] | [redacted] | [redacted] |
| **Q.9 Level of arthritis interference on household work productivity in the last month[c]** | | | |
| **Baseline** | | | |
| Mean | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] |
| **week 48** | | | |
| Mean | [redacted] | [redacted] | [redacted] |

| AS-001 | | | |
|---|---|---|---|
| **Mean Score (SD)** | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| Median | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (95% CI) | [redacted] | [redacted] | [redacted] |
| N | [redacted] | [redacted] | [redacted] |

AS = ankylosing spondylitis; CI = confidence interval; CZP = certolizumab pegol; FAS = full analysis set; n = number of patients with event; N = number of patients; PL = placebo; Q. = question; Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation.

[a] Last observation carried forward (LOCF) was used: for patients who withdrew for any reason, patients with a missing measurement, or placebo patients who used escape medication, last observation before the early withdrawal or the missing measurement or before receiving CZP was carried forward. For the entire placebo group, last observation before escape was carried forward for patients escaping to CZP.

[b] Relate to work outside the home and assessed only in patients employed outside the home.

[c] Score was based on a scale of 0 (no interference) to 10 (complete interference).

### TABLE 22: SUBGROUP ANALYSES IN AS-001 – ANKYLOSING SPONDYLITIS SUBPOPULATION (RANDOMIZED SET WITH IMPUTATION)

| AS-001 | | | |
|---|---|---|---|
| **Prior TNF-antagonist Exposure – Yes** | | | |
| | **CZP 200 mg Q2W (n = 11)** | **CZP 400 mg Q4W (n = 9)** | **PL (n = 16)** |
| **ASAS 20 at week 12** | | | |
| Responders (%) | [redacted] | [redacted] | [redacted] |
| Difference to PL (%) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **ASAS 20 at week 24** | | | |
| Responders (%) | [redacted] | [redacted] | [redacted] |
| Difference to PL (%) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASDAI at week 12** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASDAI at week 24** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |

| AS-001 | | | |
|---|---|---|---|
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASFI at week 12** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASFI at week 24** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASMI linear at week 12** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASMI linear at week 24** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **Prior TNF-antagonist Exposure – No** | | | |
| | **CZP 200 mg Q2W (n = 54)** | **CZP 400 mg Q4W (n = 47)** | **PL (n = 41)** |
| **ASAS 20 at week 12** | | | |
| Responders (%) | [redacted] | [redacted] | [redacted] |
| Difference to PL (%)[a] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **ASAS 20 at week 24** | | | |
| Responders (%) | [redacted] | [redacted] | [redacted] |
| Difference to PL (%) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASDAI at week 12** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |

| AS-001 | | | |
|---|---|---|---|
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASDAI at week 24** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASFI at week 12** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASFI at week 24** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASMI linear at week 12** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASMI linear at week 24** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **Baseline CRP Level – (≤ 15 mg/L)** | | | |
| | **CZP 200 mg Q2W (n = 38)** | **CZP 400 mg Q4W (n = 34)** | **PL (n = 26)** |
| **ASAS 20 at week 12** | | | |
| Responders (%) | [redacted] | [redacted] | [redacted] |
| Difference to PL (%)[a] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |

| AS-001 | | | |
|---|---|---|---|
| **ASAS 20 at week 24** | | | |
| Responders (%) | [redacted] | [redacted] | [redacted] |
| Difference to PL (%) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASDAI at week 12** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASDAI at week 24** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASFI at week 12** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASFI at week 24** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASMI linear at week 12** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASMI linear at week 24** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |

| AS-001 | | | |
|---|---|---|---|
| **Baseline CRP level – > 15 mg/L** | | | |
| | **CZP 200 mg Q2W (n = 27)** | **CZP 400 mg Q4W (n = 22)** | **PL (n = 31)** |
| **ASAS 20 at week 12** | | | |
| Responders (%) | [redacted] | [redacted] | [redacted] |
| Difference to PL (%)[a] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **ASAS 20 at week 24** | | | |
| Responders (%) | [redacted] | [redacted] | [redacted] |
| Difference to PL (%) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASDAI at week 12** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASDAI at week 24** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASFI at week 12** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASFI at week 24** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **BASMI linear at week 12** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |

| AS-001 | | | |
|---|---|---|---|
| **BASMI linear at week 24** | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| LS mean change from baseline (SE) | [redacted] | [redacted] | [redacted] |
| LS mean difference to PL (SE) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |

AS = ankylosing spondylitis; ASAS = Assessment in Ankylosing Spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; CI = confidence interval; CRP = C-reactive protein; CZP = certolizumab pegol; n = number of patients with event; *P* = probability; PL = placebo; Q2W = every two weeks; Q4W = every four weeks; SE = standard error; TNF = tumour necrosis factor.
Note: Baseline values are based on entire AS population and not subgroups.

### TABLE 23: OTHER ASSESSMENT IN ANKYLOSING SPONDYLITIS COMPONENTS: PATIENT GLOBAL ASSESSMENT AND SPINAL PAIN IN AS-001 DOUBLE-BLIND PHASE – ANKYLOSING SPONDYLITIS SUBPOPULATION

| AS-001 | | | |
|---|---|---|---|
| | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** | **PL (n = 57)** |
| **Patient global assessment week 12** (FAS with imputation[a]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| Mean change from baseline (SD)[b] | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (SD)[b] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **Patient global assessment at week 24** (FAS with imputation[a]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| Mean change from baseline (SD)[b] | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (SD)[b] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **Total spinal pain at week 12** (FAS with imputation[a]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| Mean change from baseline (SD)[b] | [redacted] | [redacted] | [redacted] |
| Mean difference to PL (SD)[b] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **Total spinal pain at week 24** (FAS with imputation[a]) | | | |
| Mean at baseline | [redacted] | [redacted] | [redacted] |
| Mean change from baseline (SD)[b] | [redacted] | [redacted] | [redacted] |

| AS-001 | | | |
|---|---|---|---|
| Mean difference to PL (SD)[b] | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |

AS = ankylosing spondylitis; CI = confidence interval; CZP = certolizumab pegol; FAS = full analysis set; n = number of patients with event; *P* = probability; PL = placebo; Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation.
[a] Last observation carried forward (LOCF) was used: for patients randomized to placebo, the last response while on placebo was carried forward. For patients randomized to CZP 200 mg or CZP 400 mg, the response at previous time measurement (or last observation after previous time measurement carried forward) was used.
[b] Treatment difference: CZP 200 mg minus PL, CZP 400 mg minus PL, and CZP 200 mg plus 400 mg minus PL (and corresponding 95% CI and *P* value) were estimated using a standard two-sided Wald asymptotic test with a five per cent alpha level.

### TABLE 24: OTHER ASSESSMENT IN ASSESSMENT IN ANKYLOSING SPONDYLITIS COMPONENTS: PATIENT GLOBAL ASSESSMENT AND SPINAL PAIN IN AS-001 DOSE-BLIND PHASE – ANKYLOSING SPONDYLITIS SUBPOPULATION

| AS-001 | | |
|---|---|---|
| | **CZP 200 mg Q2W (n = 65)** | **CZP 400 mg Q4W (n = 56)** |
| **Patient global assessment at week 48** | | |
| Mean at baseline | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] |
| **Total spinal pain at week 48** | | |
| Mean at baseline | [redacted] | [redacted] |
| Mean change from baseline (SD) | [redacted] | [redacted] |

AS = ankylosing spondylitis; CZP = certolizumab pegol; n = number of patients with event; Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation.

### TABLE 25: HARMS AT WEEK 48 (END OF DOSE-BLIND) IN AS-001 – ANKYLOSING SPONDYLITIS SUBPOPULATION (SAFETY SET)

| AS-001 | | |
|---|---|---|
| | **CZP 200 mg Q2W (n = 91)** | **CZP 400 mg Q4W (n = 83)** |
| **DEATHS** | [redacted] | [redacted] |
| **SAEs, N (%)** | [redacted] | [redacted] |
| Infections and infestations | [redacted] | [redacted] |
| **WDAEs, N (%)** | [redacted] | [redacted] |
| Mycobacteria identification and serology | [redacted] | [redacted] |
| **AEs[a], N (%)** | [redacted] | [redacted] |
| Infections and infestations | [redacted] | [redacted] |
| Gastrointestinal disorders | [redacted] | [redacted] |
| Investigations | [redacted] | [redacted] |

AEs = adverse events; AS = ankylosing spondylitis; CZP = certolizumab pegol; n = number of patients with event; N = number of patients; Q2W = every two weeks; Q4W = every four weeks; WDAEs = withdrawals due to adverse events.
[a] Frequency greater than five per cent of patients.

**TABLE 26: SENSITIVITY ANALYSES FOR POTENTIALLY UNBLINDED AND PATIENTS TAKING PROHIBITED CONCOMITANT MEDICATION INTAKE IN ANKYLOSING SPONDYLITIS SUBPOPULATION**

| AS-001 | | | |
|---|---|---|---|
| **Excluding Patients Who May Have Been Potentially Unblinded** | | | |
| | **CZP 200 mg Q2W (n = 48)** | **CZP 400 mg Q4W (n = 43)** | **PL (n = 18)** |
| **ASAS 20 at week 12** | | | |
| Responders (%) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| Difference to PL (%) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |
| **Excluding Patients Taking Prohibited Concomitant Medication Intake** | | | |
| | **CZP 200mg Q2W (n = 65)** | **CZP 400mg Q4W (n =56)** | **PL (n = 57)** |
| **ASAS 20 at week 12** | | | |
| Responders (%) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| Difference to PL (%) | [redacted] | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] | [redacted] |
| *P* value | [redacted] | [redacted] | [redacted] |

AS = ankylosing spondylitis; ASAS = Assessment in Axial SpondyloArthritis International Society; CI = confidence interval; CZP = certolizumab pegol; n = number of patients with event; *P* = probability; PL = placebo; Q2W = every two weeks; Q4W = every four weeks.

# APPENDIX 5: VALIDITY OF OUTCOME MEASURES

### Aim

To summarize the validity of the following outcome measures:

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- Bath Ankylosing Spondylitis Functional Index (BASFI)
- Bath Ankylosing Spondylitis Metrology Index (BASMI)
- Assessment in Ankylosing Spondylitis (ASAS) improvement criteria (including ASAS 20, ASAS 40, and ASAS 5/6)
- Ankylosing Spondylitis Quality of Life assessment (ASQoL)
- Short-form 36-item Health Survey (SF-36)
- EuroQol 5-Dimensions Questionnaire (EQ-5D)
- Modified Stokes Ankylosing Spondylitis Spine Score (mSASSS)
- Rheumatoid Arthritis-specific Work Productivity Survey (WPS-RA)

### Findings

| Instrument | Type | Evidence of Validity | MCID | References |
|---|---|---|---|---|
| BASDAI | Self-administered 6-question instrument addressing fatigue, spinal, and peripheral joint pain, localized tenderness and morning stiffness on 10 cm VAS | Yes | 10 mm to 20 mm on VAS or 22.5% of the baseline score | [22-24] |
| BASFI | Self-administered 8-question instrument addressing physical function and patient's ability to cope with everyday life on 10 cm VAS | Yes | 7 mm on VAS or 17.5% of the baseline score | [24,26] |
| BASMI | Composite instrument including five clinical measurements: tragus-to-wall distance, modified Schober's lumbar forward flexion, cervical rotation, lumbar side flexion, intermalleolar distance | Yes | Unknown | [31] |
| ASAS improvement criteria | 4-domain instrument: measures of physical function (BASFI), pain, PtGADA, spinal stiffness/inflammation (2 questions from BASDAI) | Yes | Unknown | [15,25,32] |
| ASQoL | 18-item disease-specific QoL questionnaire including items related to the impact of disease on sleep, mood, motivation, coping, activities of daily living, independence, relationships, and social life. | Yes | Unknown | [17] |

| Instrument | Type | Evidence of Validity | MCID | References |
|---|---|---|---|---|
| SF-36 | Generic QoL instrument with 36 items assessing 8 domains: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations | Yes | 2.5 to 5.0 in the PCS and MCS; 5 to 10 points in the domain scores | [29,30] |
| EQ-5D | Generic QoL instrument consisting of 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a VAS for rating health today; weighted scoring produces an EQ-5D index score | No | Unknown | [20,21] |
| mSASSS | Score obtained by assessing anterior sites of the lumbar (L1 to L5) and cervical spine (C2 to T1) on a lateral view; each site gets a score from 0 (normal) to 3 (bridging syndesmophytes), which gives a total score range of 0 to 72 | Yes | Unknown | [33] |
| WPS-RA | 9 self-reported questions addressing 8 items including employment status, productivity within and outside the home, and daily activities | No | Unknown | [34] |

ASAS = Assessment in Ankylosing Spondylitis – Response Criteria; ASQoL = Ankylosing Spondylitis Quality of Life; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; EQ-5D = EuroQol 5-Dimensions Questionnaire; MCID = minimal clinically important difference; MCS = mental component score; mSASSS = modified Stoke Ankylosing Spondylitis Spinal Score; PCS = Physiological Component Score; QoL = quality of life; SF-36 = Short-form-36-item Health Survey; VAS = visual analogue scale; WPS-RA = Rheumatoid Arthritis-specific Work Productivity Survey.

**Assessment tools for disease activity**

**Bath Ankylosing Spondylitis Disease Activity Index**

The most common and widely used validated measure of inflammatory activity of ankylosing spondylitis (AS) is the BASDAI.[22] This instrument for disease activity is a self-administered patient questionnaire. The BASDAI is a composite index that records patients' responses to major symptoms of AS. It was designed by a multidisciplinary team (rheumatologists, physiotherapists, and research associates) with input from patients. It includes six questions addressing five major symptoms: fatigue, axial (spinal) and peripheral joint pain, localized tenderness, and morning stiffness (both degree of stiffness and length of time that stiffness persists).[23] Patients' responses are recorded on a 10-unit horizontal numerical rating scale (NRS) or 10 cm visual analogue scale (VAS) or a numeric response scale (1 to 10). The scores for questions 5 and 6 (severity and duration of morning stiffness) are averaged; the result is then averaged with the scores from the remaining four questions. The final BASDAI score has a range from 0 to 10: the

higher the score, the greater the measured degree of disease activity. A reduction in the BASDAI score is considered improvement.

BASDAI 20, 50, 70, and 90 reflect an improvement of greater than or equal to 20%, 50%, 70%, and 90% respectively during an initial assessment at a given point in time of treatment of an AS patient.

The 2005 International ASAS consensus statement for the use of anti-tumour necrosis factor (TNF) drugs in patients with AS recommends the BASDAI follow after initiation of treatment. The definition of treatment response includes a change in the BASDAI value defined as two units (on a 0 to 10 scale) of the BASDAI.[35]

**Validity of BASDAI**

Garrett et al. (1994) developed as well as evaluated this instrument through analysis of user friendliness, reliability (consistency), score distribution, sensitivity to change and comparisons, to a previous Bath Disease Activity Index and the Newcastle Enthesitis Index.[23] In this assessment, the BASDAI was completed by 154 patients receiving three weeks of intensive physiotherapy (inpatients and outpatients). It was found by patients to be relatively quick (mean 67 seconds, range 30 seconds to 120 seconds) and simple to complete. Bath Ankylosing Spondylitis Disease Activity Index appeared to be sensitive to change, reflecting a 16% (mean) improvement in in-patient scores after three weeks of intensive physiotherapy treatment.

Haywood et al. (2005) completed a structured review of the measurement properties for all disease-specific multi-item, patient-assessed health instruments in patients with AS, including BASDAI.[36] In this investigation, systematic literature searches were made to identify instruments, using predefined criteria relating to reliability (measurement stability over time), validity (instrument measures what is intended, content, and face), responsiveness (ability of an instrument to measure clinically important change), and precision.[36] The investigators report 72 published instrument evaluations following completion by patients with AS (including 17 for reliability and 37 for validity). Their assessment of reliability, validity, and responsiveness for BASDAI is presented in Table 27.

**TABLE 27: HAYWOOD ET AL. REVIEW: SUMMARY OF MEASUREMENT PROPERTIES FOR ANKYLOSING SPONDYLITIS INSTRUMENTS[36]**

| Instrument | Reliability | | Validity | | Responsiveness | |
|---|---|---|---|---|---|---|
| | Thoroughness | Results | Thoroughness | Results | Thoroughness | Results |
| **BASDAI (Disease Activity)** | +++ | +++ | +++ | +++ | +++ | +++ |
| **BASFI (Function)** | +++ | +++ | +++ | +++ | +++ | +++ |
| **BAS-G (Global Well-being)** | ++ | ++ | ++ | + | ++ | ++ |
| **ASQoL (HRQoL)** | ++ | ++ | ++ | ++ | ++ | ++ |

ASQoL = Ankylosing Spondylitis Quality of Life; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BAS-G = Bath Ankylosing Spondylitis Patient Global Score; HRQoL = health-related quality of life.

Note: Thoroughness of Evaluation: 0 = no published evidence; + = basic information only; ++ = several types of test, or several evaluations in different populations; +++ = all major forms of validity, reliability/responsiveness reported, several good-quality evaluations in different populations.

Results of Evaluation: 0 = no published numerical results; + = weak evidence only; ++ = moderate evidence; +++ = strong evidence.

Maravic et al. also evaluated the psychometric properties of different translated versions of the BASDAI available (English, Turkish, French, Swedish, and Spanish), including assessing face validity, content validity, construct validity (factorial analysis, convergent and divergent validity), reliability (test-retest, Cronbach's coefficient alpha, which indicates the degree of relatedness between items), and responsiveness.[37] Face validity was validated in all versions. The authors' indicated that no version initially defined the dimensions for content validity and construct validity was partially studied and validated in English, French, and Spanish. Reliability was validated in English, French, and Turkish. Responsiveness was demonstrated in all versions except for French.

Calin et al. (1999) set out to answer the question of whether the composite index is an accurate reflection of the components parts or whether weighting would provide increased accuracy of assessment. Four hundred and seventy-three (473) patients with AS randomly received placebo or nonsteroidal anti-inflammatory drug (NSAID) therapy for six weeks. Disease activity was assessed using BASDAI and the individual components of BASDAI relating to morning stiffness, pain, fatigue, and discomfort—analyzed separately. A principle component analysis (PCA) was used to explore the best combination of variables and to assess whether a simple sum — as is currently used for the BASDAI index—or a weighted index would best define disease activity. The BASDAI as a simple sum of its components was found to have excellent content validity.[38]

Madsen et al. (2010) examined the reproducibility of BASDAI in anti-TNF-treated spondyloarthritis (SpA) patients already familiar with the use of the indice.[39] Testing was performed twice on two different days (median interval seven days, range 4 days to 10 days) under standardized conditions in 26 out-clinic patients (median age 39 years, range 22 years to 56 years). Limits of agreement were calculated as the 95% likely range for the difference between paired scores. Test-retest results were significantly intercorrelated with r (s) = 0.90 for BASDAI. Limit of agreement for BASDAI was +/- 1.8. Internal consistency reliability and construct validity of BASDAI was deemed acceptable by the authors. The authors concluded that, in a sample of anti-TNF-treated patients experienced with the use of BASDAI, random measurement errors of BASDAI was not negligible.[39]

Pavy et al. (2005) investigated the minimal clinically important difference (MCID) of BASDAI and BASFI.[24] They administered both questionnaires to 125 patients with AS at baseline and two weeks after an intensive physiotherapy program. Along with the final assessment, a global validated 15-point rating scale was used to examine each domain. Receiver operating characteristic (ROC) curves were used to determine the score change that most accurately classified patients with respect to a clinically meaningful change. According to analyses of ROC curves, the MCID was 10 mm or 22.5% for BASDAI with sensitivity = 0.65 and specificity = 0.82. Regression analysis showed that MCID values were independent of the patients' baseline scores.[24]

Cohen et al. (2006) conducted a survey of patients' perceptions about current disease control.[40] One thousand questionnaires were mailed to members of a spondyloarthropathic patients organization to estimate the best BASDAI cutoff for discriminating between poor and well-controlled groups, from a patient's perspective. A proportion of 55.3% perceived inadequate control of their disease. The mean BASDAI in the overall population was 43.5 +/- 22.9, 30.4 +/- 19.9 in the well-controlled group, and 54 +/- 19.4 in the poorly controlled group *(P* < 0.001). From the ROC curve, the best BASDAI cutoff for discriminating between patients in the two groups was found to be 39 (sensitivity 74.6% and specificity 72.4%). According to gender, the best cutoff was 44 for women and 36 for men.[40]

**Assessment tools for physical function**

**Bath Ankylosing Spondylitis Functional Index**

The BASFI is a validated, patient self-administered, composite instrument widely used in AS to assess physical function. The BASFI consists of eight specific questions regarding function in AS and two questions reflecting the patient's ability to cope with everyday life.[26] Each question is answered on a 10 cm horizontal VAS or a numeric response scale (0 to 10), the mean of which gives the BASFI score (on a scale of 0 to 10). The higher the BASFI score, the greater the degree of functional impairment with reductions from baseline indicating improvement.

**Validity of BASFI**

Calin et al. (1994) developed the BASFI and evaluated it in comparison to the published Douglas Functional Index (DFI).[26] In this investigation, the questionnaire was completed 257 times in total, once by 116 outpatients and by 47 inpatients on three occasions during a three-week intensive physiotherapy course. The BASFI was analyzed in terms of all validity criteria and compared with the DFI. Patient scores covered 95% of the BASFI range, producing a normal distribution of results. Sensitivity results of the BASDAI in comparison to DFI were reported. The DFI and BASFI took an equivalent time to complete (maximum 100 seconds).[26] During the three-week period of in-patient treatment, the BASFI revealed a significant improvement in function (20%, $P = 0.004$) while there was less change in the DFI (6%, $P = 0.03$).

Spoorenberg et al. (1999) conducted a comparative study of the usefulness of BASFI and the DFI in an assessment of AS in 191 outpatients in Europe.[41] The external criterion for disease activity was both patient and physician assessment on a VAS and the BASDAI. The external criterion for damage was two radiological scores of the spine (Bath Ankylosing Spondylitis Radiology Index spine [BASRI-s]) and a modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). Both BASFI and DFI appeared to correlate equally well with disease activity and damage. The average correlation with disease activity variables was 0.42 for BASFI and 0.41 for DFI. The correlation for both BASFI and DFI with BASRI-s was 0.42 and with mSASSS 0.36. Sensitivity for the BASFI and DFI was between 76% and 94% for distinguishing between patients with high and low disease activity, while specificity was between 66% and 87%.[41]

The study carried out by Madsen et al. (2010) also examined the reproducibility of BASFI in anti-TNF-treated SpA patients.[39] With the same study population and protocol that have been mentioned for BASDAI, test-retest results showed significant intercorrelation with r (s) = 0.92 for BASFI. Limit of agreement for BASFI was +/- 1.4. Internal consistency reliability and construct validity of BASFI was deemed acceptable by the authors, but they also mentioned that random measurement error of BASFI was not negligible.[39]

In a review of AS instruments, Haywood et al. (2005) reported on 70 published instrument evaluations for BASFI following completion by patients with AS.[36] The authors comment that BASFI is one of three AS assessment instruments with the most extensive evidence for validity through comparison with instruments that measure similar or related constructs, and/or with measures of mobility.[36]

As mentioned for BASDAI, Pavy et al. (2005) investigated the MCID of BASFI in 125 AS patients undergoing an intensive physiotherapy program.[24] Using that protocol and according to analyses of ROC curves, the MCID was 7 mm or 17.5% for BASFI with sensitivity = 0.60 and specificity = 0.85. As shown by regression analysis, MCID values were independent of the patients' baseline scores.

**Assessment tools for spinal mobility**

**Bath Ankylosing Spondylitis Metrology Index**

The BASMI is a composite index and instrument for the assessment of axial status that is sensitive to changes in spinal movement.[31] Five clinical measurements are included in this instrument including: tragus-to-wall distance, modified Schober's lumbar forward flexion, cervical rotation, lumbar side flexion, and intermalleolar distance. Higher BASMI scores (from 0 to 10) denote more severe patient limitation of movement due to AS. It should be noted that the BASMI does not assess chest expansion (cm between full inspiration and expiration, improvement in spinal mobility is seen with an increase in chest expansion).

**Validity of BASMI**

Jenkinson et al. (1994) developed and evaluated the BASMI in 193 AS patients.[31] Metrology was performed on 327 occasions. The measurement tool was assessed for reliability, speed, and both inter and intraobserver variability. The investigators reported that the instrument was quick to complete (seven minutes) and was reproducible and sensitive to change across the disease spectrum of AS. When tested on a new group of 40 patients, the measures were demonstrated to be accurate and reproducible for both intraobserver variability (r = 0.99*, P* < 0.001) and interobserver variability (r = 0.97*, P* < 0.001).[31] In a further 56 admitted inpatients, a BASMI improvement from 3.34 (standard deviation [SD] 2.71) to 2.16 (SD 2.42) was noted during a period of three weeks, which indicated a sensitivity to change (chi-square = 6.55, *P* < 0.001).

Kennedy et al. (1995) compared the BASMI with radiology as a measure of disease outcome in 53 patients.[42] Patients were blindly and independently assessed using BASMI and a radiology score of four main spinal areas affected by AS. Bath Ankylosing Spondylitis Metrology Index correlated positively with the total radiology score (r = 0.74).

Martindale et al. (2012) explored the inter and intraobserver reliability of BASMI across raters from different clinical centres using a consensus-based standardized approach to assessment.[43] One hundred and thirty BASMI assessments were completed on the same day. Thirteen physiotherapists from 10 hospitals assessed 26 participants (19 patients, seven healthy volunteers). Overall, the mean (SD) BASMI total score was 3.11 (2.04). The constituent components of SD were 0.37 ("residual" inconsistency; i.e., between observer), 0.34 (between replicates), at least 0.06 (between observer means), and 2.03 (between participants). This suggests that the repeatability of BASMI assessments is 0.95 if the same observer is used and 1.05 if different observers are used.[43]

**Other instruments and scores for ankylosing spondylitis**

**Assessment in ankylosing spondylitis – response criteria**

The ASAS working group developed a composite set of response criteria that is commonly used in AS clinical trials. The ASAS working group is an international group of rheumatologists, epidemiologists, patients with AS, and pharmaceutical industry representatives from more than 21 countries.[44,45] During the OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trial) Conference in 1998, the ASAS working group selected "core sets" of AS outcome measures to be used in AS trials in order to create uniformity, allow standardization of measures, and to allow direct comparison and pooling of results among trials.[32,44,46] Distinctions were made between disease-controlling antirheumatic therapy (DC-ART) and symptom-modifying antirheumatic drugs (SMARD). Disease-controlling antirheumatic therapy was defined as: "therapy that changes the course of AS; i.e., both improve and sustain function in association with decreased inflammatory manifestations, and prevent or significantly decrease the rate of progression of structural damage. These changes must be sustained for a minimum of one year."[44] In contrast, SMARD was defined as therapy that "improves the symptoms and clinical features of inflammatory manifestations in AS."[44]

The ASAS working group has defined a core set of six domains that are important in assessing "symptomatic" outcome in AS. These domains include: measures of physical function, pain, patient's global assessment, spinal mobility, spinal stiffness/inflammation, and fatigue.[25,46] For each domain, one or more assessment instruments are recommended and are represented in Table 28.

**TABLE 28: ASSESSMENT IN ANKYLOSING SPONDYLITIS CORE SET OF DOMAINS AND INSTRUMENTS FOR ASSESSING SIGNS AND SYMPTOMS FOR EACH DOMAI**

| Domain[a] | Recommended Instrument[a] |
|---|---|
| Physical function | BASFI VAS; DFI |
| Pain | 2 separate questions: total pain in the spine due to AS, and pain in the spine at night due to AS |
| Patient's global assessment of disease activity | |
| Spinal mobility | Four instruments: occiput-to-wall distance; chest expansion; modified Schober test; lateral lumbar flexion, or BASMI |
| Spinal stiffness/inflammation | Average of morning stiffness duration and intensity (from BASDAI questions 5 and 6) |
| Fatigue | Fatigue question from BASDAI |

AS = ankylosing spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; DFI = Douglas Functional Index; VAS = visual analogue scale.
[a] Adapted from van der Heijde et al.[25]

It should be noted that the ASAS working group has further designated other domains that should be assessed in addition to the six domains of the symptom-modifying core set for therapies assessed to have proposed disease-modifying properties. These additional domains include: acute-phase reactants (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP] level), number of swollen peripheral joints based on a 44-joint count, and enthesitis (assessed on a validated enthesitis score).[25]

The ASAS response criteria was developed to establish a uniform minimum core set of variables for inclusion in all research projects that may help prevent dilemmas, e.g., AS studies that may have employed inconsistent and excessive numbers of assessment methods.[47] This approach is hoped to help prevent such dilemmas by ensuring: change occurrences of statistically significant differences between groups are minimized; investigators do not introduce bias by selectively publishing only favourable variables; and comparisons can be made between studies including meta-analyses.[47]

**ASAS improvement criteria**

The ASAS improvement criteria (ASAS-IC), a composite score for symptom modification suggested for use in clinical trials, consist of four distinct domains:[15,25,32]

- Physical function (measured with BASFI)
- Spinal pain (measured on a 100 mm VAS)
- Patient global assessment (100 mm VAS)
- Inflammation (mean of the last two questions from BASDAI concerning both the intensity and duration of morning stiffness)

**ASAS 20 (symptom-modifying response)**

ASAS 20 response criteria is defined as improvement as greater than or equal to 20% and greater than or equal to 10 units of absolute change (10 VAS points improvement on the 0 to 100 scale) in at least three of the four domains, with no worsening of greater than or equal to 20% and greater than or equal to 10 VAS points in the fourth domain. The four domains are: Patient's Global Assessment of Disease Activity represented by the VAS global assessment score (0 to 100 scale); pain represented by the Total Back Pain VAS score (0 to 100 scale); function represented by the BASFI score (0 to 10 scale); and inflammation represented by the mean of the two morning stiffness-related BASDAI VAS scores (i.e., mean of questions five and six of the BASDAI).

For drugs proposed to possess disease-modifying capabilities, two separate response criteria were recommended in addition to the ASAS 20 response criteria:[25]

- **ASAS 40 criteria** (at least 40% improvement and 20 units of absolute change in three of four domains, using the same domain as the ASAS response criteria, without any worsening in the fourth domain)[25] or
- **ASAS 5/6 criteria** (20% improvement in five of six domains—the same four domains as the ASAS 20 response criteria plus two extra domains: spinal mobility and acute-phase reactants)[25]

**ASAS partial remission criteria**

Sustained durability of a clinical response can be assessed by partial remission (low disease activity). The ASAS partial remission criteria is defined as a value of less than 20 on a 0 to 100 scale in each of the four ASAS 20 domains.[15,25] In contrast, remission implies a state of complete absence of disease activity.[25] Durability of remission is designated as a period of at least six months.

**Validity and evaluation of ASAS improvement criteria**

Anderson et al. (2001) developed and evaluated criteria (later recognized as ASAS-IC) for the short-term symptomatic improvement in AS.[15] These criteria were developed using outcome domain data from five placebo-controlled trials of NSAIDs in AS patients. Patient data were used to assess equivalence, reliability, and responsiveness of multiple items in the five outcome domains of AS treatment: physical function, pain, spinal mobility, patient global assessment, and inflammation. It was found that at least one measure per domain was responsive, except for the spinal mobility domain, which was subsequently omitted from the criteria. The investigators developed and tested candidate improvement criteria in a random 2/3 subset from the three largest trials (n = 923 patients in total) and used the remaining 1/3 for validation.[15] Worsening in a domain was defined as a change of $\geq$ 20% and a net change of $\geq$ 10 points on a scale of 0 to 100. Partial remission was defined as an end of trial value of < 20 out of 100 in each of the four domains (for comparison purposes). Study results demonstrated that among 20 candidate criteria, a change of $\geq$ 20% and $\geq$ 10 units in each of the three domains, and absence of worsening in the fourth domain discriminated best in the development subset. Results were then confirmed by the validation subset of patients. For comparison purposes, almost all the patients satisfying the partial disease remission criteria at the end of the trial had also improved as assessed by the derived criteria set. The authors suggest that this multiple domain-based measure of improvement is useful for AS since many of the relevant outcome measures taken individually have poor reliability. The investigators outline that a potential limitation of the proposed criteria is the absence of a measure of spinal mobility (as spinal mobility constitutes a domain that is specific to AS with axial involvement).

van Tubergen et al. (2003) investigated whether the ASAS-IC reflected a clinically relevant improvement according to the opinion of an expert panel.[32] In this study, ASAS-IC scores in the four domains of 55 patients with AS who had participated in NSAID efficacy trial were presented to an international expert panel. The assessment was performed with a three-round Delphi exercise. The number of

nonresponders as designated by ASAS-IC was compared with the experts' final consensus. The most important domains in the opinion of the experts were identified, and also selected with discriminant analysis. In the study, 40 experts completed the three rounds.

Overall, all ASAS-IC designated responders (n = 21 patients) were considered responders by the exert panel.[32] However, the experts designated twice as many patients to be responders than the ASAS-IC (42 of 55 versus 21 of 55 patients). Overall agreement between the experts and ASAS-IC was 62%. Since the consensus of the experts differed from the ASAS-IC, a number of provisional criteria sets were defined to select criteria sets that best represented the consensus of the experts. Out of a total of 36 criteria sets, 19 showed an accuracy rate of ≥ 80% with the consensus of the experts, and were therefore tested for discriminative properties. Provisional criteria sets with an agreement of ≥ 80% with the experts' consensus showed a high placebo response rate (27% to 42%). In contrast, the ASAS-IC had a placebo response rate of 25%. In comparison to end of trial efficacy assessments, the provisional criteria sets showed an agreement of 71% to 82%, sensitivity of 67% to 83%, and a specificity of 81% to 88%. The ASAS-IC demonstrated an agreement of 70%, a sensitivity of 62%, and a specificity of 89%. The investigators further conclude that patients who are "considered as 'responders' by the ASAS-IC are acknowledged as such by the expert panel as well as trial efficacy assessments (patient and physician judgments) and are therefore likely to be true responders (clinically relevant response), which makes ASAS-IC particularly important for clinical trials."[32]

There a number of limitations to this type of evaluation completed by van Tubergen et al. including the fact that only 40 of the 57 experts completed the three Delphi rounds. It should be noted that opinions among the experts varied considerably (most experts in this investigation considered improvement in only two domains sufficient to acknowledge a patient to be a responder).

Stone et al. (2004) evaluated the ASAS criteria against what expert physicians considered a dramatic response. To do this, 40 consecutive AS patients who were being treated in an open-label protocol with infliximab were evaluated for one year. For the purpose of this study patients were assessed as having a good response if they achieved an ASAS 50 and were defined as having a dramatic response if they achieved an ASAS 70. Experts also evaluated the patients using predetermined measures of good and dramatic response based on patient and physician global assessments of disease activity. In this study, 12 out of the 40 patients met the ASAS 70 response criteria whereas only eight out of the 40 patients met the expert definition of dramatic response based on physician global scores. Agreement was poor between ASAS 50 and ASAS 70 and physician global scores but better agreement was found with patient global scores. The authors concluded that while ASAS relative improvement criteria are valid for use in detection improvements experienced by AS patients treated with TNF inhibitors, patient global assessment of disease activity might also be adequate.[48]

**Tools for assessment of quality of life in ankylosing spondylitis**

**ASQoL**

The ASQoL is an 18-item validated disease-specific questionnaire for measuring health-related quality of life (HRQoL) in patients with AS.[17] Items assess the impact of disease on sleep, mood, motivation, coping, activities of daily living, independence, relationships and social life. The self-reported questionnaire is composed of yes/no questions; hence the ASQoL overall score ranges from 0 to 18 with higher score indicating worse HRQoL. The instrument showed excellent internal consistency (alpha = 0.89 –0.91), test-retest reliability (r(s) = 0.91-0.92) and validity.[17] Another publication reported high test-retest reliability (> 0.90) for ASQoL and its good correlation with BASDAI (0.79).[49]

**SF-36**

The Short-form 36-item Health Survey (SF-36) is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[50] The SF-36 consists of eight health domains: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical challenges, and emotional challenges.[29] For each of the eight categories, a subscale score can be calculated. The SF-36 also provides two component summaries, the physical component summaries (PCS) and the mental component summary (MCS). The PCS and MCS scores range from 0 to 100, with higher scores indicating better health status. The summary scales are scored using norm-based methods, with regression weights and constants derived from the general US population. Both the PCS and MCS scales are transformed to have a mean of 50 and a SD of 10 in the general US population. Changes between 2.5 to 5.0 points in the PCS and MCS of the SF-36 are considered to be clinically relevant, as are changes of 5 to 10 points in the domain scores.[30]

**The validity of SF-36**

This instrument is validated and performs well in patients with rheumatoid arthritis.[51] Turan et al.[52] reported that the SF-36 had a strong correlation with the Mander Enthesitis Index, and the BASDAI in 46 patients with AS in an study conducted to investigate which parameters of disease activity, functional condition, and other clinical parameters had a greater effect on quality of life.[52] The internal consistency, construct validity, and responsiveness to change of SF-36 has been assessed in two RCTs comparing adalimumab with placebo for the treatment of AS.[53] SF-36 had a good internal consistency (alpha = 0.74 to 0.92). At baseline, the SF-36 score correlated with ASQoL scores (r = –0.36 to –0.66; $P < 0.0001$). SF-36 scores varied by indicators of clinical severity, with greater impairment observed for more severe degrees of clinical activity (all $P < 0.0001$).

**EQ-5D**

The European Quality of Life 5-Dimensions (EQ-5D) Scale is a generic quality of life (QoL) instrument that may be applied to a wide range of health conditions and treatments.[20,21] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing “no problems,” “some problems,” and “extreme problems,” respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[20,21] The second part is a 20 cm visual analogue scale (EQ-VAS) that has end points labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state.” Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

- A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- A population preference-weighted health index score based on the descriptive system
- A self-reported assessment of health status based on the EQ-VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK algorithm and –0.109 for the US algorithm). Scores less than 0 represent health states that are valued by

society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Reported MCIDs for this scale have ranged from 0.033 to 0.074.[54]

**The validity of EQ-5D**

The validity of EQ-5D was compared with the Short-form 6-dimensions (SF-6D) and the well-being rating scale in 254 patients with AS (134 patients from an observational cohort and 120 from a RCT).[55] The median score was 0.69 (range; −0.08 to −1.00) for the EQ-5D. Intraclass correlation coefficients were of moderate agreement (0.46 to 0.55). Instruments correlated equally with disease activity, functioning, and quality of life. Compared with EQ-5D and RS, SF-6D showed smaller average differences in utility between patients with better and worse disease. The smallest detectable differences in the control group of RCT were 0.36, 0.17, and 0.33 for EQ-5D, SF-6D and RS, respectively. The ability to detect treatment effect in the intervention trial showed standardized effect sizes that were moderate for EQ-5D and SF-6D (0.63 and 0.64) and low for the RS (0.23).[55]

EQ-5D and SF-6D were compared in patients (n = 448) with inflammatory arthropathies from a longitudinal study investigating treatments with biological drugs (n = 373) and DMARDs (n = 75).[56] At baseline, patients had a bimodal distribution (mean 0.42, median 0.59). After three months, EQ-5D change was 0.18 (SD 0.34). A significant but moderate correlation was found between BASDAI and BASFI changes and EQ-5D. Compared with SF-6D, EQ-5D was better able to discriminate between different levels of disease activity. Also, in patients with the most improvement in BASDAI, EQ-5D demonstrated twice the utility gain of SF-6D.[56]

**Tools for assessment of radiologic change**

In AS, radiographic findings include erosions, sclerosis, syndesmophyte formation, and ankylosis of the sacroiliac joints (SI) and vertebrae. MRI is used to visualize inflammation of the SI joints and the spine and for structural damage; whereas, ultrasound is used for enthesitis, synovitis, and occasionally boney changes. Conventional radiographs are also used in clinical practice. In general, progression in AS is slow. After two years up to 46% of AS patients showed progression of structural damage and after four years, the number increased to 56%. The ASAS recommends radiographs once every two years.[57]

MRI has an advantage compared with radiographs because it can detect abnormalities earlier than conventional radiographs and can also access the thoracic spine, which is frequently involved in AS and is difficult to access with conventional radiographs. In research, MRI is the tool of choice for monitoring AS progression.[57]

For study purposes, several scoring systems have been developed. In AS, modified Stokes Ankylosing Spondylitis Spinal Score (mSASSS)[33] is preferred for use in clinical trials to detect ASAS.[57] The mSASSS score is obtained by assessing anterior sites of the lumbar (L1-L5) and cervical spine (C2-T1) on a lateral view. Each site gets a score from 0 (normal) to 3 (bridging syndesmophytes), which gives a total score range of 0-72. It does not score the thoracic spine.

**Validity of mSASSS**

A 48-week NSAID study of 57 patients was used to evaluate the validity of this scale. In this study, interobserver correlations of the lumbar and cervical spine scores were good ($r > 0.95$). The interobserver duplicate error was 0.55 in a range from 0 to 36. The mean change in the cervical and lumbar spine scores between weeks 0 and 48 of all patients was 1.45 (range 0 to 6.0) and 1.06 (0 to 5.0), respectively (paired t testing, $P < 0.001$). Change in radiological score was seen in 36 of 57 (63%) patients (lumbar and cervical spine 11, cervical spine 12, lumbar spine 13 patients). The conclusion was that

mSASSS is useful for assessing extensive radiographic damage in AS and it was reliable, it detected changes over 48 weeks, and it showed a satisfactory face and construct validity.[27]

Salaffi et al. (2007) compared the mSASSS scoring method with the Bath Ankylosing Spondylitis Radiology Index (BASRI) using two observers for 95 AS patients.[58] mSASSS showed better intra- and interobserver correlation coefficients, a better correlation with BASFI, and a more sensitive to change score than BASRI. Similarly, Ramiro et al. (2013) compared mSASSS with the Radiographic AS Spinal Score (RASSS) on 195 AS patients using two independent readers.[59] Results showed that RASSS was frequently found to be impossible to determine. The contribution of the vertebral corners in the RASSS were found to be negligible. Therefore, the use of mSASSS remains justified.

**Tools for assessment of work productivity**

**The Rheumatoid Arthritis-Specific Work Productivity Survey**

The WPS-RA has been developed by UCB Pharma to measure the impact of rheumatoid arthritis and treatment on patient productivity inside and outside the home. It contains nine self-reported questions addressing employment status, productivity inside and outside the home, and daily activities during a one-month recall period. The eight items addressed in the questionnaire are analyzed separately.[34]

**The validity of WPS-RA**

The discriminant validity, responsiveness, and reliability of the WPS-RA in patients with active RA have been evaluated in 220 patients enrolled in a phase 3 RCT using CZP.[34] Patients with lower Health Assessment Questionnaire — Disability Index (HAQ-DI) or SF-36 scores generally had statistically greater RA-associated losses in productivity inside and outside the home compared with patients with higher scores (25 of 32 were statistically significant). Smallest differences between groups were seen in work absenteeism and days with outside help. At week 24, ACR 20 and HAQ-DI responders reported significant improvements in productivity inside and outside the home; non-responders reported mainly a worsening in productivity ($P \leq 0.05$). Effect size for productivity changes in ACR 20 or HAQ-DI responders was moderate to large for six out of eight items (Standardized response mean [SRM] = 0.48 to 1.12). The effect size was small for work absenteeism and days with outside help (SRM = 0.4 and 0.24, respectively). In non-responders, the magnitude of change was small (SRM < 0.3).[34]

The psychometric properties of WPS-RA in axial spondyloarthritic patients have recently been investigated by UCB Pharma in patients enrolled in the RAPID-axSpA study.[60] The association coefficients between all WPS-RA questions and different continuous measures assessing the disease activity, physical functioning, and HRQoL were low (< 0.3) to moderate (≥ 0.3 to 0.5) indicating divergent validity. The Kendall association coefficients indicated that better productivity at work and inside the home was associated with better HRQoL, less fatigue, better physical functioning or less pain. Significantly larger improvements in productivity inside and outside the home were reported by ASAS 20 responders compared with ASAS 20 non-responders, except with regard to absenteeism, presenteeism, and days missed of family, social or leisure activities. Particularly for absenteeism, ASAS 20 non-responders had a numerically higher change from baseline. The effect sizes of the changes in productivity, measured by the SRM, in ASAS 20 responders were small (SRM < 0.5) for absenteeism, presenteeism and days with outside help, but moderate to large for the other WPS-RA questions. The WPS-RA needs further validation for AS.[60]

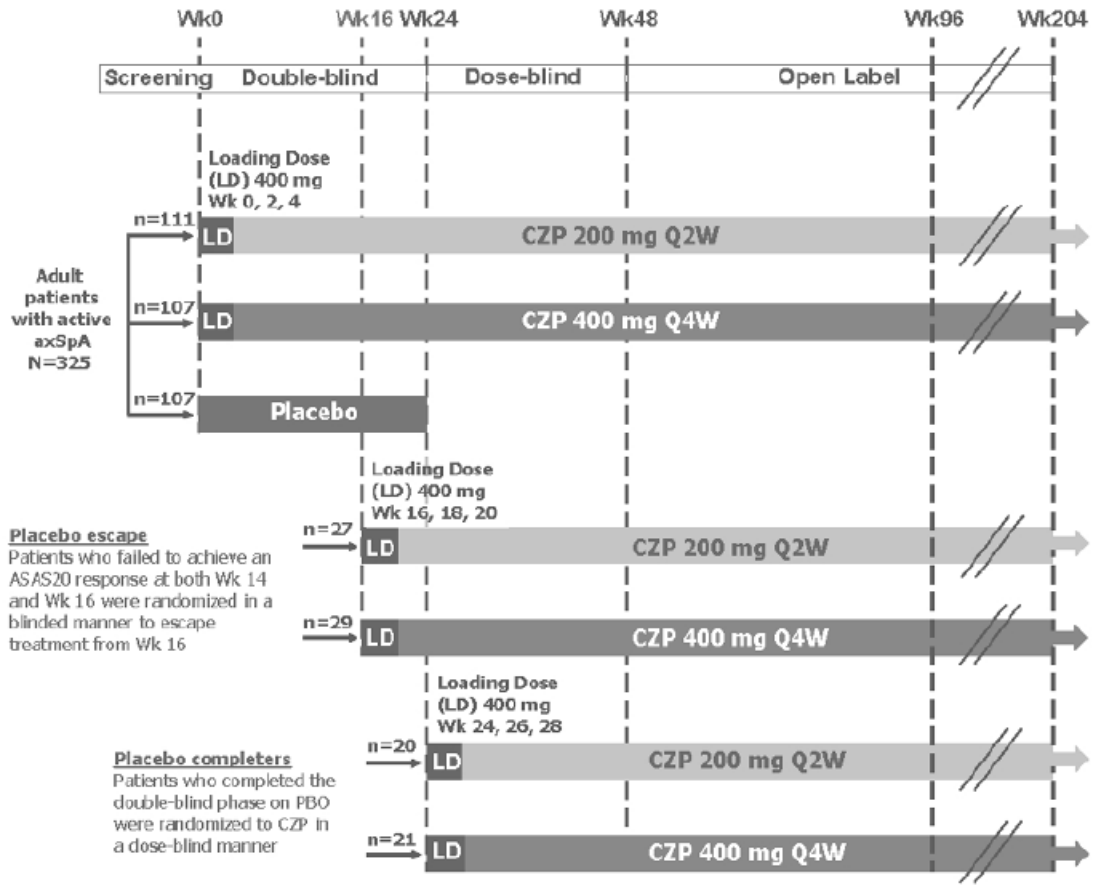
**Conclusions**

- The BASDAI is validated and sensitive to changes in disease activity. It is the most common and widely used assessment tool in AS. The reported MCID is 10 mm or 22.5% of the baseline score.
- The BASFI is a validated composite instrument for the assessment of physical function. The higher the score, the greater the degree of functional impairment. The BASFI is considered one of the best instruments for the measure of mobility in AS patients. The reported MCID is 7 mm or 17.5% of the baseline score.
- The BASMI is a composite index sensitive to changes in spinal mobility and spinal involvement. BASMI correlates positively with radiologic changes.
- ASAS response criteria are commonly used in AS clinical trials. The core sets of outcomes were selected by the ASAS working group in order to create uniformity, allow standardization of measures, and allow direct comparison and pooling results from clinical trials. The core data set includes six domains including measures of physical function, pain, patient's global assessment, spinal mobility, spinal stiffness/inflammation, and fatigue; it also recommends the tools to be used. The ASAS defines response at differing levels (20, 40, 50, and 70) and remission criteria.
- The ASQoL is a validated AS specific quality of life questionnaire. It has shown excellent internal consistency and test-retest reliability.
- The generic quality of life SF-36 instrument is a validated tool in rheumatic diseases. It appears to have a correlation with BASDAI and ASQoL and a good internal consistency/reliability in the assessment of AS patients.
- Radiographic changes appear to occur slowly in AS. Of the radiologic tools available, MRI appears to be the most sensitive and extensive. The mSASSS is the index of choice in the evaluation of radiographic changes in AS clinical trials. It has good reliability and validity.
- The WPS-RA is an instrument originally developed by UCB Pharma to measure the impact of RA on patient productivity within and outside the home. The use of this instrument in AS revealed mitigated results and further validation would be needed.

# APPENDIX 6: SUMMARY OF THE EXTENDED PHASE OF STUDY AS-001

This section summarizes the extended phase of study AS-001 up to week 96 as reported in the manuscript provided by the manufacturer.[61] The AS-001 study had a double-blind placebo-controlled phase up to week 24, after which all patients were re-randomized on CZP (dose-blind) until week 48 (Figure 6). After that point, it was an open-label treatment period that was conducted up to week 24. The primary objective of that study was to evaluate the long-term efficacy and safety of two CZP dosing regimens (200 mg Q2W and 400 mg Q4W) in AS patients.

**FIGURE 6: AS-001 STUDY DESIGN**




ASAS = Assessment in Ankylosing Spondylitis; axSpA = axial spondyloarthritis; CZP = certolizumab pegol; LD = loading dose; PBO = placebo; Q2W = twice a week; Q4W = four times a week; Wk = week.

### Study characteristics and study design

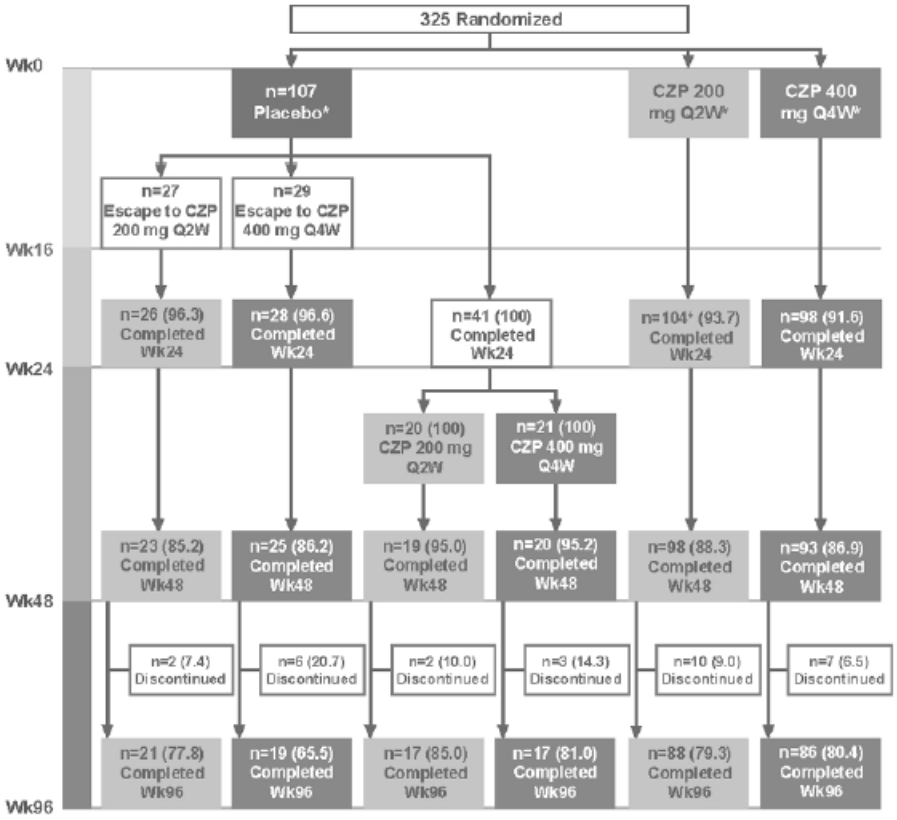
Study and patients characteristics were described in the 3.2 section (included study) of this report.

### Patient disposition

Patient disposition after 48 weeks was reported for AS (n = 178, 55%) and nr-axSpA (n = 147, 45%) patients together (Figure 7). A total of 325 patients were randomized at the beginning of AS-001. Of these patients, 107 received placebo, 111 received CZP 200 mg Q2W, and 107 received CZP 400 mg

Q4W on day 1. Overall, 246 patients (76%) completed the study to week 96. From the patients who were originally randomized to CZP (218 patients), 174 (80%) completed to week 96. From the patients who were randomized to placebo and who escaped early at week 16 (56 patients), 40 completed to week 96. From the patients who were originally randomized to placebo and who completed week 24 in the placebo group (41 patients), 32 patients completed to week 96. 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.

**FIGURE 7: AS-001 PATIENT DISPOSITION**




AS = ankylosing spondylitis; CZP = certolizumab pegol; Q2W = every two weeks; Q4W = every four weeks; Wk = week.
Data shown are n (%). Note: All patients received allocated treatment.

**Efficacy**

Efficacy outcomes up to week 96 were reported for the two dosages combined. Improvements in ASAS 20, ASAS 40, and ASAS-PR as seen in AS patients at week 48 had a numerical decrease (no *P* value reported) at week 96 in the open-label extension (Table 29). For disease activity (BASDAI), spinal mobility (BASMI) and function (BASFI), improvements from baseline to week 48 were maintained throughout the open-label extension to week 96 (Table 30). Similarly, improvements in patient-reported outcomes (PROs) observed at week 24 were maintained up to week 96 (Table 31).

**TABLE 29: PERCENTAGE OF AS PATIENTS ACHIEVING AN ASAS 20, ASAS 40, AND ASAS-PR RESPONSE TO WEEK 96**

| Week | 12 (NRI) | 24 (NRI) | 48 (NRI) | 96 (NRI) |
|---|---|---|---|---|
| **ASAS 20** | **59.5** | **66.9** | **73.6** | **64.5** |
| **ASAS 40** | **43.8** | **51.2** | **57.9** | **50.4** |
| **ASAS-PR** | **19.8** | **28.1** | **29.8** | **24.8** |

ASAS 20 = assessment of Axial SpondyloArthritis international Society 20% response criteria; ASAS 40 = assessment of Axial SpondyloArthritis international Society 40% response criteria; ASAS-PR = ASAS partial remission; NRI = non-responder imputation; OC = observed case.
Note: Observed case data for week 96 (n = 93). Results reported for the randomized set.

**TABLE 30: IMPROVEMENTS TO WEEK 96 IN THE AS POPULATION IN BASMI LINEAR SCORE, BASDAI SCORE AND BASFI SCORE (LOCF)**

| Week | 12 (LOCF) | 24 (LOCF) | 48 (LOCF) | 96 (LOCF) |
|---|---|---|---|---|
| **BASMI Mean Score** | 3.7 | 3.6 | 3.6 | 3.6 |
| **BASDAI Mean Score** | 3.8 | 3.4 | 3.1 | 3.1 |
| **BASFI Mean Score** | 3.8 | 3.3 | 3.1 | 3.0 |

AS = ankylosing spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; LOCF = last observation carried forward.
Observed case data for week 96 (n = 97). Results reported for the randomized set.

**TABLE 31: AS PATIENT-REPORTED OUTCOMES TO WEEK 96 (LOCF)**

| Week | 12 | 24 | 96 |
|---|---|---|---|
| **SF-36 PCS** | [redacted] | [redacted] | [redacted] |
| **SF-36 MCS** | [redacted] | [redacted] | [redacted] |
| **ASQoL** | [redacted] | [redacted] | [redacted] |

AS = ankylosing spondylitis; ASQoL = Ankylosing Spondylitis Quality of Life; LOCF = last observation carried forward; MCS = mental component summary; PCS = physical component summary; SF-36 = Short-form 36-item Health Survey.

Similar efficacy responses were observed in patients with and without prior anti-TNF exposure at week 96, particularly in ASAS 40 (50.0% with versus 50.5% without) and BASDAI (–3.5 with versus –3.4 without).

**Safety**

The safety results were presented for AS and nr-axSpA patients together. AEs occurred in 279 patients (88.6%; event rate per 100 patient per year [ER/100 PY] = 360.3) and were predominantly mild (74.9%) (Table 32). Serious AEs (SAEs) occurred in 41 patients (13.0%; ER/100 PY = 10.9), including one case of cardiac disorder (0.3%; ER/100 PY = 0.2) and two cases of nervous system disorder in one patient (0.3%; ER/100 PY 0.4). Serious infections were the most common SAEs and occurred in 12 patients (3.8%; ER/100 PY = 2.7). No new safety signals were observed, and no deaths, malignancies, or cases of demyelinating disease were reported during the 96-week trial period.

**TABLE 32: ADVERSE EVENTS DURING THE 96-WEEK TRIAL BY TREATMENT GROUP AT ORIGIN (SAFETY SET)**

| | 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 |
| **SAEs** | 13 (11.7) | 8.2 | 14 (13.1) | 9.1 | 41 (13.0) | 10.9 |
| **Most frequent SAEs** | | | | | | |
| GI disorders | 0 | 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) | |
| **Deaths** | 0 | | 0 | | 0 | |

AE = adverse event; CZP = certolizumab pegol; ER/100 PY = event rate per 100 patient years; GI = gastrointestinal; Q2W = every two weeks; Q4W = every four weeks; SAE = serious adverse event.

Of the patients treated with CZP, 215 were tested for the presence of anti-CZP antibodies and 9 (4.2%) were tested positive at week 96. Numbers were similar in both CZP dosing regimens with 2.7% (Q2W) and 5.8% (Q4W).

**Critical appraisal**

CZP-treated patients and patients who received placebo could be compared until week 24. The AS-001 trial only allowed for comparison between the two CZP dosing regimens after that point. The absence of a placebo group for comparison is then an important limitation. Moreover, after week 24, patients were not blinded in terms of treatment allocation. Instead, they were blinded in regard to the dosing regimen. Therefore, the results from the patient-reported components of ASAS, BASDAI, and BASFI may be biased once the patient is unblinded. The internal validity of data gathered after that point is then strongly limited.

**Conclusions**

Although there was no comparator beyond week 24, the effectiveness of the two dosing regimens of CZP for the treatment of patients with AS appeared to be maintained up to week 96. However the open-label extension phase had limitations in regard to its internal validity. At week 96, the rate of AEs reached 88.6% and the rate of SAEs was 13.0%. The most common SAE was serious infections with a rate of 3.8%. No new safety signals were observed during the extension phase.

# APPENDIX 7: SUMMARY OF MANUFACTURER-SUBMITTED MIXED TREATMENT COMPARISON

The manufacturer conducted a mixed treatment comparison (MTC) based on a systematic review to evaluate the relative efficacy and safety of certolizumab pegol 200 mg every two weeks (Q2W) or 400 mg every 4 weeks (Q4W) compared with other biologic DMARDs (anti-TNF drugs) for the treatment of axSpA (including both AS and nr-axSpA subpopulations). However, only the results for the AS subpopulation were highlighted in their submitted report. This brief provides a summary and critical appraisal of the methods and main findings of the MTC.

## Summary of network meta-analysis

[redacted][62]

## Methods

### Eligibility criteria

[redacted]

### Mixed treatment comparison

[redacted]

[redacted]

[redacted]

**Results**

**Study and patient characteristics**

[redacted] (Figure 8 and Table 33), [redacted]

[redacted]

[redacted]

[redacted]

[redacted][63]

in Table 34, [redacted]

[redacted]

**Results of the meta-analysis**

[redacted]

[redacted] (Table 35 to Table 40). [redacted]

[redacted]

[redacted]

[redacted]

**Critical appraisal of network meta-analysis**

[redacted][64]

Table 41..

**Strengths**

[redacted][63]

**Limitations**

[redacted]

**Summary**

[redacted]

**FIGURE 8: AS POPULATION EVIDENCE NETWORK DIAGRAM**

***Figure 8 contained confidential information and has been removed at the request of the manufacturer.***

**TABLE 33: DESCRIPTION OF INCLUDED STUDIES ASSESSING BIOLOGICAL DMARDS**

| Trial Name | Author, Year, Journal | Study Design | Randomized Interventions | Number of patients | PL- and Active-controlled RCT Durations | Early Escape, Crossover, and Open-label Extensions |
|---|---|---|---|---|---|---|
| [redacted] | | | | | | |
| [redacted] | | | | | | |
| [redacted] | | | | | | |
| [redacted] | | | | | | |
| [redacted] | | | | | | |
| [redacted] | | | | | | |
| [redacted] | | | | | | |
| [redacted] | | | | | | |
| [redacted] | | | | | | |

| Trial Name | Author, Year, Journal | Study Design | Randomized Interventions | Number of patients | PL- and Active-controlled RCT Durations | Early Escape, Crossover, and Open-label Extensions |
|---|---|---|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

[redacted]

**TABLE 34: QUALITY ASSESSMENT OF THE INCLUDED RCTS**

| Trial | Random Sequence Generation | Allocation Concealment | Blinding of Participants and Personnel | Blinding of Outcome Assessment | Incomplete Outcome Data | Selective Reporting | Other Source of Bias |
|---|---|---|---|---|---|---|---|
| [redacted] | | | | | | | |
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| Trial | Random Sequence Generation | Allocation Concealment | Blinding of Participants and Personnel | Blinding of Outcome Assessment | Incomplete Outcome Data | Selective Reporting | Other Source of Bias |
|---|---|---|---|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

[redacted]

**TABLE 35: RESULTS OF MTC ANALYSIS – [redacted]**

| [redacted] | [redacted] | |
|---|---|---|
| Comparison OR (95% CrI) | [redacted] | [redacted] |
| [redacted] | | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

[redacted] CrI = credible interval; [redacted] OR = odds ratio; [redacted]

**TABLE 36: RESULTS OF MTC ANALYSIS –** [redacted]

| | [redacted] | |
|---|---|---|
| **Comparison OR (95% CrI)** | [redacted] | [redacted] |
| [redacted] | | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

[redacted] CrI = credible interval; [redacted] OR = Odds ratio; [redacted].

**TABLE 37: RESULTS OF MTC ANALYSIS —** [redacted]

| Comparison Difference of Mean Change (95% CrI) | [redacted] | [redacted] |
|---|---|---|
| [redacted] | | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
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| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

[redacted] CrI = credible interval; [redacted]

[redacted]

[redacted]

[redacted]

**TABLE 38: RESULTS OF MTC ANALYSIS —** [redacted]

| | [redacted] | |
|---|---|---|
| **Comparison Difference of Mean Change (95% CrI)** | [redacted] | [redacted] |
| [redacted] | | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

[redacted] CrI = credible interval; [redacted]

[redacted]

[redacted]

[redacted]

**TABLE 39: RESULTS OF MTC ANALYSIS –** [redacted]

| | | |
|---|---|---|
| **Comparison Difference of Mean Change (95% CrI)** | [redacted] | [redacted] |
| [redacted] | | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
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| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

[redacted] CrI: credible interval; [redacted]

[redacted]

[redacted]

[redacted]

**TABLE 40: RESULTS OF MTC ANALYSIS –** [redacted]

| | [redacted] | |
|---|---|---|
| **Comparison Difference of Mean Change (95% CrI)** | [redacted] | [redacted] |
| [redacted] | | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
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| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

[redacted] CrI = credible interval; [redacted]

[redacted]

[redacted]

[redacted]

**TABLE 41: APPRAISAL OF NETWORK META-ANALYSIS USING ISPOR CRITERIA**

| ISPOR Checklist Item | | Details and Comments |
|---|---|---|
| 1. | Are the rationale for the study and the objectives stated clearly? | [redacted] |
| 2. | Does the methods section include the following?<br>• Eligibility criteria<br>• Information sources<br>• Search strategy<br>• Study selection process<br>• Data extraction<br>• Validity of individual studies | [redacted] |
| 3. | Are the outcome measures described? | [redacted] |
| 4. | Is there a description of methods for analysis/synthesis of evidence?<br>• Description of analyses methods/models<br>• Handling of potential bias/inconsistency<br>• Analysis framework | [redacted] |
| 5. | Are sensitivity analyses presented? | [redacted] |
| 6. | Do the results include a summary of the studies included in the network of evidence?<br>• Individual study data?<br>• Network of studies? | [redacted] |
| 7. | Does the study describe an assessment of model fit? | [redacted] |
| 8. | Are the results of the evidence synthesis presented clearly? | [redacted] |
| 9. | Sensitivity/scenario analyses | [redacted] |

CI = confidence interval; DIC = deviance information criterion; IFX = infliximab; ISPOR = International Society for Pharmacoeconomics and Outcomes Research.

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