Common Drug Review
Clinical Review Report

April 2015

Drug	certolizumab pegol (Cimzia) SC
Indication	For use alone, or in combination with methotrexate (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 who have failed one or more disease-modifying antirheumatic drugs (DMARDs).
Listing request	As per indication
Manufacturer	UCB Canada Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

TABLE OF CONTENTS

Tables

Figures

ABBREVIATIONS

ACE	Arthritis Consumer Experts
ACR	American College of Rheumatology
ADA	adalimumab
AE	adverse event
AS	ankylosing spondylitis
BRM	biologic response modifier
BSA	body surface area
CAPA	Canadian Arthritis Patient Alliance
CI	confidence interval
CRP	C-reactive protein
CSA	Canadian Spondylitis Association
CZP	certolizumab pegol
DAS 28	Disease Activity Score in 28 Joints
DB	double-blind
DMARD	disease-modifying antirheumatic drug
ESR	erythrocyte sedimentation rate
ETN	etanercept
EULAR	European League Against Rheumatism
FASCA	Fatigue Assessment Scale
FEM	fixed-effects model
GOL	golimumab
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire – Disability Index
HRQoL	health-related quality of life
IFX	infliximab
LDI	Leeds Dactylitis Index
LEI	Leeds Enthesitis Index
LOCF	last observation carried forward
MCID	minimal clinically important difference
MCS	mental component summary
MTC	mixed-treatment comparison
mTSS	modified Total Sharp Score
MTX	Methotrexate
NMA	network meta-analysis
NSAID	nonsteroidal anti-inflammatory drug
OLE	open-label extension
PASI	Psoriasis Area and Severity Index
PBO	placebo
PCS	physical component summary

PF	physical functioning
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
PsAQoL	Psoriatic Arthritis Quality of Life
PtAAP	Patient's Assessment of Arthritis Pain
Q2W	every two weeks
Q4W	every four weeks
RA	rheumatoid arthritis
RCT	randomized controlled trial
REM	random-effects model
SAE	serious adverse event
SC	subcutaneously
SD	standard deviation
SF-36	Study Short Form (36) Health Survey
SpA	spondyloarthritis
TEAE	treatment-emergent adverse event
TNF	tumour necrosis factor
UST	ustekinumab
VAS	visual analogue scale
WDAE	withdrawal due to adverse event
WPS	Work Productivity Survey

EXECUTIVE SUMMARY

Introduction

Psoriatic arthritis (PsA) is a heterogeneous disease associated with multiple and variable clinical features. Patients suffer from chronic inflammatory peripheral arthritis, and may also suffer from skin and nail disease, axial disease, dactylitis, and enthesitis, highlighting how this disease can have an impact on more than just the patient's joints.[1,2] The prevalence of PsA is suggested to be similar to that of rheumatoid arthritis;[3] it is estimated to affect 0.3% to 1% of the population.[1]

Certolizumab pegol (Cimzia) (CZP) is a pegylated Fc-free, anti-tumour necrosis factor (TNF) for the treatment of PsA.[4] The Health Canada Notice of Compliance is to be used as monotherapy or in combination with methotrexate (MTX) to reduce signs and symptoms and inhibit the progression of structural damage as assessed by X-ray in adult patients with moderately to severely active PsA who have failed one or more disease-modifying antirheumatic drugs (DMARDs). CZP is also approved for use in adult patients with moderately to severely active rheumatoid arthritis (RA) and in adult patients with active ankylosing spondylitis (AS) who have had an inadequate response to conventional therapy.[4] 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 PsA is 200 mg every two weeks or 400 mg every four weeks.[4]

The objective of this review is to perform a systematic review of the beneficial and harmful effects of CZP for the treatment of adult patients with moderately to severely active PsA who have failed one or more DMARDs.

Results and Interpretation

Included Studies

RAPID-PsA, 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, adult-onset PsA of six months' duration or longer. RAPID-PsA (N = 409), a three-group superiority study, evaluated the efficacy and safety of CZP 200 mg administered subcutaneously (SC) every two weeks (Q2W) or CZP 400 mg administered SC every four weeks (Q4W) compared with placebo SC injection during a double-blinded duration of 24 weeks. The co-primary outcomes were the proportion of patients achieving a 20% improvement in American College of Rheumatology response (ACR 20) at week 12 and change from baseline in modified Total Sharp Score (mTSS) at week 24. Patients are considered ACR 20 responders if they achieve a 20% improvement from baseline in swollen and tender joint counts as well as in any three of the five ACR criteria.

The mTSS measures radiographic changes in joints. Scores range from 0 to 528, with higher scores indicating greater disease severity. Both CZP groups received a loading dose of 400 mg SC at baseline (week 0), week 2, and week 4. Placebo patients who did not achieve at least a minimal response (defined as failing to achieve at least a 10% decrease in both tender joints and swollen joints) at both week 14 and week 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. During the dose-blind period (weeks 24 to 48), patients originally randomized to placebo and not re-randomized to escape treatment at week 16 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. RAPID-PsA includes an ongoing, open-label extension (OLE) from week 48 to week 216, where patients continued to receive the same dosing regimen of CZP as 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 PsA trials due to ethical considerations, potentially limits the interpretation and clinical relevance of the trial data after week 16. 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 nonresponder imputation and with around 43% 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; however, it is not possible to determine the direction of the bias. Furthermore, a hierarchical testing procedure was used for select efficacy outcomes (ACR 20 at weeks 12 and 24; Health Assessment Questionnaire – Disability Index [HAQ-DI] at week 24; change from baseline in mTSS at week 24 and week 48; and Psoriasis Area and Severity Index 75 [PASI 75] at week 24). Thus, all other outcomes, as well as subgroup analyses, were not adjusted for multiplicity, and should be interpreted with caution. In addition, change from baseline in mTSS, which is a co-primary outcome in this study, was ranked as number six.

Efficacy

Both CZP regimens were statistically significantly superior to placebo in the proportion of patients achieving ACR 20 response. The mean absolute difference between CZP 200 mg and placebo was 33.7% (95% confidence interval [CI], 22.8% to 44.6%); and between CZP 400 mg and placebo, 27.6% (95% CI, 16.5% to 38.7%) at 12 weeks. The mean absolute difference between CZP 200 mg and placebo was 40.2% (95% CI, 29.5% to 51.0%) and between CZP 400 mg and placebo was 32.8% (95% CI, 21.8% to 43.8%) at 24 weeks. In addition, the proportion of patients achieving ACR 50, ACR 70, Disease Activity Score in 28 Joints (DAS 28), European League Against Rheumatism (EULAR) response of good, Psoriatic Arthritis Response Criteria (PsARC) responders, change from baseline in LEI, and change from baseline in LDI for both CZP regimens were also statistically significantly superior to placebo at weeks 12 and 24. Statistically significantly should be interpreted with caution for these tests because they were not included in the statistical analysis hierarchy, and hence the level of significance may be inflated.

Psoriasis Area and Severity Index (PASI) was used to assess psoriatic skin response. PASI is a measure of the extent and severity of psoriasis lesions. PASI 75 responders are those with a 75% improvement from baseline scores. The proportion of patients achieving PASI 75 and PASI 90 responses in both CZP regimens were also statistically significantly superior to placebo at weeks 12 and 24. “Statistically significantly” should be interpreted with caution for PASI 75, because it was ranked after the mTSS at 24 weeks, which failed to show statistical significance, and PASI 90 was not included in the statistical analysis hierarchy; hence, their level of significance may be inflated.

Results of the health-related quality of life [(HRQoL) short Form (36) survey (SF-36) scores] revealed an improvement from baseline in mental component summary (MCS) scores and physical component summary (PCS) scores for both CZP regimens that exceeded the established minimal clinically important difference (MCID). The improvement in MCS and PCS scores did not exceed the MCID in placebo treatment group. The mean changes from baseline to week 12 and week 24 in SF-36 PCS and SF-36 MCS

scores for both CZP treatment groups were statistically significantly higher than in the placebo group. Similarly, results from the PsA Quality of Life (PsAQoL) instrument indicated that both CZP 200 mg Q2W and CZP 400 mg Q4W treatment groups had statistically significantly better improvements relative to placebo for mean score change from baseline at weeks 12 and 24. No MCID has been defined for the PsAQoL; therefore, the clinical significance of these findings is uncertain. Moreover, statistically significant results for SF-36 and PsAQoL should be interpreted with caution, because they were not included in the statistical analysis hierarchy; hence, their level of significance may be inflated.

There were statistically significantly more patients achieving improvements in physical function (≥ 0.30 improvement HAQ-DI score), arthritis pain as assessed using Patient's Assessment of Arthritis Pain (PtAAP) visual analogue scale (VAS), and fatigue as assessed using the Fatigue Assessment Scale (FASCA) in CZP 200 mg Q2W and CZP 400 mg Q4W treatment groups compared with placebo at weeks 12 and 24. Statistically significant results for these tests should be interpreted with caution because they were not included in the statistical analysis hierarchy; hence, their level of significance may be inflated.

Overall, improvements in work productivity were demonstrated, as there was a statistically significant difference for five of eight questions in the Work Productivity Survey (WPS) among the CZP 200 mg Q2W group, and three of eight questions for the CZP 400 mg 4QW group when compared with placebo at week 12. There was a statistically significant difference for all eight questions among the CZP 200 mg Q2W group, and for five of eight questions for the CZP 400 mg 4QW group when compared with placebo at week 24. This outcome was not included in the statistical analysis hierarchy; hence, their results should be interpreted with caution.

There was no statistically significant difference between the CZP and placebo groups in the primary radiographic end point change from baseline in mTSS at week 24 when the prespecified imputation methods to account for missing data were used. In a post-hoc analysis, using the median mTSS change from baseline in the whole study population to impute missing values, CZP was associated with a statistically significant reduction in radiographic progression compared with placebo (least squares means mTSS change from baseline: combined CZP groups 0.06, placebo group 0.28, $P = 0.007$). Further post-hoc analyses using the mean mTSS change from baseline and maximum mTSS change from baseline in the whole study population to impute missing values supported these results. However, the results have uncertain clinical significance, given that the difference between combined CZP groups and placebo is 0.22 on a scale that ranges from 0 to 528 following 24 weeks of treatment. In addition, inhibition of progression of structural damage by CZP for up to 48 weeks was maintained only in a subgroup of patients at higher risk of radiographic progression (patients with a baseline mTSS score > 6).

Subgroup analyses were performed for prior TNF-alpha exposure for efficacy outcome ACR 20 and change from baseline in mTSS. It was found that regardless of whether or not patients were previously exposed to TNF inhibitors, ACR 20 responders for CZP 200 mg Q2W and CZP 400 mg Q4W were still statistically significantly higher than placebo in both CZP regimens. There was less progression of radiographic change in the CZP 200 mg Q2W + CZP 400 mg Q4W group compared with the placebo group in the subgroup of patients with prior use of TNF inhibitors, while in the subgroup of patients with no prior exposure to TNF inhibitors, the difference was not statistically significant compared with placebo.

We were unable to identify any studies in which CZP was compared directly or indirectly with any other biologic response modifiers (BRMs) in patients with PsA. The manufacturer conducted a Bayesian mixed-treatment comparison (MTC) that compared the efficacy of CZP with other BRMs. Despite the fact that

patient populations were somewhat heterogeneous, and despite certain potential methodological limitations, overall, CZP demonstrated similar efficacy compared with other BRMs in terms of ACR response, PASI and PsARC. This is potentially mostly applicable to the outcomes assessed at weeks 12 to 16, given the early-escape designs used in some of the studies included in the MTC.

Harms

Two deaths occurred in the double-blind period, one in each CZP treatment group; both deaths were considered unrelated to study medication by investigators. Over 24 weeks, the overall frequency of serious adverse events (SAEs) was 5.8%, 9.6%, and 4.4% in the CZP 200 mg Q2W, CZP 400 mg Q4W, and placebo groups, respectively. The overall frequency of withdrawals due to adverse events (WDAEs) was 2.9%, 4.4%, and 1.5% in the CZP 200 mg Q2W, CZP 400 mg Q4W, and placebo groups respectively. The overall frequency of treatment-emergent adverse events (TEAEs) was 68.1%, 71.1%, and 67.6% in the CZP 200 mg Q2W, CZP 400 mg Q4W, and placebo groups respectively. [redacted]. The safety profile of CZP in PsA during the 96 weeks was consistent with that observed during 24 weeks, with no new safety signals reported.

Conclusions

Based on one double-blind randomized controlled trial (RCT) in patients with active PsA, treatment with CZP (either 200 mg Q2W or 400 mg Q4W) resulted in statistically significant and clinically meaningful improvements in clinical response (ACR 20 and PASI) at weeks 12 and 24 when compared with placebo. Statistically and clinically significant improvements were also seen in quality of life, physical function, pain, and fatigue at 12 and 24 weeks. However, except for HAQ-DI, adjustment for multiplicity was not done for these other outcomes; hence, results for these outcomes should be interpreted with caution. Statistically significant improvements in work productivity were also demonstrated, but the clinical meaningfulness of these results remains uncertain; in addition, this analysis was not adjusted for multiplicity. Overall, the incidence of TEAEs was similar to placebo for both CZP groups, although the study was not designed to identify between-group differences in safety. Moreover, PsA 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, while typically used in recent PsA 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 nonresponder imputation for assessments at week 24, results for the patient-reported outcomes at week 24 are potentially biased.

TABLE 1: SUMMARY OF RESULTS

RAPID-PsA						
	Week 12			Week 24		
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO (n=136)	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO (N = 136)
ACR 20[a]						
% (95% CI)	58.0 (49.7 to 66.2)	51.9 (43.4 to 60.3)	24.3 (17.1 to 31.5)	63.8 (55.7 to 71.8)	56.3 (47.9 to 64.7)	23.5 (16.4 to 30.7)
Difference from PBO, % (95% CI)[b]	33.7 (22.8 to 44.6)	27.6 (16.5 to 38.7)	—	40.2 (29.5 to 51.0)	32.8 (21.8 to 43.8)	—
P value[b]	< 0.001	< 0.001	—	< 0.001	< 0.001	—
EULAR RESPONSE OF GOOD, N (%)[c]						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO, % (95% CI)[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSARC RESPONDERS[a]						
N (%)	[redacted]	[redacted]	[redacted]	108 (78.3)	104 (77.0)	45 (33.1)
Difference from PBO, % (95% CI)[b]	[redacted]	[redacted]	[redacted]	45.2 (34.7 to 55.7)	43.9 (33.3 to 54.6)	—
P value[b]	[redacted]	[redacted]	[redacted]	< 0.001	< 0.001	—
PASI 75 RESPONDERS[a]						
N (%)	[redacted]	[redacted]	[redacted]	56 (62.2)	46 (60.5)	13 (15.1)[f]
Difference from PBO, % (95% CI)[b]	[redacted]	[redacted]		47.1 (34.6 to 59.7)	45.4 (32.1 to 58.8)	—
P value[b]	[redacted]	[redacted]		< 0.001	< 0.001	—
CHANGE FROM BASELINE IN HAQ-DI[fg]						
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from PBO (SE)[h]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHANGE FROM BASELINE IN PSAQOL[f]						
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from PBO (SE)[h]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHANGE FROM BASELINE IN SF-36 PCS[f]						
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from PBO (SE)[h]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

RAPID-PsA						
	Week 12			Week 24		
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO (n=136)	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO (N = 136)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHANGE FROM BASELINE IN SF-36 MCS[f]						
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from PBO (SE)[h]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHANGE FROM BASELINE IN PTAAP-VAS[f]						
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from PBO (SE)[h]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHANGE FROM BASELINE IN FASCA[f]						
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference from PBO (SE)[h]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHANGE FROM BASELINE AT WEEK 24 IN MTSS (PRESPECIFIED ANALYSES)[l]						
PRESPECIFIED ANALYSES						
LS mean change from baseline (SE)			18.28 (6.07)[j]	11.5 (7.59)	25.1 (7.92)	28.9 (7.73)
P value			0.203[j]	0.071	0.688	
POST-HOC PRIMARY ANALYSIS WITH ANCOVA: MEDIAN MTSS CHANGE FROM BASELINE OF ALL PATIENTS OBSERVED						
LS mean change from baseline (SE)[h]			0.06 (0.06)[j]	0.01 (0.07)	0.11 (0.08)	0.28 (0.07)[k]
95% CI			(–0.06 to 0.17)[j]	(−0.14 to 0.15)	(−0.04 to 0.26)	(0.13 to 0.42)[k]
LS mean difference from PBO (SE)[h]			–0.22 (0.08)[j]	−0.27 (0.09)	−0.17 (0.09)	
95% CI			(–0.38 to –0.06)[j]	(−0.45 to −0.08)	(−0.35 to 0.02)	
P value			0.007[j]	0.004	0.072	
HARMS						
N	—	—	—	[redacted]	[redacted]	[redacted]
Deaths	—	—	—	[redacted]	[redacted]	[redacted]

RAPID-PsA						
	Week 12			Week 24		
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO (n=136)	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO (N = 136)
SAEs, N (%)	—	—	—	[redacted]	[redacted]	[redacted]
WDAEs, N (%)	—	—	—	[redacted]	[redacted]	[redacted]
Notable harms	—	—	—			
Serious infections	—	—	—	[redacted]	[redacted]	[redacted]
Malignancy	—			[redacted]	[redacted]	[redacted]
Increased ALT	—			[redacted]	[redacted]	[redacted]
Increased AST	—	—	—	[redacted]	[redacted]	[redacted]
Hepatic enzyme increased	—	—	—	[redacted]	[redacted]	[redacted]
Blood CPK increased	—	—	—	[redacted]	[redacted]	[redacted]

ACR = American College of Rheumatology; ALT = alanine aminotransferase; AST = aspartate transaminase; CI = confidence interval; CPK = creatinine phosphokinase; CZP = certolizumab pegol; DAS 28 (CRP) = Disease Activity Score-28 joint count (C-reactive protein); EULAR = European League Against Rheumatism; HAQ-DI = Health Assessment Questionnaire – Disability Index; LS = least squares; PASI = Psoriasis Area and Severity Index; PBO = placebo; PsARC = Psoriatic Arthritis Response Criteria; Q2W = every two weeks; Q4W = every four weeks; RS = randomized set; SD = standard devision; SE = standard error.

[a] Patients who withdrew for any reason, or placebo patients who used escape medication, were considered as nonresponders from the time they dropped out or when escape therapy was initiated. Patients who had missing data at a visit were counted as nonresponders for the respective visit.

[b] Treatment difference and corresponding 95% CI and *P* value were estimated using a standard two-sided Wald asymptotic test with a 5% alpha level.

[c] A EULAR response of "good" was defined as an improvement in DAS 28(CRP) of > 1.2 and a score of ≤ 3.2 (possible scores range from 0 to 28).

[d] Calculated by CADTH using Review Manager; positive values indicate that more patients in the CZP treatment group achieved response in comparison with patients in the placebo treatment group.

[e] Placebo patients who escaped to CZP utilized the missing category from the time the escape medication was initiated.

[f] For patients who withdrew for any reason, patients with a missing measurement, or placebo patients who used escape medication, the last observation prior to the early withdrawal or the missing measurement or before receiving CZP was carried forward.

[g] HAQ-DI score range 0–3; reduction in score indicates improvement.

[h] Analysis of covariance model with treatment, region, and prior TNFα-antagonist exposure (yes/no) as factors and baseline score as a covariate.

[i] mTSS score range 0 to 528; mTSS nonprogressors defined as participants with a change in score of ≤ 0 from baseline (predefined) or ≤ 0.5 (post hoc).

[j] For CZP 200 mg Q2W + CZP 400 mg Q4W groups combined.

[k] For the entire placebo group, linear extrapolations were used for patients escaping to CZP.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Psoriatic Arthritis (PsA) is a heterogeneous disease, associated with multiple and variable clinical features. Patients suffer from chronic inflammatory peripheral arthritis and in addition, may also suffer from skin and nail disease, axial disease, dactylitis, and enthesitis, highlighting how this disease can have an impact on more than just the patients' joints.[1,2] It can result in significant disease burden, functional impairment, increased comorbidity and mortality, and reduced health-related quality of life (HRQoL).[2,5,6] The prevalence of PsA is suggested to be similar to that of rheumatoid arthritis(RA);[3] it is estimated to affect 0.3% to 1% of the population.[1] With effective treatment, functional disabilities and quality of life can effectively be improved;[7] however, there is no one treatment regimen that works on every person. Hence, different treatment options are required.

1.2 Standards of Therapy

Clinical practice guidelines provide definitions of mild, moderate, and severe PsA, but these definitions vary with the symptoms being considered.[2] For example, with respect to peripheral arthritis, mild disease is considered involvement of fewer than five joints, with no damage as assessed by X-ray; moderate disease is considered to be involvement of five or more joints, with damage assessed by X-ray and moderate impact on function and quality of life; severe disease is considered to be involvement of five or more joints with severe damage visible on X-ray and a severe impact on function and quality of life.

With respect to psoriasis, body surface area (BSA) involvement < 5% and a Psoriasis Area and Severity Index (PASI) > 5 are considered mild disease; non-response to topical treatments and with a PASI < 10 is considered moderate disease; BSA involvement > 10% and a PASI > 10 is considered severe disease. With respect to enthesitis, mild disease is considered involvement of one or two sites with no loss of function; moderate disease is considered involvement of more than two sites or loss of function; severe disease is considered loss of function or involvement of more than two sites and failure of response. Other symptoms that should be assessed for severity include spinal disease and dactylitis. Therefore, severity of disease in PsA is difficult to classify and can depend on how the disease manifests itself in each person and the severity of different symptoms.

Several drug classes are employed in the treatment of PsA, including nonsteroidal anti-inflammatory drugs (NSAIDs); disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX), sulfasalazine, and leflunomide; immunosuppressives (cyclosporine); and tumour necrosis factor α (TNFα) inhibitors, such as etanercept, infliximab, golimumab, adalimumab, certolizumab, and ustekinumab. Even though there were only two small controlled trials of inadequate power that evaluated MTX for PsA, it remains the primary treatment post-NSAIDs.[8] The next line of treatment involves the biologic TNFα inhibitors, should the DMARDs fail or if there are contraindications. If the first TNFα inhibitor fails, then another TNFα inhibitor can be offered.[2]

1.3 Drug

Certolizumab pegol (CZP) (Cimzia) is a TNFα inhibitor consisting of a recombinant, humanized antibody Fab' fragment with specificity for human TNFα, conjugated to polyethylene glycol (PEG).[4] In Canada, CZP is indicated: 1) 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 PsA who have failed one or more DMARDs; 2) in combination with 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 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) for reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) who have had an inadequate response to conventional therapy.[4] 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 PsA is 200 mg every two weeks or 400 mg every four weeks.[4] In addition to CZP, five other anti-TNFα drugs — etanercept, infliximab, golimumab, adalimumab, and ustekinumab — are currently approved in Canada to treat PsA patients (Table 2).

Indication under review
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 who have failed one or more DMARDs.
Listing criteria requested by sponsor
As per indication.

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

	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab	Ustekinumab
Mechanism of Action	A recombinant human IgG1 monoclonal antibody that inhibits binding of TNF to TNF receptors	A recombinant, humanized antibody Fab' fragment that inhibits binding of TNF to TNF receptors	A dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) TNF receptor linked to the Fc portion of human IgG1; 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	A fully human IgG1κ monoclonal antibody that binds to the shared p40 subunit of human cytokines IL-12 and IL-23, preventing them from binding to the IL-12Rβ1 receptor protein on surface immune cells
Indication[a]	Reducing the signs and symptoms of active arthritis; inhibiting the progression of structural damage; and improving the physical function in adult PsA patients. It can be used in combination with MTX in patients who do not respond adequately to MTX alone.	Reducing the signs and symptoms and inhibiting the progression of structural damage as assessed by X-ray in adult patients with moderately to severely active PsA who have failed one or more DMARDs. It can be used alone or in combination with MTX.	Reducing the signs and symptoms and inhibiting the progression of structural damage of active arthritis, and improving physical function in adult patients with PsA. It can be used in combination with MTX in adult patients who do not respond adequately to MTX alone.	Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active PsA. It can be used in combination with MTX in patients who do not respond adequately to MTX alone.	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with PsA.	Treatment of adult patients with active PsA. It can be used alone or in combination with MTX.

	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab	Ustekinumab
Route of Administration	SC				IV	SC
Recommended Dose	40 mg administered every other week as a SC injection	Loading dose of 400 mg (given as two SC injections of 200 mg each) initially (week 0) and at weeks 2 and 4 followed by a maintenance dose of 200 mg every two weeks or 400 mg every four weeks	50 mg per week in one SC injection or two 25 mg SC injections on the same day, once weekly or three or four days apart	50 mg SC once a month on the same date each month	5 mg/kg given as an IV infusion followed with additional similar doses at two and six weeks after the first infusion, then every eight weeks thereafter	45 mg administered at weeks 0 and 4, then every 12 weeks thereafter. Alternately, 90 mg may be used in patients with a body weight > 100 kg.
Serious Side Effects or Safety Issues	Infections, particularly opportunistic ones and TB Malignancies Allergic reactions Injection or infusion site reactions					Infections; reactivation of latent infections; injection site reactions; malignancies; RPLS

DMARD = disease-modifying antirheumatic drug; IgG1 = immunoglobin G1; IV = intravenous injection; MTX = methotrexate; PsA = psoriatic arthritis; RPLS = Reversible Posterior Leukoencephalopathy Syndrome; SC = subcutaneous injection; TB = tuberculosis; TNF = tumour necrosis factor.

[a] Health Canada indication.

Source: Health Canada product monographs.[4,9-13]

2. OBJECTIVES AND METHODS

2.1 Objective

To perform a systematic review of the beneficial and harmful effects of CZP at recommended doses, alone or in combination with MTX in adult patients with moderately to severely active PsA who have failed one or more DMARDs.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Other studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with moderate to severely active PsA who have failed ≥ 1 DMARDs. **Subgroups of interest:** • Body weight at baseline (< 100 KG versus > 100 KG) • Region • Number of prior DMARDs and/or biologic response modifiers • Disease severity (based on DAS 28)
Intervention	Certolizumab pegol at recommended doses, alone or in combination with MTX
Comparators	Individual or combination therapy with: • Biological response modifiers (e.g., infliximab, etanercept, adalimumab, golimumab, ustekinumab) • Other DMARDs, including MTX
Outcomes	**Efficacy outcomes:** • Outcome measures of psoriatic arthritis symptoms (e.g., ACR 20/50/70, DAS 28, PsARC) • Health-related quality of life (e.g., SF-36, HAQ-DI, PsAQoL, EQ-5D) • Work productivity • Psoriatic outcome measures (e.g., PASI, NAPSI) • Radiographic changes **Harms outcomes:** • Mortality, SAEs, AEs, WDAEs • Notable harms: serious infections (including tuberculosis), malignancies, heart failure, hypersensitivity reactions, and hepatotoxicity (liver function tests)
Study Design	Published and unpublished phase 3 RCTs

ACR = American College of Rheumatology; AE = adverse event; DAS = Disease Activity Score; DB = double-blind; DMARD = disease-modifying antirheumatic drugs; EQ-5D = EuroQoL Health Status Questionnaire; HAQ-DI = Health Assessment Questionnaire – Disability Index; MTX = methotrexate; NAPSI = Nail Psoriasis Severity Index; PASI = Psoriasis Area and Severity Index; PsAQoL = Psoriatic Arthritis Quality of Life; PsARC = Psoriatic Arthritis Response Criteria; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; SF-36 = Short Form (36) Health Survey; 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 Subject Headings), and keywords. The main search concepts were certolizumab (Cimzia) and PsA.

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 November 19, 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/en/resources/finding-evidence-is/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 drug manufacturer was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (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; excluded studies (with reasons) are presented in Appendix 3: EXCLUDED STUDIES.

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 studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in Appendix 3: EXCLUDED STUDIES.

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

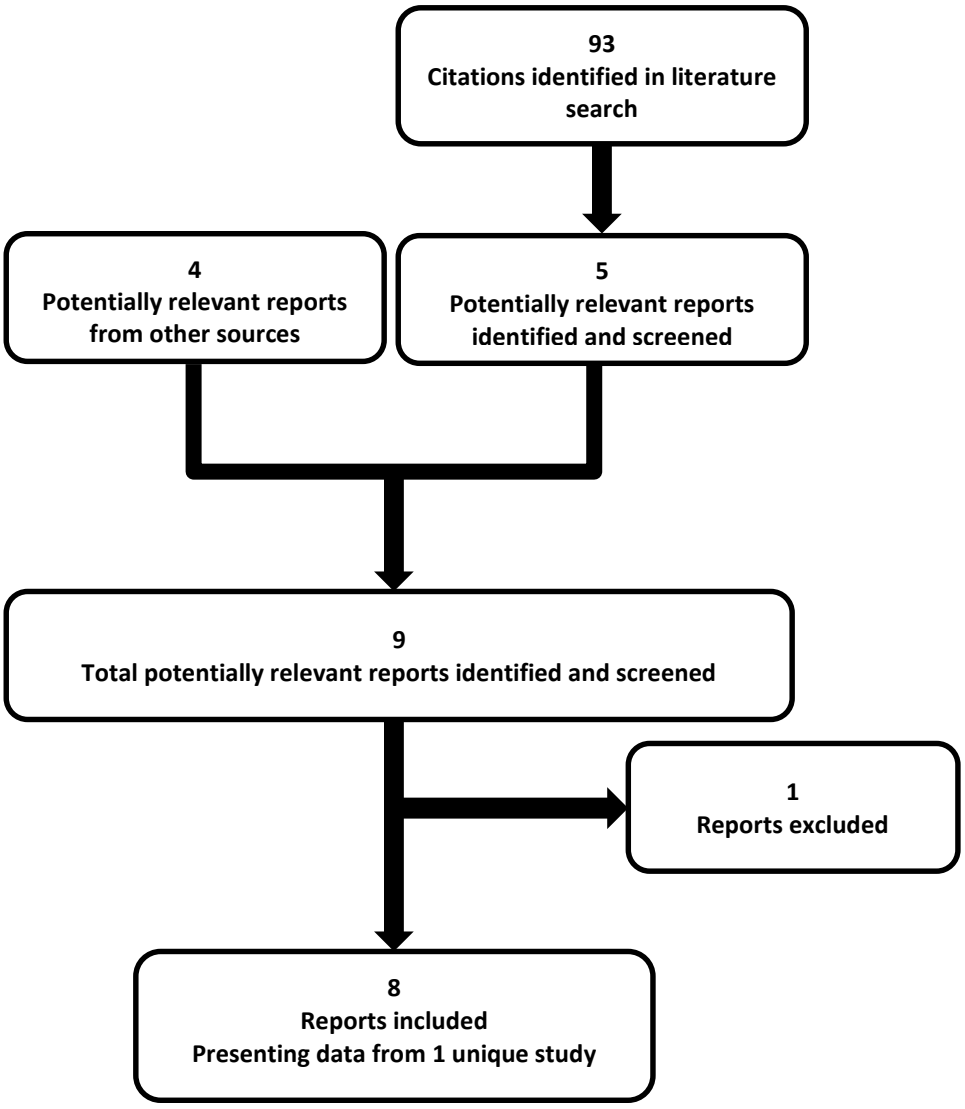


TABLE 4: DETAILS OF INCLUDED STUDIES

		RAPID-PsA
DESIGNS & POPULATIONS	**Study Design**	Phase 3, placebo-controlled, DB, multi-centre RCT
	Locations	92 centres in USA, Canada, Argentina, Brazil, Belgium, Czech Republic, France, Germany, Hungary, Ireland, Italy, Mexico, Poland, Spain, UK
	Randomized (N)	409
	Inclusion Criteria	Adults (aged ≥ 18 years) with a diagnosis of adult-onset PsA (defined by the CASPAR criteria) of at least six months' duration. Must have arthritis defined as ≥ 3 tender and ≥ 3 swollen joints at screening and at baseline, and either ESR ≥ 28 mm/h or CRP > upper limit of normal; have previously failed ≥ 1 DMARD; and have active psoriatic skin lesions or a documented history of psoriasis. Up to 40% of patients could have received a TNF inhibitor previously.
	Exclusion Criteria	• Other inflammatory diseases, previous exposure to > 1 TNF inhibitor or > 2 biologics for the treatment of PsA or psoriasis, or primary failure to any TNF inhibitor • Evidence of latent or active TB • Chronic or clinically significant infections, demyelinating disease of the central nervous system, or malignancy • Breastfeeding, pregnant, or planning a pregnancy during the study or within 3 months of receiving the last administration of study drug
DRUGS	**Intervention**	CZP 400 mg SC loading dose at week 0 (baseline), week 2, and week 4, followed by either: • CZP 200 mg Q2W SC or • CZP 400 mg Q4W SC
	Comparator(s)	Placebo pre-filled syringe administered as Q2W SC
DURATION	**Phase**	
	Double-blind	24 weeks (week 0 to 24)
	Dose-blind	24 weeks (week 24 to 48)
	Open-label	168 weeks (week 48 to 216) (ongoing)
	Follow-up	10 weeks (week 216 to 224) (safety follow-up)
OUTCOMES	**Primary End Point**	Co-primary: • ACR 20 response at week 12 • Change from baseline in mTSS at week 24
	Other End Points	• ACR 20 response at week 24 • PsARC responder at weeks 12, and 24 • Change from baseline in DAS 28 • Change from baseline in HAQ-DI at week 24 • Change from baseline in PsAQoL at weeks 12 and 24 • Change from baseline in SF-36 through week 48 • Change from baseline in PtAAP-VAS at weeks 12 and 24 • Change from baseline in FASCA at weeks 12 and 24 • Scores on the Work Productivity Survey at weeks 4, 12, and 24 • PASI 75 response at weeks 12 and 24[a] • PASI 90 response at weeks 12 and 24[a] • Change from baseline in the LDI at weeks 12 and 24 • Change from baseline in the LEI at weeks 12 and 24 • Change from baseline in mTSS at week 48

NOTES	**Publications**	Mease et al.[14]

ACR = American College of Rheumatology; CASPAR = Classification Criteria for Psoriatic Arthritis; CRP = C-reactive protein; DAS = Disease Activity Score; CZP = certolizumab pegol; DB = double-blind; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; FASCA = Fatigue Assessment Scale; HAQ-DI = health assessment questionnaire-disability index; LDI = Leeds Dactylitis Index; LEI = Leeds Enthesitis Index; mTSS = modified Total Sharp Score; PASI = Psoriasis Area and Severity Index; PsAQoL = Psoriatic Arthritis Quality of Life; PsARC = Psoriatic Arthritis Response Criteria; PtAAP = Patient's Assessment of Arthritis Pain; Q2W = every two weeks; Q4W = every four weeks; RCT = randomized controlled trial; SC = subcutaneous; TB = tuberculosis; TNF = tumour necrosis factor; VAS = visual analogue scale.

[a] In the subgroup of patients with PSO involving at least 3% BSA at baseline.

Source: Mease et al.,[14] Clinical Study Report, week 24.[15]

* Six additional reports were included: van der Heijde et al.,[16] Kavanaugh et al.,[17] Gladman et al.,[18] Clinical Study Protocol;[19] CDR submission;[20] Health Canada reviewer's report.[21]

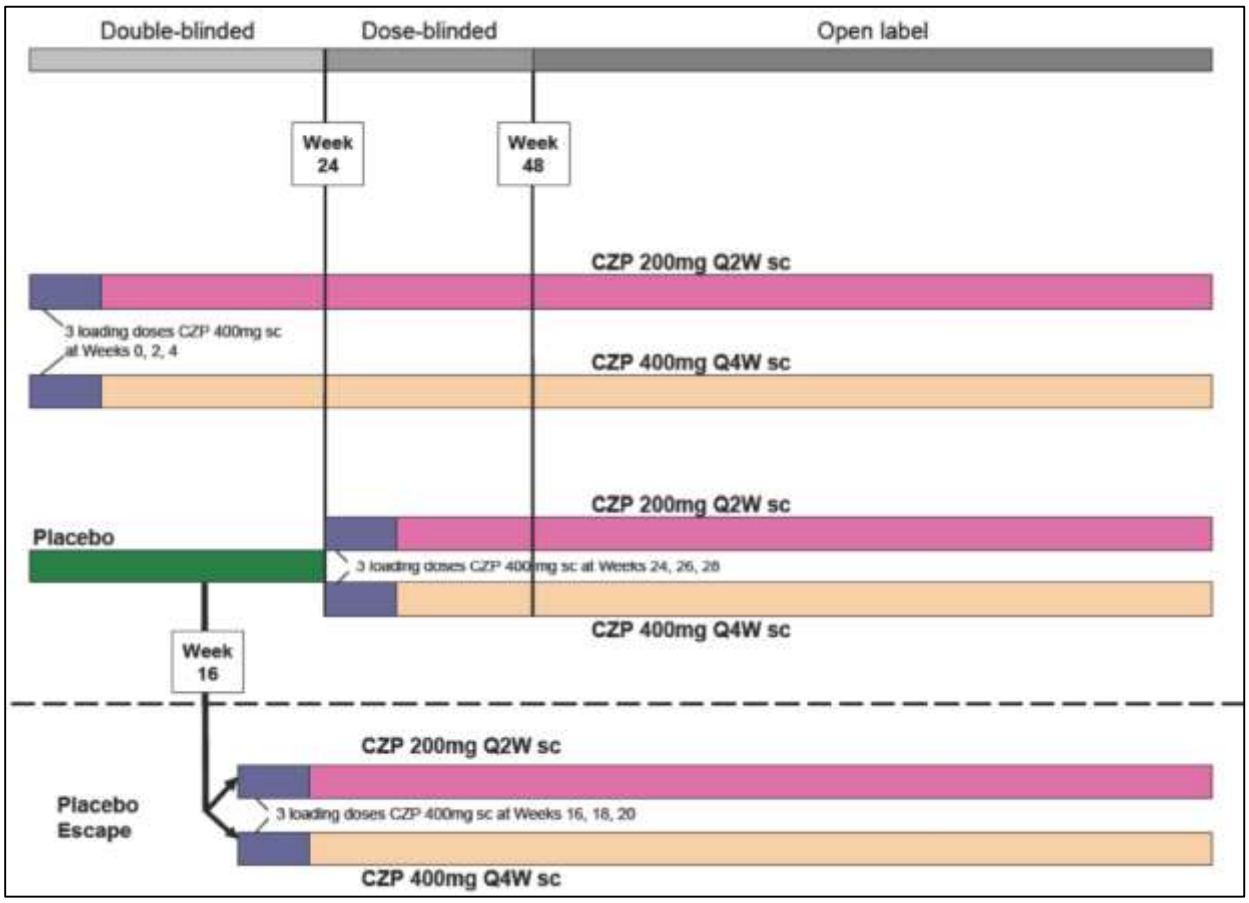
3.2 Included Studies

3.2.1 Description of Studies

RAPID-PsA, a phase 3, multi-centre, randomized, double-blind, placebo-controlled study, met the inclusion criteria for this systematic review. RAPID-PsA (N = 409), 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 during a double-blinded duration of 24 weeks. Both CZP groups received a loading dose of 400 mg SC at baseline (week 0), week 2, and week 4. Placebo patients who did not achieve at least a minimal response (defined as patients who failed to achieve at least a 10% decrease in both tender joints and swollen joints) 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, receiving loading doses of CZP 400 mg SC at weeks 16, 18, and 20, followed by either CZP 200 mg Q2W or CZP 400 mg Q4W) in a blinded fashion from week 16 onward. Study treatments were administered by unblinded trained site personnel. Randomization was stratified by site and prior exposure to a TNF inhibitor.

During the dose-blind period (weeks 24 to 48), patients originally randomized to placebo and not re-randomized to escape treatment in week 16 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. RAPID-PsA includes an ongoing, open-label extension (OLE) from week 48 to week 216 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 RAPID-PsA can be found below (Figure 2).

FIGURE 2: RAPID-PSA SCHEMATIC DESIGN



CZP = certolizumab pegol; Q2W = every two weeks; Q4W = every four weeks; SC = subcutaneous.
Source: Clinical Study Report RAPID-PsA week 24.[15]

3.2.2 Populations

a) Inclusion and exclusion criteria

RAPID-PsA included patients 18 years of age or older with adult-onset PsA of at least six months' duration as defined by the Classification of Psoriatic Arthritis (CASPAR) criteria. Patients had to have active psoriatic skin lesions or a documented history of psoriasis, and had to have active arthritis as defined by each of the following: 1) three or more tender joints; 2) three or more swollen joints; 3) either erythrocyte sedimentation rate (ESR) ≥ 28 mm/h or C-reactive protein (CRP) above the upper limit of normal (7.9 mg/L). Patients must have failed one or more DMARDs. No more than 40% of patients could have received a prior TNF inhibitor. Patients were excluded if they had: a diagnosis of any other inflammatory arthritis; a secondary, non-inflammatory condition symptomatic enough to interfere with the evaluation of CZP for PsA; received prior treatment with more than one anti-TNF drug or more than two biological response modifiers for PsA or psoriasis; chronic/recent infection or a high risk of infection; a history of malignancy, demyelinating disease, or class 3/4 congestive heart failure.

b) Baseline characteristics

The treatment groups in the RAPID-PsA trial were generally balanced with respect to demographics and baseline characteristics across the treatment groups in all patients. The placebo group had a lower mean duration of PsA (7.9 years) compared with the CZP 200 mg Q2W (9.6 years) and 400 mg Q4W (8.1 years) groups at baseline. The majority of patients were Caucasian (~ 98%) and approximately 55% of patients were female. There were 19.1%, 22.5%, and 17.0% of patients with prior anti-TNF exposure in the placebo, CZP 200 mg Q2W, and CZP 400 mg Q4W treatment groups, respectively. In addition, 61.8%, 63.8%, and 65.2% of patients were on concomitant MTX in the placebo, CZP 200 mg Q2W, and CZP 400 mg Q4W treatment groups, respectively (Table 5).

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Characteristics	RAPID-PsA		
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO (N = 136)
Demographic Characteristics			
Age, mean (SD)	48.2 (12.3)	47.1 (10.8)	47.3 (11.1)
Female, N (%)	74 (53.6)	73 (54.1)	79 (58.1)
Weight, kg, mean (SD)	85.8 (17.7)	84.8 (18.7)	82.6 (19.9)[a]
Race, white, N (%)	135 (97.8)	133 (98.5)	132 (97.1)
Disease Characteristics			
PsA duration in years, mean (SD)	9.6 (8.5)	8.1 (8.3)	7.9 (7.7)
CRP (mg/L), median (min, max)	7.0 (0.2, 238.0)	8.7 (0.1, 87.0)	9.0 (0.2, 131.0)
ESR (mm/h), median (min, max)	35.0 (5.0, 125.0)	33.0 (4.0, 120.0)	34.0 (6.0, 125.0)
Tender joint count (0–68 joints), mean (SD)	21.5 (15.3)	19.6 (14.8)	19.9 (14.7)
Swollen joint count (0–66 joints), mean (SD)	11.0 (8.8)	10.5 (7.5)	10.4 (7.6)
DAS 28(CRP)	5.04	4.99	4.99
mTSS	18.0 (30.6)	22.8 (46.5)	24.4 (49.7)
PtAAP by VAS, mm, mean (SD)	59.7 (20.7)	61.1 (18.5)	60.0 (22.0)
HAQ-DI (range 0–3), mean (SD)	1.3 (0.7)	1.3 (0.6)	1.3 (0.7)
Enthesitis, N (%)	88 (63.8)	84 (62.2)	91 (66.9)
Dactylitis, N (%)	47 (34.1)	47 (34.8)	45 (33.1)
Psoriasis BSA ≥ 3%, N (%)	90 (65.2)	76 (56.3)	86 (63.2)
PASI, median (min, max)	7.1 (0.3, 55.2)	7.0 (0.6, 72.0)	8.1 (0.6, 51.8)
Nail psoriasis, N (%)	92 (66.7)	105 (77.8)	103 (75.7)
Prior and Concomitant Medication Use			
Concomitant MTX at baseline, N (%)	88 (63.8)	88 (65.2)	84 (61.8)
No concomitant DMARDs at baseline, N (%)	39 (28.3)	35 (25.9)	48 (35.3)

Characteristics	RAPID-PsA		
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO (N = 136)
Prior use of DMARDs, N (%)			
1	61 (44.2)	72 (53.3)	74 (54.4)
≥ 2	73 (52.9)	60 (44.5)	60 (44.1)
Prior TNF inhibitor exposure, (%)	31 (22.5)	23 (17.0)	26 (19.1)

BSA = body surface area; CRP = C-reactive protein; CZP = certolizumab pegol; DAS = Disease Activity Score; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; HAQ-DI = health assessment questionnaire-disability index; mTSS = modified Total Sharp Score; MTX = methotrexate; PASI = Psoriasis Area and Severity Index; PBO = placebo; PsA = psoriatic arthritis; PtAAP = Patient's Assessment of Arthritis Pain; Q2W = every two weeks; Q4W= every four weeks; SD = standard deviation; TNF = tumour necrosis factor; VAS = visual analogue scale.
[a] N = 135.
Source: Mease et al.,[14] Interim Clinical Study Report, week 24.[15]

3.2.3 Interventions

Study treatments (including placebo) were administered at weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22. Patients randomized to receive CZP received CZP administered SC at the dose of CZP 400 mg Q2W at weeks 0, 2, and 4, followed by either CZP SC 200 mg Q2W (starting at week 6) or CZP SC 400 mg Q4W (starting at week 8). Starting at week 6, all patients received single injections every four weeks, where patients in CZP 400 mg Q4W and placebo treatment groups received one placebo injection while patients in CZP 200 mg Q2W received one injection of CZP 200 mg. Starting at week 8, all patients received two injections every four weeks, where patients in the CZP 400 mg Q4W treatment group received two injections of CZP 200 mg each, patients in CZP 200 mg Q2W treatment group received one injection of CZP 200 mg and one injection of placebo, and patients in the placebo group received two injections of saline. [redacted]

NSAIDs, cyclooxygenase-2 inhibitors, analgesics, and DMARDs (sulfasalazine, MTX, or leflunomide) were permitted during the study. Corticosteroids and phototherapy as well as topical medications for psoriasis were permitted to be used after the first 48 weeks of the study.

3.2.4 Outcomes

The two primary efficacy end points were the 20% improvement in American College of Rheumatology response (ACR 20) at week 12 (200 mg Q2W and 400 mg Q4W separately) and change from baseline in modified Total Sharp Score (mTSS) at week 24 (200 mg Q2W and 400 mg Q4W combined).

a) American College of Rheumatology 20/50/70

The ACR criteria[22] for assessing joint status (originally developed for RA patients) provide a composite measure of ≥ 20%, ≥ 50%, or ≥ 70% improvement in both swollen and tender joint counts and at least three of five additional disease criteria, including: patient and physician global assessments of disease activity (10 cm visual analogue scale [VAS]), health assessment questionnaire (HAQ), patient assessment

of pain intensity, and levels of CRP or ESR. ACR 20 is generally accepted as the minimal clinically important difference (MCID) indicating a response to treatment. ACR 20 at week 12 was a co-primary outcome.

b) Psoriatic Arthritis Response Criteria

The Psoriatic Arthritis Response Criteria (PsARC)[23] measure the signs and symptoms of PsA assessed by tender and/or swollen joint count, physician global assessment (0 to 5 Likert scale), and patient global assessment (0 to 5 Likert scale). To be a considered a PsARC "responder," a patient must have at least a 30% reduction in tender or swollen joint count, as well as a 1-point reduction on the 5-point patient and/or physician global assessment scales, and no worsening on any score.

c) Disease Activity Score 28 and C-reactive Protein

The Disease Activity Score in 28 Joints (DAS 28) includes a 28-item assessment of tender and swollen joints along with a patient global assessment of well-being to evaluate a patient's response to treatment and CRP.[24,25] The score ranges from 0 to 9.4 with higher scores indicating greater disease activity.

The threshold values are 2.6, 3.2, and 5.1 for remission, low disease activity, and high disease activity, respectively.[26] Patients were considered DAS responders if they had a good or moderate response defined according to baseline DAS values:[25]

Current DAS 28	Improvement in DAS 28 From Baseline		
	> 1.2	> 0.6 to ≤ 1.2	≤ 0.6
≤ 3.2	Good	Moderate	None
3.2 to ≤ 5.1	Moderate	Moderate	None
5.1	Moderate	None	None

d) Psoriasis Area and Severity Index

The PASI is a widely used instrument in psoriasis trials that assesses and grades the severity of psoriatic lesions and the patient's response to treatment. It produces a numeric score ranging from 0 to 72. In general, a PASI score of 5 to 10 is considered moderate disease and a score higher than 10 is considered severe. A 75% reduction in the score (PASI 75) is the current benchmark for most clinical trials in psoriasis and is the criterion for efficacy of new psoriasis treatments approved by the FDA.[27]

e) Health Assessment Questionnaire

The HAQ was developed to assess physical disability and pain in RA[28] and has been used extensively in arthritis randomized controlled trials (RCTs), including for PsA. Through a self-assessed questionnaire covering eight domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities), patients' difficulty in performing these activities is scored from 0 (without any difficulty) to 3 (unable to do). The MCID for the HAQ ranges from 0.3 to 0.35.[29,30]

f) Medical Outcomes Study Short Form 36

The Medical Outcome Study Short Form (36) Health Survey (SF-36) is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[31] The SF-36 consists of eight health domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH).[32] The eight domains are aggregated to create two component summaries: the physical component summaries (PCS) and the mental component summary (MCS), with scores ranging from 0 to 100, with higher scores indicating better health status. The MCID for either the PCS or MCS of the SF-36 is typically between 2.5 and 5 points.[33-35] Leung et al.[36] reported MCIDs of 3.74 and 1.77 in PsA patients treated with anti-TNFα drugs

for the PCS and MCS subsections, respectively. In the RAPID-PsA trial, a patient was considered a PCS or MCS responder if the patient had an increase of ≥ 2.5 points from baseline.

g) Psoriatic Arthritis Quality of Life

The Psoriatic Arthritis Quality of Life (PsAQoL) is a quality of life instrument specific to psoriatic arthritis.[37] The PsAQoL comprises 20 items so that the score ranges from 0 to 20, with higher scores indicating worse HRQoL.[15] It has been used in clinical studies and trials to assess the impact of interventions for PsA. It is well accepted by patients and has acceptable scaling and psychometric properties.[37]No MCID for PsAQoL was identified.

h) Patient's Assessment of Arthritis Pain – VAS (PtAAP-VAS)

The Patient's Assessment of Arthritis Pain – Visual Analogue Scale (PtAAP-VAS) is part of ACR core set of measures in arthritis.[15,38] The PtAAP-VAS consists of a horizontal line 100 mm in length on which patients are asked to indicate the level of their arthritis pain at the day of the visit, between 0 ("no pain") and 100 ("most severe pain").[15] The MCID for the pain was defined as a 10-point decrease from baseline.[18,39]

i) Fatigue Assessment Scale

The Fatigue Assessment Scale (FASCA) is a validated Numeric Rating Scale — a single-item instrument consisting of numerals from 0 to 10 on a horizontal line, with 0 representing "no fatigue" and 10 representing "fatigue as bad as you can imagine." Participants were asked to rate their fatigue (weariness, tiredness) during the previous week on the scale, choosing a single number from 0 to 10.[40] A 1-point decrease from baseline was suggested as MCID for FAS.[18]

j) Leeds Dactylitis Index

Dactylitis, the swelling of an entire digit related to articular and periarticular inflammation, is a characteristic of inflammatory spondyloarthropathies, including PsA. The presence of dactylitis was assessed using the Leeds Dactylitis Index (LDI) basic, which evaluates for a ≥ 10% difference in the circumference of a digit compared with the opposite digit.[15,41,42] No MCID for LDI was identified.

k) Leeds Enthesitis Index

Enthesitis, the inflammation at the bone insertion of a tendon or ligament, is common in PsA. The Leeds Enthesitis Index (LEI) is a new enthesitis index designed for use in PsA[15,43] and recently adopted for use in randomized controlled studies involving patients with PsA. Enthesitis was assessed by palpation on the lateral humeral epicondyles (elbows), medial femoral epicondyles (knees), and Achilles tendons (heels) bilaterally, and scored as 0 (no pain) and 1 (painful).[15] No MCID for LEI was identified.

l) Work Productivity Survey

The Work Productivity Survey (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.

m) Modified Total Sharp Score (mTSS)

The modified Total Sharp Score (mTSS) allows for the assessment of two different aspects of joint damage: articular erosions (representing direct invasion of cartilage and bone by the proliferating synovial pannus) and joint space narrowing (representing destruction of surface cartilage). The van der Heijde erosion score includes 16 joints from the hands and wrists (graded from 0 to five) and six joints from the feet (graded from 0 to 10). The joint space narrowing score includes 15 areas from the hands and wrists (graded from 0 to 4) and six areas from the feet (also graded from zero to four). The mTSS Score was modified for PsA by adding hand distal interphalangeal joints. The maximum possible scores were 320 for erosions, 208 for JSN, and 528 for the total score. Radiographs tend to change slowly in RA, requiring at least six months to a year to detect changes in a single patient. Inter-rater and intra-rater reliability is also a concern, due to the subtle nature of changes and subjective interpretation. The images themselves can also vary between samples, due to positioning and quality. An MCID of 4.6 units for the Sharp/van der Heijde method was determined, using a panel of experts.[44] In RAPID-PsA, all enrolled patients were required to have radiographs taken of both hands and both feet at baseline; at weeks 12 and 24; and at early withdrawal. Radiographs were read centrally and independently by two experienced readers. A change from baseline in mTSS at week 24 (200 mg Q2W and 400 mg Q4W combined) was a co-primary outcome.

3.2.5 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.

3.2.6 Statistical Analysis

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.3 Patient Disposition

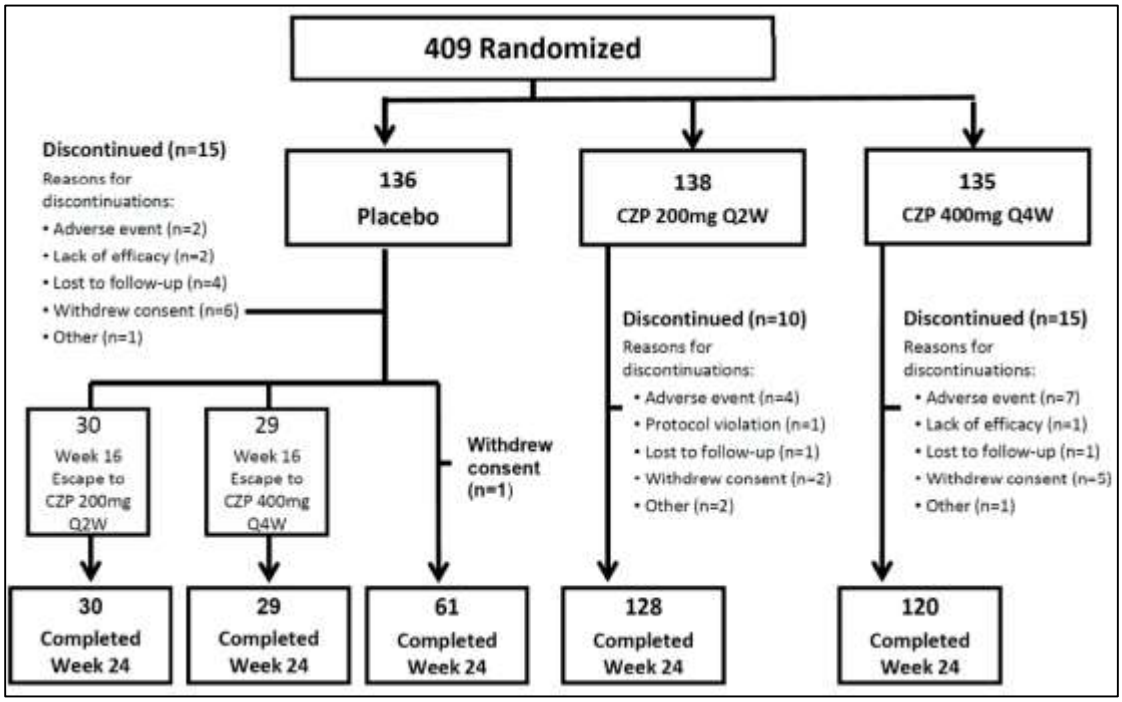
Patient disposition is summarized in Table 6. In the double-blind phase (up to week 24), a total of 409 patients were randomized. Overall, the number of premature discontinuations was higher in the CZP 400 mg Q4W and placebo groups (11.1% and 11.8%) than in the CZP 200 mg Q2W treatment group (7.2%). The most common cause of discontinuation in CZP treatment groups was AEs (ranging from 2.9% to 5.2%), while in the placebo treatment group, it was consent withdrawal (5.1%). At week 16, 22.1% and 21.3% of patients in the placebo group escaped to the CZP 200 mg Q2W and CZP 400 mg Q4W groups respectively. The completion rate at week 24 was similar across treatment groups (ranging from 88.2% to 92.8%).

TABLE 6: PATIENT DISPOSITION

Characteristics	RAPID-PsA		
	CZP 200 mg Q2W	CZP 400 mg Q4W	PBO
Screened, N	[redacted]		
Randomized, N	138	135	136
Discontinued before week 24 (end of double-blind), N (%)	10 (7.2)	15 (11.1)	16 (11.8)
Adverse event	4 (2.9)	7 (5.2)	2 (1.5)
Lack of efficacy	0	1 (0.7)	2 (1.5)
Protocol violation	1 (0.7)	0	0
Withdrew consent	2 (1.4)	5 (3.7)	7 (5.1)
Lost to follow-up	1 (0.7)	1 (0.7)	4 (2.9)
Other	2 (1.4)	1 (0.7)	1 (0.7)
Escape to CZP 200 mg Q2W at week 16	NA	NA	30 (22.1)
Escape to CZP 400 mg Q4W at week 16	NA	NA	29 (21.3)
Completed, week 24	128 (92.8)	120 (88.9)	120 (88.2)[a]
RS, N	[redacted]	[redacted]	[redacted]
CS	[redacted]	[redacted]	[redacted]
FAS, N	[redacted]	[redacted]	[redacted]
PP, N	[redacted]	[redacted]	[redacted]
Safety, N	[redacted]	[redacted]	[redacted]

CS = completer set; CZP = certolizumab pegol; FAS = full analysis set; PBO = placebo; PPS = per-protocol set; Q2W = every two weeks; Q4W = every four weeks; RS = randomized set.
Source: Mease et al.,[14] Interim Clinical Study Report, week 24.[15]
[a] Includes those who escaped to CZP.
[b] For the entire placebo group, data from placebo patients escaping to CZP were not utilized.

FIGURE 3: PATIENT DISPOSITION IN RAPID-PSA UP TO END OF DOUBLE-BLIND PHASE (WEEK 24)



CZP = certolizumab pegol; Q2W = every two weeks; Q4W = every four weeks.
Source: RAPID-PsA Clinical Study Report week 24.[15]

3.4 Exposure to Study Treatments

[redacted]

TABLE 7: EXTENT OF EXPOSURE IN DOUBLE-BLIND PERIOD AT 24 WEEKS (SAFETY SET)

	RAPID-PsA		
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO (N = 136)
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]

CZP = certolizumab pegol; PBO = placebo; Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation.
[a] Number of doses received = dose days (PBO 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.
Source: Interim Clinical Study Report, week 24.[15]

TABLE 8: CONCOMITANT MEDICATION USE IN DOUBLE-BLIND PERIOD (WEEK 24)[a]

	RAPID-PsA		
N (%)	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO[b] (N = 136)
NSAID	[redacted]	[redacted]	[redacted]
Concomitant Medication (Other Than DMARDs and NSAIDs)	[redacted]	[redacted]	[redacted]
DMARDs	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]
Leflunomide	[redacted]	[redacted]	[redacted]
Suflasalazine	[redacted]	[redacted]	[redacted]
Methotrexate sodium	[redacted]	[redacted]	[redacted]
Hydroxychloroquine	[redacted]	[redacted]	[redacted]

CZP = certolizumab pegol; DMARD = disease-modifying antirheumatic drug; PBO = placebo; Q2W = every two weeks; Q4W = every four weeks.
[a] Randomized set.
[b] For the entire placebo group, data from placebo patients escaping to CZP were not utilized.
Source: Interim Clinical Study Report, week 24.[15]

3.5 Critical Appraisal

3.5.1 Internal Validity

RAPID-PsA was randomized and double-blinded up to week 24, and dose-blinded up to week 48. Randomization was stratified by site and prior TNF inhibitor exposure (yes/no). The investigators and patients remained blinded to the allocated CZP dose regimens until patients reached their week 48 visits. Study treatments were administered by dedicated, unblinded trained site personnel. Pharmacokinetic data and antibody data were to be provided only once the study was unblinded.

[redacted]

A hierarchical test procedure for eight ranked primary and secondary outcomes was used in order to control the type 1 error rate, in which — conditional on the first test being significant — the second hypothesis was tested with the same alpha level of 5%. Statistical testing for the hypotheses was performed only if the previous null hypothesis in the hierarchy could be rejected.

The problem with this approach is that only certain outcomes were selected; hence, the hierarchical approach did not take into consideration all outcomes measured in the study, including PsARC, SF-36, PASI 90, PsAQoL, PtAAP, FASCA, LDI, and LEI. These latter outcomes were not adjusted for multiplicity; hence, given the large number of comparisons in the study, a statistically significant finding (*P* value < 0.05) for the comparison between CZP treatment groups and placebo for these outcomes is more likely subject to inflated type 1 error rate (alpha). In addition, no criteria were stated with regard to how the outcomes were ranked. Of note, the ranking tested for the statistical significance of the co-primary outcome, change from baseline in mTSS at week 24, as the sixth outcome assessed in the hierarchical procedure. This is somewhat unusual; in similar types of analysis, a primary or co-primary outcome would typically be at the top of the list, not sixth.

Around 43% of patients in the placebo group changed their assigned treatments at week 16 after meeting the criteria for early escape. This limits the ability to make assertions about 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 PsA, for ethical considerations. Patients treated with CZP were not

eligible for early escape; therefore, if they would otherwise have been assessed as nonresponders at week 16, they were still able to continue to week 24 and have the opportunity (potentially) to be responders at the final outcome assessment. Placebo patients did not have this opportunity. Nevertheless, early escape potentially biased results in favour of the CZP treatment groups at week 24 outcome assessments, because only those in the placebo group were evaluated for early escape at week 16 and use of nonresponder imputation.

To adjust for missing data for the (ACR, PsARC, PASI, and SF-36 responders) end points, patients who withdrew for any reason, or placebo patients who used escape medication, were considered nonresponders from the time they dropped out or when escape therapy was initiated. For all other end points, the last observation carried forward (LOCF) approach was used to impute missing data, assuming the patient's scores at the time of dropout would be the same at the end of study. While this assumption is generally not correct, it does tend to produce a conservative bias. Concern regarding the appropriateness of this approach for outcomes measured at 12 weeks is mitigated given the low proportion of dropouts (approximately 11%) before week 16.

Subgroup analyses for prior TNF-alpha exposure and region were performed for ACR 20 and change from baseline in mTSS. Results should be interpreted with caution, as they are likely not adequately powered given the small sample sizes, and were not adjusted for multiplicity. On the other hand, randomization was stratified by centre and prior TNF-alpha exposure; hence, it is expected that patients would be equally distributed between treatment groups based on prior TNF-alpha exposure and centres.

The predefined rules for the across-patient imputation led to physiologically implausible changes in mTSS. To correct for the imputation rules that were applied, a different imputation approach was applied post hoc, along with a specified minimum time interval between radiographs subjected to imputation. In addition, there were 10 mTSS values missing at week 0, 27 mTSS values missing at week 12, and 44 mTSS values missing at week 24. The number of missing values was similar between treatment groups; however, this large number of missing values (around 10% at week 24) might have affected results in the physiologically implausible changes in mTSS using the predefined rules.

The prespecified analysis of change from baseline in mTSS at week 24 did not indicate that CZP is statistically significantly better than placebo; hence, from a statistical point of view, no other statistical test should have been undertaken after this analysis; i.e., statistical testing should have been stopped after outcome number six on the hierarchical. From a clinical point of view, it seems that the prespecified imputation methods used were not appropriate, and the post-hoc imputation method is more appropriate as it is discussed above, the post-hoc imputation methods yielded statistically significant results in favour of CZP, then it is legitimate to continue testing.

3.5.2 External Validity

RAPID-PsA required patients to have ESR ≥ 28 mm/hour or CRP > upper limit of normal to qualify for entry. According to the clinical expert involved in the review, a substantial proportion of patients seen in clinical practice do not have inflammatory markers elevated to this degree, yet still require treatment with biologic response modifiers (BRMs). Hence, the generalizability of the study may be limited.

Baseline characteristics of enrolled patients were consistent with what has been seen in other PsA trials. However, the clinical expert consulted for this review indicated that trial patients had, on average, greater disease severity than patients treated with biologic therapies in clinical practice, and may not be

representative of patients in the real world. Thus, study results may not be generalizable to PsA patients who exhibit lower disease activity.

Baseline HAQ-DI scores were higher than what is seen in clinical practice. These high scores would increase the change of achieving improvement in the HAQ-DI scores.

Patients with a primary failure to any TNF inhibitor were excluded from RAPID-PsA. Thus, study results are not generalizable to PsA patients who had prior primary failure to a TNF inhibitor.

Both dosages and regimens of CZP used in RAPID-PsA were consistent with what is recommended by Health Canada.

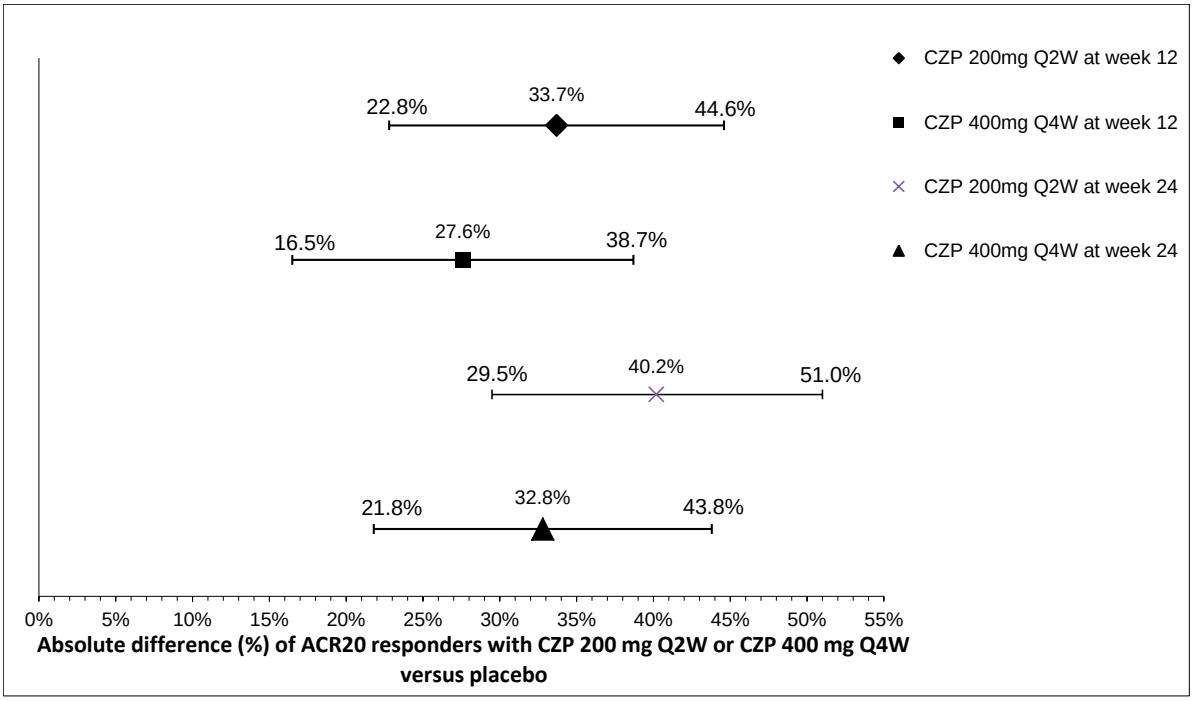
3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported in this review (Section 2.2, Table 3). See Appendix 4: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Outcomes Related to Psoriatic Arthritis

Results for the absolute difference in percentage of ACR 20 responders for CZP 200 mg Q2W and CZP 400 mg Q4W compared with placebo at weeks 12 and 24 are presented in Figure 4. Both CZP regimens were statistically significantly superior to placebo, with a mean absolute difference of 33.7% (95% confidence interval [CI], 22.8% to 44.6%) and 27.6% (95% CI, 16.5% to 38.7%) at 12 weeks and 40.2% (95% CI, 29.5% to 51.0%) and 32.8% (95% CI, 21.8% to 43.8%) at 24 weeks for the CZP 200 mg Q2W and CZP 400 mg Q4W groups respectively (Table 10). The plot of ACR 20 response over time is shown in Figure 5 (Appendix 4: DETAILED OUTCOME DATA).

FIGURE 4: MEAN ABSOLUTE DIFFERENCE (%) BETWEEN CERTOLIZUMAB PEGOL AND PLACEBO FOR ACR 20 RESPONDERS AT 12 AND 24 WEEKS IN RAPID-PSA (RANDOMIZED SET WITH IMPUTATION)



CZP = certolizumab pegol; Q2W = every two weeks; Q4W = every four weeks.

The proportion of patients who achieved ACR 50 and ACR 70 at weeks 12 and 24 for both CZP regimens was also statistically significantly superior to placebo (Table 10).

a) DAS 28

The proportion of patients achieving DAS 28 European League Against Rheumatism (EULAR) response of good was higher for both CZP regimens than for the placebo group. [redacted] Table 12 [redacted]

b) PsARC

There were statistically significantly greater proportions of PsARC responders in the CZP 200 mg Q2W and CZP 400 mg Q4W groups compared with placebo, [redacted] $P < 0.001$ for all comparisons (Table 13).

c) HAQ-DI

Baseline mean HAQ scores ranged from 1.29 to 1.33 across treatment groups. At weeks 12 and 24, the mean change in scores decreased (improved) from baseline for all treatment groups, including placebo. Both CZP 200 mg Q2W and CZP 400 mg Q4W groups were statistically significantly improved relative to placebo for mean score change from baseline at weeks 12 and 24. [redacted]. The proportion of patients with an improvement of ≥ 0.3 was statistically significantly greater in the CZP 200 mg Q2W (45.7% at week 12, and 49.3% at week 24) and CZP 400 mg Q4W (48.9% at week 12, and 48.1% at week 24) groups relative to placebo (21.3% at week 12 and 15.4% at week 24) (Table 14).

d) LEI

The analysis was performed only in patients with LEI ≥ 1. LEI change from baseline at weeks 12 and 24 favoured the CZP 200 mg Q2W and CZP 400 mg Q4W groups compared with placebo ($P < 0.05$) (Table 19).

e) LDI

The analysis was performed only in patients with ≥ 1 dactylitis digit with a ≥ 10% difference in the circumference of the digit compared with the opposite digit. LDI change from baseline at weeks 12 and 24 favoured the CZP 200 mg Q2W and CZP 400 mg Q4W groups compared with placebo ($P < 0.05$) (Table 19).

3.6.2 Outcomes Related to Psoriasis

a) PASI

PASI is a measure of the extent and severity of psoriasis lesions; absolute scores range from 0 to 72, with higher scores representing more severe psoriasis. PASI 75 responders are those with a 75% improvement from baseline scores. Only patients with a BSA involvement ≥ 3% at baseline had a PASI assessment (approximately 62% of all randomized patients). The proportion of patients achieving a

PASI 75 response in CZP compared with placebo was statistically significantly higher for both doses at weeks 12 and 24. The absolute differences for CZP 200 mg Q2W and CZP 400 mg Q4W groups versus placebo were 32.7% and 33.4% at 12 weeks and 47.1 % and 45.4% at 24 weeks respectively (Table 18). Similarly, statistically significantly more patients achieved a PASI 90 response in both CZP groups compared with placebo at weeks 12 and 24 (Table 18).

3.6.3 Health-Related Quality of Life and Other Patient-Reported Outcomes

Short Form (36) Health Survey

Results for the mean change from baseline in SF-36 MCS and PCS at weeks 12 and 24 are presented in Table 15. The mean change from baseline at week 12 for SF-36 MCS was 4.87 points, 2.40 points, and 1.36 points in the CZP 200 mg Q2W, CZP 400 mg Q4W, and placebo groups respectively, with the

[redacted]

Table 16[redacted]

The percentage of SF-36 PCS responders was greater in the CZP 200 mg Q2W and CZP 400 mg Q4W groups compared with placebo at weeks 12 and 24 ($P < 0.001$). The percentage of SF-36 MCS responders was greater in the CZP 200 mg Q2W group compared with placebo at weeks 12 and 24 ($P < 0.001$), while the percentage of SF-36 MCS responders was statistically significantly greater in the CZP 400 mg Q4W group compared with placebo only at week 24.

a) PsAQoL

At weeks 12 and 24, the mean change in scores decreased (improved) from baseline for all treatment groups, including placebo. Both the CZP 200 mg Q2W and CZP 400 mg Q4W groups had statistically significantly greater improvement relative to placebo for mean score change at weeks 12 and 24 (Table 15).

b) PtAAP

At weeks 12 and 24, the mean change in scores decreased (improved) from baseline for all treatment groups, including placebo. Both the CZP 200 mg Q2W and CZP 400 mg Q4W groups were statistically significantly improved relative to placebo for mean score change at weeks 12 and 24 (Table 15).

c) FASCA

At weeks 12 and 24, the mean change in scores decreased (improved) from baseline for all treatment groups, including placebo. Both the CZP 200 mg Q2W and CZP 400 mg Q4W groups were statistically significantly improved relative to placebo for mean score change at weeks 12 and 24 (Table 15).

3.6.4 Work Productivity

a) Work Productivity Survey

Results for work productivity scores for the individual questions (questions 2 to 9) at baseline and at weeks 12 and 24 are presented in Table 17. As seen in Table 17, there was a statistically significant improvement in "household work days missed due to arthritis in the last month" (question 5) and "level of arthritis interference on household work productivity in the last month" (question 9) among both CZPs groups at week 12. Additionally, there were statistically significant improvements in "work days missed due to arthritis in the last month" (question 2) among the CZP 400 mg Q4W group when compared with placebo at week 12. Also, there were statistically significant improvements in "work days with productivity reduced by at least half due to arthritis in the last month" (question 3), "level of arthritis interference on work productivity in the last month" (question 4), and "household work days with productivity reduced by at least half due to arthritis in the last month" (question 6) among the CZP 200 mg Q2W group when compared with placebo at week 12. There was a statistically significant improvement for questions two through nine among the CZP 200 mg Q2W group, and questions four, five, six, seven, and nine for the CZP 400 mg Q4W group when compared with placebo at week 24.

3.6.5 Radiographic Changes

a) mTSS

Results for the change in mTSS at week 24 can be found in Table 20. The mean changes from baseline in the prespecified analysis were 11.5 points, 25.1 points, and 18.28 points for the CZP 200 mg Q2W, CZP 400 mg Q4W, and placebo groups respectively. There was no statistically significant difference between CZP treatment groups and placebo. This change from baseline in mTSS scores was considered physiologically implausible; hence, post-hoc analyses using different imputation methods were performed.

In the post-hoc analyses, missing mTSS values were imputed using median change from baseline in the entire study population (in this case 0), and a minimum time interval of eight weeks between radiographs was defined to perform a meaningful linear interpolation or extrapolation. There was less progression of radiographic changes in the CZP 200 mg Q2W and CZP 400 mg Q4W groups compared with the placebo group (0.01, and 0.11 versus 0.28); the differences from placebo were –0.27 ($P = 0.004$) and –0.17 ($P = 0.072$) points respectively. There was less progression of radiographic changes in the CZP 200 mg Q2W and CZP 400 mg Q4W groups compared with the placebo group (0.06 versus 0.28 points); the difference from placebo was –0.22 points ($P = 0.007$).

The mTSS response at week 24 was analyzed using the post-hoc imputation rules. A patient was considered an mTSS responder if the patient had a change from baseline to week 24 in mTSS of ≤ 0; escapers were treated as if they had a change > 0. There were statistically significantly greater proportions of mTSS responders in the CZP 200 mg Q2W and CZP 400 mg Q4W groups compared with the placebo group at weeks 12 and 24 ($P < 0.001$) (Table 20).

Results for the change in mTSS at week 48 can be found in Table 23. Radiographic progression remained low in both CZP 200 mg Q2W and CZP 400 mg Q4W patients to week 48 (0.16 [95% CI, –0.07 to 0.39] and 0.12 [95% CI, –0.12 to 0.37], respectively) compared with earlier time points. The projected rate of

progression was also low for placebo patients (0.34 [95% CI, 0.10 to 0.58]). In a post-hoc analysis in a subgroup of patients with baseline radiographic damage (mTSS > 6), radiographic progression was significantly lower for CZP-treated patients (0.27 [95% CI, –0.10 to 0.65]) compared with that projected for patients treated with placebo (0.82 [95% CI, 0.32 to 1.33]).

3.6.6 Subgroup Analyses

Subgroup analyses for prior TNF-alpha exposure (at week 12 and week 24), concomitant use of DMARDs at baseline, and region at week 12 were performed for ACR 20 efficacy outcomes, and are presented in Table 11. The percentage of ACR 20 responders for the CZP 200 mg Q2W and CZP 400 mg Q4W groups was statistically significant compared with placebo in the subgroup of patients with or without prior use of TNF, with or without concomitant use of DMARDs at baseline. In the subgroup of patients in Latin America, CZP 200 mg Q2W and CZP 400 mg Q4W were not statistically significantly better than placebo; however, these results should be interrupted with caution due to the small number of patients.

Subgroup analyses for prior TNF-alpha exposure were performed for change from baseline in mTSS at week 24 (Table 21). There was less progression of radiographic change in the CZP 200mg Q2W and CZP 400 mg Q4W groups compared with the placebo group in the subgroup of patients with prior use of TNF inhibitors ([redacted]); the difference versus placebo was [redacted]). In the subgroup of patients with no prior exposure to TNF inhibitors, the difference versus placebo was not significant [redacted].

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See Appendix 4: DETAILED OUTCOME DATA for detailed harms data.

3.7.1 Adverse Events

Over week 24, the overall frequency of treatment-emergent adverse events (TEAEs) was 68.1%, 71.1%, and 67.6% in the CZP 200 mg Q2W, CZP 400 mg Q4W, and placebo groups respectively (Table 9). The most common reasons for AEs reported for all three groups were nasopharyngitis (13.0%, 6.7%, and 7.4% in the CZP 200 mg 2QW, CZP 400 mg 4QW, and placebo groups respectively) and upper respiratory tract infection (8.7%, 9.6%, and 5.1% in the CZP 200 mg 2QW, CZP 400 mg 4QW, and placebo groups respectively) (Table 24).

3.7.2 Serious Adverse Events

Over week 24, the overall frequency of serious adverse events (SAEs) was 5.8%, 9.6%, and 4.4% in the CZP 200 mg Q2W, CZP 400 mg Q4W, and placebo groups, respectively (Table 9). The most common reasons for SAEs were infections and infestations, with 1.4%, 1.5%, and 0.7% in the CZP 200 mg Q2W, CZP 400 mg Q4W, and placebo groups respectively.

3.7.3 Withdrawals Due to Adverse Events

Over week 24, the overall frequency of withdrawals due to adverse events (WDAEs) was 2.9%, 4.4%, and 1.5% in the CZP 200 mg Q2W, CZP 400 mg Q4W, and placebo groups respectively (Table 9). No individual AE leading to permanent study medication discontinuation was reported for more than one patient.

3.7.4 Mortality

Two deaths were reported during the 24-week double-blind treatment period. One death due to cardiac arrest was reported in the CZP 200mg Q2W treatment group, and one sudden death was reported in the

CZP 400mg Q4W treatment group. Both deaths were considered unrelated to study medication by investigators. No death was reported in the placebo group.

3.7.5 Notable Harms

Over week 24, two patients in the CZP 200 mg Q2W group, two patients in the CZP 400 mg Q4W group, and one patient in the placebo group experienced serious infection. One patient in the CZP 400 mg Q4W group experienced malignancy. Increased alanine aminotransferase (defined as > 3 lower limit of normal [ULN]) was reported in 4, 7, and two patients, while increased aspartate aminotransferase (defined as > 3 ULN) was reported in 4, 6, and one patients in the CZP 200 mg Q2W, CZP 400 mg Q4W, and placebo groups respectively. There were no congestive heart failure events (Table 9).

TABLE 9: HARMS OVER WEEK 24 (END OF DOUBLE-BLIND) IN RAPID-PSA (SAFETY SET)

	RAPID-PsA		
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO (N = 136)
Deaths	1 (0.7)	1 (0.7)	0
SAEs, N (%)	8 (5.8)	13 (9.6)	6 (4.4)
WDAEs, N (%)	4 (2.9)	6 (4.4)	2 (1.5)
Patients With > 0 AEs, N (%)	94 (68.1)	96 (71.1)	92 (67.6)
Notable Harms			
Serious infections	2 (1.4)	2 (1.5)	1 (0.7)
Malignancy	0	1 (0.7)	0
Congestive heart failure	0	0	0
Alanine aminotransferase increased	4 (2.9)	7 (5.2)	2 (1.5)
Aspartate aminotransferase increased	4 (2.9)	6 (4.4)	1 (0.7)
Hepatic enzyme increased	5 (3.6)	4 (3.0)	2 (1.5)
Blood CPK increased	5 (3.6)	6 (4.4)	4 (2.9)

AE = adverse event; CZP = certolizumab pegol; SAE = serious adverse event; Q2W = every two weeks; Q4W = every four weeks; WDAE = withdrawal due to adverse event.
Source: Interim Clinical Study Report, week 24.[15]

4. DISCUSSION

4.1 Summary of Available Evidence

One published, manufacturer-sponsored, double-blind, placebo-controlled RCT was included in this systematic review: RAPID-PsA.[14] In RAPID-PsA, patients (N = 409) received active treatment with subcutaneous injections of CZP or placebo-pre-filled 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. No trials directly comparing CZP with other BRMs were found in the scientific literature. RAPID-PsA had an appropriate randomization strategy, with generally similar treatment groups at baseline. Overall, study discontinuation was low and similar across treatment groups; however, 43.4% of patients in the placebo group escaped to CZP treatment groups after week 16. Subgroup analyses for patients with prior TNF-alpha exposure and region were performed. No subgroup analyses for baseline body weight disease severity were performed.

4.2 Interpretation of Results

4.2.1 Efficacy

The co-primary efficacy outcome in RAPID-PsA was ACR 20 response at week 12 (defined as an improvement of at least 20% in both swollen and tender joint counts and at least three of five additional disease criteria). Both CZP treatment groups were statistically significantly superior to placebo for ACR 20 response at week 12. The clinical expert involved in the review noted that the difference in ACR 20 response compared with placebo at 12 and 24 weeks was clinically meaningful. Other clinical response outcomes (ACR 50, ACR 70, DAS 28, PsARC, PASI 75, PASI 90, LEI, and LDI) at weeks 12 and 24 also demonstrated a statistically significant and clinically meaningful difference favouring both CZP treatment groups compared with placebo. The effectiveness of the two dosing regimens of CZP for the treatment of PsA patients appeared to be similar up to week 96 (as was reported in the extension study), as was observed at week 24 (Appendix 6: SUMMARY OF FINDINGS AT 96 WEEKS of Study RAPID-). However, the lack of a comparator limits the conclusions that may be drawn from the dose-blind and extension phases. The outcome measures ACR 50, ACR 70, PsARC, PASI 90, LEI, and LDI were not part of the hierarchical analysis plan; therefore, they were not adjusted for multiple comparisons. In addition, change from baseline in mTSS, which was ranked sixth in the hierarchical analysis procedure, was not statistically significant; hence, statistical testing for other hypotheses that are ranked lower or not on the hierarchical analysis procedure should not have been performed, because the null hypothesis of mTSS in the hierarchy was rejected.

Common themes seen as important in the patient-group input were improvements in quality of life and work productivity (Appendix 1: PATIENT INPUT SUMMARY). In RAPID-PsA, SF-36 was used to assess health-related quality of life. Statistically significantly greater improvements were observed in the MCS and PCS scores of the SF-36 among CZP 200 mg Q2W and CZP 400 mg Q4W patients compared with those in the placebo group at weeks 24. Patients in both treatment groups (CZP 200 mg Q2W and CZP 400 mg Q4W) exceeded the MCID for the SF-36 improvement, which is typically 3.74 points for PCS and 1.77 points for MCS, while the patients in the placebo group did not exceed the established MCIDs. Also, there were statistically significantly more patients achieving improvements in health-related quality of life (change in SF-36 score) in the CZP 200 mg Q2W and CZP 400 mg Q4W treatment groups compared with placebo. The PsAQoL a quality of life instrument specific to psoriatic arthritis indicated that both the CZP 200 mg Q2W and CZP 400 mg Q4W groups had statistically significant greater improvement compared with placebo for mean score change at weeks 12 and 24. There is no MCID specified for PsAQoL; hence, it is difficult to determine if the differences in results between CZP regimens and

placebo were clinically meaningful. The outcome measures SF-36 and PsAQoL were not part of the hierarchical analysis plan; therefore, they were not adjusted for multiple comparisons; hence, the level of significance is inflated and results should be interpreted with caution.

Improvement in productivity within and outside the home was generally seen in both CZP treatment regimens when compared with placebo at weeks 12 and 24, though results only reached statistical significance for five out of eight questions, and three out of eight questions for the CZP 200 mg Q2W and CZP 400 mg Q4W groups respectively when compared with placebo at week 12. At week 24, all questions and five out of eight questions reached statistical significance for the CZP 200 mg Q2W and CZP 400 mg Q4W respectively when compared with placebo. This outcome measure was not part of the hierarchical analysis plan; therefore, it was not adjusted for multiple comparisons. Also it is worth noting that there is 8 test applied for the WPS, one test per question; hence, alpha should have been divided by eight in order to adjust for inflation. Moreover, without a confirmed MCID for the WPS instrument, it remains unclear whether or not the differences were clinically meaningful.

In addition to improvement in HRQoL, there were statistically significantly more patients achieving improvements in physical function (≥ 0.30 improvement HAQ-DI score) in the CZP 200 mg Q2W and CZP 400 mg Q4W treatment groups compared with placebo at weeks 12 and 24. Arthritis pain in patients was assessed using the PtAAP-VAS. Patients in all treatment groups exceeded the MCID, which is typically 10 points; but the magnitude of the improvement in the CZP 200 mg Q2W and CZP 400 mg Q4W treatment groups was more than twice that of the placebo group. Fatigue was assessed using FASCA. Patients in both treatment groups (CZP 200 mg Q2W and CZP 400 mg Q4W) exceeded the MCID for FASCA improvement, which is typically 1 point at weeks 12 and 24, while patients in the placebo group did not exceed the established MCID. PtAAP and FASCA were not part of the hierarchical analysis plan; therefore, they were not adjusted for multiple comparisons; hence, their level of significance is inflated and results should be interpreted with caution.

There was no statistically significant difference between the CZP and placebo groups in the primary radiographic end point change from baseline in mTSS at week 24 when the prespecified imputation methods to account for missing data were used. Van der Heijde et al.[16] indicated that the prespecified imputation method led to unrealistic increases in mTSS in participants with missing values and overestimated the extent of radiographic progression in all treatment groups. In a post-hoc analysis, using the median mTSS change from baseline in the whole study population to impute missing values, CZP was associated with a statistically significant reduction in radiographic progression compared with placebo (least squares mean mTSS change from baseline: combined CZP groups 0.06; placebo group 0.28; $P = 0.007$).

Further post-hoc analyses using the mean and maximum mTSS change from baseline in the whole study population to impute missing values supported these results. However, a statistically significant difference between the combined CZP and placebo groups was found at week 24 when the maximum mTSS change from baseline by treatment group to impute missing values was used. The Health Canada Reviewers' Report also indicated that the prespecified imputation method resulted in implausibly high least squares mean changes from baseline across all groups, and that the post-hoc imputation method provided a realistic representation of the data.[21] On the other hand, the sample size calculation for RAPID-PsA was based on the assumption that the difference from placebo for the active treatment groups in mean change from baseline in the mTSS would be greater than 1.0; this assumption was based on published data from other TNF inhibitors. However, none of the post-hoc analyses yielded a difference in mean change from baseline in the mTSS greater than 1.0.

In addition, the European public assessment report indicated that inhibition of progression of structural damage by CZP for up to 48 weeks has not been formally established in the overall study population. However, in a subgroup of patients at higher risk of radiographic progression (patients with a baseline mTSS score > 6), inhibition of radiographic progression was maintained with CZP up to week 48.[45]

The clinical expert confirmed that measurement of radiographic change at week 24 is not a sufficient duration to determine a clinically meaningful improvement. Furthermore, Haraoui et al.[46] argued that highly sensitive imaging techniques must be added to complement standard radiographs for a better assessment of new highly effective therapies after the failure of conventional DMARD, because it has become difficult to show statistically significant reduction of structural damage by the active comparator or DMARD. Also, Bykerk indicated that radiographic progression is minimal once patients failing DMARD are treated with TNF inhibitors.[47]

Subgroup analyses for prior TNF-alpha exposure for efficacy outcome ACR 20 and change from baseline in mTSS. It was found that regardless of whether or not patients were previously exposed to TNF inhibitors, ACR 20 responders for CZP 200 mg Q2W and CZP 400 mg Q4W were still statistically significant compared with placebo in both subgroups. There was less progression of radiographic change in the CZP 200 mg Q2W and CZP 400 mg Q4W groups compared with the placebo group in the subgroup of patients with prior use of TNF inhibitors, while in the subgroup of patients with no prior exposure to TNF inhibitors, the difference compared with placebo was not significant.

Without adequate head-to-head trial data for CZP with other BRMs, the manufacturer conducted a Bayesian mixed-treatment comparison (MTC) analysis based on a systematic review of RCTs to compare the efficacy of CZP with adalimumab, etanercept, golimumab, infliximab, and ustekinumab. The systematic review and MTC were found to demonstrate some methodological rigour on International Society for Pharmacoeconomics and Outcomes Research (ISPOR) criteria. Despite the heterogeneity of patient populations as well as certain potential methodological limitations, overall CZP demonstrated similar efficacy compared with other BRMs in terms of ACR response, PASI, and PsARC. This is potentially mostly applicable to the outcomes assessed at weeks 12 to 16, as those at week 24 may be less valid because many studies had an early-escape design. It is uncertain how well meta-regression adjustment by placebo response would have controlled for the potential bias introduced by early escape in outcomes at week 24.

The study design of RAPID-PsA did not allow for comparison between the two Health Canada–approved CZP dosing regimens, as no statistical testing was performed. The clinical expert confirmed there is no reason to expect a clinical difference in the two CZP treatment groups, as trough levels are the same. The clinical expert noted that inclusion criteria for RAPID-PsA and other PsA studies tend to enrol patients with more severe disease activity than typically seen in clinical practice; therefore, the results may not be generalizable to PsA patients who exhibit lower disease activity.

There were limitations regarding the internal validity of efficacy results after week 12. Although the study design to include early escapers in the placebo group is required by ethics committees, the effect of placebo escapers may yield potentially biased results in favour of the CZP treatment groups, because patients treated with CZP were not eligible for early escape; therefore, if they otherwise would have been assessed as nonresponders at week 16, they were still able to continue to week 24, and had the opportunity (potentially) to be responders at the final outcome assessment. Placebo patients did not have this opportunity. Nevertheless, early escape potentially biased results in favour of the CZP treatment groups at week 24 outcome assessments, because only those in the placebo group were

evaluated for early escape at week 16 and use of nonresponder imputation. Furthermore, after week 24, patients were no longer blinded to treatment allocation. Thus, 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.

[redacted].

4.2.2 Harms

During the double-blind period over week 24, the frequency of SAEs was low; it was similar in the CZP 200 mg Q2W and placebo groups, but higher in the CZP 400 mg Q4W treatment group. The most common SAEs were infections and infestations. WDAEs were also low, but marginally greater among the CZP treatment groups compared with placebo. TEAEs were relatively similar between treatment groups; the most common infectious AEs were nasopharyngitis and upper respiratory tract infection, while the most common non-infectious AEs were diarrhea and headache. Notable harms, such as serious infection or malignancy, were similar between treatment groups; but increased alanine aminotransferase and increased aspartate aminotransferase were marginally greater among the CZP treatment groups compared with placebo. Two deaths occurred in the double-blind period, one in each CZP treatment group; both were considered unrelated to study medication by investigators. The safety profile of CZP in PsA over 96 weeks was consistent with that observed during 24 weeks, with no new safety signals reported.

No MTC analysis for safety outcomes was reported in the manufacturer-submitted network meta-analysis (NMA). A NMA by Singh et al.[48] that assessed the potential AEs of biological drugs (including CZP) used to treat various conditions or diseases in adults found CZP was associated with a statistically significantly higher risk of SAEs compared with adalimumab and abatacept, and a statistically significantly higher risk of serious infections compared with abatacept, adalimumab, etanercept, golimumab, and rituximab. However, these findings should be interpreted with caution, because trials differed in terms of patient populations, BRM dose, concomitant use of DMARDs, prior failed therapies, and trial duration; in addition, event rates were often low.

5. CONCLUSIONS

Based on one double-blind randomized controlled trial in patients with active PsA, treatment with CZP (either 200 mg Q2W or 400 mg Q4W) resulted in statistically significant and clinically meaningful improvements in clinical response (ACR 20 and PASI) at weeks 12 and 24 when compared with placebo. Statistically significant and clinically significant improvements were in quality of life, physical function, pain, and fatigue were also seen at 12 and 24 weeks. However, except for HAQ-DI, adjustment for multiplicity was not done for these other outcomes; hence, results for these outcomes should be interpreted with caution. Statistically significant improvements in work productivity were also demonstrated, though the clinical meaningfulness of these results remains uncertain; in addition, this analysis was not adjusted for multiplicity. 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, PsA 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, while typically used in recent PsA 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 nonresponder imputation for assessments at week 24, results for the patient-reported outcomes at week 24 are potentially biased.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Three patient groups submitted inputs for this review: the Canadian Spondylitis Association (CSA), Arthritis Consumer Experts (ACE), and the Canadian Arthritis Patient Alliance (CAPA).

CSA is a volunteer-run patient association for those living with spondyloarthritis (SpA), including ankylosing spondylitis (AS) and psoriatic arthritis (PsA). The majority of CSA members are patients with AS, but there are also patients with PsA. CSA advocates for SpA patients nationally and provincially; provides a national resource centre for information relevant to the SpA community; and provides a national forum for partnerships between the medical and patient communities. CSA has received funding from Abbvie (unrestricted and restricted grants), Janssen (restricted educational grants), and UCB Canada (a restricted travel grant). However, CSA declared no conflict of interest in the preparation of its submission.

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 and comprehensible to the general public, government and media; and to train individuals with arthritis to be able to contribute meaningfully to research initiatives and government decision-making. ACE provides programs in both official languages. It receives unrestricted grants-in-aid from public and private sector organizations as well as unsolicited funding from individual donors, including: AbbVie Corporation, Amgen Canada, Arthritis Research Centre of Canada, BIOTECanada, Bristol-Myers Squibb Canada, Canadian Institutes of Health Research, the Canadian Rheumatology Research Consortium, Celgene Inc., GlaxoSmithKline, Hoffmann-La Roche Canada Ltd., Janssen Inc., Pfizer Canada, Purdue Pharma L.P., and the University of British Columbia. ACE declared no conflicts of interest in the preparation of its submission.

CAPA is a patient-driven, independent, national organization with members across Canada. CAPA creates links between Canadians with arthritis. CAPA believes the first expert on arthritis is the individual who has the disease. CAPA has received both restricted and unrestricted funding and in-kind support from: Abbvie, Amgen, Hoffmann-La Roche, Janssen, Novartis, Pfizer Canada, UCB Pharma, Rx&D, the Ontario Rheumatology Association, the Canadian Rheumatology Association, the Arthritis Society, Canadian Institutes for Health Research, Schering Canada, Scleroderma Society, and STA Communications. However, CAPA declared no conflict of interest in the preparation of its submission.

2. Condition and Current Therapy-Related Information

CSA collected the information from its general membership and board of directors through patient forums, newsletters, and its website and Facebook pages. ACE gathered the information through a request for patient input from JointHealth members and subscribers sent through email and posted on the JointHealth website. The submission was based on previous patient inputs and interviews conducted throughout ACE's 15 years as an organization. CAPA obtained the information through personal experiences of the CAPA board and membership.

PsA is a type of inflammatory arthritis and an autoimmune disease. It usually starts slowly, gradually spreading from one joint to others. The is often in the teenage years or early twenties; it is often preceded by psoriasis (30% of patients with psoriasis will develop PsA). The symptoms are generally pain; morning stiffness and swelling in the peripheral joints, particularly the fingers and toes (dactylitis) but including the knees, ankles and lower back; pitted and discoloured fingernails and toenails; discoloured and scaly skin; and extreme fatigue. Iritis and uveitis are frequently experienced. Patients with PsA often have difficulties performing daily self-care activities, such as getting out of bed, doing house chores, getting up and down stairs or in and out of the bathtub, cooking, and getting dressed. PsA can affect a patient's lifestyle, including their sleep patterns and relationships with friends and family members. The skin manifestations associated with PsA are very visible and can cause heightened anxiety and depression. The chronic pain of PsA, together with fatigue and depression, significantly reduces the quality of life for patients. PsA symptoms and the unpredictable nature of the disease may prevent patients from going to work. It can be very stressful for the patient, as they have to think about work flexibility, benefit packages, and the possibility of being put on disability pension.

Caregivers of patients with PsA have indicated that time is always a concern for them. They need to arrange and plan their schedules to accommodate emergency requests from the person living with PsA. They have to help with house chores when the patient is in extreme pain, as well as fulfill their own and household financial responsibilities.

Patients realize there is no cure for PsA. Available treatment options will only slow the progression of the disease by controlling inflammation and improving quality of life. Existing therapies include nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, non-biologic disease-modifying antirheumatic drugs (DMARDs), biologics, and exercise. Many patients with milder disease will do well on NSAIDs and appropriate exercise. DMARDs are effective with peripheral disease. For patients with more severe disease, biologics have proved very effective in many cases. Many patients are on the biologics approved for PsA: Remicade (infliximab), Enbrel (etanercept), Humira (adalimumab), and Simponi (golimumab). The patient groups pointed out that existing biologics do not work for everyone, and it is important to have as large an arsenal of biological drugs as possible for PsA patients. Patients expressed concerns about experiencing adverse effects over prolonged periods; the intolerance to methotrexate in combination with other medications; how their medication is administered; the loss of efficacy of their medications over time; and the time commitment required from them as a patient. Side effects reported for biologics are most commonly allergic reactions, infections, and cold-like symptoms.

Patients believe that the more options, the better. Having more options could mean better access to medication, having a backup plan in case the current therapy stops working, and having an economically sound solution in case the current treatment is no longer covered under an insurance plan. As well, they feel that the best treatment is one that has the fewest adverse effects. Infusion or injection treatments are disruptive and time-consuming. The cost of biologic drug therapy is expensive, and for patients without a health insurance plan (or one that only partially covers drug costs), or who only have access to provincial health insurance, the cost can be prohibitive.

3. Related Information About the Drug Being Reviewed

None of the three groups reported using certolizumab pegol in patients with PsA. They do believe that Cimzia will offer an additional choice, which is important to the patient community. Patients with PsA would like other options because everyone responds differently and because drugs that have been effective in managing symptoms can suddenly stop working. In patients' opinions, access to certolizumab pegol means a new chance for them to have a treatment that may be more effective in managing their disease if another biologic(s) used previously fails. Allowing access to the medication can also give professionals more tools to help patients achieve remission. There is a need for increased research activity into the causes and possible cures for the disease.

Patients hope that certolizumab pegol will lessen their PsA pain so they can manage day-to-day activities. They concluded with a plea to the health care system to find medications that help people with PsA achieve remission. In remission, patients can live normal lives free from adverse effects, and maximize their full potential as human beings.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	November 19, 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 Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; 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 subject 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 or HSDB-7848 or HSDB7848 or CZP).ti,ab,ot,sh,rn,hw,nm.
2	(428863-50-7 or UMD07X179E or 339184-10-0 or 1132819-27-2).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 or HSDB-7848 or HSDB7848 or CZP).ti,ab.
7	5 or 6
8	7 use oemezd
9	8 not conference abstract.pt.
	Combine MEDLINE and Embase results
10	4 or 9
	Combine with terms for psoriatic arthritis, remove non-human studies
11	Arthritis, Psoriatic/ use pmez
12	psoriatic arthritis/ use oemezd
13	((psoriatic or psoriasis or psoriatica) adj3 (arthrit* or arthropath* or polyarthrit* or rheumat*)).ti,ab.
14	"PsA".ti,ab.
15	or/11-14
	Cimzia for Psoriatic
16	10 and 15
17	exp animals/
18	exp animal experimentation/ or exp animal experiment/
19	exp models animal/
20	nonhuman/
21	exp vertebrate/ or exp vertebrates/
22	animal.po.
23	or/17-22
24	exp humans/
25	exp human experimentation/ or exp human experiment/
26	human.po.
27	or/24-26
28	23 not 27
29	16 not 28
30	Remove duplicates from 29

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	November 17, 2014
Keywords:	certolizumab (Cimzia), psoriatic arthritis & synonyms
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Osterhaus JT, Purcaru O. Arthritis Res Ther. 2014;16(4):R140.[49]	Outcome not of interest

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 10: PROPORTION OF PATIENTS WITH ACR 20, ACR 50 AND ACR 70 RESPONSES AT WEEK 12 AND WEEK 24 (RANDOMIZED SET WITH IMPUTATION)

	RAPID-PsA					
	Week 12[a]			Week 24[a]		
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO (N = 136)	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO (N = 136)
ACR 20						
%, 95% CI	58.0 (49.7 to 66.2)	51.9 (43.4 to 60.3)	24.3 (17.1 to 31.5)	63.8 (55.7 to 71.8)	56.3 (47.9 to 64.7)	23.5 (16.4 to 30.7)
Difference from PBO, % (95% CI)[b]	33.7 (22.8 to 44.6)	27.6 (16.5 to 38.7)		40.2 (29.5 to 51.0)	32.8 (21.8 to 43.8)	
P Value[b]	< 0.001	< 0.001		< 0.001	< 0.001	
ACR 50						
%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO, % (95% CI)[c]	[redacted]	[redacted]		[redacted]	[redacted]	
P Value[b]	[redacted]	[redacted]		[redacted]	[redacted]	
ACR 70						
%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO, % (95% CI)[c]	[redacted]	[redacted]		[redacted]	[redacted]	
P Value[b]	[redacted]	[redacted]		[redacted]	[redacted]	

ACR 20 = American College of Rheumatology; CI = confidence interval; CZP = certolizumab pegol; PBO = placebo; Q2W = every two weeks; Q4W = every four weeks; RS = randomized set.

[a] Patients who withdrew for any reason, or placebo patients who used escape medication, were considered as nonresponders from the time they dropped out or when escape therapy was initiated. Patients who had missing data at a visit were counted as nonresponders for the respective visits.

[b] Treatment difference and corresponding 95% CI and *P* value were estimated using a standard two-sided Wald asymptotic test with a 5% alpha level.

[c] Calculated by CADTH using Review Manager; positive values indicate that more patients in the CZP treatment group achieved response in comparison with patients in the placebo treatment group.

Source: Mease et al.,[14] Interim Clinical Study Report, week 24.[15]

FIGURE 5: ACR 20 RESPONSE RATES OVER TIME

[Figure presenting the Proportion of Patients Achieving ACR 20, Responses Over Time was removed because the figure was copyrighted.]

Q2W = every two weeks; Q4W = every four weeks.
**P* value ≤ 0.001 versus placebo.
Source: Mease et al.[14]

TABLE 11: SUBGROUP ANALYSIS OF PROPORTION OF PATIENTS WITH ACR 20 RESPONSES AT WEEK 12 AND WEEK 24 (RANDOMIZED SET WITH IMPUTATION)

	RAPID-PsA					
	Week 12			Week 24		
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N =135)	PBO (N =136)	CZP 200 mg Q2W (N =138)	CZP 400 mg Q4W (N =135)	PBO (N =136)
PRIOR TNF THERAPY						
NO						
n/N, (%)	66/107 (61.7)	55/112 (49.1)	29/110 (26.4)	69/107 (64.5)	63/112 (56.3)	29/110 (26.4)
Difference from PBO, % (95% CI)	35.3 (23.0 to 47.7)	22.7 (10.4 to 35.1)		38.1 (25.9 to 50.4)	29.9 (17.5 to 42.2)	
P Value	< 0.001	< 0.001		< 0.001	< 0.001	
YES						
n/N, (%)	14/31 (45.2)	15/23 (65.2)	4/26 (15.4)	19/31 (61.3)	13/23 (56.5)	3/26 (11.5)
Difference from PBO, % (95% CI)	29.8 (7.4 to 52.1)	49.8 (25.9 to 73.7)		49.8 (28.7 to 70.8)	45.0 (21.3 to 68.7)	
P Value	0.012	< 0.001		< 0.001	< 0.001	
CONCOMITANT USE OF DMARDS AT BASELINE						
NO						
n/N, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO, % (95% CI)	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
P Value	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Yes						
n/N, (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO, % (95% CI)	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
P Value	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]

RAPID-PsA						
	Week 12			Week 24		
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N =135)	PBO (N =136)	CZP 200 mg Q2W (N =138)	CZP 400 mg Q4W (N =135)	PBO (N =136)
PRIOR USE OF SDMARDS						
1, n/N, (%)	42/61 (68.9)	42/72 (58.3)	22/74 (29.7)	NR	NR	NR
Difference from PBO, % (95% CI)	39.1 (23.5 to 54.7)	28.6 (13.2 to 44.0)		NR	NR	NR
P Value	< 0.001	< 0.001		NR	NR	NR
≥ 2, n/N, (%)	38/73 (52.1)	28/60 (46.7)	11/60 (18.3)	NR	NR	NR
Difference from PBO, % (95% CI)	33.7 (18.6 to 48.8)	28.3 (12.4 to 44.3)		NR	NR	NR
P Value	< 0.001	< 0.001		NR	NR	NR
REGION						
North America, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO, % (95% CI)	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
P Value	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Latin America, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO, % (95% CI)	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
P Value	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
West Europe, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO, % (95% CI)	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
P Value	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
East Europe, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO, % (95% CI)	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
P Value	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]

CI = confidence interval; CZP = certolizumab pegol; NR = not reported; PBO = placebo; Q2W = every two weeks; Q4W = every four weeks; sDMARD = synthetic disease-modifying antirheumatic drug; TNF = tumour necrosis factor alpha.
Source: Interim Clinical Study Report, week 24.[15]

TABLE 12: PROPORTION OF PATIENTS WITH DAS 28 EUROPEAN LEAGUE AGAINST RHEUMATISM RESPONSE OF GOOD AT WEEK 12 AND WEEK 24 (RANDOMIZED SET WITH IMPUTATION)

RAPID-PsA			
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N =135)	PBO[a] (N =136)
EULAR RESPONSE OF GOOD, N (%)			
Week 12			
N (%)	[redacted]	[redacted]	[redacted]
Difference from PBO, % (95% CI)[b]	[redacted]	[redacted]	
P Value[b]	[redacted]	[redacted]	
Week 24			
N (%)	[redacted]	[redacted]	[redacted]
Difference from PBO, % (95% CI)[b]	[redacted]	[redacted]	
P Value[b]	[redacted]	[redacted]	

CZP = certolizumab pegol; DAS 28(CRP) = Disease Activity Score in 28 Joints (C-reactive protein); EULAR = European League Against Rheumatism; PBO = placebo; Q2W = every two weeks; Q4W = every four weeks.
[a] For the entire placebo group, missing was used for patients escaping to CZP.
[b] Calculated by CADTH using Review Manager; positive values indicate that more patients in the CZP treatment group achieved response in comparison with patients in the placebo treatment group.
Source: Interim Clinical Study Report, week 24[15]

TABLE 13: PSARC RESPONDER RATE AT WEEK 12 AND WEEK 24 (RANDOMIZED SET WITH IMPUTATION)

RAPID-PsA						
	Week 12[a]			Week 24[a]		
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N =135)	PBO (N =136)	CZP 200 mg Q2W (N =138)	CZP 400 mg Q4W (N =135)	PBO (N =136)
PSARC RESPONDERS						
N (%)	[redacted]	[redacted]	[redacted]	[redacted] (78.3)	[redacted] (77.0)	[redacted] (33.1)
Difference from PBO, % (95% CI)[b]	[redacted]	[redacted]		[redacted]	[redacted]	
P Value[b]	[redacted]	[redacted]		< 0.001	< 0.001	
SUBGROUP OF PATIENTS WITH CONCOMITANT USE OF DMARDS AT BASELINE						
n/N (%)	73/99 (73.7)	63/100 (63.0)	37/88 (42.0)			
SUBGROUP OF PATIENTS WITH NO CONCOMITANT USE OF DMARDS AT BASELINE						
n/N (%)	28/39 (71.8)	26/35 (74.3)	15/48 (31.3)			

CI = confidence interval; CZP = certolizumab pegol; DMARD = disease-modifying antirheumatic drug; PBO = placebo; PsARC = Psoriatic Arthritis Response Criteria; Q2W = every two weeks; Q4W = every four weeks.
[a] Patients who withdrew for any reason or placebo patients who used escape medication were considered as nonresponders from the time they dropped out or when escape therapy was initiated. Patients who had missing data at a visit were counted as nonresponders for the respective visits.
[b] Treatment difference and corresponding 95% CI and *P* value were estimated using a standard two-sided Wald asymptotic test with a 5% alpha level.
Source: Mease et al.,[14] Interim Clinical Study Report, week 24.[15]

TABLE 14: HEALTH ASSESSMENT QUESTIONNAIRE – DISABILITY INDEX SCORE

RAPID-PsA						
	Week 12			Week 24		
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO (N = 136)	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO (N = 136)
% OF PATIENTS ACHIEVING A DECREASE OF ≥ 0.30 IN HAQ-DI SCORE FROM BASELINE[ab]						
N (%)	63 (45.7)	66 (48.9)	29 (21.3)	68 (49.3)	65 (48.1)	21 (15.4)
Difference from PBO, % (95% CI)[c]	24.3 (13.5 to 35.1)	27.6 (16.7 to 38.5)		33.8 (23.5 to 44.2)	32.7 (22.3 to 43.1)	
P Value[c]	< 0.001	< 0.001		< 0.001	< 0.001	
CHANGE FROM BASELINE IN HAQ-DI (RANDOMIZED SET WITH IMPUTATION)[d]						
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO[e]						
LS mean (SE)	[redacted]	[redacted]		[redacted]	[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	[redacted]	
P value	[redacted]	[redacted]		[redacted]	[redacted]	

CI = confidence interval; CZP = certolizumab pegol; HAQ-DI = Health Assessment Questionnaire – Disability Index; PBO = placebo; PsARC = Psoriatic Arthritis Response Criteria; Q2W = every two weeks; Q4W = every four weeks.

[a] Randomized set with imputation.

[b] Patients who withdrew for any reason or placebo patients who used escape medication were considered as nonresponders from the time they dropped out or when escape therapy was initiated. Patients who had missing data at a visit were counted as nonresponders for the respective visits.

[c] Treatment difference and corresponding 95% CI and *P* value were estimated using a standard two-sided Wald asymptotic test with a 5% alpha level.

[d] For patients who withdraw for any reason, patients with a missing measurement, or placebo patients who used escape medication, last observation prior to the early withdrawal or the missing measurement or before receiving CZP was carried forward.

[e] Analysis of covariance model with treatment, region, and prior TNFα-antagonist exposure (yes/no) as factors and baseline score as a covariate.

Source: Interim Clinical Study Report, week 24.[15]

TABLE 15: CHANGE FROM BASELINE IN PSAQOL, SF-36, PTAAP-VAS, AND FASCA AT WEEKS 12 AND 24 (RANDOMIZED SET WITH IMPUTATION)

RAPID-PsA						
	Week 12			Week 24		
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N =135)	PBO[a] (N =136)	CZP 200 mg Q2W (N =138)	CZP 400 mg Q4W (N =135)	PBO[a] (N =136)
CHANGE FROM BASELINE IN PSAQOL[b]						
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO[c]						
LS mean (SE)	[redacted]	[redacted]		[redacted]	[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	[redacted]	
P value	[redacted]	[redacted]		[redacted]	[redacted]	
CHANGE FROM BASELINE IN SF-36 PCS[b]						
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO[c]						
LS mean (SE)	[redacted]	[redacted]		[redacted]	[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	[redacted]	
P value	[redacted]	[redacted]		[redacted]	[redacted]	
CHANGE FROM BASELINE IN SF-36 MCS[b]						
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO[c]						
LS mean (SE)	[redacted]	[redacted]		[redacted]	[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	[redacted]	
P value	[redacted]	[redacted]		[redacted]	[redacted]	
CHANGE FROM BASELINE IN PTAAP-VAS[b]						
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

RAPID-PsA						
	Week 12			Week 24		
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N =135)	PBO[a] (N =136)	CZP 200 mg Q2W (N =138)	CZP 400 mg Q4W (N =135)	PBO[a] (N =136)
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO[c]						
LS mean (SE)	[redacted]	[redacted]		[redacted]	[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	[redacted]	
P value	[redacted]	[redacted]		[redacted]	[redacted]	
CHANGE FROM BASELINE IN FASCA[b]						
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO[c]						
LS mean (SE)	[redacted]	[redacted]		[redacted]	[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	[redacted]	
P value	[redacted]	[redacted]		[redacted]	[redacted]	

CI = confidence interval; CZP = certolizumab pegol; FASCA = Fatigue Assessment Scale; LS = least square; PBO = placebo; PsAQoL = Psoriatic Arthritis Quality of Life; PtAAP = Patient's Assessment of Arthritis Pain; Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale.

[a] For the entire placebo group, last observation prior to escape was carried forward for patients escaping to CZP.

[b] For patients who withdraw for any reason, patients with a missing measurement, or placebo patients who used escape medication, last observation prior to the early withdrawal or the missing measurement or before receiving CZP was carried forward.

[c] Analysis of covariance model with treatment, region, and prior TNFα-antagonist exposure (yes/no) as factors and baseline score as a covariate.

Source: Interim Clinical Study Report, week 24.[15]

TABLE 16: SHORT FORM (36) HEALTH SURVEY PCS AND MCS RESPONDERS AT WEEKS 12 AND 24 (RANDOMIZED SET WITH IMPUTATION)

RAPID-PsA						
MCID ≥ 2.5 points	Week 12			Week 24		
	CZP 200 mg Q2W (N = 138)	**CZP 400 mg Q4W (N =135)**	**PBO[a] (N =136)**	**CZP 200 mg Q2W (N =138)**	**CZP 400 mg Q4W (N =135)**	**PBO[a] (N =136)**
SF-36 PCS[b]						
Responders, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO[c], % (95% CI)	[redacted]	[redacted]		[redacted]	[redacted]	
P value	[redacted]	[redacted]		[redacted]	[redacted]	
SF-36 MCS[b]						
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO[c], % (95% CI)	[redacted]	[redacted]		[redacted]	[redacted]	
P value	[redacted]	[redacted]		[redacted]	[redacted]	

CI = confidence interval; CZP = certolizumab pegol; MCID = minimal clinically important difference; PBO = placebo; Q2W = every two weeks; Q4W = every four weeks; SF-36 = Short Form (36) Health Survey.

[a] For the entire placebo group, nonresponder imputation was used for patients escaping to CZP.

[b] Patients who withdrew for any reason or placebo patients who used escape medication were considered as nonresponders (i.e., not reaching MCID criteria) from the time they dropped out or when escape therapy was initiated. Patients who had missing data at a visit were counted as nonresponders for the respective visits.

[c] Treatment difference: CZP 200 mg Q2W – PBO; CZP 400 mg Q4W – PBO; and CZP 200 mg Q2W + CZP 400 mg Q4W – PBO (and corresponding 95% CI and *P* value) were estimated using a standard two-sided Wald asymptotic test with a 5% alpha level. The corresponding 95% CI for the differences were constructed using their asymptotic standard errors (asymptotic Wald confidence limits).

Source: Interim Clinical Study Report, week 24.[15]

TABLE 17: IMPROVEMENTS IN PRODUCTIVITY IN THE WORKPLACE AND WITHIN THE HOME AT WEEKS 12 AND 24 (RANDOMIZED SET, LOCF)

	RAPID-PsA					
	Week 12			Week 24		
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO[a] (N = 136)	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO[a] (N = 136)
Q2. WORK DAYS MISSED DUE TO ARTHRITIS IN THE LAST MONTH (EMPLOYED PATIENTS ONLY)						
N	[redacted]	[redacted]	[redacted]	84	84	76
Mean (SD)	[redacted]	[redacted]	[redacted]	0.2 (0.8)	0.6 (2.0)	1.6 (5.1)
Mean difference from PBO, (95% CI), *P* Value[b]	[redacted]	[redacted]		–1.4 (–3.4 to –0.6) < 0.001	–1.0 (–2.8 to –0.1) 0.060	
Q3. DAYS WITH WORK PRODUCTIVITY REDUCED BY ≥ 50% DUE TO ARTHRITIS IN THE LAST MONTH (EMPLOYED PATIENTS ONLY)						
N	[redacted]	[redacted]	[redacted]	84	84	76
Mean (SD)	[redacted]	[redacted]	[redacted]	1.3 (2.8)	2.1 (6.0)	3.5 (6.8)
Mean difference from PBO, (95% CI), *P* Value[b]	[redacted]	[redacted]		–2.2 (–4.1 to –0.7) 0.003	–1.4 (–3.4 to 0.6) 0.176	
Q4. RATE OF ARTHRITIS INTERFERENCE WITH WORK PRODUCTIVITY IN THE LAST MONTH (EMPLOYED PATIENTS ONLY)						
N	[redacted]	[redacted]	[redacted]	84	84	76
Mean (SD)	[redacted]	[redacted]	[redacted]	1.7 (2.0)	1.9 (2.5)	3.2 (3.0)
Mean difference from PBO, (95% CI), *P* Value[b]	[redacted]	[redacted]		–1.4 (–2.3 to –0.7) < 0.001	–1.2 (–2.1 to –0.4) 0.004	
Q5. DAYS WITH NO HOUSEHOLD WORK DUE TO ARTHRITIS IN THE LAST MONTH (ALL PATIENTS)						
N	[redacted]	[redacted]	[redacted]	138	135	136
Mean (SD)	[redacted]	[redacted]	[redacted]	2.4 (6.3)	2.5 (6.4)	4.7 (7.8)
Mean difference from PBO, (95% CI), *P* Value[b]	[redacted]	[redacted]		–2.3 (–4.0 to –0.7) 0.007	–2.2 (–3.9 to –0.6) 0.010	
Q6. DAYS WITH HOUSEHOLD WORK PRODUCTIVITY REDUCED BY ≥ 50% DUE TO ARTHRITIS IN THE LAST MONTH (ALL PATIENTS)						
N	[redacted]	[redacted]	[redacted]	138	135	136
Mean (SD)	[redacted]	[redacted]	[redacted]	2.9 (6.0)	3.5 (7.0)	6.8 (9.0)
Mean difference from PBO, (95% CI), *P* Value[b]	[redacted]	[redacted]		–3.9 (–5.8 to –2.2) < 0.001	–3.4 (–5.3 to –1.5) < 0.001	
Q7. DAYS WITH FAMILY, SOCIAL, OR LEISURE ACTIVITIES MISSED DUE TO ARTHRITIS IN THE LAST MONTH						
N	[redacted]	[redacted]	[redacted]	138	135	136
Mean (SD)	[redacted]	[redacted]	[redacted]	1.1 (3.6)	1.0 (3.9)	2.8 (6.6)

RAPID-PsA						
	Week 12			Week 24		
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO[a] (N = 136)	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO[a] (N = 136)
Mean difference from PBO, (95% CI), *P* Value[b]	[redacted]	[redacted]		–1.7 (–3.1 to –0.5) 0.005	–1.8 (–3.2 to –0.6) 0.004	
Q8. Days With Outside Help Needed Due to Arthritis in the Last Month						
N	[redacted]	[redacted]	[redacted]	138	135	136
Mean (SD)	[redacted]	[redacted]	[redacted]	0.7 (2.6)	1.5 (5.6)	1.9 (5.6)
Mean difference from PBO, (95% CI), *P* Value[b]	[redacted]	[redacted]		–1.2 (–2.4 to –0.3) 0.008	–0.4 (–1.7 to 1.0) 0.582	
Q9. Level of Arthritis Interference on Household Work Productivity in the Last Month						
N	[redacted]	[redacted]	[redacted]	138	135	136
Mean (SD)	[redacted]	[redacted]	[redacted]	2.2 (2.7)	2.6 (2.7)	4.1 (3.0)
Mean difference from PBO, (95% CI), *P* Value[b]	[redacted]	[redacted]		–1.8 (–2.5 to –1.2) < 0.001	–1.5 (–2.1 to –0.8) < 0.001	

CI = confidence interval; CZP = certolizumab pegol; LOCF = last observation carried forward; PBO = placebo; Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation.

[a] For the entire placebo group, last observation prior to escape was carried forward for patients escaping to CZP.

[b] Bootstrap *P* value and 95% CI for mean difference from placebo are based on a non-parametric bootstrap-t method with a variance stabilizing transformation (10,000 bootstrap replications).

Source: Interim Clinical Study Report, week 24.[15]

TABLE 18: PASI 75 AND PASI 90 RESPONDERS AT WEEKS 12 AND 24 FOR PATIENTS WITH AT LEAST 3% PSORIASIS BODY SURFACE AREA AT BASELINE (RANDOMIZED SET WITH IMPUTATION)

	RAPID-PsA					
	Week 12[a]			Week 24[a]		
	CZP 200 mg Q2W (N = 90)	CZP 400 mg Q4W (N = 76)	PBO (N = 86)	CZP 200 mg Q2W (N = 90)	CZP 400 mg Q4W (N = 76)	PBO (N = 86)
PASI 75						
Responders, N (%)	42 (46.7)	36 (47.4)	12 (14.0)	56 (62.2)	46 (60.5)	13 (15.1)
Difference from PBO, % (95% CI)[b]	32.7 (20.1 to 45.4)	33.4 (20.0 to 46.8)		47.1 (34.6 to 59.7)	45.4 (32.1 to 58.8)	
P Value[b]	< 0.001	< 0.001		< 0.001	< 0.001	
PASI 90						
Responders, N (%)	20 (22.2)	15 (19.7)	4 (4.7)	42 (46.7)	27 (35.5)	5 (5.8)
Difference from PBO, % (95% CI)[b]	17.6 (7.9 to 27.2)	15.1 (5.1 to 25.1)		40.9 (29.4 to 52.3)	29.7 (17.9 to 41.6)	
P Value[b]	< 0.001	0.004		< 0.001	< 0.001	

CI = confidence interval; CZP = certolizumab pegol; PASI = Psoriasis Area and Severity Index; PBO = placebo; Q2W = every two weeks; Q4W = every four weeks.

[a] Patients who withdrew for any reason or placebo patients who used escape medication were considered as nonresponders from the time they dropped out or when escape therapy was initiated. Patients who had missing data at a visit were counted as nonresponders for the respective visits.

[b] Treatment difference and corresponding 95% CI and *P* value were estimated using a standard two-sided Wald asymptotic test with a 5% alpha level.

Source: Mease et al.,[14] Interim Clinical Study Report, week 24.[15]

TABLE 19: CHANGE FROM BASELINE IN LEEDS DACTYLITIS INDEX AND LEEDS ENTHESITIS INDEX AT WEEKS 12 AND 24 (RANDOMIZED SET WITH IMPUTATION)

RAPID-PsA						
	Week 12			Week 24		
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO[a] (N = 136)	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO[a] (N = 136)
CHANGE FROM BASELINE IN LDI[b]						
N	[redacted]	[redacted]	[redacted]	35	38	35
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	45.30 (36.00)	56.82 (75.86)	65.60 (90.41)
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	–40.69 (34.62)	–53.47 (69.09)	–22.04 (46.87)
Difference from PBO[c]						
LS mean (SE)	[redacted]	[redacted]		[redacted]	[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	[redacted]	
P value	[redacted]	[redacted]		0.002	< 0.001	
CHANGE FROM BASELINE IN LEI[b]						
N	[redacted]	[redacted]	[redacted]	88	84	91
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	3.1 (1.7)	2.9 (1.6)	2.9 (1.6)
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	–2.0 (1.8)	–1.8 (1.9)	–1.1 (1.8)
Difference from PBO[c]						
LS mean (SE)	[redacted]	[redacted]		[redacted]	[redacted]	
95% CI	[redacted]	[redacted]		[redacted]	[redacted]	
P value	[redacted]	[redacted]		< 0.001	0.003	

CI = confidence interval; CZP = certolizumab pegol; LDI = Leeds Dactylitis Index; LEI = Leeds Enthesitis Index; LS = least square; PBO = placebo; Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation; SE = standard error.

[a] For the entire placebo group, last observation prior to escape was carried forward for patients escaping to CZP.

[b] For patients who withdraw for any reason, patients with a missing measurement, or placebo patients who used escape medication, last observation prior to the early withdrawal or the missing measurement or before receiving CZP was carried forward.

[c] Analysis of covariance model with treatment, region, and prior TNFα-antagonist exposure (yes/no) as factors and baseline score as a covariate.

Source: Interim Clinical Study Report, week 24.[15]

TABLE 20: CHANGE FROM BASELINE AT WEEK 24 IN MTSS

RAPID-PsA				
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	CZP 200 mg Q2W + CZP 400 mg Q4W (N = 273)	PBO (N = 136)
PRESPECIFIED ANALYSES				
LS mean change from baseline (SE)	11.5 (7.59)	25.1 (7.92)	18.28 (6.07)	28.9 (7.73)
P value	0.071	0.688	0.203	
RANDOMIZED SET WITH OBSERVED CASES[a]				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO[c]				
LS mean (SE)	[redacted]	[redacted]	[redacted]	
95% CI	[redacted]	[redacted]	[redacted]	
P value	[redacted]	[redacted]	[redacted]	
POST-HOC PRIMARY ANALYSIS WITH ANCOVA: MEDIAN MTSS CHANGE FROM BASELINE OF ALL PATIENTS OBSERVED				
Change from baseline[c]				
LS mean (SE)	0.01 (0.07)	0.11 (0.08)	0.06 (0.06)	0.28 (0.07)[b]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO[c]				
LS mean (SE)	–0.27 (0.09)	–0.17 (0.09)	–0.22 (0.08)	
95% CI	[redacted]	[redacted]	[redacted]	
P value	0.004	0.072	0.007	
ANALYSIS WITH ANCOVA UTILIZING CZP DATA FOR PLACEBO-ESCAPE PATIENTS: MEDIAN MTSS CHANGE FROM BASELINE OF ALL PATIENTS OBSERVED				
Change from baseline[d]				
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO[c]				
LS mean (SE)	[redacted]	[redacted]	[redacted]	
95% CI	[redacted]	[redacted]	[redacted]	
P value	[redacted]	[redacted]	[redacted]	
POST HOC: IMPUTATION OF MISSING VALUES USING MEAN CHANGE FROM BASELINE IN ENTIRE STUDY POPULATION[e]				
Change from baseline				
LS mean (SE)	0.01 (0.07)	0.11 (0.08)	0.06 (0.06)	0.28 (0.07)[b]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Difference to PBO				
LS mean (SE)	–0.27 (0.09)	–0.17 (0.09)	–0.22 (0.08)	
95% CI	[redacted]	[redacted]	[redacted]	
P value	0.004	0.072	0.007	
POST HOC: IMPUTATION OF MISSING VALUES BY USING WORST CHANGE FROM BASELINE IN ENTIRE STUDY POPULATION[f]				
Change from baseline				
LS mean (SE)	0.18 (0.13)	0.52 (0.13)	0.35 (0.10)	0.66 (0.13)[b]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO				

RAPID-PsA				
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	CZP 200 mg Q2W + CZP 400 mg Q4W (N = 273)	PBO (N = 136)
LS mean (SE)	−0.48 (0.16)	−0.14 (0.16)	–0.31 (0.14)	
95% CI	[redacted]	[redacted]	[redacted]	
P value	0.003	0.380	0.028	
POST HOC: IMPUTATION OF MISSING VALUES BY USING WORST CHANGE FROM BASELINE IN SAME TREATMENT GROUP[g]				
Change from baseline				
LS mean (SE)	0.14 (0.11)	0.49 (0.12)	0.31 (0.09)	0.39 (0.11)[b]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Difference to PBO				
LS mean (SE)	−0.25 (0.14)	0.10 (0.14)	–0.08 (0.12)	
95% CI	[redacted]	[redacted]	[redacted]	
P value	0.077	0.483	0.538	
POST HOC: EXCLUSION OF PATIENTS WITH < 2 AVAILABLE VALUES[h]				
Change from baseline				
N	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE)	0.01 (0.08)	0.12 (0.08)	0.06 (0.06)	0.29 (0.08)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Difference from PBO				
LS mean (SE)	−0.29 (0.10)	−0.17 (0.10)	–0.23 (0.09)	
95% CI	[redacted]	[redacted]	[redacted]	
P value	[redacted]	[redacted]	[redacted]	

ANCOVA = analysis of covariance; CI = confidence interval; CZP = certolizumab pegol; LS = least square; mTSS = modified Total Sharp Score; Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation; SE = standard error.

[a] Analysis included slotting approach without a specified minimum window between radiograph time points. Placebo mean change value is biased because it includes only patients who performed well on placebo therapy (i.e., did not escape to CZP).

[b] For the entire placebo group, linear extrapolations were used for patients escaping to CZP.

[c] The change from baseline data represents an ANCOVA model with treatment, region, and prior TNFα-antagonist exposure (yes/no) as factors and baseline score as covariate.

[d] For the analysis with ANCOVA utilizing CZP data for placebo-escape patients, for patients who withdrew for any reason or patients with a missing week 24 measurement, the scores were linearly extrapolated from the last two radiographs before week 24 or the early withdrawal visit.

[e] For patients with < 2 radiographs, mean change from baseline to week 24 in mTSS was utilized.

[f] For patients with < 2 radiographs, worst change from baseline to week 24 in mTSS was utilized.

[g] For patients with < 2 radiographs, worst change from baseline to week 24 in mTSS by treatment was utilized.

[h] The randomized set was restricted to patients with at least two radiograph visit values, which were at least eight weeks apart.

Source: van der Heijde et al.,[16] Interim Clinical Study Report, week 24.[15]

TABLE 21: CHANGE FROM BASELINE AT WEEK 24 IN MODIFIED TOTAL SHARP SCORE BY SUBGROUPS OF PRIOR EXPOSURE TO TNF INHIBITORS (RANDOMIZED SET WITH IMPUTATION; POST-HOC ANALYSIS)

	RAPID-PsA			
	CZP 200mg Q2W (N = 138)	CZP 400mg Q4W (N = 135)	CZP 200mg Q2W + CZP 400mg Q4W (N = 273)	PBO (N = 136)
PRIOR EXPOSURE TO TNF THERAPY				
NO				
N	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference to PBO, LS mean (SE)	[redacted]	[redacted]	[redacted]	
P Value	[redacted]	[redacted]	[redacted]	
Yes				
N	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference to PBO, LS mean (SE)	[redacted]	[redacted]	[redacted]	
P Value	[redacted]	[redacted]	[redacted]	

ANCOVA = analysis of covariance; CZP = certolizumab pegol; LS = least square; mTSS = modified Total Sharp Score; PBO=placebo; Q2W = every two weeks; Q4W = every four weeks; SE = standard error; TNFα = tumour necrosis factor alpha.
Note: Linear extrapolation was used. For patients who withdrew for any reason, patients with a missing week 24 measurement, or placebo patients who used escape medication, the scores were linearly extrapolated from the last two radiographs before week 24, from the early withdrawal visit, or before receiving CZP. For patients with fewer than two radiographs, median change from baseline to week 24 in mTSS was utilized.
Note: For the entire placebo group, linear extrapolations were used for patients escaping to CZP.
Note: The change from baseline data represent an ANCOVA model with treatment, region, and prior TNFα-antagonist exposure (yes/no) as factors and baseline score as covariate, except for the subgroup analysis by region and prior TNFα-antagonist exposure. For the subgroup analysis by region and prior TNFα-antagonist exposure, treatment and prior TNFα-antagonist exposure or treatment and region are the factors for the ANCOVA model.
Source: Interim Clinical Study Report, week 24.[15]

TABLE 22: MODIFIED TOTAL SHARP SCORE RESPONDERS AT WEEK 24 (RANDOMIZED SET WITH IMPUTATION)

RAPID-PsA			
	CZP 200mg Q2W (N = 138)	CZP 400mg Q4W (N = 135)	PBO (N = 136)
Responders[a], % (95% CI)[b]	[redacted]	[redacted]	[redacted]
Difference from PBO[c], % (95% CI)	[redacted]	[redacted]	
P value	< 0.001	< 0.001	

CI = confidence interval; CZP = certolizumab pegol; mTSS = modified Total Sharp Score; PBO = placebo; Q2W = every two weeks; Q4W = every four weeks.

Note: Nonresponder imputation was used: patients who withdrew for any reason, or placebo patients who used escape medication, were considered as nonresponders from the time they dropped out or when escape therapy was initiated. Patients who had missing data at visits were counted as nonresponders for the respective visits.

Note: For patients with fewer than two radiographs, median change from baseline to week 24 in mTSS was utilized.

[a] A patient was considered an mTSS responder if the patient had a change from baseline to week 24 in mTSS of ≤ 0 (a patient was considered a nonresponder if there was a change from baseline to week 24 in mTSS > 0); escapers were treated as if they had a change > 0.

[b] Asymptotic Wald confidence limits.

[c] Treatment differences: CZP 200mg Q2W – PBO; CZP 400mg Q4W – PBO; and CZP 200mg Q2W + CZP 400mg Q4W – PBO (and corresponding 95% CI and *P* values) were estimated using a standard two-sided Wald asymptotic test with a 5% alpha level. The corresponding 95% CIs for the differences were constructed using their asymptotic standard errors (asymptotic Wald confidence limits).

Source: Interim Clinical Study Report, week 24.[15]

TABLE 23: MODIFIED TOTAL SHARP SCORE AT WEEK 48

RAPID-PsA			
	CZP 200 mg Q2W	CZP 400 mg Q4W	PBO
CHANGE FROM BASELINE (ALL PATIENTS)			
N			
LS mean			
95% CI			
CHANGE FROM BASELINE (PATIENTS WITH BASELINE MTSS > 6)			
N			
LS mean			
95% CI			
CHANGE FROM BASELINE (PATIENTS WITH BASELINE MTSS ≤ 6)			
N			
LS mean			
95% CI			
NON-PROGRESSION (≤ 0) (ALL PATIENTS)			
N			
% nonresponders			
95% CI			
NON-PROGRESSION (≤ 0) (PATIENTS WITH BASELINE MTSS > 6)			
N			
% nonresponders			
95% CI			
NON-PROGRESSION (≤ 0) (PATIENTS WITH BASELINE MTSS ≤ 6)			
N			
% nonresponders			
95% CI			

CZP = certolizumab pegol; mTSS = modified Total Sharp Score; PBO = placebo; Q2W = every two weeks; Q4W = every four weeks.
Source: Mease et al.[50]

TABLE 24: TREATMENT-EMERGENT ADVERSE EVENTS WITH AN INCIDENCE OF > 3% IN EITHER CZP GROUP DURING THE 24-WEEK DOUBLE-BLIND PERIOD

RAPID-PsA			
	CZP 200 mg Q2W (N = 138)	CZP 400 mg Q4W (N = 135)	PBO (n=136)
Diarrhea	[redacted]	[redacted]	[redacted]
Abdominal pain (upper)	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]
Hepatic enzyme increased	[redacted]	[redacted]	[redacted]
Blood CPK increased	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]

Source: Interim Clinical Study Report, week 24.[15]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

1. Objective

The objective was to provide information on the characteristics, validity, and clinically important differences of the scales and surrogate outcomes measured in the trials included in the CADTH Common Drug Review (CDR) systematic review. These include the American College of Rheumatology (ACR) 20/50/70, Psoriatic Arthritis Response Criteria (PsARC), Disease Activity Score in 28 Joints (DAS 28) based on C-reactive protein (CRP), Psoriasis Area and Severity Index (PASI), Leeds Dactylitis Index (LDI), Leeds Enthesitis Index (LEI), Health Assessment Questionnaire (HAQ), Short Form (36) Health Survey (SF-36), and the Work Productivity Survey (WPS).

2. Findings

Currently available outcome measures in PsA have largely been adopted from other conditions, such as rheumatoid arthritis (RA) and psoriasis. Hence, validity and reliability data specific to PsA are sparse. To complicate matters further, there are many different parameters of disease activity in PsA; and no single evaluation tool assesses all components of PsA, necessitating the use of multiple outcome measures in clinical trials. The various outcome measures are summarized below.

American College of Rheumatology 20/50/70

The ACR criteria[22] for assessing joint status (originally developed for RA patients) provide a composite measure of ≥ 20%, ≥ 50%, or ≥ 70% improvement in both swollen and tender joint counts and at least three of five additional disease criteria, including: patient and physician global assessments of disease activity (10 cm visual analogue scale [VAS]), HAQ, patient assessment of pain intensity, and levels of CRP or erythrocyte sedimentation rate (ESR). The ACR joint count assesses 68 joints for tenderness and 66 joints for swelling. Assessment of the proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints of the hands and feet (i.e., 78 joints for tenderness and 76 for swelling) is not typically included for PsA because of the difficulty in distinguishing it from PIP and DIP joint inflammation in the toes.[51] The ACR has been shown to have good inter- and intra-observer reliability in PsA,[52,53] and was shown to be a valid outcome measure in randomized controlled trials (RCTs).[54] The ACR 20 is generally accepted as the minimal clinically important difference (MCID) indicating a response to treatment, while the ACR 50 and ACR 70 more likely reflect truly important change for the long-term management of arthropathy. Of note, the ACR is a general measure of clinical response of peripheral joint disease, and does not include assessment of enthesitis, dactylitis, the spine, or the skin. Consequently, it represents only part of the clinical features of PsA, necessitating the use of additional assessment instruments.

Psoriatic Arthritis Response Criteria

PsARC[23] measures the signs and symptoms of PsA assessed by tender or swollen joint count, physician global assessment (0 to 5 Likert scale), and patient global assessment (0 to 5 Likert scale). To be a PsARC responder, a patient must have at least a 30% reduction in tender or swollen joint count, as well as a 1-point reduction on the 5-point patient and/or physician global assessment scales, and no worsening on any score. PsARC has been shown to be a responsive and discriminate outcome instrument in PsA RCTs.[54] However, the PsARC tends to have a higher percentage response than the ACR 20, which may be explained by the requirement that tender *or* swollen joint change is required, not both, and possibly by the absence of the HAQ score and measurement of ESR or CRP.[55] As with the ACR, the PsARC does not account for psoriasis severity, and is only a general assessment of clinical status.

Disease Activity Score in 28 Joints and C-reactive Protein

The Disease Activity Score in 28 Joints (DAS 28) includes an assessment of 28 joints for tenderness and swelling along with a patient global assessment of well-being to evaluate a patient's response to treatment.[24,25] The score ranges from 0 to 9.4 and is calculated using clinical values of either ESR or CRP; the reviewed trial used CRP, where TJC28 and SJC28 are the tender and swollen joint counts and PtGA is the patient global assessment:

$$DAS\ 28 = 0.56(\sqrt{TJC28}) + 0.28(\sqrt{SJC28}) + 0.36Ln(CRP + 1) + 0.014(PtGA)$$[24]

The threshold values are 2.6, 3.2, and 5.1 for remission, low disease activity, and high disease activity, respectively.[26] DAS 28 and change from baseline DAS 28 values are used to derive the European League Against Rheumatism (EULAR)[25] response criteria. Responders include patients with moderate or good response:

TABLE 25: IMPROVEMENT IN DAS 28 FROM BASELINE

Current DAS 28	Improvement in DAS 28 From Baseline		
	> 1.2	> 0.6 to ≤ 1.2	≤ 0.6
≤ 3.2	Good	Moderate	None
3.2 to ≤ 5.1	Moderate	Moderate	None
5.1	Moderate	None	None

DAS 28 = Disease Activity Score in 28 Joints.

The DAS components correlate well with each other and with the ACR,[24,56-58] and have been shown to be discriminant and responsive in trials.[59] However, the DAS 28 does not include assessment of DIP or lower extremity disease; thus, it may not describe the full extent of a patient's disease status. The DAS 28 using ESR is better established versus using CRP, and the DAS 28-ESR has been validated for use as an outcome measure in several RA trials.[24,26,54,60] The DAS 28-ESR has shown the ability to discriminate between placebo and treatment in PsA trials,[59] although no formal validation has been conducted in PsA thus far.

The DAS 28-CRP shows general agreement with the ESR equation in RA trials, though the DAS 28-CRP tends to yield better response criteria results than the DAS 28-ESR when disagreements occur between the two.[61-63] CRP may be a more desirable clinical measurement than ESR because CRP levels are sensitive to short-term changes in disease activity, whereas ESR can be influenced by such factors as age, gender, or plasma proteins.[64] As with the ACR and PsARC, the DAS 28 is only a general assessment of clinical response.

Psoriasis Area and Severity Index

The PASI is a widely used instrument in psoriasis trials that assesses and grades the severity of psoriatic lesions and the patient's response to treatment. It produces a numeric score ranging from 0 to 72. In general, a PASI score of 5 to 10 is considered moderate disease, and a score higher than 10 is considered severe. A 75% reduction in the PASI score (PASI 75) is the current benchmark for most clinical trials in psoriasis and is the criterion for the efficacy of new psoriasis treatments approved by the FDA.[27]

In calculating the PASI, severity is determined by dividing the body into four regions: head (h), upper extremities (u), trunk (t), and lower extremities (l). These account for 10%, 20%, 30%, and 40% of the total body surface area (BSA), respectively.[65] Each of these areas is assessed separately for erythema,

induration, and scaling, which are rated on a scale of 0 (none) to 4 (very severe). Extent of psoriatic involvement is graded as follows: 0 = no involvement; 1 = 1% to 9%; 2 = 10% to 29%; 3 = 30% to 49%; 4 = 50% to 69%; 5 = 70% to 89%; and 6 = 90% to 100%. The following formula is used to calculate the PASI score:

PASI = 0.1 (Eh + lh + Sh) Ah + 0.2 (Eu + lu + Su) Au + 0.3 (Et +lt + St) At + 0.4 (El +ll +Sl) Al[65]

where E = erythema, I = induration, S = scaling, A = area, h = head score, t = trunk score, u = upper extremities, and l = lower extremities score. PASI 75 is a dichotomous scale (Yes/No; patient achieved ≥ 75% improvement from baseline PASI score).

A number of limitations of the PASI have been identified:

- The PASI has been criticized as not correlating the clinical extent of the disease with quality of life and the psychological stress caused by psoriasis. The patient's measure of quality of life is often worse than the physician-rated clinical severity.[66]
- There are significant inter-rater reliability issues regarding the measurement of BSA.[67,68]
- It often fails to predict severity as seen from the patient's perspective.[67,68]
- Improvements in PASI score are not linearly related to severity or improvements in psoriasis.[67,68] The extent of psoriatic involvement is measured using a scale of one to six, and the areas corresponding to each score are nonlinear.
- Some severe disease (clinically) may be scored low. For example, scores as low as three (on palms and soles) may represent psoriasis that disables a patient from work and other life activities.
- Most patients fall into a narrow band of scores, thereby decreasing the usefulness of the full range of scores (i.e., scores above 40 are rare).[67]
- There is little research on the reliability of the assessments for erythema, desquamation, and induration together with overall PASI scores.[67]
- Criterion validity is restricted by the lack of a "gold standard" measure of psoriatic severity.[69]
- The PASI lacks sensitivity as erythema, desquamation, and induration are scored with equal weight within each of the four body regions. Thus, a reduction in scaling with a concomitant increase in skin erythema could be recorded with the same PASI score.
- Improvement of the histological phenotype of psoriasis can be underestimated by the per cent improvement in PASI (e.g., reduction of T cells, loss of K16 expression, and reduction in epidermal thickness).[27]
- Little work has been done to determine the clinical relevance of derived PASI scores.[67]

Health Assessment Questionnaire

The HAQ was developed to assess physical disability and pain in RA,[28] and has been used extensively in arthritis RCTs, including for PsA. Through a self-assessed questionnaire covering eight domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities), patients' difficulty in performing these activities is scored from zero (without any difficulty) to three (unable to do). The scores are adjusted for the use of aids, devices, or persons who help with the activity, and are then summed and divided by the number scores answered. Scores are evaluated based on change from baseline. The MCID for the HAQ has been estimated from a phase 3 trial of etanercept in PsA[29] to be 0.3 (as opposed to 0.22 for RA). Further expanding on this analysis, Mease et al.[30] determined that the MCID for the HAQ Disability Index [HAQ-DI] was 0.35, up 0.05 from their preliminary estimate. The MCID from Kwok et al. was also in this range, at 0.309.[70] Blackmore et al. have shown the HAQ adequately captures clinically important changes in functional status and pain.[28,29] Because the HAQ focuses on physical disability, however, it may not adequately capture disability in patients with predominantly skin disease.

Also, it may not adequately measure the activities affected in patients with different patterns of PsA.[71] This observation has not been evaluated in other studies to date. Modified versions of the HAQ (the HAQ-S includes spinal domains and the HAQ-SK includes assessment of skin disease) have not proven to be significantly better for assessing health status in PsA than the original HAQ.[71,72] Of note, the HAQ-SK correlated poorly with the PASI, though it does correlate with patient- and physician-assessed psoriasis severity.[72]

Medical Outcomes Study Short Form (36) Health Survey

The SF-36 is a 36-item general health status instrument that has been used extensively in clinical trials in many disease areas.[31] The SF-36 consists of eight health domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH).[32] For each of the eight categories, a subscale score can be calculated. The SF-36 also provides two component summaries: the physical component summary (PCS) and the mental component summary (MCS), derived from aggregating the eight domains according to a scoring algorithm. 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 standard deviation of 10 in the general US population. Therefore, all scores above/below 50 are considered above/below average for the general US population. Husted et al.[73] and Leung et al.[36] reported that the SF-36 is reliable and valid for assessment of patients with PsA, and could be used to distinguish PsA patients from patients without PsA. In addition, the PCS and MCS summary scores support the SF-36 validity.[36] The SF-36 is equally or more responsive than the HAQ to short-term changes in perceived health status and inflammatory disease activity in patients with PsA.[74]

The MCID for either the PCS or MCS of the SF-36 is typically between 2.5 and 5 points.[33-35] Leung et al.[36] reported MCIDs of 3.74 and 1.77 in PsA patients treated with anti- tumour necrosis factor alpha (TNF-alpha) drugs for the PCS and MCS subsections, respectively. The MCS has also been observed to be weaker in differentiating drug and placebo effects as shown in phase 3 trial.[36] Limitations to consider with regard to this study include small sample size (N = 17) and the fact that MCIDs may change with either clinic settings or baseline disease severity.[36]

Modified Total Sharp Score

The Sharp scoring system, first developed in 1971, has undergone modifications over time and is now referred to as the modified Total Sharp Score (mTSS). This method allows for the assessment of two different aspects of joint damage: articular erosions (representing direct invasion of cartilage and bone by the proliferating synovial pannus) and joint space narrowing (representing destruction of surface cartilage). Data on the progression of joint structural damage are obtained by taking X-rays of specific joints (typically in the hands and feet) before treatment and at various points after treatment has been initiated.

TABLE 26: THE SHARP SCORING SYSTEM

Sharp/van der Heijde[75]	
Erosions	
0	Normal
1	Discrete erosions
2 to 3	Larger erosions according to surface area involved
4	Erosion extending over the middle of the bone
5	Complete collapse
Joint space narrowing	
0	Intact bony outlines and normal joint space
1	Erosion < 1 mm in diameter or JSN
2	One or several small erosions (diameter > 1 mm)
3	Marked erosions
4	Severe erosions (usually no joint space left and the original bony outlines are only partly preserved)
5	Mutilating changes (the original bony outlines have been destroyed)

The most recent modification of the Sharp scoring system was performed by van der Heijde.[76] Van der Heijde scores erosions as listed in the above table.

The van der Heijde erosion score includes 16 joints from the hands and wrists (graded from 0 to 5) and six joints from the feet (graded from 0 to 10). The joint space narrowing score includes 15 areas from the hands and wrists (graded from 0 to 4) and six areas from the feet (also graded from 0 to 4). The maximum erosion score is 160 for hands and wrists and 120 for feet, while the maximum joint space narrowing score is 120 for hands and 48 for feet.[77] Maximum total scores for both erosion and joint space narrowing are as follows:

Erosion = (32 joints in hands and wrists x 5) + (12 joints in feet x 10) = 280
Joint space narrowing = (30 joints in hands and wrists x 4) + (12 joints in feet x 4) = 168

The van der Heijde modification has become the most commonly used for a few reasons: it includes both hands and feet; it measures erosions and joint space narrowing; and it covers a broad spectrum of joints, providing sensitivity to change.[78]

In the early stages of RA, inflammation appears to be the main contributor to increased disability, rather than actual damage to joints.[79,80] The relationship between radiological and functional changes has been studied. A reanalysis of published data performed by Welsing et al. found that patients must reach a certain amount of radiological damage before an increase in damage will impact disability. The authors also found that changes in Sharp scores had a greater impact on disability with advancing age. A study by Sabin et al. found that radiologic damage assessed using the van der Heijde method was highly correlated with HAQ scores in a population with a mean disease duration of seven years. They also cited findings from another study that found that Sharp scores became correlated with HAQ after six years' disease duration. At the other end of the spectrum, a study by Clarke et al. found that radiological scores assessed using the Genant method were positively correlated with HAQ in patients with 20 years' disease duration.[81] Therefore, radiological changes assessed by Sharp scores and functional changes assessed by the HAQ do not correlate with each other early in RA, but after several years of disease.

Several limitations exist in the use of radiographs to assess clinical status in RA. Radiographs tend to change slowly in RA, requiring at least six months to a year to detect changes in a single patient. Inter-

rater and intra-rater reliability are also a concern due to the subtle nature of changes and subjective interpretation. The images themselves can also vary between samples, due to positioning and quality. Radiographs should be read in random order to reduce the potential bias of interpretation at different time points.[82] Given these limitations, beginning in the early 1990s, the use of magnetic resonance imaging (MRI) was being examined as an alternative for assessing disease progression.[83] However, the use of MRI for assessing clinical status of RA is limited due to cost and accessibility.

In a study by Bruynesteyn, authors determined an MCID of 4.6 units for the Sharp/van der Heijde method, using a panel of experts.[44] They defined the MCID as a progression in radiologic joint damage that makes a rheumatologist change therapy. This MCID was equal to, or slightly lower than, the smallest detectable difference (SDD) for this scoring system. The SDD represents the smallest change score that can be reliably discriminated from the measurement error of the scoring method.[84] The authors also note that with improvements in disease-modifying therapies, such as the biologics, the magnitude of progression will continue to shrink, requiring increasingly sensitive measures.

Psoriatic Arthritis Quality of Life

The Psoriatic Arthritis Quality of Life (PsAQoL) is a quality of life instrument specific to psoriatic arthritis.[37] The PsAQoL comprises 20 items so that the score ranges from 0 to 20, with higher scores indicating worse health-related quality of life (HRQoL).[15] It has been used in clinical studies and trials to assess the impact of interventions for PsA. It is well accepted by patients and has acceptable scaling and psychometric properties.[37] Although HRQoL measures may provide valuable information about treatment benefits in patient well-being, it was observed that patient-reported outcomes, such PsAQoL, correlate very poorly with clinical outcomes in PsA. It indicated that patients who respond clinically do not necessarily report improvements in their HRQoL and vice versa.[18] No MCID for PsAQoL was identified.

Patient's Assessment of Arthritis Pain-VAS (PtAAP-VAS)

The Patient's Assessment of Arthritis Pain – Visual Analogue Scale (PtAAP-VAS) is part of the ACR core set of measures in arthritis.[15,38] The PtAAP-VAS consists of a horizontal line 100 mm in length on which patients are asked to indicate the level of their arthritis pain at the day of the visit between 0 ("no pain") and 100 ("most severe pain").[15] The MCID for the pain was defined as a 10-point decrease from baseline for pain.[18,39]

Fatigue Assessment Scale

The Fatigue Assessment Scale (FAS or FASCA) is a validated Numeric Rating Scale (NRS) — that is, a single-item instrument consisting of numerals from 0 to 10 on a horizontal line, with 0 representing "no fatigue" and 10 representing "fatigue as bad as you can imagine." Patients were asked to rate their fatigue (weariness, tiredness) during the previous week on the scale, choosing a single number from 0 to 10.[40] A 1-point decrease from baseline was suggested as MCID for FASCA.[18]

Leeds Dactylitis Index

Dactylitis, the swelling of an entire digit related to articular and periarticular inflammation, is a characteristic of inflammatory spondyloarthropathies, including PsA. Presence of dactylitis was assessed using the LDI basic, which evaluates for a $\geq$ 10% difference in the circumference of the digit compared with the opposite digit.[15,41,42] No MCID for LDI was identified.

Leeds Enthesitis Index

Enthesitis, the inflammation at the bone insertion of a tendon or ligament, is common in PsA. The LEI is a new enthesitis index designed for use in PsA[15,43] and recently adopted for use in RCTs involving patients with PsA. Enthesitis was assessed by palpation on the lateral humeral epicondyles (elbows), medial femoral epicondyles (knees), and Achilles tendons (heels) bilaterally, and scored as 0 (no pain) and 1 (painful).[15] No MCID for LEI was identified.

3. The Validity of WPS

The WPS is a nine-question instrument used to assess the impact of arthritis on productivity within and outside the home during the preceding month.[15] One question on the WPS concerns employment status; three questions relate to work productivity outside the home; and five questions concern 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).[15]

The discriminant validity, responsiveness, and reliability of the arthritis-specific WPS in patients with active PsA have been evaluated in 409 patients enrolled in a phase 2 RCT using certolizumab pegol (CZP).[49] Patients with a higher disease activity [higher DAS 28 (CRP) or PASI], worse HRQoL (lower SF-36 scores or higher PsAQoL or DLQI), or lower PF (higher HAQ-DI and lower SF-36 scores) generally had greater PsA-associated losses in productivity within and outside the home as well as a significantly higher interference of arthritis per month compared with patients with lower disease activity, better HRQoL, or higher PF.

At week 12, ACR 20 responders reported significantly greater improvement in household and patient workplace productivity in comparison with nonresponders (except in work days missed and days with outside help). Similar results were reported for HAQ-DI and ACR 50 responders. The effect size for change in productivity scores in ACR 20 responders was moderate to small (0.5 < standardized response mean (SRM) < 0.8), while it was negligible (SRM < 0.1) or small (SRM < 0.5) in nonresponders.[49] The MCID is currently unknown.

APPENDIX 6: SUMMARY OF FINDINGS AT 96 WEEKS OF STUDY RAPID-PSA

Aim

To summary the findings of the study **RAPID-PsA** at 96 weeks[50] provided by manufacturer: effect of certolizumab pegol over 96 weeks in patients with PsA with and without prior anti-TNF exposure.[50]

Findings

Study and Baseline Disease Characteristics

Baseline study and disease characteristics were reported in the main text. Briefly, RAPID-PsA is a phase 3 trial, randomized, double-blind and placebo-controlled to week 24, dose-blind to week 48, and open-label extension (OLE) to week 216. Patients were randomized to placebo or subcutaneous CZP 400 mg at week 0, 2, and 4 (loading dose) followed by either CZP 200 mg every two weeks (Q2W) or CZP 400 mg every four weeks (Q4W). Patients originally randomized to CZP continued on their assigned dose in the dose-blind phase and OLE. Placebo patients who failed to achieve at least a 10% improvement from baseline in tender and swollen joint counts at both week 14 and week 16 (early escape) were re-randomized at week 16 to CZP 200 mg Q2W or CZP 400 mg Q4W, following the CZP loading dose. The remaining placebo patients were re-randomized in a similar manner at week 24. The primary clinical outcomes were the ACR 20 response at week 12 and mTSS at week 24. [redacted]

Patient Disposition

In RAPID-PsA, a total of 409 patients were randomized, of whom 273 received CZP (200 mg Q2W or 400 mg Q4W) from week 0 (baseline). Of the patients randomized to CZP at baseline, 248 (90.8%) completed to week 24 [redacted].

Results: Efficacy and Harms

Efficacy

American College of Rheumatology Response

[redacted]

Table 27[redacted].

Modified Total Sharp Score
No mTSS results were reported at week 96.

Psoriasis Area and Severity Index

.

Disease Activity Score in 28 Joints, Health Assessment Questionnaire – Disability Index, Pain, Fatigue, and Short Form (36) Health Survey
The efficacy observed at week 24 in terms of DAS 28, HAQ-DI, Pain, Fatigue and SF-36 (Table 27).

TABLE 27: CLINICAL AND PATIENT-REPORTED OUTCOMES AT WEEK 96 FOR PATIENTS RANDOMIZED TO CZP AT BASELINE (200 MG Q2W AND 400 MG Q4W DOSES COMBINED)

Outcomes	CZP 200 mg + 400 mg
	Week 96 (Imputation)
ACR 20, N (%) (NRI)	[redacted]
TNF-naive[a]	[redacted]
TNF-experienced[b]	[redacted]
ACR 50, N (%) (NRI)	[redacted]
TNF-naive[a]	[redacted]
TNF-experienced[b]	[redacted]
ACR 70, N (%) (NRI)	[redacted]
TNF-naive[a]	[redacted]
TNF-experienced[b]	[redacted]
PASI 75, N (%)[c] (NRI)	[redacted]
PASI 90, N (%)[c] (NRI)	[redacted]
MDA, N (%) (NRI)	[redacted]
ΔBL DAS 28(CRP) (LOCF)	[redacted]
DAS 28(CRP) ≤ 3.2, N (%)(LOCF)	[redacted]
ΔBL LEI[d] (LOCF)	[redacted]
ΔBL LDI[e] (LOCF)	[redacted]
ΔBL mNAPSI[f] (LOCF)	[redacted]
ΔBL HAQ-DI (LOCF)	[redacted]
ΔBL Pain (LOCF)	[redacted]
ΔBL Fatigue (LOCF)	[redacted]
ΔBL PsAQoL (LOCF)	[redacted]
ΔBL SF-36 PCS (LOCF)	[redacted]
ΔBL SF-36 MCS (LOCF)	[redacted]

ΔBL = change from baseline; ACR = American College of Rheumatology; CZP = certolizumab pegol; DAS 28 = Disease Activity Score in 28 Joints; HAQ = Health Assessment Questionnaire; LDI = Leeds Dactylitis Index; LEI = Leeds Enthesitis Index; LOCF = last observation carried forward; MCS = mental component summary; NA = not available; NAPSI = Nail Psoriasis Severity Index; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PCS = physical component summary; PsAQoL = Psoriatic Arthritis Quality of Life; Q2W = every two weeks; Q4W = every four weeks; SF-36 = Short Form (36) Health Survey; TNF = tumour necrosis factor.

Note: Data shown as mean (standard deviation) unless otherwise specified.

[a] TNF-naive patients, N = 219.

[b] TNF experienced patients, N = 54.

[c] PASI data presented for patients with baseline BSA ≥ 3% (N = 166).

[d] LEI reported for patients with enthesitis at baseline (N = 172).

[e] LDI reported for patients with ≥1 dactylitic digit with a circumference ≥ 10% larger compared with the contralateral digit (N = 73).

[f] mNAPSI reported for patients with nail involvement at baseline (N = 197).

Source: T2 in Mease at al. 2014.[50]

Safety and Tolerability

The safety set consisted of 393 patients who received at least one dose of CZP [redacted]. The total exposure for all patients treated with CZP in RAPID-PsA [redacted] Table 29)

TABLE 28: TREATMENT-EMERGENT ADVERSE EVENTS DURING 96 WEEKS OF THE RAPID-PSA TRIAL

	CZP 200 mg Q2W N = 198n (%) (ER)	CZP 400 mg Q4W N = 195n (%) (ER)	All CZP N = 393n (%) (ER)
Any TEAE	[redacted]	[redacted]	[redacted]
TEAEs by intensity[a]			
Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]
Drug-related TEAEs	[redacted]	[redacted]	[redacted]
Infections[b]	[redacted]	[redacted]	[redacted]
Upper respiratory infections[c]	[redacted]	[redacted]	[redacted]
Serious infections	[redacted]	[redacted]	[redacted]
Serious TEAEs	[redacted]	[redacted]	[redacted]
Withdrawal due to TEAEs	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]

ER = event rate per 100 patient-years; TEAE = treatment-emergent adverse event.
[a] As determined by the investigator.
[b] System Organ Class.
[c] Preferred term.
Source: T2 in Mease at al. 2014.[50]

TABLE 29: TREATMENT-EMERGENCY ADVESRE EVENTS LEADING TO WITHDRAWAL DURING 96 WEEKS OF THE RAPID-PSA TRIAL

	CZP 200 mg Q2W N = 198n (%)	CZP 400 mg Q4W N = 195n (%)	All CZPN = 393 n (%)
Any TEAE	[redacted]	[redacted]	[redacted]
TEAEs by system organ class			
Cardiac disorders	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified			
Including cysts and polyps	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]
Pregnancy, puerperium, and perinatal conditions	[redacted]	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]

TEAE = treatment-emergent adverse event.
Source: T2 in Mease at al. 2014.[50]

Limitation

Although the study was randomized and double-blinded until week 24, dose-blinded until week 48, and the baseline characteristics were comparable between treatment groups, the main limitation for the findings at week 96 involves the open-label portion, which has no placebo control. It is particularly problematic for the interpretation of PROs and subjective outcomes. [redacted].

Summary

The improvements in clinical and patient-reported outcomes, which were observed over 24 weeks of the RAPID-PsA trial in both CZP dosing regimens, [redacted].

Due to the nature of the open-label period, the efficacy findings reported at week 96 should be interpreted with caution.

APPENDIX 7: SUMMARY AND APPRAISAL OF MANUFACTURER-SUBMITTED MIXED-TREATMENT COMPARISION

The manufacturer conducted a mixed-treatment comparison (MTC) based on a systematic review[85-89] to evaluate the relative efficacy of certolizumab pegol (CZP) and its relevant active comparators, adalimumab (ADA), etanercept (ETN), golimumab (GOL) and infliximab (IFX), as well as placebo in the treatment of PsA. The MTC was conducted, at least in part, because no RCTs have compared CZP with other biologic response modifiers (BRMs). The following is a summary and critical appraisal of the methods and main findings of the MTC.

Summary of Network Meta-Analysis

Methods

Eligibility Criteria

The MTC was based on a systematic review. The literature search included both electronic and manual components. [redacted] (Table 30).

Mixed-Treatment Comparison

[redacted]87

[redacted]90,91

[redacted]92

[redacted]92

[redacted]

[redacted]

[redacted]

[redacted]

Results

Study and Patient Characteristics

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Results of the MTC Analysis

[redacted]

Table 32. [redacted]

Table 35 and Table 36 respectively. [redacted]

[redacted]

Table 37. [redacted]

[redacted]

Table 38 [redacted]

[redacted] Table 39.

[redacted]

[redacted] Table 40 and Table 41. [redacted]

[redacted]

[redacted] Table 42. [redacted]

[redacted]

[redacted]

Safety

[redacted] 14,59,94-104 [redacted] 93 [redacted] Figure 7, Figure 8 and

Figure 9.

Critical Appraisal of Network Meta-Analysis

The quality of the manufacturer-submitted network meta-analysis (NMA) was assessed according to recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[107] Commentary for each of the relevant items identified by ISPOR is provided in Table 43.

Strengths

[redacted]

Limitations

[redacted]

[redacted]

[redacted]

15

[redacted]

[redacted]

[redacted]

Summary

[redacted]

TABLE 30: INTERVENTIONS AND COMPARATORS INCLUDED IN SYSTEMATIC REVIEW

Interventions	Comparators	
Biologic Response Modifiers	Biologic Response Modifiers	DMARDs
[redacted]	[redacted]	[redacted]

DMARD = disease-modifying antirheumatic drug; IL = interleukin; TNF-alpha = tumour necrosis factor alpha.

FIGURE 6: GENERAL EVIDENCE NETWORK DIAGRAM

Figure 6 contained confidential information and was removed at the request of the manufacturer.

[redacted]

TABLE 31: INCLUDED STUDIES AND THE COVARIATES REPORTED BY TRIALS

Trials			Disease Duration		Pasi Score At Baseline	
	Active Arm	Publication Year	Biologic	Placebo	Biologic	Placebo
[redacted]						

[redacted]

TABLE 32: STUDY CHARACTERISTICS

Trial Name	Author, Year	Country	Study Design	Industrial Sponsorship	Interventions	Number of Patients	Early Escape, Crossover, and Open-Label Extensions
ADEPT[99]							
GO-REVEAL[103]							
IMPACT[59]							
IMPACT 2[101]							
M02-570[102]							
NCT00317499[100]							
University of Washington[104]							
PSA001[15]							
PSUMMIT-1[105]							
PSUMMIT-2[106]							

[redacted]

TABLE 33: RISK OF BIAS IN INCLUDED RANDOMIZED CONTROLLED TRIALS

Trial	Biologic DMARD of Interest	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Source of Bias
ADEPT[99]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GO-REVEAL[103]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IMPACT[59]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IMPACT 2[101]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
M02-570 Study[102]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NCT00317499[99]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
University of Washington (Seattle, US)[104]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSA001[15]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSUMMIT-1[105]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSUMMIT-2[106]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

TABLE 34: PROBABILITY OF ACHIEVING AMERICAN COLLEGE OF RHEUMATOLOGY RESPONSE IN ANTI-TNF – NAIVE PSORIATIC ARTHRITIS PATIENTS – BAYESIAN MIXED-TREATMENT COMPARISON ([redacted])

Intervention	Probability of Achieving Response (95% CrI)					
	ACR 20		ACR 50		ACR 70	
	12 to 16 weeks	24 weeks	12 to 16 weeks	24 weeks	12 to 16 weeks	24 weeks
[redacted]						

[redacted]

TABLE 35: ODDS RATIO OF ACHIEVING ACR 20 RESPONSE IN ANTI-TNF–NAIVE PSORIATIC ARTHRITIS PATIENTS – BAYESIAN MIXED-TREATMENT COMPARISON ([redacted]) ([redacted])

Intervention	[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]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

TABLE 36: ODDS RATIO OF ACHIEVING ACR 50 RESPONSE IN ANTI-TNF–NAIVE PSORIATIC ARTHRITIS PATIENTS – BAYESIAN MIXED-TREATMENT COMPARISON ([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]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

TABLE 37: HEALTH ASSESSMENT QUESTIONNAIRE – DISABILITY INDEX: [redacted]

Intervention	[redacted]		[redacted]	
	[redacted]			
[redacted]				
[redacted]				
[redacted]				
[redacted]				
	[redacted]			
[redacted]				
[redacted]				
[redacted]				
[redacted]				

[redacted]

TABLE 38: PROBABILITY OF ACHIEVING PASI RESPONSE IN ANTI-TNF–NAIVE PSORIATIC ARTHRITIS PATIENTS – CLASSICAL MIXED-TREATMENT COMPARISON ([redacted])

[redacted]	[redacted]					
	[redacted]		[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

[redacted]

TABLE 39: ODDS RATIO OF ACHIEVING PASI 75 RESPONSE IN ANTI-TNF–NAIVE PSORIATIC ARTHRITIS PATIENTS – MIXED-TREATMENT COMPARISON ANALYSES ( )

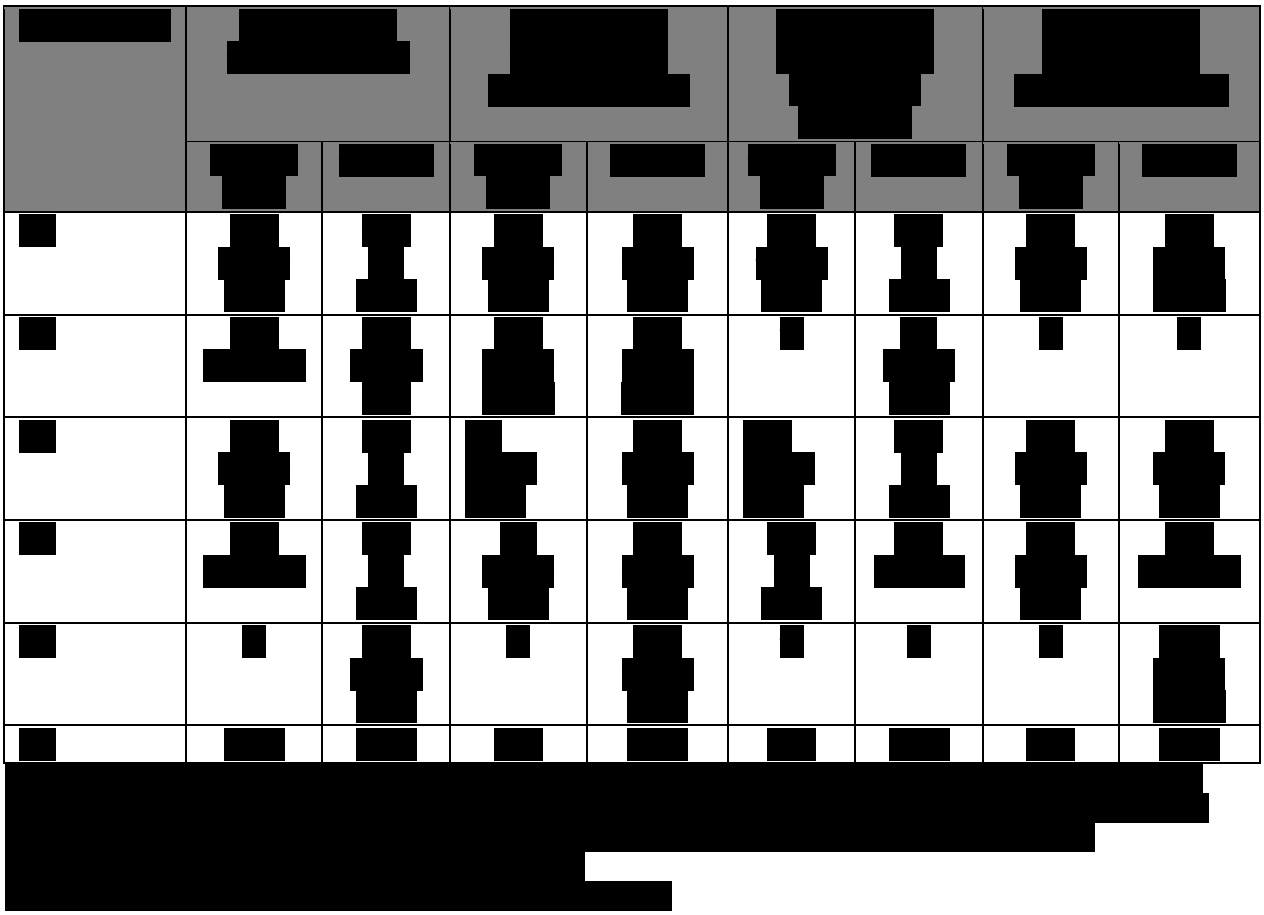


TABLE 40: PSORIATIC ARTHRITIS RESPONDER CRITERIA RESPONSE (ODDS RATIOS) –

TABLE 41: PSORIATIC ARTHRITIS RESPONDER CRITERIA RESPONSE (ODDS RATIOS) –

TABLE 42: SHORT FORM 36 PHYSICAL COMPONENT SUMMARY (DIFFERENCE OF MEAN CHANGE) – [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]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

FIGURE 7: PROPORTION OF PATIENTS EXPERIENCING SERIOUS ADVERSE EVENTS IN RANDOMIZED CONTROLLED TRIALS

Figure 7 contained confidential information and was removed at the request of the manufacturer.

[redacted]

FIGURE 8: RATE OF ALL-CAUSE DISCONTINUATIONS IN RANDOMIZED CONTROLLED TRIALS

Figure 8 contained confidential information and was removed at the request of the manufacturer.

[redacted]

FIGURE 9: PROPORTION OF PATIENTS EXPERIENCING UPPER RESPIRATORY TRACT INFECTION IN RANDOMIZED CONTROLLED TRIALS

Figure 9 contained confidential information and was removed at the request of the manufacturer.

TABLE 43: APPRAISAL OF NETWORK META-ANALYSIS USING INTERNATIONAL SOCIETY FOR PHARMACOECONOMICS AND OUTCOMES RESEARCH 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? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	[redacted]
3.	Are the outcome measures described?	[redacted]
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • 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? • Individual study data? • 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]

[redacted]

REFERENCES

1. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis [Internet]. 2005 Mar [cited 2015 Jan 14];64 Suppl 2:ii14-ii17. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1766874/pdf/v064p0ii14.pdf
2. Ritchlin CT, Kavanaugh A, Gladman DD, Mease PJ, Helliwell P, Boehncke WH, et al. Treatment recommendations for psoriatic arthritis. Ann Rheum Dis [Internet]. 2009 Sep [cited 2015 Jan 14];68(9):1387-94. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2719080/pdf/ARD-68-09-1387.pdf
3. Dandorfer SW, Rech J, Manger B, Schett G, Englbrecht M. Differences in the patient's and the physician's perspective of disease in psoriatic arthritis. Semin Arthritis Rheum. 2012 Aug;42(1):32-41.
4. Cimzia® (certolizumab pegol): solution for injection in a single-use pre-filled glass syringe, 200mg/mL [product monograph]. Oakville (ON): UCB Canada, Inc.; 2014 Jan 15.
5. Rosen CF, Mussani F, Chandran V, Eder L, Thavaneswaran A, Gladman DD. Patients with psoriatic arthritis have worse quality of life than those with psoriasis alone. Rheumatology (Oxford) [Internet]. 2012 Mar [cited 2015 Jan 14];51(3):571-6. Available from: http://rheumatology.oxfordjournals.org/content/51/3/571.full.pdf+html
6. Husted JA, Tom BD, Farewell VT, Schentag CT, Gladman DD. A longitudinal study of the effect of disease activity and clinical damage on physical function over the course of psoriatic arthritis: Does the effect change over time? Arthritis Rheum [Internet]. 2007 Mar [cited 2015 Jan 14];56(3):840-9. Available from: http://onlinelibrary.wiley.com/doi/10.1002/art.22443/pdf
7. Diagnosis and management of psoriasis and psoriatic arthritis in adults [Internet]. Edinburgh: Scottish Intercollegiate Guidelines Network; 2010 Oct. [cited 2015 Jan 14]. Available from: http://www.sign.ac.uk/pdf/sign121.pdf
8. National Guideline Clearinghouse [Internet]. Rockville (MD): National Guideline Clearinghouse; 1997 -. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents.; 2009 [cited 2015 Jan 14]. Available from: http://www.guideline.gov/content.aspx?id=15650
9. Simponi (golimumab): solution for injection 50 mg/0.5mL, 100mg/1.0mL [product monograph on the Internet]. Toronto (ON): Janssen Inc.; 2014 Nov 25. [cited 2015 Jan 26]. Available from: http://www.janssen.ca/product/187
10. Enbrel (etanercept): solution for injection in a prefilled syringe 50 mg/mL and lyophilized powder for reconstitution in a vial 25 mg/vial [product monograph on the Internet] [Internet]. Thousand Oaks (CA): Immunex Corporation; 2013 Sep 13. [cited 2015 Jan 14]. Available from: https://www.amgen.ca/Enbrel_PM.pdf
11. Humira (adalimumab): 40 mg in 0.8 mL sterile solution (50 mg/mL) subcutaneous injection [product monograph] [Internet]. St-Laurent (QC): AbbVie Corporation; 2014 Jan 17. [cited 2015 Jan 26]. Available from: http://www.abbvie.ca/content/dam/abbviecorp/ca/english/docs/HUMIRA_PM_EN.pdf
12. Inflectra (infliximab): powder for solution, sterile, lyophilized, 100 mg/vial [product monograph]. Saint-Laurent (QC): Hospira Healthcare Corporation; 2014 Jun 4.
13. PrStelara® (ustekinumab): 45 mg/0.5 mL, 90 mg/1.0 mL [product monograph]. Toronto: Janssen Inc.; 2014 Sep 16.

14. Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, Kielar D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis [Internet]. 2014 Jan [cited 2015 Jan 26];73(1):48-55. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3888622

15. Clinical Study Report: PsA001, week 24. Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of certolizumab pegol in subjects with adult-onset active and progressive psoriatic arthritis (PsA) [**CONFIDENTIAL** internal manufacturer's report]. Oakville (ON): UCB Biociences; 2013 Apr 24. 273 p.

16. van der Heijde D, Fleischmann R, Wollenhaupt J, Deodhar A, Kielar D, Woltering F, et al. Effect of different imputation approaches on the evaluation of radiographic progression in patients with psoriatic arthritis: results of the RAPID-PsA 24-week phase III double-blind randomised placebo-controlled study of certolizumab pegol. Ann Rheum Dis [Internet]. 2014 Jan [cited 2015 Jan 26];73(1):233-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3888591

17. Kavanaugh A, Gladman D, van der HD, Purcaru O, Mease P. Improvements in productivity at paid work and within the household, and increased participation in daily activities after 24 weeks of certolizumab pegol treatment of patients with psoriatic arthritis: results of a phase 3 double-blind randomised placebo-controlled study. Ann Rheum Dis. 2015 Jan;74(1):44-51. Epub ahead of print 2014 Jun 18.

18. Gladman D, Fleischmann R, Coteur G, Woltering F, Mease PJ. Effect of certolizumab pegol on multiple facets of psoriatic arthritis as reported by patients: 24-week patient-reported outcome results of a phase III, multicenter study. Arthritis Care Res (Hoboken) [Internet]. 2014 Jul [cited 2014 Nov 21];66(7):1085-92. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4171746/pdf/acr0066-1085.pdf

19. Clinical Study Protocol: PsA001. Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of certolizumab pegol in subjects with adult-onset active and progressive psoriatic arthritis (PsA) [**CONFIDENTIAL** internal manufacturer's report]. Oakville (ON): UCB Biociences; 2010 Nov 22. 137 p.

20. CDR submission: Cimzia® (certolizumab pegol), 200mg/mL pre-filled syringe. Company: UCB Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Oakville (ON): UCB Canada Inc.; 2014 Aug 29.

21. Health Canada reviewer's report: Cimzia (certolizumab pegol) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2014.

22. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995 Jun;38(6):727-35.

23. Clegg DO, Reda DJ, Mejias E, Cannon GW, Weisman MH, Taylor T, et al. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. Arthritis Rheum. 1996 Dec;39(12):2013-20.

24. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995 Jan;38(1):44-8.

25. van Gestel AM, Prevoo ML, van't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health

Organization/International League Against Rheumatism Criteria. Arthritis Rheum. 1996 Jan;39(1):34-40.

26. van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum. 1998 Oct;41(10):1845-50.
27. Carlin CS, Feldman SR, Krueger JG, Menter A, Krueger GG. A 50% reduction in the Psoriasis Area and Severity Index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis. J Am Acad Dermatol. 2004 Jun;50(6):859-66.
28. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980 Feb;23(2):137-45.
29. Mease PJ, Ganguly R, Wanke L, Yu E, Singh A. How much improvement in functional status is considered important by patients with active psoriatic arthritis: applying the outcome measures in rheumatoid arthritis clinical trials (OMERACT) group guidelines. Ann Rheum Dis. 2004 Jun 9;63(Sup 1):391-2. Annual European Congress of Rheumatology (EULAR).
30. Mease PJ, Woolley JM, Bitman B, Wang BC, Globe DR, Singh A. Minimally important difference of Health Assessment Questionnaire in psoriatic arthritis: relating thresholds of improvement in functional ability to patient-rated importance and satisfaction. J Rheumatol. 2011 Nov;38(11):2461-5.
31. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. conceptual framework and item selection. Med Care. 1992 Jun;30(6):473-83.
32. Mease PJ, Menter MA. Quality-of-life issues in psoriasis and psoriatic arthritis: outcome measures and therapies from a dermatological perspective. J Am Acad Dermatol. 2006 Apr;54(4):685-704.
33. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. Ann Med. 2001 Jul;33(5):350-7.
34. Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. PharmacoEconomics. 1999 Feb;15(2):141-55.
35. Strand V, Singh JA. Improved health-related quality of life with effective disease-modifying antirheumatic drugs: evidence from randomized controlled trials. Am J Manag Care. 2008 Apr;14(4):239-53.
36. Leung YY, Ho KW, Zhu TY, Tam LS, Kun EW, Li EK. Testing scaling assumptions, reliability and validity of medical outcomes study short-form 36 health survey in psoriatic arthritis. Rheumatology (Oxford) [Internet]. 2010 Aug [cited 2014 Dec 8];49(8):1495-501. Available from: http://rheumatology.oxfordjournals.org/content/49/8/1495.full.pdf+html
37. McKenna SP, Doward LC, Whalley D, Tennant A, Emery P, Veale DJ. Development of the PsAQoL: a quality of life instrument specific to psoriatic arthritis. Ann Rheum Dis [Internet]. 2004 Feb [cited 2015 Jan 9];63(2):162-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1754880
38. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum. 1993 Jun;36(6):729-40.
39. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008 Feb;9(2):105-21.

40. Tack BB. Self-reported fatigue in rheumatoid arthritis. A pilot study. Arthritis Care Res. 1990 Sep;3(3):154-7.

41. Healy PJ, Helliwell PS. Measuring dactylitis in clinical trials: which is the best instrument to use? J Rheumatol. 2007 Jun;34(6):1302-6.

42. Helliwell PS, Firth J, Ibrahim GH, Melsom RD, Shah I, Turner DE. Development of an assessment tool for dactylitis in patients with psoriatic arthritis. J Rheumatol. 2005 Sep;32(9):1745-50.

43. Healy PJ, Helliwell PS. Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis. Arthritis Rheum. 2008 May 15;59(5):686-91.

44. Bruynesteyn K, van der Heijde D, Boers M, Saudan A, Peloso P, Paulus H, et al. Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. Arthritis Rheum. 2002 Apr;46(4):913-20.

45. Committee for Medicinal Products for Human Use (CHMP). Assessment report. Cimzia [Internet]. London: European Medicines Agency; 2013 Oct 24. [cited 2014 Dec 19]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/001037/WC500159001.pdf Procedure no. EMEA/H/C/001037/II/27.

46. Haraoui B, Karsh J, Pope JE, Thorne JC, Keystone EC. Is structural damage evaluation by traditional radiographs still relevant in rheumatoid arthritis clinical trials? J Rheumatol [Internet]. 2014 Nov [cited 2014 Dec 19];41(11):2325. Available from: http://www.jrheum.org/content/41/11/2325.full.pdf

47. Bykerk VP. Radiographic progression in rheumatoid arthritis: does it still happen and does it matter? J Rheumatol [Internet]. 2014 Dec [cited 2014 Dec 19];41(12):2337-9. Available from: http://www.jrheum.org/content/41/12/2337.full.pdf

48. Singh JA, Wells GA, Christensen R, Tanjong GE, Maxwell L, MacDonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev [Internet]. 2011;(2):CD008794.

49. Osterhaus JT, Purcaru O. Discriminant validity, responsiveness and reliability of the arthritis-specific Work Productivity Survey assessing workplace and household productivity in patients with psoriatic arthritis. Arthritis Res Ther [Internet]. 2014 [cited 2014 Nov 21];16(4):R140. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4226958

50. Mease P, Deodhar A, Fleischmann R, Wollenhaupt J, Gladman D, Ieszczynski P, et al. Effect of certolizumab pegol over 96 Weeks in patients with psoriatic arthritis with and without prior anti-tumor necrosis factor exposure. In: CDR submission: Cimzia® (certolizumab pegol), 200mg/mL pre-filled syringe. Company: UCB Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Oakville (ON): UCB Canada, Inc.; 2014.

51. Gladman DD, Mease PJ, Healy P, Helliwell PS, FitzGerald O, Cauli A, et al. Outcome measures in psoriatic arthritis. J Rheumatol. 2007 May;34(5):1159-66.

52. Gladman DD, Farewell V, Buskila D, Goodman R, Hamilton L, Langevitz P, et al. Reliability of measurements of active and damaged joints in psoriatic arthritis. J Rheumatol. 1990 Jan;17(1):62-4.

53. Gladman DD, Cook RJ, Schentag C, Feletar M, Inman RI, Hitchon C, et al. The clinical assessment of patients with psoriatic arthritis: results of a reliability study of the spondyloarthritis research consortium of Canada. J Rheumatol. 2004 Jun;31(6):1126-31.

54. Fransen J, Antoni C, Mease PJ, Uter W, Kavanaugh A, Kalden JR, et al. Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomized, controlled trials of two TNF inhibitors. Ann Rheum Dis [Internet]. 2006 Apr 27 [cited 2014 Dec 8];65(10):1373-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1798317/pdf/1373.pdf

55. Mease PJ, Antoni CE, Gladman DD, Taylor WJ. Psoriatic arthritis assessment tools in clinical trials. Ann Rheum Dis. 2005 Mar;64 Suppl 2:ii49-ii54.

56. van der Heijde DM, van 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis. 1990 Nov;49(11):916-20.

57. van der Heijde DM, van 't Hof MA, van Riel PL, van Leeuwen MA, van Rijswijk MH, van de Putte LB. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. Ann Rheum Dis. 1992 Feb;51(2):177-81.

58. van Gestel AM, Anderson JJ, van Riel PL, Boers M, Haagsma CJ, Rich B, et al. ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. J Rheumatol. 1999 Mar;26(3):705-11.

59. Antoni CE, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheum. 2005 Apr;52(4):1227-36.

60. Vander CB, Van Looy S, Wyns B, Westhovens R, Durez P, Van den Bosch F, et al. DAS28 best reflects the physician's clinical judgment of response to infliximab therapy in rheumatoid arthritis patients: validation of the DAS28 score in patients under infliximab treatment. Arthritis Res Ther. 2005;7(5):R1063-R1071.

61. Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis. 2009 Jun;68(6):954-60.

62. Inoue E, Yamanaka H, Hara M, Tomatsu T, Kamatani N. Comparison of Disease Activity Score (DAS)28- erythrocyte sedimentation rate and DAS28- C-reactive protein threshold values. Ann Rheum Dis [Internet]. 2007 Mar [cited 2014 Dec 8];66(3):407-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1856019/pdf/407.pdf

63. Matsui T, Kuga Y, Kaneko A, Nishino J, Eto Y, Chiba N, et al. Disease Activity Score 28 (DAS28) using C-reactive protein underestimates disease activity and overestimates EULAR response criteria compared with DAS28 using erythrocyte sedimentation rate in a large observational cohort of rheumatoid arthritis patients in Japan. Ann Rheum Dis [Internet]. 2007 Sep [cited 2014 Dec 8];66(9):1221-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1955164/pdf/1221.pdf

64. Kushner I. C-reactive protein in rheumatology. Arthritis Rheum. 1991 Aug;34(8):1065-8.

65. Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. Ann Rheum Dis [Internet]. 2005 [cited 2014 Dec 8];64(Suppl 2):ii65-ii68. Available from: http://ard.bmj.com/content/64/suppl_2/ii65.full.pdf

66. Choi J, Koo JY. Quality of life issues in psoriasis. J Am Acad Dermatol. 2003 Aug;49(2 Suppl):S57-S61.

67. Ashcroft DM, Wan Po AL, Williams HC, Griffiths CE. Clinical measures of disease severity and outcome in psoriasis: a critical appraisal of their quality. Br J Dermatol. 1999 Aug;141(2):185-91.
68. Feldman SR, Menter A, Koo JY. Improved health-related quality of life following a randomized controlled trial of alefacept treatment in patients with chronic plaque psoriasis. Br J Dermatol. 2004 Feb;150(2):317-26.
69. Jacobson CC, Kimball AB. Rethinking the Psoriasis Area and Severity Index: the impact of area should be increased. Br J Dermatol. 2004 Aug;151(2):381-7.
70. Kwok T, Pope JE. Minimally important difference for patient-reported outcomes in psoriatic arthritis: Health Assessment Questionnaire and pain, fatigue, and global visual analog scales. J Rheumatol. 2010 May;37(5):1024-8.
71. Blackmore MG, Gladman DD, Husted J, Long JA, Farewell VT. Measuring health status in psoriatic arthritis: the Health Assessment Questionnaire and its modification. J Rheumatol. 1995 May;22(5):886-93.
72. Husted JA, Gladman DD, Long JA, Farewell VT. A modified version of the Health Assessment Questionnaire (HAQ) for psoriatic arthritis. Clin Exp Rheumatol. 1995 Jul;13(4):439-43.
73. Husted JA, Gladman DD, Farewell VT, Long JA, Cook RJ. Validating the SF-36 health survey questionnaire in patients with psoriatic arthritis. J Rheumatol. 1997 Mar;24(3):511-7.
74. Husted JA, Gladman DD, Cook RJ, Farewell VT. Responsiveness of health status instruments to changes in articular status and perceived health in patients with psoriatic arthritis. J Rheumatol. 1998 Nov;25(11):2146-55.
75. Guillemin F, Billot L, Boini S, Gerard N, Odegaard S, Kvien TK. Reproducibility and sensitivity to change of 5 methods for scoring hand radiographic damage in patients with rheumatoid arthritis. J Rheumatol. 2005 May;32(5):778-86.
76. Boini S, Guillemin F. Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages. Ann Rheum Dis. 2001 Sep;60(9):817-27.
77. Sokka T. Radiographic scoring in rheumatoid arthritis: a short introduction to the methods. Bull NYU Hosp Jt Dis. 2008;66(2):166-8.
78. Landewe R, van der Heijde D. Radiographic progression in rheumatoid arthritis. Clin Exp Rheumatol. 2005 Sep;23(5 Suppl 39):S63-S68.
79. Voskuyl AE, Dijkmans BA. Remission and radiographic progression in rheumatoid arthritis. Clin Exp Rheumatol. 2006 Nov;24(6 Suppl 43):S37-S40.
80. Drossaers-Bakker KW, de Buck M, van Zeben D, Zwinderman AH, Breedveld FC, Hazes JM. Long-term course and outcome of functional capacity in rheumatoid arthritis: the effect of disease activity and radiologic damage over time. Arthritis Rheum. 1999 Sep;42(9):1854-60.
81. Sahin F, Kotevoglu N, Taspinar S, Yilmaz F, Kuran B. Comparison of functional disability scales and their relevance to radiological progression in patients with rheumatoid arthritis in remission. Clin Exp Rheumatol. 2006 Sep;24(5):540-5.
82. Swinkels HL, Laan RF, van 't Hof MA, van der Heijde DM, de Vries N, van Riel PL. Modified sharp method: factors influencing reproducibility and variability. Semin Arthritis Rheum. 2001 Dec;31(3):176-90.
83. Foley-Nolan D, Stack JP, Ryan M, Redmond U, Barry C, Ennis J, et al. Magnetic resonance imaging in the assessment of rheumatoid arthritis--a comparison with plain film radiographs. Br J Rheumatol. 1991 Apr;30(2):101-6.

84. Landewe R, van der Heijde D. Is radiographic progression a realistic outcome measure in clinical trials with early inflammatory arthritis? Clin Exp Rheumatol. 2003 Sep;21(5 Suppl 31):S37-S41.

85. Fahrbach K, Xu Y, Ashaye AO. Cimzia© and biologic DMARDs in the treatment of psoriatic arthritis: an adjusted mixed treatment comparison analysis. Version 2.2. In: CDR submission: Cimzia® (certolizumab pegol), 200mg/mL pre-filled syringe. Company: UCB Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Lexington (MA): Evidera; 2014 Jul 31.

86. Xu Y, Fahrbach K, Zhang J, Di Tanna GL, Becker B, Strand L. Statistical analysis plan for mixed treatment comparison of Cimzia© and biological DMARDs in the treatment of psoriatic arthritis. Version 2.1. In: CDR submission: Cimzia® (certolizumab pegol), 200mg/mL pre-filled syringe. Company: UCB Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Lexington (MA): United BioSource Corporation; 2013 May 30.

87. Blieden M, Fahrbach K, Strand L, Becker B, Tater K, Xu Y. A feasibility assessment for mixed treatment comparison analyses in psoriatic arthritis. Version 2.0. In: CDR submission: Cimzia® (certolizumab pegol), 200mg/mL pre-filled syringe. Company: UCB Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Lexington (MA): United BioSource Corporation; 2013 Jan 11.

88. Xu Y, Blieden M, John S, Strand L. A protocol for a systematic review of Cimzia© and biological DMARDs in the treatment of psoriatic arthritis. In: CDR submission: Cimzia® (certolizumab pegol), 200mg/mL pre-filled syringe. Company: UCB Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Lexington (MA): United BioSource Corporation; 2012 May 31.

89. Becker B, Strand L, Tater K, Xu Y, Ashaye AO. A systematic review of Cimzia© and biologic DMARDs in the treatment of psoriatic arthritis. Version 3.0. In: CDR submission: Cimzia® (certolizumab pegol), 200mg/mL pre-filled syringe. Company: UCB Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Bethesda (MD): Evidera; 2013 Oct 4.

90. Brooks SP, Gelman A. Alternative methods for monitoring convergence of iterative simulation. J Comput Graph Stat. 1998;7(4):434-55.

91. Gelman A. Inference and monitoring convergence. In: Gilks WR, Richardson S, Spiegelhalter DJ, editors. Markov chain Monte Carlo in practice. London: Chapman & Hall; 1996. p. 131-43.

92. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials [Internet]. London: National Institute for Health and Care Excellence; 2011. [cited 2014 Dec 4]. Available from: http://www.nicedsu.org.uk/TSD2%20General%20meta%20analysis%20corrected%2015April2014.pdf

93. Thaler KJ, Gartlehner G, Kien C, Van Noord MG, Thakurta S, Wines RCM, et al. Drug Class Review: targeted immune modulators: final update 3 report [Internet]. Portland (OR): Oregon Health & Science University; 2012 Mar. [cited 2014 Nov 21]. (Drug Class Reviews). Available from: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0049852/pdf/TOC.pdf

94. Atteno M, Peluso R, Costa L, Padula S, Iervolino S, Caso F, et al. Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic drugs. Clin Rheumatol. 2010 Apr;29(4):399-403.

95. Baranauskaite A, Raffayova H, Kungurov NV, Kubanova A, Venalis A, Helmle L, et al. Infliximab plus methotrexate is superior to methotrexate alone in the treatment of psoriatic arthritis in methotrexate-naive patients: the RESPOND study. Ann Rheum Dis [Internet]. 2012 Apr [cited 2015 Jan 26];71(4):541-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3298666

96. Combination of adalimumab (ADL) with cyclosporine-a (CSA) against single therapy in refractory psoriatic arthritis: an interim analysis of an ongoing, 12-month open, three-arm, randomized study. Ann Rheum Dis. 2014 [cited 2014 Dec 3];68(Suppl 3):138. Available from: http://www.abstracts2view.com/eular/view.php?nu=EULAR09L_OP-0200&terms=

97. Kimball AB, Bensimon AG, Guerin A, Yu AP, Wu EQ, Okun MM, et al. Efficacy and safety of adalimumab among patients with moderate to severe psoriasis with co-morbidities: Subanalysis of results from a randomized, double-blind, placebo-controlled, phase III trial. Am J Clin Dermatol. 2011 Feb 1;12(1):51-62.

98. Mease P, Genovese MC, Gladstein G, Kivitz AJ, Ritchlin C, Tak PP, et al. Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. Arthritis Rheum. 2011 Apr;63(4):939-48.

99. Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2005 Oct;52(10):3279-89.

100. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum. 2004 Jul;50(7):2264-72.

101. Antoni C, Krueger GG, de VK, Birbara C, Beutler A, Guzzo C, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis [Internet]. 2005 Aug [cited 2015 Jan 26];64(8):1150-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1755609

102. Genovese MC, Mease PJ, Thomson GT, Kivitz AJ, Perdok RJ, Weinberg MA, et al. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. J Rheumatol. 2007 May;34(5):1040-50.

103. Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009 Apr;60(4):976-86.

104. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet. 2000 Jul 29;356(9227):385-90.

105. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet. 2013 Aug 31;382(9894):780-9.

106. Ritchlin CT, McInnes IB, Kavanaugh A, Puig L, Rahman P, Brodmerkel C, et al. Maintenance of efficacy and safety of ustekinumab in patients with active psoriatic arthritis despite prior conventional nonbiologic and anti-TNF biologic therapy: 1-year results of a phase 3, multicenter, double-blind, placebo-controlled trial. Arthritis Rheum [conference abstract on the Internet]. 2013 [cited 2014 Dec 4];65(Suppl 10):302. Available from: http://www.blackwellpublishing.com/acrmeeting/abstract.asp?MeetingID=799&id=107669 (Presented at The American College of Rheumatology/Association of Rheumatology Health Professionals Annual Meeting; 2014 October 25-30; San Diego (CA)).

107. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health. 2011 Jun;14(4):417-28.