CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

Certolizumab Pegol (Cimzia)

(UCB Canada Inc.)

Indication: Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy

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Abbreviations

AE	adverse event
BSA	body surface area
CAPP	Canadian Association of Psoriasis Patients
CDA	Canadian Dermatology Association
CDR	CADTH Common Drug Review
CMH	Cochran–Mantel–Haenszel
CPN	Canadian Psoriasis Network
CSPA	Canadian Skin Patient Alliance
CZP	certolizumab pegol
DLQI	Dermatology Life Quality Index
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels questionnaire
EQ VAS	EuroQol Visual Analogue Scale
HRQoL	health-related quality of life
IL	interleukin
ITC	indirect treatment comparison
IVRS	interactive voice response system
LOCF	last observation carried forward
MCS	mental component summary
MCID	minimal clinically important difference
NMA	network meta-analysis
PASI	Psoriasis Area and Severity Index
PCS	physical component summary
PEG	polyethylene glycol
PGA	Physician's Global Assessment
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse event
SC	subcutaneous
SF-36	Short Form (36) Health Survey
sPGA	static Physician's Global Assessment
TEAE	treatment-emergent adverse event
TNF	tumour necrosis factor
VAS	visual analogue scale
WDAE	withdrawal due to adverse event

Drug	Certolizumab Pegol (Cimzia)
Indication	Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy
Reimbursement request	As per indication
Dosage form(s)	400 mg by subcutaneous injection (SC) every 2 weeks OR 400 mg SC initially (week 0) and at weeks 2 and 4 followed by 200 mg every two weeks
NOC date	August 16, 2018
Manufacturer	UCB Canada Inc.

Executive Summary

Introduction

Psoriasis is a chronic, inflammatory, immune-mediated skin disorder that affects more than 500,000 people in Canada.[1] Plaque psoriasis is the most common form of psoriasis and is characterized by silvery scales, redness, erythematous patches, papules, and plaques on the extensor surfaces, trunk, and scalp that are often pruritic.[2] Approximately 17% of those with psoriasis have moderate-to-severe disease.[3] Moderate-to-severe plaque psoriasis can be defined by: the extent of skin coverage, with involvement of more than 5% to 10% of body surface area (BSA); location, i.e., involvement of the face, palm, groin, or sole; or severity, with a Psoriasis Area and Severity Index (PASI) score of more than 10.[4] Psoriasis has a multitude of psychosocial and emotional effects on patients, including decreased self-esteem, increased self-consciousness, frustration, fatigue, depression, and suicidal ideation. As a result, patients frequently report sleeping problems, difficulties at work, problems interacting with family members, disrupted leisure activities, and sexual difficulties.[5-9] In addition, psoriasis patients are at an increased risk of a wide variety of serious comorbidities and inflammatory conditions, including cardiovascular disease, metabolic syndrome, psoriatic arthritis, and even early mortality.[1,4,10]

Certolizumab pegol (CZP) is a recombinant, humanized antibody Fab' fragment that specifically targets human tumour necrosis factor (TNF) alpha, a key pro-inflammatory cytokine implicated in the pathogenesis of psoriasis. CZP has been approved in Canada for rheumatoid arthritis since 2009, and for psoriatic arthritis and ankylosing spondylitis since 2014. On August 2018, CZP received a Health Canada Notice of Compliance (NOC) for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy. The recommended dose of CZP for plaque psoriasis is 400 mg by subcutaneous injection (SC) every two weeks. A dose of 400 mg initially (week 0) and at weeks 2 and 4 followed by 200 mg every two weeks may be considered.[11] The objective of this report was to perform a systematic review of the beneficial and harmful effects of CZP 400 mg and 200 mg every two weeks administered as an SC injection for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy.

Results and Interpretation

Included Studies

Three multi-centre, phase III, double-blind (DB), randomized controlled trials (RCTs) that evaluated the efficacy and safety of CZP were included in this systematic review: CIMPASI-1 (N = 234),[12,13] CIMPASI-2 (N = 227),[12,14] and CIMPACT (N = 559).[15,16] The trials had similar inclusion and exclusion criteria and enrolled adult patients (≥ 18 years) with chronic psoriasis, with PASI ≥ 12, BSA ≥ 10%, and a Physician's Global Assessment (PGA) score ≥ 3. The trials used doses of both CZP 200 mg and 400 mg every two weeks and were separated into five similarly designed periods: screening (five weeks), initial treatment period (week 0 to 16), maintenance treatment period (week 16 to 48), open-label treatment period (week 48 to 144), and safety follow-up period. The CIMPASI trials differed from the CIMPACT trial in the treatment assignment and schedule during the initial and maintenance treatment periods, described subsequently.

CIMPASI-1 and CIMPASI-2 were two identically designed RCTs with a DB placebo–controlled initial treatment period followed by a dose-blind maintenance treatment period. During the initial treatment period, patients were randomized in a 2:2:1 ratio to receive CZP 200 mg or 400 mg every two weeks, or placebo. The treatment received during the maintenance period was blinded or open-label based on the randomized treatment and the response to treatment at week 16. Patients initially randomized to either CZP doses and achieving at least a 50% reduction from baseline in PASI score (PASI 50) continued the same dose, whereas placebo-treated patients who achieved PASI 50 but not at least a 75% reduction from baseline in PASI (PASI 75) started CZP 200 mg every two weeks or continued to receive placebo if they achieved PASI 75.

CIMPACT was a DB, parallel-group RCT, with a DB-placebo but open-label active-controlled initial treatment period, followed by a DB placebo–controlled maintenance period. During the initial treatment period, patients were randomized in a 3:3:3:1 ratio to receive CZP 200 mg or CZP 400 mg every two weeks (through week 14), etanercept 50 mg twice weekly (through week 11.5), or placebo (through week 14). At the subsequent maintenance treatment period, the treatment assignment was blinded or open-label, based on the treatment received and response shown at week 16. Among patients who achieved PASI 75 at week 16:

- The patients initially randomized to etanercept were re-randomized (2:1) to either CZP 200 mg every two weeks or placebo.
- The patients initially randomized to CZP 200 mg every two weeks were re-randomized (2:2:1) to CZP 200 mg every two weeks, CZP 400 mg every four weeks, or placebo.
- The patients initially randomized to CZP 400 mg every two weeks were re-randomized (2:2:1) to CZP 200 mg every two weeks, CZP 400 mg every two weeks, or placebo.
- The patients in the placebo arm continued to receive placebo.

Patients who did not achieve PASI 75 at week 16 started escape treatment.

Following the maintenance period, all patients received an additional 96 weeks of open-label CZP treatment (currently ongoing; data not available), with dose determined and adjusted through this period depending on patients' PASI response. All patients started CZP 200 mg every two weeks with a CZP 400 mg loading dose (i.e., CZP 400 mg every two weeks for the first four weeks) followed by CZP 200 mg every two weeks thereafter,

regardless of treatment period or week. Patients who did not achieve PASI 50 (CIMPASI-1 and -2) or PASI 75 (CIMPACT) at week 16 underwent escape treatment, i.e., open-label CZP 400 mg at the loading dose followed by CZP 200 mg every two weeks. In all trials, those who did not achieve PASI 50 from week 32 through week 48 were withdrawn from the study. All patients who underwent escape treatment at week 48 continued to receive CZP 400 mg every two weeks or had their dose reduced to 200 mg if they achieved PASI 75. Finally, all patients, including those who discontinued the treatment, were followed up for an additional 10 weeks after the final dose of study medication.

In CIMPASI-1 and -2, the following co-primary and secondary outcomes were measured at week 16 to evaluate the superiority of CZP 200 mg and 400 mg every two weeks to placebo parallelly, in the following sequence: 75% reduction in the PASI score from baseline (PASI 75), PGA response (defined as clear or almost clear, with a corresponding score of 0 or 1), PASI 90 (at least a 90% reduction from baseline in PASI score), and change from baseline in Dermatology Life Quality Index (DLQI) score. In CIMPACT, the following co-primary and secondary outcomes were assessed first at week 12 and then at week 16 to evaluate the superiority of CZP 400 mg and 200 mg every two weeks over placebo sequentially, in the following order: PASI 75, PGA response, and PASI 90. If the null hypotheses were rejected at that point, PASI 75 response at week 12 was evaluated between CZP 400 mg and etanercept first, followed by CZP 200 mg and etanercept, for noninferiority and superiority. In addition to the symptoms-related scores, a number of health-related quality-of-life (HRQoL) measures were used as end points, including DLQI, Hospital Anxiety and Depression Scale for anxiety (HADS-A) and depression (HADS-D), EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L), and the Short Form (36) Health Survey (SF-36). These were included as other secondary outcomes, but the statistical analyses of them were not controlled for multiplicity (with the exception of DLQI in the CIMPASI trials only). All the aforementioned end points were also measured through week 48; however, no statistical comparisons were made between the CZP groups and placebo. Additionally, the provision to reassign treatment doses during the maintenance period resulted in few patients receiving CZP 200 mg or 400 mg exclusively. Therefore, the data during the maintenance period are not the primary focus of this CADTH Common Drug Review (CDR) of CZP.

Efficacy

CIMPASI-1 and -2 found CZP 200 mg and 400 mg every two weeks were superior to placebo for the primary and secondary efficacy outcomes at week 16: achievement of PASI 75 response, PGA response (clear or almost clear, i.e., a score of 0 or 1), PASI 90 response, and improvements in DLQI score from baseline. At week 16, statistically significantly higher PASI 75 rates were observed for CZP 400 mg (CIMPASI-1 and CIMPASI-2: 75.8% and 82.6%, respectively) and CZP 200 mg (66.5% and 81.4%, respectively) compared with placebo (6.5% and 11.6%, respectively) ($P < 0.0001$ for all). There were statistically significantly higher PGA responder rates for CZP 400 mg (CIMPASI-1 and CIMPASI-2: 57.9% and 71.6%, respectively) and CZP 200 mg (47.0% and 66.8%, respectively) compared with placebo (4.2% and 2.0%, respectively) ($P < 0.0001$ for all).

In the CIMPACT study, 61.3% and 66.7% of patients in the CZP 200 mg and 400 mg groups, respectively, achieved PASI 75 response at week 12 compared with 53.3% of patients who received etanercept and 5.0% who received placebo. The odds ratios for being a PASI 75 responder were statistically significantly higher for both CZP groups versus

placebo ($P < 0.0001$). CZP 400 mg was found to be superior to etanercept (odds ratio 1.76; 95% confidence interval [CI], 1.11 to 2.77; $P = 0.015$) and CZP 200 mg was found to be noninferior to etanercept. Noninferiority was based on a −10% noninferiority margin for the difference in proportions (mean difference 8%; 95% CI, −2.9% to 18.9%). CIMPACT found that 39.8% and 50.3% of patients in the CZP 200 mg and 400 mg groups achieved PGA response at week 12, respectively, compared with 1.9% of patients in the placebo group ($P = 0.0004$ and $P < 0.0001$, respectively). PGA response was achieved by 39.2% of patients in the etanercept group at week 12; however, no statistical comparison was made between CZP and etanercept or between etanercept and placebo.

In all three trials, data through week 48 suggest that patients who responded to CZP treatment (either dose) at week 12 (CIMPACT) or week 16 (CIMPASI-1 and -2) continued to have a good response to treatment, as shown by PASI and PGA score as well as a number of HRQoL measures. However, week 48 results may overstate the effect of CZP due to the focus on the enriched population of responders. In addition, no statistical comparisons between treatment arms were made for any post–week 16 (CIMPASI-1 and -2) or post–week 12 (CIMPACT) end points; therefore, results for the maintenance period should be interpreted descriptively.

Of the subgroups identified as relevant by the review team, data were available for previous systemic treatment experience only. Analysis of primary outcomes (PASI 75 and PGA responder rates) by previous systemic treatment experience showed no consistent pattern, although a statistical comparison was not done.

According to patient group input, the most significant physical symptoms of psoriasis include scales, flaking, itching, joint pain, cracking and bleeding, and pain. The input also suggests that lesions affect psychological well-being. Assessment of the disease-specific DLQI instrument and generic EQ-5D-3L, HADS-A and HADS-D, and the SF-36 physical component and mental component summaries suggest that improvements in the symptoms of plaque psoriasis (demonstrated by PASI and PGA) resulted in improvements in HRQoL for CZP-treated patients compared with placebo at week 12 or week 16. However, statistical comparisons for these outcomes were not adjusted for multiplicity, with the exception of DLQI score change from baseline in CIMPASI-1 and -2. No statistical comparisons for HRQoL measures were made between CZP and etanercept. A number of biologics are currently available on the market to treat moderate-to-severe psoriasis, including anti-TNF drugs (adalimumab, etanercept, and infliximab), interleukin (IL)-12 and IL-23 inhibitors (ustekinumab, risankizumab), and the IL-17A inhibitors (brodalumab, secukinumab, and ixekizumab). The CIMPACT trial included as a comparator only one of many options for plaque psoriasis: etanercept. To address the lack of direct comparative evidence from other drug treatments for psoriasis, CDR reviewed and critically appraised the manufacturer's submitted indirect treatment comparison. [redacted]

Harms

The percentage of patients who experienced treatment-emergent adverse events during the first 16 weeks ranged from 46% to 70% across the trials, with a balanced incidence between treatment groups within each trial. Infection was the most frequent adverse event,

which is known with anti–TNF alpha medications. The overall frequency of serious adverse events and events leading to study discontinuation were low (< 10%) across treatment groups. The safety profile remained largely similar through the maintenance period. Overall, the safety profile of CZP in patients with psoriasis was consistent with that observed in the other inflammatory conditions for which the drug is approved.

Potential Place in Therapy[1]

CZP is an anti-TNF biologic indicated for the treatment of moderate-to-severe psoriasis. Currently, there are 10 biologics (including CZP) approved for this indication. CZP is one of three anti-TNF drugs. Unlike other anti-TNF drugs, CZP is Fc-free and does not transfer across the placenta. Hence, it is believed to be safe in pregnancy.

There is a paucity of data on the transfer of biologics across the placenta and into breast milk. In clinical practice, it is generally accepted (based on clinical experience) that biologics are safe in the first two trimesters of pregnancy; their withdrawal is generally advisable in the third trimester. It is believed that the oral bioavailability of biologics is minimal, and mothers can breastfeed while on biologics. CZP is the only anti-TNF with formal pharmacokinetic studies on placental and breast-milk transfer. These studies provide more reassuring data to clinicians and pregnant and nursing women that CZP is safe in pregnancy and lactation.

CZP provides another biologic choice for patients and physicians. The currently available biologics, especially the newer drugs (anti-IL-17 and anti-IL-23), provide good efficacy and a durable response. Less than 10% to 20% of patients fail to respond to one of the biologics or lose efficacy or have a contraindication. CZP may be tried when another drug fails or is not appropriate.

Biologics are currently used as continuous therapy. When a patient is started on a biologic, the treatment is expected to be continuous and lifelong. A major unmet need is a treatment that is remittive or would work well on an intermittent “as-needed” basis. So far, neither CZP nor any of the biologics are able to fulfill this need.

Conclusions

Based on the results of three phase III RCTs in adults with moderate-to-severe plaque psoriasis, compared with placebo and etanercept, CZP 200 mg and CZP 400 mg resulted in statistically significant and clinically important improvements in skin clearance and dermatological symptoms over the short-term initiation phase, as measured by the PASI and PGA. [redacted]. Long-term comparative efficacy data from RCTs is lacking, as results beyond week 16 had limited interpretability. The safety profile of CZP in patients with psoriasis is consistent with its other indications.

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Table 1: Summary of Results at Week 16 for CIMPASI-1, CIMPASI-2, and CIMPACT

	CIMPASI-1			CIMPASI-2			CIMPACT			
	PBO	CZP 200	CZP 400	PBO	CZP 200	CZP 400	PBO	ETN	CZP 200	CZP 400
N	51	95	88	49	90	87	57	170	165	167
PASI 75 Responder Rate Versus Placebo										
Responder rate (%)	6.5	66.5	75.8	11.6	81.4	82.6	3.8	NA	68.2	74.7
Estimate (95% CI) for difference in proportion of responders vs. PBO		[redacted]	[redacted]		[redacted]	[redacted]			[redacted]	[redacted]
Odds ratio vs. PBO (97.5% CI)[a]		28.96 (6.97 to 120.37)	45.66 (10.66 to 195.63)		33.41 (9.97 to 111.98)	36.21 (10.69 to 122.71)			55.41 (13.14 to 233.78)[b]	76.28 (17.95 to 324.09)[b]
P value vs. PBO		< 0.0001	< 0.0001		< 0.0001	< 0.0001			< 0.0001	< 0.0001
PASI 90 Responder Rate										
Responder rate (%)	0.4	35.8	43.6	4.5	52.6	55.4	0.3	NR	39.8	49.1
Estimate (95% CI) for difference in proportion of responders vs. PBO		35.4 (20.85 to 49.87)	43.1 (27.56 to 58.71)		48.1 (35.04 to 61.26)	51.0 (37.75 to 64.19)			39.5 (25.58 to 53.38)	48.8 (34.22 to 63.41)
Odds ratio vs. PBO (97.5% CI)[a]		36.67 (5.72 to 235.20)	50.61 (7.88 to 324,988)		24.28 (4.39 to 134.43)	27.20 (4.90 to 151.20)			49.53 (10.00 to 245.26)	72.28 (14.65 to 356.60)
P value		< 0.0001	< 0.0001		< 0.0001	< 0.0001			< 0.0001	< 0.0001
PGA										
Responder rate (%)	4.2	47.0	57.9	2.0	66.8	71.6	3.4	NR	48.3	58.4
Estimate (95% CI) for difference in proportion of responders vs. PBO		42.8 (30.70 to 54.86)	53.6 (41.33 to 65.94)		64.8 (52.16 to 77.46)	69.6 (57.48 to 81.77)			44.9 (35.39 to 54.49)	55.0 (45.59 to 64.35)
Odds ratio vs. PBO (97.5% CI)[a]		20.12 (3.70 to 109.40)	31.14 (5.69 to 170.55)		106.23 (9.57 to 1,178.84)	133.16 (11.90 to 1,489.58)			27.17 (6.50 to 113.45)[b]	40.72 (9.74 to 170.20)[b]
P value		< 0.0001	< 0.0001		< 0.0001	< 0.0001			< 0.0001	< 0.0001

CI = confidence interval; CSR = Clinical Study Report; CZP = certolizumab pegol; ETN = etanercept; MCMC = Markov chain Monte Carlo; NR = not reported; PASI 75, PASI 90 = at least a 75% or 90% reduction in Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; PBO = placebo; vs. = versus.

[a] Logistic regression model with treatment group, region, and prior biologic exposure (yes/no) as factors, with MCMC methods used to impute missing data.

[b] Ninety-five per cent CI.

Source: CIMPASI-1 CSR,[13] CIMPASI-2 CSR;[14] CIMPACT.[16]

Table 2: Summary of Harms

	CIMPASI-1			CIMPASI-2			CIMPACT			
	PBO	CZP 200	CZP 400	PBO	CZP 200	CZP 400	PBO	ETN	CZP 200	CZP 400
N	51	95	88	49	90	87	57	170	165	167
Harms										
Any TEAEs	28 (54.9)	72 (72.0)	111 (77.1)	33 (67.3)	73 (76.8)	103 (79.8)	32 (56.1)	78 (46.4)	78 (47.3)	82 (49.1)
Serious TEAEs	1 (2.0)	4 (4.0)	11 (7.6)	0	7 (7.4)	7 (5.4)	5 (8.8)	1 (0.6)	1 (0.6)	4 (2.4)
Patient discontinuations due to TEAEs	0	0	5 (3.5)	0	8 (8.4)	8 (6.2)	0	4 (2.4)	1 (0.6)	1 (0.6)
Related TEAEs	4 (7.8)	14 (14.0)	28 (19.4)	4 (8.2)	24 (25.3)	27 (20.9)	7 (12.3)	20 (11.9)	16 (9.7)	22 (13.2)
Severe TEAEs	0	6 (6.0)	11 (7.6)	4 (8.2)	7 (7.4)	6 (4.7)	3 (5.3)	5 (3.0)	0	3 (0.9)
All deaths	0	0	1 (0.7)	0	0	0	0	0	0	0
Deaths (TEAEs leading to death)	0	0	1 (0.7)	0	0	0	0	0	0	0

CSR = Clinical Study Report; CZP = certolizumab pegol; ETN = etanercept; PBO = placebo; TEAE = treatment-emergent adverse event.

In the CIMPASI studies, the PBO data is through week 16 only and the CZP 200 and CZP 400 data is through 48 weeks. Data for the CIMPACT trial (all arms) is through 12 weeks.

Source: CIMPASI-1 CSR,[13] CIMPASI-2 CSR,[14] CIMPACT.[16]

Introduction

Disease Prevalence and Incidence

Psoriasis is a chronic, inflammatory, immune-mediated skin disorder that affects more than 500,000 people in Canada.[1] Various forms of psoriasis exist, including plaque, guttate, inverse, pustular, and erythrodermic. Plaque psoriasis is the most common, comprising approximately 80% to 90% of all cases. Approximately 17% of those with psoriasis have moderate-to-severe disease.[3] Moderate-to-severe plaque psoriasis can be defined by: the extent of skin coverage, with involvement of more than 5% to 10% of body surface area (BSA); location, i.e., involvement of the face, palm, groin or sole; or severity, with Psoriasis Area and Severity Index (PASI) score of more than 10.[4]

The disease is characterized by a series of linked cellular changes in the skin: hyperplasia of epidermal keratinocytes, vascular hyperplasia and ectasia, and infiltration of T lymphocytes, neutrophils, and other types of leucocytes in affected skin. Although the pathophysiology of psoriasis is not fully understood, the importance of T cells and inflammatory cytokines has been demonstrated by the clinical benefit provided by therapies directed at these targets[17] and, in particular, inhibition of Th17 T cells by the tumour necrosis factor (TNF) alpha inhibitors.[18]

Growing scientific evidence links psoriasis to cardiovascular disease (Gelfand et al., 2007), metabolic syndrome,[19] and autoimmune diseases such as Crohn's disease.[20] Psoriatic arthritis also is an important comorbidity in up to 30% of psoriasis patients.[21] Recent evidence has suggested an increased overall risk of mortality in patients with severe psoriasis.[22]

Psoriasis has a multitude of psychosocial and emotional effects on patients, including decreased self-esteem, increased self-consciousness, frustration, fatigue, depression, and suicidal ideation. As a result, patients frequently report sleeping problems, difficulties at work, problems interacting with family members, disrupted leisure activities, and sexual difficulties.[5-9]

Standards of Therapy

The treatment decision for psoriasis depends on the stage of the disease. According to the Canadian Guidelines for the Management of Plaque Psoriasis by the Canadian Dermatology Association (CDA),[1] first-line therapies for mild presentation include topical therapies, such as corticosteroids, calcipotriol, tazarotene, anthralin, and tars, used alone or in combination. Calcipotriol/betamethasone is not recommended for use on facial, flexural, or genital areas.[1,4] Moderate-to-severe plaque psoriasis is defined on the basis of the BSA or PASI cut-offs described previously; however, the CDA guideline recommends the use of the following definition in clinical and daily practices to diagnose patients with moderate-to-severe plaque psoriasis: ". . . if [the patient] cannot achieve, or would not be expected to achieve, adequate control using topical agents, with adequacy defined by the patient's own perception of the disease and its burdens."[1,4]

Moderate-to-severe plaque psoriasis requires the use of systemic therapies, often administered concomitantly with topical drugs. Psoriasis is essentially an immune disorder; therefore, the systemic therapies all work by suppressing components of the immune system. The common oral systemic drugs include acitretin, cyclosporine, and methotrexate;

prescription of these drugs is based on careful consideration of their clinical benefits and side effects.[1,4,23] Acitretin is often given in combination with other topical drugs for rapid and complete control; however, acitretin is highly teratogenic and strictly contraindicated in pregnancy. Cyclosporine is an immunosuppressant that is highly effective in severe disease, but may induce renal toxicity, hypertension, and hypertriglyceridemia; therefore, it is recommended for intermittent rather than continuous long-term use.[1,4,23] Methotrexate is an immunomodulatory and anti-proliferative drug that may be used for long-term management; however, this is associated with liver and systemic toxicity and is strictly contraindicated in pregnancy due to teratogenic and abortifacient effects.[1,4,23]

Biologics were the next systemic therapies to be developed. Initially, all of these drugs targeted TNF, a key mediator of inflammation. TNF-alpha inhibitors include adalimumab, etanercept, and infliximab, all of which have been approved for use in moderate-to-severe plaque psoriasis by Health Canada. However, they may be associated with an elevated risk of certain cancers, demyelinating disorders, and tuberculosis with long-term use.[1,4,23] The newest biological drugs target interleukins (ILs) and include ustekinumab (targets IL-12 and IL-23), guselkumab and risankizumab (both target IL-23), ixekizumab, brodalumab, and secukinumab (all three target IL-17). Additional details regarding these treatment options are in Table 3.

Phototherapy is also used for the treatment of moderate-to-severe psoriasis and involves ultraviolet A (UVA) with psoralen (PUVA) and ultraviolet B (UVB) therapy. In PUVA therapy, psoralen is administered orally or by immersing the affected areas in a psoralen solution before UVA exposure (oral versus bath PUVA, respectively). While successful in achieving skin clearance and durable response for at least six months following treatment cessation, PUVA is associated with non-melanoma skin cancer; therefore, it is recommended to be combined with other drugs to reduce ultraviolet exposure.[1,4,23] Broadband UVB has traditionally been used in the past; it is now often applied using a more effective option, narrow-band irradiation, which has been shown to have a more benign safety profile and to offer remission for at least six to 12 months. However, it is recommended to be given in combination with topical, systemic, or biologic drugs for more rapid and complete control, potentially reducing exposure to both ultraviolet light and other therapeutic drugs.[1,4,23]

Drug

Certolizumab pegol (CZP) is a recombinant, humanized antibody Fab' fragment, with specificity for human TNF alpha. The Fab' fragment is manufactured in *Escherichia coli* and then purified and conjugated to polyethylene glycol (PEG). PEGylation extends the half-life to approximately 14 days, increases bioavailability, and prolongs circulation time in the blood. TNF alpha is a key pro-inflammatory cytokine. CZP has a high affinity to both membrane-associated and soluble TNF and, therefore, selectively neutralizes TNF and the downstream pro-inflammatory cytokines and disease processes involved in chronic inflammatory diseases.

CZP has been approved in Canada for rheumatoid arthritis since 2009 and psoriatic arthritis and ankylosing spondylitis since 2014. CZP received a Health Canada Notice of Compliance (NOC) for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy on August 16, 2018. The recommended dose of CZP for plaque psoriasis is 400 mg by subcutaneous injection (SC) every two weeks. A dose of 400 mg initially (week 0) and at weeks 2 and 4 followed by 200 mg every two weeks may be considered.[11]

Table 3: Key Characteristics of Biologic Drugs for the Treatment of Psoriasis

	Mechanism of Action	Health Canada–Approved Indication	Recommended Dose	Serious Side Effects / Safety Issues
Infliximab	TNF inhibitor	Treatment of adult patients with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, infliximab should be used if phototherapy has been shown to be ineffective or inappropriate. When assessing the severity of psoriasis, the physician should consider the extent of involvement, location of lesions, response to previous treatments, and impact of disease on the patient's quality of life.	5 mg/kg given as an IV infusion followed by additional similar doses at 2 weeks and 6 weeks after the first infusion, then every 8 weeks thereafter. If a patient shows no response at 24 weeks, no additional treatment with infliximab should be given.	• Infection • Cancer
Adalimumab	TNF inhibitor	Treatment of adult patients with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, adalimumab should be used if phototherapy has been shown to be ineffective or inappropriate.	80 mg administered SC, followed by 40 mg SC given every other week starting one week after the initial dose. Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period.	• Infection • Cancer
Etanercept	TNF inhibitor	Treatment of adult patients with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.	50 mg dose given twice weekly SC (administered 3 or 4 days apart) for 3 months followed by a reduction to a maintenance dose of 50 mg SC per week. A maintenance dose of 50 mg SC given twice weekly has also been shown to be efficacious.	• Infection • Cancer
Ustekinumab	IL-12 and IL-23 inhibitor	Treatment of patients with chronic moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy.	45 mg SC at week 0 and week 4, then every 12 weeks thereafter. Alternatively, 90 mg SC may be used in patients with a body weight > 100 kg. For patients who respond inadequately to administration every 12 weeks, consideration may be given to treating as often as every 8 weeks.	• Infection • Cancer • Serious hypersensitivity reactions • Immunization
Guselkumab	IL-23 inhibitor	Treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.	100 mg administered SC at week 0 and week 4, followed by maintenance administration every 8 weeks thereafter.	• Infection

	Mechanism of Action	Health Canada–Approved Indication	Recommended Dose	Serious Side Effects / Safety Issues
Secukinumab	IL-17A inhibitor	Treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.	300 mg SC with initial administration at weeks 0, 1, 2, and 3, followed by monthly maintenance administration starting at week 4.	• Infection • Serious hypersensitivity reactions • Vaccination • Crohn's disease
Ixekizumab	IL-17A inhibitor	Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.	160 mg SC at week 0 followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks.	• Infection • Serious hypersensitivity reactions • IBD • Vaccination
Brodalumab	IL-17 RA	Treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.	210 mg administered by SC injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks.	• Infection • Suicidal ideation and behaviour
Risankizumab	IL-23 inhibitor	Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.	150 mg (two 75 mg injections) administered by SC at weeks 0 and 4 and every 12 weeks thereafter.	• Infection

IBD = inflammatory bowel disease; IL = interleukin; IV = intravenous; RA = receptor antibody; SC = subcutaneous; TNF = tumour necrosis factor.

Source: Product monographs for Cosentyx,[24] Enbrel,[25] Humira,[26] Remicade,[27] Siliq,[28] Skyrizi,[29] Stelara,[30] Taltz,[31] and Tremfya.[32]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of CZP (400 mg SC every two weeks, or a dose of 400 mg initially [week 0] and at weeks 2 and 4, followed by 200 mg every two weeks) for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to the CADTH Common Drug Review (CDR) and Health Canada, as well as those meeting the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient Population	Adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy. Subgroups of interest: • body weight (< 100 kg, ≥ 100 kg) • patients with psoriatic arthritis • patients with previous exposure to systemic therapy • patients whose condition failed to respond to previous systemic therapy • pregnant or nursing women
Intervention	Certolizumab pegol as a subcutaneous injection: • certolizumab pegol 400 mg every 2 weeks OR • certolizumab pegol 400 mg at weeks 0, 2 and 4 followed by 200 mg every 2 weeks
Comparators	Monotherapy or combination therapy (including adjunctive topical therapy) with: • **non-biologic systemic drugs:** acitretin, apremilast, cyclosporine, methotrexate • **biologic drugs targeting TNF alpha:** adalimumab, etanercept, infliximab • **biologic drugs targeting interleukins:** Ixekizumab, secukinumab, ustekinumab, guselkumab, risankizumab, brodalumab
Outcomes	**Key efficacy outcomes:** • health-related quality of life by a validated instrument (e.g., DLQI, SF-36, EQ-5D) • skin clearance / psoriasis score (e.g., PASI response, global assessment) • patient-reported symptoms (e.g., PSI) **Harms outcomes:** • mortality, AEs, SAEs, WDAEs **Notable harms, including but not limited to:** • infections • injection-site reactions • inflammatory bowel disease • serious hypersensitivity reactions • malignancy • cardiovascular and cerebrovascular events • suicidal ideation
Study Design	Published and unpublished phase III and IV RCTs

AE = adverse event; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-Dimensions questionnaire; PASI = Psoriasis Area and Severity Index; PSI = Psoriasis Symptom Inventory; 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.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 5, excluded studies (with reasons) are presented in Appendix 3.

Results

Findings From the Literature

A total of 317 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

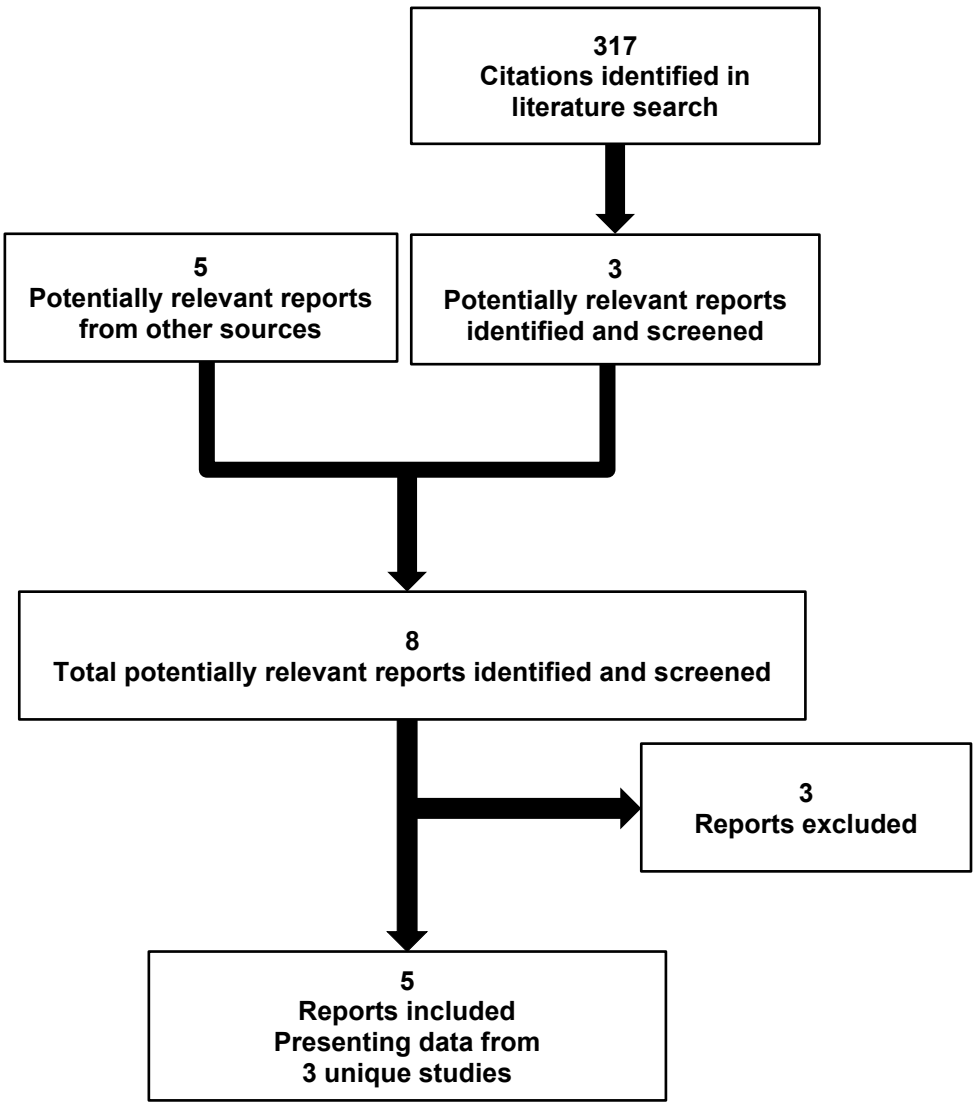


Table 5: Details of Included Studies

		CIMPASI-1	CIMPASI-2	CIMPACT
Designs and Populations	**Study Design**	DB RCT (main phase); followed by dose-blind phase and open-label maintenance phase		DB RCT
	Locations	30 centres in Canada, the US, Czech Republic, German, and Hungary	23 centres in Canada, the US, Austria, and Poland	70 centres in the US and Western and Eastern Europe
	Randomized (N)	234	227	559
	Inclusion Criteria	• Adult patients ≥ 18 years • Chronic psoriasis for at least 6 months • PASI ≥ 12, BSA ≥ 10% and PGA ≥ 3 • Women with no risk of pregnancy		
	Exclusion Criteria	• Patients who are breastfeeding, pregnant, or planning to become pregnant • Receiving any live (includes attenuated) vaccination within the 8 weeks prior to baseline • Primary failure to any biologic therapy • Secondary failure to more than one biologic therapy • History of serious infection, tuberculosis, or other clinically significant conditions or comorbidities		
Drugs	**Intervention**	CZP SC 400 mg q.2.w. or CZP SC 400 mg at week 0, 2, and 4 followed by CZP 200 mg q.2.w.		
	Comparator(s)	Placebo		Placebo ETN SC biweekly at a cumulative weekly dose of 100 mg
Duration	**Phase**			
	Screening	5 weeks		
	Double-blind	16 weeks		12 weeks
	Blinded maintenance	32 weeks (dose-blinded)		32 weeks
	Open-label maintenance	96 weeks		96 weeks
Outcomes	**(Co-)Primary End Point**	• PASI 75 at week 16 • PGA clear or almost clear (with at least two-category improvement) at week 16		• PASI 75 at week 12
	Other End Points	• PASI 90/100 at week 16 • PGA clear or almost clear (with at least two-category improvement) at week 48 • Change from baseline in DLQI at week 16, percentage of patients achieving ≥ 4-point change and absolute score of ≤ 1 • Change from baseline in SF36 all domains, and percentage of patients achieving 2.5 points • Responses to EQ-5D-3L • PASI 75 at week 48 for those achieving PASI 75 at week 16		• PASI 75/90/100 at week 16 • PASI 90 at week 12 and week 16 • PGA clear or almost clear (with at least a 2-category improvement) at week 12 • PGA clear or almost clear (with at least a 2-category improvement) at week 16 • PASI 75 at week 48 for those achieving PASI 75 at week 16

		CIMPASI-1	CIMPASI-2	CIMPACT
Notes	**Publications**	Gottlieb AB et al. 2018[13,14,33]		Lebwohl M et al. 2018[16,34]

BSA = body surface area; CSR = Clinical Study Report; CZP = certolizumab pegol; DB = double-blind; DLQI = Dermatology Life Quality Index; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; ETN = etanercept; PASI = Psoriasis Area and Severity Index; PASI 75/90/100 = at least a 75%, 90%, or 100% reduction from baseline in Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; PBO = placebo; q.2.w. = every 2 weeks; RCT = randomized controlled trial; SC = subcutaneous.

Source: CIMPASI-1 CSR,[13] CIMPASI-2 CSR,[14] CIMPACT.[16]

Included Studies

Description of Studies

A total of three phase III, double-blind (DB), multi-centre, randomized controlled trials (RCTs) that evaluated the efficacy and safety of CZP were included in this systematic review: CIMPASI (N = 234), CIMPASI-2 (N = 227), and CIMPACT (N = 559). All three trials had similar inclusion and exclusion criteria and enrolled patients aged ≥ 18 years with chronic psoriasis, with PASI ≥ 12, BSA ≥ 10%, and Physician's Global Assessment (PGA) ≥ 3 (Table 5). The studies had five similarly designed periods: screening (five weeks), initial treatment period (week 0 to 16), maintenance treatment period (week 16 to 48), open-label treatment (week 48 to 144), and a safety follow-up period. The major difference between CIMPASI-1/2 and CIMPACT was the different treatment regimens used in the initial, maintenance, and open-label treatment period.

CIMPASI-1 and CIMPASI-2 were two identically designed RCTs with a DB placebo–controlled initial treatment period, followed by a dose-blind maintenance treatment period. Beginning with the screening period, patients underwent clinical and laboratory assessments to determine eligibility to enter the respective trial. The five-week screening period also allowed washout of any prohibited medications for use during the study. The initial treatment period of 16 weeks was used to evaluate the efficacy of CZP over placebo. Patients were randomized in a 2:2:1 ratio to receive CZP 200 mg every two weeks, CZP 400 mg every two weeks, or placebo every two weeks. During the subsequent dose-blind maintenance treatment period, the efficacy of CZP beyond initial treatment was assessed from week 16 to 48. Patients who received CZP 200 mg or 400 mg every two weeks during the first 16 weeks and achieved at least a 50% reduction in PASI score (PASI 50) from baseline continued CZP treatment at the same dose. Patients receiving placebo who achieved PASI 75 (a 75% reduction in PASI from baseline) continued to receive placebo, whereas those who achieved PASI 50 but not PASI 75 at week 16 started CZP 400 mg at the loading dose and thereafter received CZP 200 mg every two weeks. During the maintenance period, treatments were administered in a dose-blind manner. Patients who completed the maintenance period and responded to the treatment (i.e., achieved PASI 50 at week 48) received open-label treatment for up to an additional 96 weeks. During the open-label period, patients who completed and responded to the treatment at week 48 received CZP 200 mg every two weeks. CZP dose adjustment was allowed during the open-label period at the investigator's discretion, depending on patients' PASI response. CZP dose was increased from 200 mg to 400 mg every two weeks for ≥ 12 weeks among nonresponders; patients were withdrawn from the study if no response continued. A CZP dose increase from 200 mg to 400 mg every two weeks was also allowed among responders in order to

improve their PASI response from PASI 50 to PASI 75, whereas CZP dose was reduced among patients with PASI 75.

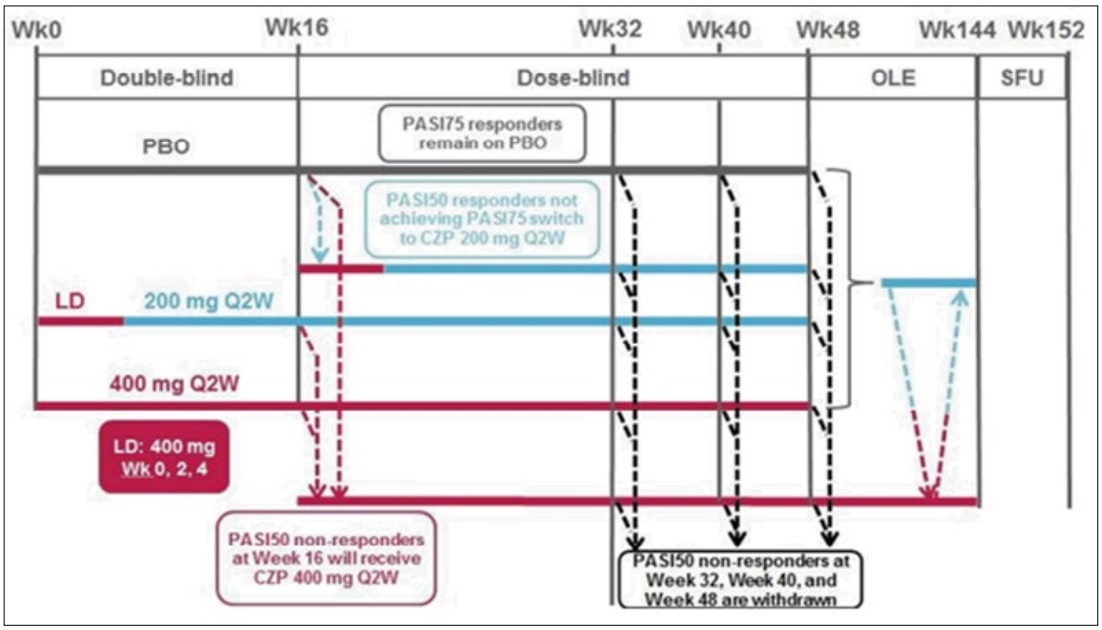
CIMPACT was a DB, parallel-group RCT with a DB-placebo and open-label active-controlled initial treatment period, followed by a DB placebo–controlled maintenance period. With the exception of the initial treatment period and maintenance period, the design of CIMPACT was largely similar to the CIMPASI trials. Following the screening period, patients were randomized in a 3:3:3:1 ratio to receive CZP 200 mg every two weeks through week 14, CZP 400 mg every two weeks through week 14, etanercept 50 mg twice weekly through week 11.5, or placebo every two weeks through week 14. At the subsequent maintenance treatment period, patients were re-randomized to receive CZP or placebo based on their treatment assignment and response at the end of week 16 (i.e., initial treatment period). Patients receiving placebo who achieved PASI 75 since baseline continued to receive blinded placebo. Patients initially randomized to etanercept were re-randomized (2:1) to either CZP 200 mg every two weeks or placebo. Patients initially randomized to CZP 200 mg every two weeks were re-randomized (2:2:1) to either CZP 200 mg every two weeks, CZP 400 mg every four weeks, or placebo. Patients initially randomized to CZP 400 mg every two weeks were re-randomized (2:2:1) to either CZP 200 mg every two weeks, CZP 400 mg every two weeks, or placebo. Patients who completed or relapsed (i.e., did not achieve PASI 50 at any point) during the maintenance period entered the subsequent 96-week open-label treatment period. Patients who completed the maintenance period without a relapse initiated open-label CZP 200 mg every two weeks, whereas those who relapsed or were undergoing escape treatment at week 48 received CZP 400 mg every two weeks. CZP dose was increased from 200 mg to 400 mg every two weeks for ≥ 12 weeks among nonresponders; patients were withdrawn from the study if no response continued. A CZP dose increase from 200 mg to 400 mg every two weeks was also allowed among responders in order to improve their PASI response from PASI 50 to PASI 75, whereas CZP dose was reduced among patients with PASI 75.

All patients started CZP 200 mg every two weeks with a CZP 400 mg loading dose (i.e., CZP 400 mg every two weeks for the first four weeks) followed by CZP 200 mg every two weeks thereafter, regardless of treatment period or week. Patients who did not achieve PASI 50 (CIMPASI-1 and -2) or PASI 75 (CIMPACT) at week 16 underwent escape treatment, i.e., open-label CZP 400 mg at the loading dose followed by CZP 200 mg every two weeks. In all trials, those who did not achieve PASI 50 from week 32 through week 48 were withdrawn from the study. All patients who underwent escape treatment at week 48 continued to receive CZP 400 mg every two weeks or had their dose reduced to 200 mg if they achieved PASI 75. Finally, all patients, including those who discontinued the treatment, were followed up for an additional 10 weeks after the final dose of study medication.

Participants in all three trials were randomized based on a predetermined production randomization and/or packaging schedule provided by the sponsor. An interactive voice/Web response system (IVRS/IWRS) was used to assign a treatment regimen, which was also used to change a patient's dose. Notably, patients received unblinded etanercept during the initial treatment period, since it was available only in commercial form and thus posed a challenge for study blinding. During the initial treatment period and maintenance treatment period (i.e., up to week 48), all study medications were administered by unblinded study personnel, although they were not involved in the study in any other way. It was mentioned that all sites used a dedicated, blinded assessor for the primary efficacy assessments. During the blinded period of each study, the sponsor provided blinded and unblinded site monitors in order to verify efficacy, safety, and treatment administration

records until patients reached week 48, when the database was locked for primary analysis. However, it was mentioned that the study monitors and study site personnel are blinded to treatment assignment did not discuss or have access to any study medication–related information.

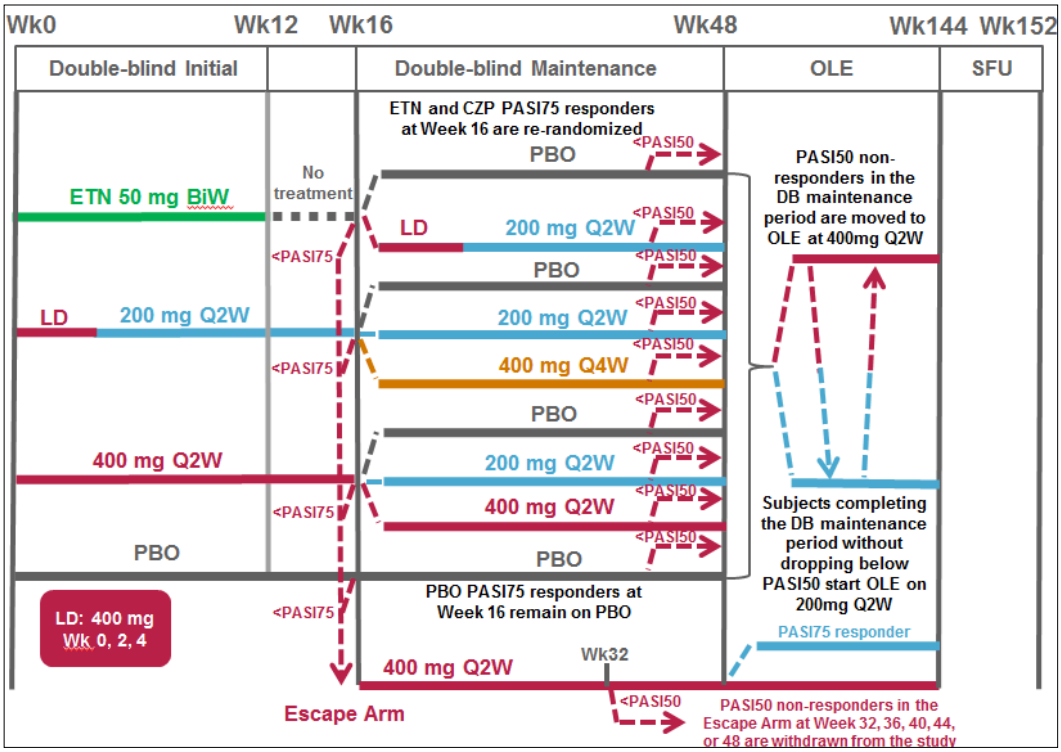
Figure 2: Study Design and Treatment Schema (CIMPASI-1 and CIMPASI-2)



CZP = certolizumab pegol; LD = loading dose; OLE = open-label extension; PASI50 = at least a 50% reduction from baseline in Psoriasis Area and Severity Index; PASI75 = at least a 75% reduction from baseline in Psoriasis Area and Severity Index; PBO = placebo; Q2W = every 2 weeks; SFU = safety follow-up; Wk = week.

Source: CIMPASI-1 Clinical Study Report.[13]

Figure 3: Study Design and Treatment Schema (CIMPACT)



BiW = biweekly; CZP = certolizumab pegol; DB = double-blind; ETN = etanercept; LD = loading dose; OLE = open-label extension; PASI 50 = at least a 50% reduction from baseline in Psoriasis Area and Severity Index; PASI 75 = at least a 75% reduction from baseline in Psoriasis Area and Severity Index; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SFU = Safety follow-up; Wk = week.

Source: CIMPACT.[16]

Populations

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria of all three trials were similar and are described in Table 5. The eligibility criteria for all three studies were the same with the exception that prior use of etanercept was not allowed in CIMPACT since etanercept was used as the active comparator in that study. Key inclusion criterion included: adult men and (non-pregnant or post-menopausal) women ≥ 18 years of age with chronic plaque psoriasis for at least six months, a baseline PASI ≥ 12, BSA ≥ 10%, and a PGA score ≥ 3 who were candidates for systemic psoriasis therapy and/or phototherapy and/or chemophototherapy.

A number of exclusion criteria were in place that can be broadly categorized as criteria related to medical conditions and prior medications. Patients with the following medical conditions were excluded: erythrodermic, guttate, or a generalized pustular form of psoriasis; current and previous chronic or recurrent infections or history of serious infections; high risk of infection; concurrent hepatitis B, hepatitis C, or HIV; history of an infected joint prosthesis; recent history of any live (includes attenuated) vaccination; history of previous lymphoproliferative disorders; concurrent malignancy or history of malignancy (except basal or squamous cell carcinomas of the skin, actinic keratosis, or uterine cervical carcinoma in situ); clinically significant laboratory abnormalities; and current or recent history of severe, progressive, and/or uncontrolled renal, hepatic, hematological, endocrine,

pulmonary, cardiac, or neurological disease. Additionally, patients were excluded if they had been diagnosed with inflammatory arthritis other than psoriatic arthritis (including rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, or fibromyalgia); were taking psoriatic arthritis medications (stable doses of NSAIDs were allowed to treat psoriatic arthritis symptoms); had a known tuberculosis infection, were at high risk of acquiring tuberculosis infection, or had a latent tuberculosis infection.

Patients were also excluded if they received prior CZP (at any point in the past, irrespective of dose or indication), had taken more than two biologics for psoriatic arthritis or psoriasis prior to study entry, had what was considered as primary failure to any prior biologic (defined as no response within the first 12 weeks of treatment), or had a secondary failure (defined as patients who initially responded to therapy and then stopped treatment due to loss of response after week 12) to more than one biologic therapy. Patients using the following treatments were excluded if any of the following therapies were used within a period of two to 24 weeks prior to study entry: systemic retinoids, systemic non-biologics (including immunosuppressants, fumarate, corticosteroids, phototherapy, or photochemotherapy), anti-TNFs (including infliximab, adalimumab, golimumab, and etanercept), other biologics and systemic therapies (including alefacept, efalizumab, ustekinumab, apremilast, secukinumab), rituximab (excluded if used within two years), and topical agents (including topical corticosteroids, vitamin D analogues, topical retinoids, and keratolytic agents, such as coal tar).

Baseline Characteristics

Baseline characteristics are summarized in Table 6. Demographic characteristics were generally well balanced across study groups and were similar between studies. The only notable exception was that there were fewer males overall in CIMPASI-2 (127 patients [55.9%]) compared with CIMPASI-1 (162 patients [69.2%]) or CIMPACT (381 patients [68.2%)]). The overall mean age of patients was 45.7 years (range 18 to 80 years), with more than half (59.9%) of the patients aged 40 to 63 years; a lower percentage of patients in the placebo group were less than 40 years of age (28.0%) compared with the CZP 200 mg every two weeks and 400 mg every two weeks groups (33.6% and 34.5%, respectively). The majority of patients were male (63.9%). Most patients were white (94.0%) and not of Hispanic or Latino ethnicity (92.4%). Overall, the mean body mass index was 30.63 kg/m^2 and mean body weight was 91.13 kg; mean and median body weight and body mass index were generally similar across treatment groups.

Baseline disease characteristics were generally reflective of a population with moderate-to-severe psoriasis. Notable differences between the studies were observed for prior anti-TNF therapy, prior photochemotherapy or phototherapy use, and geographical region. A lower percentage of patients used prior anti-TNF therapy in CIMPACT (21 patients [3.8%]) compared with CIMPASI-1 (46 patients [19.7%]) and CIMPASI-2 (53 patients [23.3%]). This difference in prior anti-TNF therapy is likely related to the exclusion of patients with prior etanercept use from CIMPACT. A higher percentage of patients used photochemotherapy or phototherapy in CIMPACT (289 patients [51.7%]) compared with CIMPASI-1 (102 patients [43.2%]), and CIMPASI-2 (94 patients [41.4%]). Additionally, a higher percentage of patients were from Europe in CIMPACT (approximately 83.5%) compared with CIMPASI-1 (48.7%) and CIMPASI-2 (30.8%).

Table 6: Summary of Baseline Characteristics

Baseline Characteristics	CIMPASI-1			CIMPASI-2			CIMPACT			
	PBO	CZP 200	CZP 400	PBO	CZP 200	CZP 400	PBO	ETN	CZP 200	CZP 400
N	51	95	88	49	91	87	57	170	165	167
Age, years, mean (SD)	47.9 (12.8)	44.5 (13.1)	43.6 (12.1)	43.3 (14.5)	46.7 (13.3)	46.4 (13.5)	46.5 (12.5)	44.6 (14.1)	46.7 (13.5)	45.4 (12.4)
Male, n (%)	35 (68.6)	67 (70.5)	60 (68.2)	26 (53.1)	58 (63.7)	43 (49.4)	34 (59.6)	127 (74.7)	113 (68.5)	107 (64.1)
Race, n (%)										
White	45 (88.2)	87 (91.6)	79 (89.8)	44 (89.8)	86 (94.5)	81 (93.1)	57 (100)	163 (95.9)	158 (95.8)	162 (97.0)
Asian							0	0 1 (0.6)	3 (1.8)	3 (1.8)
Black	3 (5.9)	2 (2.1)	3 (3.4)	1 (2.0)	3 (3.3)	3 (3.4)	0	0 3 (1.8)	2 (1.2)	2 (1.2)
Weight, kg Mean (SD)	95.23 (19.52)	92.59 (20.98)	92.23 (21.68)	87.11 (26.35)	97.77 (25.57)	91.79 (27.74)	93.74 (29.71)	88.63 (20.66)	89.71 (20.62)	86.27 (20.04)
Weight group, n (%)										
≤ First quintile	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> First to ≤ second quintile	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> Second to ≤ third quintile	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> Third to ≤ fourth quintile	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> Fourth quintile	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2 Mean (SD)	32.195 (6.828)	31.142 (7.261)	30.672 (6.676)	30.155 (7.953)	32.800 (8.294)	31.650 (8.923)	31.165 (8.549)	29.475 (6.304)	29.813 (6.059)	28.943 (5.919)
Duration of psoriasis, years mean (SD)	18.47 (12.85)	16.64 (12.28)	18.39 (12.86)	15.36 (12.19)	18.77 (13.52)	18.57 (12.37)	18.942 (12.885)	17.399 (12.037)	19.467 (13.200)	17.822 (11.479)
PsA, n (%), yes	4 (7.8)	10 (10.5)	15 (17.0)	9 (18.4)	22 (24.2)	26 (29.9)	12 (21.1)	27 (15.9)	27 (16.4)	24 (14.4)
BSA, % mean (SD)	26.1 (16.1)	25.4 (16.9)	24.1 (16.6)	20.0 (9.5)	21.4 (12.2)	23.1 (11.6)	24.3 (13.8)	27.5 (15.5)	28.1 (16.7)	27.6 (15.3)
PASI, mean (SD)	19.81 (7.51)	20.05 (8.24)	19.59 (7.93)	17.34 (5.33)	18.40 (5.92)	19.51 (6.71)	19.13 (7.10)	21.04 (8.21)	21.43 (8.79)	20.79 (7.69)
sPGA, n (%)										
0, 1, or 2	–	–	–	–	–	–	–	–	–	–
3	35 (68.6)	–	–	–	–	–	–	–	–	–
4	16 (31.4)	33 (34.7)	23 (26.1)	12 (24.5)	25 (27.5)	26 (29.9)	17 (29.8)	55 (32.4)	51 (30.9)	54 (32.3)
5	–	–	–	–	–	–	–	–	–	–
DLQI total score, mean (SD)	13.9 (8.3)	13.3 (7.4)	13.1 (6.5)	12.9 (7.3)	15.2 (7.2)	14.2 (7.2)	13.2 (7.6)	14.1 (7.4)	12.8 (7.0)	15.3 (7.3)

Baseline Characteristics	CIMPASI-1			CIMPASI-2			CIMPACT			
	PBO	CZP 200	CZP 400	PBO	CZP 200	CZP 400	PBO	ETN	CZP 200	CZP 400
Prior therapy, n (%)										
Topicals (any)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Phototherapy or photochemotherapy	21 (41.2)	43 (45.3)	38 (43.2)	21 (42.9)	33 (36.3)	40 (46.0)	28 (49.1)	89 (52.4)	88 (53.3)	84 (50.3)
Non-biologic systemic	16 (31.4)	37 (38.9)	37 (42.0)	21 (42.9)	41 (45.1)	31 (35.6)	22 (38.6)	61 (35.9)	63 (38.2)	75 (44.9)
Biologics	15 (29.4)	30 (31.6)	29 (33.0)	14 (28.6)	32 (35.2)	30 (34.5)	11 (19.3)	51 (30)	44 (26.7)	48 (28.7)
One biologic	13 (25.5)	22 (23.2)	22 (25.0)	11 (22.4)	22 (24.2)	21 (24.1)	7 (12.3)	38 (22.4)	38 (23.0)	37 (22.2)
Two biologics	2 (3.9)	8 (8.4)	7 (8.0)	3 (6.1)	10 (11.0)	8 (9.2)	4 (7.0)	13 (7.6)	6 (3.6)	11 (6.6)
Anti-TNF	10 (19.6)	19 (20.0)	17 (19.3)	9 (18.4)	22 (24.2)	22 (25.3)	5 (8.8)	8 (4.7)	4 (2.4)	4 (2.4)
Prior failure of biologics (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

BMI = body mass index; BSA = body surface area; CSR = Clinical Study Report; CZP 200 = certolizumab pegol 200 mg q.2.w.; CZP 400 = certolizumab pegol 400 mg q.2.w.; DLQI = Dermatology Life Quality Index; ETN = etanercept; NR = not reported; PASI = Psoriasis Area and Severity Index; PBO = placebo; PsA = psoriatic arthritis; PSI = Psoriasis Symptom Inventory total score; q.2.w. = every two weeks; SD = standard deviation; sPGA = static Physician's Global Assessment; TNF = tumour necrosis factor.

[redacted]

Source: CIMPASI-1 CSR,[13] CIMPASI-2 CSR,[14] CIMPACT.[16]

Interventions

All investigational products (CZP and placebo) were administered using single-use, pre-filled syringes. Both CZP doses and placebo were given as two blinded injections. Notably, CZP solution has a colourless to slightly yellow appearance, whereas placebo does not. The sponsor indicated that special precautions were taken to ensure blinding due to the difference in the presentation and viscosity between CZP and placebo. Injections were administered subcutaneously to the lateral abdominal wall and upper outer thigh, with each of the two injections administered at separate sites. During the initial and maintenance treatment periods (i.e., up to week 48), administration of all investigational products was conducted by unblinded study site staff, and all subsequent injections during the open-label period were self-administered (self-administration included administration by a trained caregiver). However, etanercept was self-administered by the patient on non–study visit days if on- or off-site trained personnel were unavailable. Finally, in all studies, escape treatment was defined as unblinded treatment with CZP 400 mg every two weeks.

Treatments administered at each period in the three trials are described subsequently.

CIMPASI-1 and CIMPASI-2

Initial Treatment Period (Week 0 to Week 16)

- CZP 200 mg every two weeks, 400 mg every two weeks, or placebo (randomized in a 2:2:1 ratio).

Maintenance Treatment Period (Week 16 to Week 48)

The treatment administered during the maintenance treatment period was based on the response to treatment at week 16. During this period, patients continued to receive study medication in a dose-blind fashion.

Patients who achieved at least PASI 50 at week 16 continued treatment as follows:

- Patients randomized to CZP 200 mg or 400 mg every two weeks continued to receive CZP at the same dosage.
- Patients randomized to placebo who achieved PASI 50 but not PASI 75 started CZP 200 mg every two weeks with a 400 mg loading dose for the first four weeks.
- Patients randomized to placebo who achieved PASI 75 continued to receive placebo.

Patients who did not achieve PASI 50 at week 16 started escape treatment with CZP 400 mg every two weeks during the maintenance period and were withdrawn from the study if this non-response persisted for 16 weeks. Patients who did not achieve a PASI 50 response at week 32 or after were withdrawn from the study.

Open-label Treatment Period (Week 48 to Week 144)

During the open-label period, patients who completed and responded to the treatment (achieved PASI 50) at week 48 started open-label treatment for up to an additional 96 weeks. A CZP dose adjustment was allowed during the open-label period at the investigator's discretion, depending on patients' PASI response.

- Patients who completed week 48 with a PASI 50 response received CZP 200 mg every two weeks.
- Patients who were receiving escape treatment at week 48 continued escape therapy during the open-label period, although their dose could be reduced to 200 mg every two weeks if they achieved PASI 75.
- Patients who were receiving CZP 200 mg every two weeks and achieved PASI 50 but not PASI 75 from week 60 to week 132 had their dose increased to 400 mg. Conversely, patients who received CZP 400 mg every two weeks for ≥ 12 weeks and achieved PASI 75 had their dose reduced to 200 mg.
- Patients who were receiving CZP 200 mg every two weeks but did not achieve PASI 50 from week 60 to 132 started CZP 400 mg every two weeks for ≥ 12 weeks. These patients were withdrawn from the study if no response persisted.

CIMPACT

Initial Treatment Period (Week 0 to Week 16)

- CZP 200 mg every two weeks, 400 mg every two weeks, etanercept 50 mg twice weekly, or placebo (randomized in a 3:3:3:1 ratio). Notably, the last etanercept treatment was administered at week 11.5. No etanercept treatment was administered on weeks 12 through 14.

Maintenance Treatment Period (Week 16 to Week 48)

During this period, patients were re-randomized to receive CZP or placebo based on their treatment assignment and response at the end of week 16. Patients who did not achieve PASI 75 at week 16 started escape treatment (described subsequently) and were withdrawn from the study if they did not achieve PASI 50 at week 32. Additionally, patients

who achieved PASI 50 at week 32 but not in subsequent weeks were withdrawn from the study.

Patients who achieved at least PASI 75 at week 16 continued treatment as follows:

- Patients initially randomized to etanercept were re-randomized (2:1) to CZP 200 mg every two weeks (with a 400 mg loading dose for the first four weeks) or placebo.
- Patients initially randomized to CZP 200 mg every two weeks were re-randomized (2:2:1) to CZP 200 mg every two weeks, CZP 400 mg every four weeks (with placebo administered on alternate dosing weeks to maintain the blind), or placebo.
- Patients initially randomized to CZP 400 mg every two weeks were re-randomized (2:2:1) to CZP 200 mg every two weeks, CZP 400 mg every two weeks, or placebo.
- Patients who relapsed, i.e., did not achieve a PASI 50 response at any time point, entered the open-label period of the study.

Open-Label Treatment Period (Week 48 to Week 144)

A CZP dose adjustment was allowed during the open-label period at the investigator's discretion, depending on patients' PASI response.

- Patients who experienced a relapse during the maintenance period started CZP 400 mg every two weeks.
- Patients who completed the maintenance period without a relapse started CZP 200 mg every two weeks.
- Patients who were receiving escape treatment at week 48 continued escape therapy during the open-label period, although their dose could be reduced to 200 mg every two weeks if they achieved PASI 75.
- Patients who were receiving CZP 200 mg every two weeks and achieved PASI 50 but not PASI 75 from week 60 to week 132 had their dose increased to 400 mg every two weeks for 12 weeks. Conversely, patients who received CZP 400 mg every two weeks for ≥ 12 weeks and achieved PASI 75 had their dose reduced to 200 mg every two weeks.
- Patients who were receiving CZP 200 mg every two weeks but did not achieve PASI 50 from week 60 to week 132 started CZP 400 mg every two weeks for ≥ 12 weeks. These patients were withdrawn from the study if no response persisted.

The following concomitant medications were allowed for medical conditions (e.g., hypertension, diabetes, acute infections) or treatment of an adverse event (AE): NSAIDs, acetaminophen, paracetamol, and opioids for psoriatic arthritis. In addition, the following medications were permitted for psoriasis during the open-label period: moderate potency (class III to V) topical corticosteroids, vitamin D analogues and topical retinoids, and keratolytics, such as coal tar. Prohibited concomitant medications included the ones specified in the exclusion criteria described previously.

Notably, the start of CZP 200 mg every two weeks was always done with a loading dose of CZP 400 mg every two weeks for the first four weeks, followed by 200 mg every two weeks until the dose was changed.

Outcomes

In CIMPASI-1 and CIMPASI-2, PASI 75 and PGA responder rates (clear or almost clear, with at least a two-category improvement) at week 16 were co-primary end points. Secondary efficacy end points included PASI 90 at week 16, PGA responder rates at week 48, PASI 75 at week 48, and change from baseline in Dermatology Life Quality Index (DLQI) at week 16. For CIMPACT, the primary end point was PASI 75, which was assessed at week 12 due to the comparison with etanercept. The key secondary efficacy end points were PASI 75 at week 16, PASI 90 at week 12 and week 16, PGA responder rates at week 12 and week 16, and PASI 75 at week 48 for those achieving a PGA response at week 16.

In addition to the primary and secondary end points, the following health-related quality of life (HRQoL) end points assessed in the three trials were relevant for this review: scores for all domains of the Short Form (36) Health Survey (SF-36) as well as the physical and mental component summary scores; DLQI scores; Hospital Anxiety and Depression Scale (HADS) for anxiety (HADS-A) and depression (HADS-D) scores; and scores for the EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L) and visual analogue scale (VAS). For all these measures, change from baseline was assessed. As well, the percentage of patients achieving a set cut point (i.e., manufacturer-claimed minimal clinically important difference [MCID]) was reported, which was at least a four-point change from baseline and an absolute score of ≤ 1 for DLQI and HADS-A and HADS-D scores of < 8 points.

Appendix 5 provides a detailed description of the outcome measures used in the studies. The following is a brief description of the symptoms-related efficacy end points measured in all three trials.

Psoriasis Area and Severity Index

PASI is a widely used instrument in psoriasis trials and clinical practice that grades the severity of psoriatic lesions and the patient's response to treatment. It combines the extent of BSA involvement in four anatomical regions (head, trunk, arms, and legs) and the severity of desquamation, erythema, and plaque induration or infiltration (thickness) in each region. Patients are given a numeric score ranging from 0 to 72, where higher scores indicate worsened symptoms.[35] In general, a PASI score of 5 to 10 is considered moderate disease and a score of more 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 efficacy for new psoriasis treatments approved by the FDA.[36] However, newer biologics have been shown to be capable of achieving a 90% to 100% reduction from baseline in PASI score (PASI 90 to PASI 100).[36,37] In the three trials, PASI 50, 75, 90, 100, and the absolute and percentage change from baseline in PASI score were assessed at different time points.

Static Physician's Global Assessment

The static PGA (sPGA) is a single estimate of a physician's impression of a patient's psoriasis.[35] This is an ordinal scale where psoriatic lesions are graded for induration, erythema, and scaling based on a scale of 0 to 5, where higher scores indicate a more severe condition.[38,39] The sums of the three scales are added and divided by three to obtain a final sPGA, interpreted as:

- 0 = Cleared, except for residual discoloration
- 1 = Minimal
- 2 = Mild
- 3 = Moderate
- 4 = Marked
- 5 = Severe

No MCID for patients with plaque psoriasis was identified. However, the trials included in this review used PGA clear or almost clear (with at least a two-category improvement) as the criteria to indicated clinical response.

The following is a brief description of the HRQoL end points measured in all three trials.

Dermatology Life Quality Index

The DLQI is a widely used dermatology-specific questionnaire to assess the impact of disease on a patient's quality of life (QoL). It consists of a 10-item, patient-reported questionnaire assessing six different domains that may affect QoL: symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment.[40] The DLQI produces a numeric score that can range from 0 to 30; the higher the score, the greater the impairment in QoL.[32,33] DLQI scores are interpreted in the following way:

- 0 to 1 = no effect
- 2 to 5 = small effect
- 6 to 10 = moderate effect
- 11 to 20 = very large effect
- 21 to 30 = extremely large effect

Estimates of MCID for DLQI range from 2.2 to 6.9 to 32 to 36. The manufacturer considered a change in DLQI score of four or more points as clinically meaningful for the patient, and a DLQI absolute score of 1 or more as a cut point for DLQI remission (i.e., no or small impact of the disease on HRQoL).

Hospital Anxiety and Depression

The HADS is a widely used generic patient-reported questionnaire designed to identify anxiety disorders and depression in patients at non-psychiatric medical institutions.[41] It includes 14 questions, each of which was answered by patients using a four-point scale (from 0 to 3, with 0 indicating absence and 3 indicating extreme presence), with higher scores indicating more severe anxiety or depression symptoms. An anxiety subscale score (possible score of 0 to 21) was calculated by combining seven items from the HADS, and a depression subscale score (possible score of 0 to 21) was calculated by combining the remaining seven items.[42] For both subscales, scores of 7 or less indicate healthy state, 8 to 10 indicate borderline case, and 11 to 21 indicate diseased case. However, the manufacturer considered a score of 8 or less as normal.

EuroQol 5-Dimensions 3-Levels Questionnaire

The EQ-5D-3L is a generic, preference-based measure of HRQoL that has been applied to a wide range of health conditions and treatments, including psoriasis. It consists of two

parts: a descriptive system and a VAS.[43,44] The descriptive system consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing “no problems,” “some problems,” and “extreme problems,” respectively. Respondents are asked to choose one level that reflects their own health state for each of the five dimensions.[43,44] A scoring function is used to assign a value (EQ-5D-3L index score) to self-reported health states, with estimates of MCID for the EQ-5D-3L index score ranging from 0.09 to 0.22.[43,44] The second part of the EQ-5D-3L is a 20 cm VAS (EQ VAS) that has end points labelled 0 and 100, representing the “worst imaginable health state” and “best imaginable health state,” respectively.[37,38] Respondents are asked to rate their own health on the EQ VAS that best represents their health on that day, with reported MCIDs ranging from 3.82 to 10.34 in psoriasis patients.[43,44]

Short Form (36) Health Survey

The SF-36 is a generic measure of HRQoL that has been used extensively in clinical trials in many disease areas. It is composed of 36 items covering eight domains: physical functioning, role physical, role emotional, bodily pain, vitality, social functioning, mental health, and general health. The eight domains are aggregated to create the physical component summary (PCS) and mental component summary (MCS), with scores ranging from 0 to 100; higher scores indicate better health status. The MCIDs for the PCS and MCS in psoriasis have been reported to range between 2.57 to 3.91 and 3.89 to 6.05, respectively.[45,46] The manufacturer used an MCID for SF-36 domains and component scores of 2.5 points.

Safety

A number of safety end points were measured throughout the duration of each study and involved AEs, serious adverse events (SAEs), serious infectious events, laboratory assessments, vital signs, electrocardiograms, and antibody formation. In addition, several AEs of interest were recorded, notably including injection-site reactions, neutropenia, hypersensitivity reactions, serious cardiovascular events, congestive heart failure, and malignancies, including lymphoma.

An AE was defined as any untoward medical occurrence in a patient regardless of a causal relationship between the treatment and the AE outcome. This included worsening of pre-existing medical conditions (i.e., an increase in severity, frequency, duration), or was associated with a significantly worse outcome. Incidences of SAEs were also recorded and involved any one of the following criteria: was fatal or life-threatening, required in-patient hospitalization (overnight) or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, and any other medically important serious events.

Statistical Analysis

Analyses of Primary and Key Secondary Efficacy End Points

For the CIMPASI-1 and CIMPASI-2 trials, the co-primary efficacy outcomes were the PGA (clear or almost clear with at least a two-category improvement) and PASI 75 responses at week 16. These outcomes were analyzed based on the randomized population set using a logistic regression model with treatment group, region, and prior biological exposure (yes/no) as covariates. For the PGA and PASI response outcomes, the Markov chain Monte Carlo (MCMC) method for multiple imputation was used to impute missing data

during the 16-week initial treatment period (details of imputation methods provided subsequently).

In CIMPASI-1 and CIMPASI-2, continuous outcomes, such as the change from baseline to week 16 in the DLQI, were analyzed using an analysis of covariance (ANCOVA) model that included variables for treatment group, prior biologic exposure (yes/no), and baseline outcome score. Last observation carried forward (LOCF) was used to impute missing data.

For the CIMPACT study, the primary efficacy outcome was PASI 75 response at 12 weeks for the comparison of each CZP dose versus placebo (randomized population set). The primary outcome was analyzed using a logistic regression model that included variables for treatment group, region and prior biologic exposure (yes/no) and was reported as odds ratio with 95% confidence interval (CI) and *P* value. MCMC multiple imputation methods were used to handle missing data in the initial treatment period.

Other binary secondary outcomes were analyzed using the same method used in the CIMPACT study for primary outcome. For the comparison between CZP and etanercept, noninferiority was evaluated based on a 10% noninferiority margin for the difference in proportions. If the lower limit of the 95% CI or 97.5% CI did not extend beyond −10%, then noninferiority was met (see Table 7 for details). No information was provided to support the selection of a 10% noninferiority margin. The change from baseline to week 12 in the DLQI was analyzed using an ANCOVA model that included variables for treatment group, prior biologic exposure (yes/no) and baseline outcome score. LOCF was used for missing data.

In the CIMPACT study, the maintenance treatment period was analyzed separately from the initial treatment period, as patients were re-randomized to nine blinded treatment groups and four escape treatment groups.

Study Power

Based on a sample size of 225 patients randomized 2:2:1 to CZP 400 mg, CZP 200 mg, and placebo groups, the CIMPASI-1 and CIMPASI-2 studies had > 99% power to detect a difference between CZP 200 mg and placebo with a two-sided alpha of 0.025. In these calculations, it was assumed that 70%, 50%, and 5% of patients in the CZP 400 mg, CZP 200 mg, and placebo groups, respectively, would achieve a PGA response at week 16, based on data from a phase II trial.[47] The anticipated PASI 75 response rates (80%, 75%, and 10% for the CZP 400 mg, CZP 200 mg, and placebo groups, respectively). were higher than PGA response rates; thus, PGA response was used for the power calculations. The overall alpha of 0.05 was split between the two CZP dosage groups for the statistical testing and power calculations.

The CIMPACT study was estimated to have > 99% power for the PASI 75 responder rate for CZP 200 mg versus placebo, based on a planned sample size of 540 patients randomized 3:3:3:1 to CZP 400 mg, CZP 200 mg, etanercept, or placebo, respectively. It was assumed that 80%, 75%, 57%, and 5% of patients in the CZP 400 mg, CZP 200 mg, etanercept, and placebo groups, respectively, would achieve a PASI 75 response at week 12 based on data from two trials.[47,48] Using a two-sided significance level of 0.05, the study was estimated to have 91% power to detect a difference between CZP 200 mg and etanercept.

Subgroup Analyses

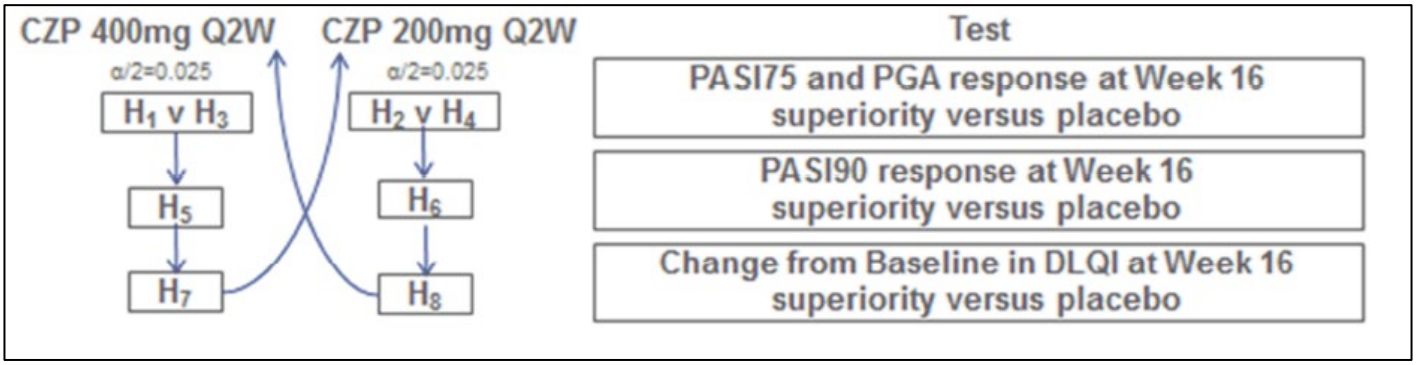
In the three included studies, numerous subgroup analyses were planned a priori, including the following: age, gender, race, ethnicity, duration of disease, geographic region, body mass index, weight, prior systemic phototherapy or photochemotherapy, prior systemic therapy (non-biologic), prior biologic exposure, prior anti-TNF exposure, any prior systemic therapy for psoriasis, previous exposure to at least two systemic treatments out of phototherapy, methotrexate, and cyclosporine (with no previous biologic exposure), PASI score at baseline, BSA at baseline, and anti–CZP antibody status. These subgroup analyses were performed on the primary efficacy outcomes and presented with descriptive statistics in the three trials.

Multiplicity

A fixed-sequence testing procedure was used to account for multiplicity in the three trials.

In CIMPASI-1 and CIMPASI-2, the statistical analysis of the co-primary efficacy outcomes and two secondary efficacy outcomes (PASI 90 response at week 16 and change from baseline to week 16 in DLQI score) were included in the fixed-sequence testing procedure that controlled the family-wise type I error rate at a two-sided alpha level of 0.05 (Figure 4). The type I error was split equally between CZP 400 mg and CZP 200 mg dosage groups so that each dose was tested at a two-sided alpha level of 0.025. The first two hypotheses tested whether each CZP dose was superior to placebo for PASI 75 response and PGA response at week 16. If the null hypothesis for both outcomes was rejected at a two-sided alpha level of 0.025, that alpha was passed to the next test in the sequence, and the testing procedure was continued. If all null hypotheses within one dosage set of hypotheses (CZP 400 mg or CZP 200 mg) were rejected, the corresponding type I error probability was passed on to the other set of hypotheses and that set was retested, if necessary, at a two-sided alpha level of 0.05.

Figure 4: Fixed-Sequence Testing Procedure in CIMPASI-1 and CIMPASI-2



CZP = certolizumab pegol; DLQI = Dermatology Life Quality Index; H = hypothesis; PASI75 = at least a 75% reduction from baseline in Psoriasis Area and Severity Index; PASI90 = at least a 90% reduction from baseline in Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; Q2W = every 2 weeks.

Source: CIMPASI-1 Clinical Study Report.[13]

In the CIMPACT trial, the statistical analyses of the primary efficacy outcome and selected secondary efficacy outcomes were tested using a fixed-sequence testing procedure that controlled the overall type I error. The sequential procedure is described in Table 7.

Table 7: Statistical Testing Hierarchy for CIMPACT Study

Testing Order	Comparison	Outcome	Time Point	Comment
1	CZP 400 mg versus placebo	PASI 75	12	2-sided; alpha 0.05
2	CZP 200 mg versus placebo	PASI 75	12	2-sided; alpha 0.05
3	CZP 400 mg versus placebo	PGA response	12	2-sided; alpha 0.05
4	CZP 200 mg versus placebo	PGA response	12	2-sided; alpha 0.05
5	CZP 400 mg versus placebo	PASI 90	12	2-sided; alpha 0.05
6	CZP 200 mg versus placebo	PASI 90	12	2-sided; alpha 0.05
7	CZP 400 mg versus placebo	PASI 75	16	2-sided; alpha 0.05
8	CZP 200 mg versus placebo	PASI 75	16	2-sided; alpha 0.05
9	CZP 400 mg versus placebo	PGA response	16	2-sided; alpha 0.05
10	CZP 200 mg versus placebo	PGA response	16	2-sided; alpha 0.05
11	CZP 400 mg versus placebo	PASI 90	16	2-sided; alpha 0.05
12	CZP 200 mg versus placebo	PASI 90	16	2-sided; alpha 0.05
13	CZP 400 mg versus etanercept	PASI 75 (noninferiority)	12	Noninferiority based on the difference in proportions using a 10% noninferiority margin (lower bound of 2-sided 95% CI)
14a	CZP 400 mg versus etanercept	PASI 75 (superiority)	12	Hochberg procedure: • if 14a is significant at alpha level 0.05 and 14b is significant based on lower bound of 95% CI, then test step 15 • if 14a is not significant at alpha 0.05 and 14b is significant based on lower bound of a 2-sided 97.5% CI; then 14b considered significant and testing procedure stopped • if 14a is significant at alpha 0.025 and 14b is non-significant based on lower bound of 95% CI, then 14a considered is significant and testing stopped • if both 14a and 14b are non-significant at alpha level 0.05, then testing concluded
14b	CZP 200 mg versus etanercept	PASI 75 (noninferiority)	12	
15	CZP 200 mg versus etanercept	PASI 75 (superiority)	12	2-sided; alpha 0.05

CI = confidence interval; CZP = certolizumab pegol; PASI 75 = at least a 75% reduction from baseline in Psoriasis Area and Severity Index; PASI 90 = at least a 90% reduction from baseline in Psoriasis Area and Severity Index; PGA = Physician's Global Assessment.

Source: CIMPACT.[16]

Imputation for Missing Data

The MCMC method for multiple imputation was used to account for missing values in the primary analysis of PGA and PASI 75 outcomes in all three trials. This method for handling intermittent or monotonic missing data assumes a missing-at-random pattern of missingness. The multiple imputation procedure for PGA response was based on the observed score on a scale from 0 to 4 (as opposed to the binary response). Similarly, for PASI 75, the multiple imputation procedure was based on the actual PASI score.

During the maintenance phase of CIMPASI-1 and CIMPASI-2, any patient who did not achieve a PASI 50 response at week 16 (i.e., met the escape criteria) was considered a nonresponder for all subsequent time points. Other missing data during the maintenance phase were imputed via the MCMC multiple imputation method. Other dichotomous

outcomes used the nonresponder imputation method to handle any missing data. Missing data for continuous outcomes were handled using LOCF. During the maintenance phase, patients who did not achieve a PASI 50 response at week 16 had their week 16 DLQI score carried forward to all subsequent time points. LOCF was used to impute other missing data for the analysis of the maintenance phase.

For the analysis of the maintenance phase of the CIMPACT study, PASI 75 response was analyzed using the nonresponder imputation method. Patients in the blinded maintenance groups who relapsed (and were withdrawn) or who withdrew for other reasons, were considered nonresponders for subsequent time point. Maintenance period data were also analyzed without imputation using observed case data. Continuous efficacy outcomes were analyzed using LOCF and observed case data for the maintenance period.

The CIMPASI-1 and CIMPASI-2 trials conducted sensitivity analyses for the co-primary outcomes that used the nonresponder imputation (patient with missing PGA [or PASI 75] value at week 16 was treated as a nonresponder) as well as a model-based multiple imputation method for the PGA (or PASI 75) responder data. Similarly, in the CIMPACT trial, nonresponder imputation and a model-based multiple imputation method were used to analyze the PASI 75 responder rate at week 12 as sensitivity analyses.

Analysis Populations

The analysis populations in all three trials were defined as follows:

- Randomized set: All patients randomized into the study.
- Safety set: All randomized patients who received at least one dose of study medication.
- Treated with CZP set: All patients who received at least one dose of CZP study medication and combined the initial treatment period and the maintenance treatment period for reporting of safety. In CIMPASI-1 and CIMPASI-2, a second group — the treated with blinded CZP group — was similar, except it excluded any patients randomized to placebo who received escape therapy with CZP after week 16.
- Maintenance set: All patients who completed the week 16 visit and had at least one efficacy assessment in the maintenance treatment period.
- Maintenance safety set: All randomized patients who received at least one dose of study medication during the maintenance treatment period.
- Per-protocol set: All randomized patients who had been in the study up to week 12 (CIMPACT) or week 16 (CIMPASI-1 and CIMPASI-2) without any important protocol deviations that could have influenced the validity of the data.

In the CIMPACT study, another analysis population was defined as follows:

- Week 16 randomized set: All patients who achieved a PASI 75 response at week 16 and were re-randomized into the double-blind, placebo-controlled maintenance treatment period.

All efficacy analyses were performed using the randomized set in CIMPASI-1 and CIMPASI-2. In the CIMPACT study, efficacy analyzes were based on the randomized set, the week 16 randomized set, and the maintenance set. The per-protocol set was used for a sensitivity analysis of the primary end points only. Safety summaries were performed using the safety set, treated with CZP set, treated with blinded CZP set, or maintenance safety set.

Patient Disposition

Of the patients screened for inclusion in the CIMPASI-1, CIMPASI-2, and CIMPACT studies, 18%, 25%, and 24% of patients, respectively, were not randomized. The most common reason for screening failure was ineligibility. Overall, 234, 227, and 559 patients were randomized to the CIMPASI-1, CIMPASI-2, and CIMPACT studies, and 4% to 7% of patients discontinued from the initial treatment phase (first 16 weeks) (Table 8). The frequency of discontinuation was generally similar between treatment groups within trials, with 4% to 10% in the placebo group, 1% to 8% in the CZP groups, and 7% in the etanercept group stopping early.

Overall, 159 (68%) and 159 (70%) patients entered the blinded maintenance phase, and 64 (27%) and 54 (24%) entered the escape maintenance phase in CIMPASI-1 and CIMPASI-2, respectively (Table 9 and Table 10). Discontinuations were generally higher among those receiving escape therapy (13% to 63%) than among those who remained on blinded treatment (0% to 40%). The percentage of patients within the blinded CZP treatment groups who discontinued ranged from 4% to 16% compared with 0% to 40% among those who had previously received placebo.

In the CIMPACT study, 310 (55%) patients entered the blinded maintenance phase and 223 (40%) entered the escape maintenance phase (Table 11). Among the blinded maintenance groups, 0% to 9% discontinued and, in the escape maintenance groups, 13% to 27% discontinued prior to week 48. The reasons for discontinuation were similar between groups.

Table 8: Patient Disposition for Initial Treatment Period

	CIMPASI-1			CIMPASI-2			CIMPACT			
	PBO	CZP 200	CZP 400	PBO	CZP 200	CZP 400	PBO	ETN	CZP 200	CZP 400
Screened, N	286			301			731			
Initial Treatment Period (Weeks 0 to 16)										
Randomized – overall, N	234			227			559			
Randomized – per group, N	51	95	88	49	91	87	57	170	165	167
Completed – per group, n (%)	46 (90.2)	92 (96.8)	87 (98.9)	45 (91.8)	84 (92.3)	83 (95.4)	55 (96.5)	159 (93.5)	159 (96.4)	162 (97.0)
Discontinued – per group, n (%)	5 (9.8)	3 (3.2)	1 (1.1)	4 (8.2)	7 (7.7)	4 (4.6)	2 (3.5)	11 (6.5)	6 (3.6)	5 (3.0)
Reason for Discontinuation: Initial Treatment Period (Weeks 0 to 16)										
Adverse event	0	0	1 (1.1)	0	3 (3.3)	1 (1.1)	0	4 (2.4)	1 (0.6)	1 (0.6)
Lack of efficacy	1 (2.0)	0	0	NA	NA	NA	0	1 (0.6)	0	0
Lost to follow-up	1 (2.0)	1 (1.1)	0	1 (2.0)	2 (2.2)	0	1 (1.8)	2 (1.2)	1 (0.6)	2 (1.2)
Consent withdrawn	3 (5.9)	2 (2.1)	0	3 (6.1)	2 (2.2)	1 (1.1)	1 (1.8)	2 (1.2)	3 (1.8)	1 (0.6)
Other	NA	NA	NA	0	0	2 (2.3)	0	1 (0.6)	1 (0.6)	1 (0.6)

CSR = Clinical Study Report; CZP 200 = certolizumab pegol 200 mg q.2.w.; CZP 400 = certolizumab pegol 400 mg q.2.w.; ETN = etanercept; q.2.w. = every two weeks.
Source: CIMPASI-1 CSR,[13] CIMPASI-2 CSR,[14] CIMPACT.[16]

Table 9: CIMPASI-1 Disposition and Discontinuation Reasons by Maintenance Treatment Group – Maintenance Treatment Period

Disposition	Blinded Maintenance Group				Escape Maintenance Group			All Patients N = 223 n (%)
	PBO/ PBO N = 3 n (%)	PBO / CZP 200 N = 5 n (%)	CZP 200 / CZP 200 N = 74 n (%)	CZP 400 / CZP 400 N = 77 n (%)	PBO / Esc CZP 400 N = 38 n (%)	CZP 200 / Esc CZP 400 N = 18 n (%)	CZP 400 Esc CZP 400 N = 8 n (%)	
Started maintenance treatment period (weeks 16 to 48)	3 (100)	5 (100)	74 (100)	77 (100)	38 (100)	18 (100)	8 (100)	223 (100)
Completed week 48	3 (100)	5 (100)	71 (95.9)	70 (90.9)	33 (86.8)	13 (72.2)	7 (87.5)	202 (90.6)
Discontinued prior to week 48	0	0	3 (4.1)	7 (9.1)	5 (13.2)	5 (27.8)	1 (12.5)	21 (9.4)
Primary Reason for Discontinuation								
Adverse event	0	0	0	0	1 (2.6)	0	0	1 (0.4)
Lost to follow-up	0	0	0	1 (1.3)	2 (5.3)	0	0	3 (1.3)
Consent withdrawn	0	0	1 (1.4)	3 (3.9)	1 (2.6)	1 (5.6)	1 (12.5)	7 (3.1)
Other	0	0	1 (1.4)	1 (1.3)	1 (2.6)	0	0	3 (1.3)
Other: Mandatory withdrawal due to not achieving a PASI 50 response	0	0	1 (1.4)	2 (2.6)	0	4 (22.2)	0	7 (3.1)

CZP 200 = certolizumab pegol 200 mg q.2.w.; CZP 400 = certolizumab pegol 400 mg q.2.w.; esc = escape; q.2.w. = every two weeks.

Source: CIMPASI-1 Clinical Study Report.[13]

Table 10: CIMPASI-2 Disposition and Discontinuation Reasons by Maintenance Treatment Group – Maintenance Treatment Period

Disposition	Blinded Maintenance Group				Escape Maintenance Group			All Patients N = 210 n (%)
	PBO / PBO N = 6 n (%)	PBO / CZP 200 N = 5 n (%)	CZP 200 / CZP 200 N = 76 n (%)	CZP 400 / CZP 400 N = 69 n (%)	PBO / Esc CZP 400 N = 34 n (%)	CZP 200 / Esc CZP 400 N = 8 n (%)	CZP 400 / Esc CZP 400 N = 12 n (%)	
Started maintenance treatment period (weeks 16 to 48)	6 (100)	5 (100)	76 (100)	69 (100)	34 (100)	8 (100)	12 (100)	210 (100)
Completed week 48	5 (83.3)	3 (60.0)	64 (84.2)	61 (88.4)	27 (79.4)	3 (37.5)	10 (83.3)	173 (82.4)
Discontinued prior to Week 48	1 (16.7)	2 (40.0)	12 (15.8)	8 (11.6)	7 (20.6)	5 (62.5)	2 (16.7)	37 (17.6)
Primary Reason for Discontinuation								
Adverse event	0	2 (40.0)	3 (3.9)	4 (5.8)	2 (5.9)	1 (12.5)	0	12 (5.7)
Lack of efficacy	0	0	2 (2.6)	1 (1.4)	0	1 (12.5)	1 (8.3)	5 (2.4)

Disposition	Blinded Maintenance Group				Escape Maintenance Group			All Patients N = 210 n (%)
	PBO / PBO N = 6 n (%)	PBO / CZP 200 N = 5 n (%)	CZP 200 / CZP 200 N = 76 n (%)	CZP 400 / CZP 400 N = 69 n (%)	PBO / Esc CZP 400 N = 34 n (%)	CZP 200 / Esc CZP 400 N = 8 n (%)	CZP 400 / Esc CZP 400 N = 12 n (%)	
Lost to follow-up	0	0	2 (2.6)	0	2 (5.9)	0	0	4 (1.9)
Consent withdrawn	1 (16.7)	0	3 (3.9)	1 (1.4)	1 (2.9)	0	1 (8.3)	7 (3.3)
Other	0	0	0	1 (1.4)	1 (2.9)	1 (12.5)	0	3 (1.4)
Other: Mandatory withdrawal due to not achieving a PASI 50 response	0	0	2 (2.6)	1 (1.4)	1 (2.9)	2 (25.0)	0	6 (2.9)

CZP 200 = certolizumab pegol 200 mg q.2.w.; CZP 400 = certolizumab pegol 400 mg q.2.w.; esc = escape; PASI 50 = at least a 50% reduction from baseline in Psoriasis Area and Severity Index; q.2.w. = every two weeks.

Source: CIMPASI-2 Clinical Study Report.[14]

Table 11: CIMPACT Disposition and Discontinuation Reasons by Maintenance Treatment Group – Maintenance Treatment Period

	Blinded Groups (N = 310)									Escape Groups (N = 223)				
Initial Treatment	**PBO**	**ETN**		**CZP 200 mg q.2.w.**			**CZP 400 mg q.2.w.**			**PBO**	**ETN**	**CZP 200 mg q.2.w.**	**CZP 400 mg q.2.w.**	**All Patients**
Maintenance Treatment	**PBO**	**PBO**	**CZP 200 mg q.2.w.**	**PBO**	**CZP 200 mg q.2.w.**	**CZP 400 mg q.4.w.**	**PBO**	**CZP 200 mg q.2.w.**	**CZP 400 mg q.2.w.**	**Esc CZP 400 mg q.2.w.**				
Disposition	**N = 2**	**N = 24**	**N = 50**	**N = 22**	**N = 44**	**N = 44**	**N = 25**	**N = 50**	**N = 49**	**N = 53**	**N = 85**	**N = 49**	**N = 36**	**N = 533**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Started maintenance treatment	2 (100)	24 (100)	50 (100)	22 (100)	44 (100)	44 (100)	25 (100)	50 (100)	49 (100)	53 (100)	85 (100)	49 (100)	36 (100)	533 (100)
Period (weeks 16 to 48)														
Completed maintenance treatment period	2	23	48	20	40	43	23	47	49	46	71	36	30	478 (89.7)
	(100)	(95.8)	(96.0)	(90.9)	(90.9)	(97.7)	(92.0)	(94.0)	(100)	(86.8)	(83.5)	(73.5)	(83.3)	
Completed without relapse[a] (does not apply to escapers)	2 (100)	7 (29.2)	44 (88.0)	12 (54.5)	36 (81.8)	41 (93.2)	13 (52.0)	42 (84.0)	48 (98.0)	NA	NA	NA	NA	245 (46.0)
Completed with relapse[a] (does not apply to escapers)	0	16 (66.7)	4 (8.0)	8 (36.4)	4 (9.1)	2 (4.5)	10 (40.0)	5 (10.0)	1 (2.0)	NA	NA	NA	NA	50 (9.4)
Discontinued prior to week 48	0	1 (4.2)	2 (4.0)	2 (9.1)	4 (9.1)	1 (2.3)	2 (8.0)	3 (6.0)	0	7 (13.2)	14 (16.5)	13 (26.5)	6 (16.7)	55 (10.3)
Primary Reason for Discontinuation														
Adverse event	0	0	0	1 (4.5)	2 (4.5)	0	0	0	0	1 (1.9)	4 (4.7)	1 (2.0)	2 (5.6)	11 (2.1)
Lack of efficacy	0	0	0	0	0	0	0	0	0	0	0	3 (6.1)	0	3 (0.6)
Lost to follow-up	0	0	0	0	0	0	0	0	0	0	1 (1.2)	0	0	1 (0.2)

	Blinded Groups (N = 310)									Escape Groups (N = 223)				
Initial Treatment	**PBO**	**ETN**		**CZP 200 mg q.2.w.**			**CZP 400 mg q.2.w.**			**PBO**	**ETN**	**CZP 200 mg q.2.w.**	**CZP 400 mg q.2.w.**	**All Patients**
Maintenance Treatment	**PBO**	**PBO**	**CZP 200 mg q.2.w.**	**PBO**	**CZP 200 mg q.2.w.**	**CZP 400 mg q.4.w.**	**PBO**	**CZP 200 mg q.2.w.**	**CZP 400 mg q.2.w.**	**Esc CZP 400 mg q.2.w.**				
Disposition	**N = 2**	**N = 24**	**N = 50**	**N = 22**	**N = 44**	**N = 44**	**N = 25**	**N = 50**	**N = 49**	**N = 53**	**N = 85**	**N = 49**	**N = 36**	**N = 533**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Consent withdrawn	0	1 (4.2)	1 (2.0)	1 (4.5)	1 (2.3)	0	1 (4.0)	2 (4.0)	0	2 (3.8)	4 (4.7)	1 (2.0)	0	14 (2.6)
Other	0	0	1 (2.0)	0	1 (2.3)	1 (2.3)	1 (4.0)	1 (2.0)	0	1 (1.9)	2 (2.4)	0	0	8 (1.5)
Other: Mandatorily withdrawn due to not achieving PASI 50 response (applies only to escapers)	NA	NA	NA	NA	NA	N A	NA	NA	NA	3 (5.7)	3 (3.5)	8 (16.3)	4 (11.1)	18 (3.4)

CZP = certolizumab pegol; esc = escaped to; ETN = etanercept; MS = maintenance set; NA = not applicable; PASI 50 = at least a 50% reduction from baseline in the Psoriasis Area and Severity Index; PBO = placebo; q.2.w. = every 2 weeks; q.4.w. = every four weeks.

[a] Relapse was defined as not achieving a PASI 50 response at some time point during the maintenance treatment period. Patients in a blinded group who relapsed completed the maintenance treatment period per-protocol by being withdrawn from that period and entered into the open-label extension upon relapse. If a patient in an escape group did not achieve a PASI 50 response at week 32, the patient was withdrawn from the study. A patient in an escape arm who achieved a PASI 50 response at week 32 but did not achieve a PASI 50 response at a later visit was withdrawn from the study at that time.

Source: CIMPACT Clinical Study Report.[16]

Exposure to Study Treatments

During the 16-week initial treatment period, the duration of exposure was similar across treatment groups within each trial as well as across trials. With the exception of patients in the etanercept arm in CIMPACT, the mean duration of exposure ranged between 106 and 112 days.

Exposure to study treatment was comparable between groups throughout the 32-week maintenance period. With the exception of the placebo arm in CIMPACT, the mean duration of exposure ranged between 197 and 224 days.

Table 12: Extent of Exposure to Study Treatment

	CIMPASI-1			CIMPASI-2			CIMPACT			
	PBO/PBO	CZP 200 mg q.2.w/CZP 200 mg q.2.w	CZP 400 mg q.2.w/CZP 400 mg q.2.w	PBO/PBO	CZP 200 mg q.2.W/CZP 200 mg q.2.w	CZP 400 mq q.2.w/CZP 400 mg q.2.w	PBO/PBO	ETN / CZP 200 mg q.2.w	CZP 200 mg q.2.w / CZP 400 mg q.2.w	CZP 400 mg q.2.w/ CZP 400 mg q.4.w.
Weeks 0 to 16										
Duration of exposure (days), n	[redacted]									
Mean (SD)	[redacted]									
Weeks 16 to 48										
Duration of exposure (days), n	[redacted]									
Mean (SD)	[redacted]									

CSR = Clinical Study Report; CZP = certolizumab pegol; ETN = etanercept; q2/4w. = every two/four weeks; SD = standard deviation.

Source: CIMPASI-1 CSR,[13] CIMPASI-2 CSR,[14] CIMPACT.[16]

Critical Appraisal

Internal Validity

Study Design, Intervention, and Comparator

All three trials used an appropriate centralized method for randomization (i.e., IVRS) independent of the study team. The centralized IVRS method of randomization helped conceal treatment allocation in all trials. However, several factors had the potential to compromise the study blinding. Study treatments were administered at the investigational sites by unblinded, dedicated study medication administration personnel. Although it was reported that the unblinded personnel were not involved in the study in any way other than treatment administration, it was not clear if these personnel could affect blinding integrity

through interactions with study participants and investigators. Furthermore, blinding of study medication could be disclosed through a difference in colour between CZP and placebo. It was reported the CZP solution could have a slightly yellow colour, while the placebo was a colourless solution. The sponsor indicated that special precautions were taken to ensure blinding, but no further clarification was provided. In CIMPACT, treatment with etanercept was not blinded; therefore, only the CZP doses and placebo were administered in a blinded manner.

There were notable imbalances across treatment arms within trials for a number of baseline variables. These include the sex ratio across treatment arms in CIMPASI-2 and CIMPACT, body weight in CIMPASI-2, the proportion of patients with psoriatic arthritis in all trials, baseline sPGA score distribution in CIMPASI-1, DLQI score distribution in CIMPASI-1 and -2, and use of prior biologics in CIMPACT. Prior failure of biologics was identified as a key prognostic factor for success with biologic treatment; however, this information was not available in any trial.

The original randomization scheme generated in the initial treatment period may have been compromised during the subsequent maintenance period. Patients were assigned to treatments during the maintenance period based on their clinical response at week 16, thereby breaking the original randomization. This resulted in an imbalanced number of patients in each arm; it is possible that the baseline characteristics that were randomized to be distributed evenly across treatment arms were imbalanced too, which would bias the results. In addition, the treatment schema during the maintenance period were very complex, and patients had the option to alternate between different dosages of CZP. This creates a challenge in identifying the patients who received one dose of the study drug exclusively through the full 48-week blinded duration of the trials. There were no statistical comparisons conducted between any of the treatment groups for any outcomes during the maintenance phase. Finally, there were fewer patients in each treatment arm during the maintenance phase after conducting a second round of randomization (CIMPACT) or reassigning doses to patients (CIMPASI-1 and -2). It is unclear if, and to what extent, the smaller sample size in each comparator arm within the trials affected the statistical power. Together, these factors limit the interpretability of the results beyond the initial treatment period.

Disposition of Patients

Overall, the proportion of patients who discontinued the study prior to the end of the initial treatment period was generally low in all three trials (< 10%) and relatively balanced between treatment groups, with a notable imbalance in study discontinuation seen in the placebo arm of CIMPASI-1 (9.8%) compared with the CZP groups (1.1% to 3.2%).

During the maintenance period, a greater proportion of patients receiving blinded CZP (both doses) discontinued from the respective trials (range: 4% to 10% in CIMPASI-1, 11% to 16% in CIMPASI-2, and 2% to 9% in CIMPACT) compared with the initial treatment period. Additionally, the proportion of dropouts among patients receiving escape therapy was also high (range 12% to 28% in CIMPASI-1, 16% to 63% in CIMPASI-2, and 13% to 27% in CIMPACT). The relatively high dropout rates, in combination with the re-randomization and reassignment of treatments in the maintenance period described previously, speaks to the possibility of imbalances in measured and unmeasured covariates across treatment groups and the resulting challenges in the interpretability of results after week 16.

Statistical Analyses

A sequential testing procedure was applied to adjust for multiple testing. All analyses for primary and secondary outcomes were conducted using data from the randomized set (intention-to-treat population), and the results were consistent with those from the per-protocol population. Additionally, a number of sensitivity analyses were performed to assess the effect of imputing missing data for all efficacy variables.

Each of the included studies had sufficient power to demonstrate statistical significance for testing of the primary and secondary outcomes. Other than the primary and secondary efficacy outcomes included in the sequential testing procedure, none of the other symptoms-related outcomes at either time point were controlled for multiple comparisons. With the exception of DLQI in CIMPASI-1 and -2, none of the HRQoL outcomes at either phase of any trial were adjusted for multiplicity. Additionally, none of the outcomes were compared statistically between any treatment groups during the maintenance phase. A number of sensitivity analyses were performed to assess the effect of imputing missing data for all efficacy variables, including a combination of MCMC, LOCF, and nonresponder imputation.

Outcomes

The outcome measures and definitions used in all three trials, including the sPGA and PASI Psoriasis Symptom Inventory response, have evidence of validity in psoriasis and are considered appropriate to evaluate treatment response in psoriasis clinical trials. Patient-reported outcome measures (i.e., DLQI, EQ-5D-3L, and SF-36) are also frequently used to capture the different aspects of patients' lives that are affected and are considered valid and reliable. A report by the National Institute for Health and Care Excellence (NICE) indicated that PASI may underestimate disease severity in people with darker skin, as redness may be less evident.[49] However, the majority of the patients in the three included trials were white; therefore, this was likely not an issue in the three trials.

External Validity

Patient Selection

Inclusion and exclusion criteria in all three trials appeared relevant and reasonable given that, according to the clinical expert consulted for this review, baseline characteristics were consistent with those of real-life patients seen in clinical practice. Notably, various groups of patients with comorbid conditions were excluded, including those with current or a history of malignant diseases, current or a history of serious infections, active or latent tuberculosis, HIV, hepatitis B, hepatitis C, and any other clinically significant disease. Therefore, the findings from these trials are not generalizable to these patients. Patients with forms of psoriasis other than plaque psoriasis (e.g. pustular, erythrodermic, guttate) were excluded from the trials; however, CZP is not indicated for those types of psoriasis, according to the product monograph.

In all three trials, following the initial treatment period, the treatment groups in the maintenance period included a selective, enriched population that responded to treatment before week 12 or 16. An FDA guidance document for industry on the approval of biologic products discussed the effect of enrichment in clinical trials.[50] Based on this guidance, the selection of responders to CZP during the induction phase for the subsequent re-randomization or treatment assignment in the maintenance phase is a form of predictive enrichment strategy. With this approach, the patients chosen for trials are more likely than the unselected general population to respond to the treatment. This leads to an increased likelihood of detecting a treatment difference with a relatively small sample size, and an

enhanced risk–benefit relationship wherein the treatment effects of a drug are magnified (in both absolute and relative terms) among responders, while exposure and potential toxicity are avoided, compared with nonresponders.

Treatment Administration, and Length of Follow-Up

Patients in all three trials received their treatment from in-office study personnel up to week 48, which may not reflect real-world use. Therefore, the results during the initial treatment period and maintenance period might not be generalizable to patient self-administration, as compliance with treatment may vary with self-administration. During the open-label period after week 48, patients were able to self-administer treatment (or do so with the help of a trained caregiver). Thus, it is unclear if the results obtained in the first 48 weeks of the study, during which treatments were administered by qualified staff members in an in-office setting, reflect the results that would be obtained with self-administration.

The total duration of the studies is more than 150 weeks; however, only data up to week 48 were available in the manufacturer submitted interim clinical report. As many recent biologics currently in the market were assessed using more than 150 to 200 weeks of data, a final clinical report by the manufacturer would be beneficial in evaluating the long-term efficacy and safety of CZP.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported (Table 4). These include results up to week 16 (initial treatment phase) for all three trials. Due to a number of design and statistical issues described previously, there is little comparative efficacy data beyond week 16 that are relevant to the current review. Additionally, due to reassigning (CIMPASI-1 and -2) or re-randomizing (CIMPACT) treatment during the maintenance period, the number of patients exclusively receiving one dose of CZP was smaller than the initial treatment period. Results through week 48 are provided in Appendix 4; however, their interpretation is limited.

Health-Related Quality-of-Life Outcomes

Dermatology Life Quality Index

DLQI total score was the common HRQoL outcome measured in all three trials and part of the statistical testing hierarchy in CIMPASI-1 and -2. Baseline scores ranged from approximately 13 to 15 across trial arms (Table 6).

Initial Treatment Period

Compared with placebo, the adjusted mean differences in DLQI score in the CZP 200 mg and 400 mg groups were −6.00 (95% CI, −8.18 to −3.81) and −6.84 (95% CI, −9.05 to −4.62), respectively, in CIMPASI-1; −6.62 (95% CI, −8.88 to −4.36) and −6.19 (95% CI, −8.46 to −3.93), respectively, in CIMPASI-2, and −7.27 (95% CI, −9.03 to −5.50) and −8.46 (95% CI, −10.22 to −6.7), respectively, in CIMPACT ($P < 0.0001$ for both comparisons). DLQI was not assessed for etanercept at any time point post-baseline. Therefore, no statistical comparison was performed between CZP and etanercept or between etanercept and placebo (Table 13).

In all three trials, the proportion of patients achieving a DLQI score ≥ 4 points from baseline as well as an absolute score of ≤ 1 was higher in both CZP doses compared with placebo.

Additionally, the percentage of patients who achieved these outcomes were numerically higher in the CZP 400 mg every two weeks group compared with the CZP 200 mg every two weeks group.

Maintenance Treatment Period

During the maintenance period, the mean change in DLQI score from baseline ranged between 7.5 to 14.5 across trials. In CIMPASI-1 and -2, approximately 60% to 70% of patients in the CZP arms achieved a change in DLQI score of ≥ 4 points from baseline. The proportion of CZP-treated patients achieving a DLQI absolute score of ≤ 1 ranged between 38% and 52% in CIMPASI-1 and -2. Notably, a numerically large proportion of patients in the CZP 400 mg arm in CIMPACT achieved a change in DLQI score of ≥ 4 points from baseline compared with CZP 200 mg (95.9% versus 65.9%) and an absolute score of ≤ 1 (77.6% versus 54.5%).

Hospital Anxiety and Depression

HADS-A and HADS-D scores were reported in CIMPASI-1 and -2; however, these outcomes were not part of the statistical testing hierarchy. At baseline, the mean HADS-A and HADS-D scores in the CZP 200 mg and 400 mg groups were similar to each other and to the placebo group in CIMPASI-1. However, patients in the CZP arms had slightly lower baseline HADS-A and HADS-D scores compared with placebo, indicating that patients in the placebo group had higher anxiety and depression (Table 6).

Initial Treatment Period

During the initial treatment period, there were numerically larger adjusted mean decreases from baseline observed in both the HADS-A and HADS-D scores at week 16 for both the CZP dose groups compared with placebo. Compared with placebo, the adjusted mean differences in HADS-A score in the CZP 200 mg and 400 mg groups were −1.00 (95% CI, −2.03 to 0.02) and −0.98 (95% CI, −2.02 to 0.06), respectively, in CIMPASI-1; and −0.55 (95% CI, −1.59 to 0.49) and −0.81 (95% CI, −1.85 to 0.24), respectively, in CIMPASI-2. Compared with placebo, the adjusted mean differences in HADS-D score in the CZP 200 mg and 400 mg groups were −1.86 (95% CI, −2.92 to −0.81) and −1.68 (95% CI, −2.75 to −0.61), respectively, in CIMPASI-1; and −1.46 (95% CI, −2.46 to −0.47) and −0.86 (95% CI, −1.86 to 0.14), respectively, in CIMPASI-2 (Table 13).

The proportion of patients achieving a HADS-A and HADS-D score of < 8 was presented in both trials; however, these data will not be reported here, since HADS was neither a primary nor secondary end point.

Maintenance Treatment Period

Results during the maintenance period are not presented here since the mean changes from baseline in HADS-A and HADS-D scores were presented by maintenance treatment group, not by their initially randomized group.

Short Form (36) Health Survey, Version 2

The PCS and MCS for the SF-36 version 2 were reported in the CIMPASI-1 and CIMPASI-2 trials. At baseline, the PCS and MCS scores in both trials were similar between both CZP doses and placebo (Table 6).

Initial Treatment Period

At week 16, there were numerically greater mean decreases from baseline observed in both the PCS and MCS scores for both the CZP 200 mg every two weeks and CZP 400 mg every two weeks groups compared with placebo. Compared with placebo, the adjusted mean differences in PCS score ranged between 2.2 and 3.05 in the CZP-treated patients in both studies. Compared with placebo, the adjusted mean differences in MCS score ranged between 3.16 and 5.17 in the CZP-treated patients in both studies (Table 13).

The proportions of patients achieving at least a 2.5-point change in both PCS and MCS scores were presented in both trials; however, these data will not be reported here, since SF-36 was neither a primary nor a secondary end point (Table 13).

Maintenance Treatment Period

Results during the maintenance period are not presented here since the mean changes from baseline in SF-36 component scores were presented by maintenance treatment group, not by their initially randomized group.

EuroQol 5-Dimensions 3-Levels Questionnaire

Results for the EQ-5D-3L and EQ VAS both were measured in the three trials. At baseline, approximately 90% of patients in all treatment groups across trials reported no problems for the EQ-5D-3L dimension score of self-care (Table 6).

Initial Treatment Period

Overall, there were small improvements in all domains of EQ-5D-3L from baseline in the treatment groups. It was reported that a numerically greater proportion of patients in the two CZP groups reported no problem in each of the five domains across trials, with the greatest improvement observed for the pain/discomfort dimension (data not presented). Similarly, results for EQ VAS showed numerically greater increases at week 16 in both CZP-treated groups compared with placebo.

Maintenance Treatment Period

Results during the maintenance period are not presented here since the mean changes from baseline in EQ-5D-3L component scores were presented by maintenance treatment group, not by their initially randomized group.

Table 13: Health-Related Quality of Life Outcomes for Initial Treatment Period (Randomized Set)

	CIMPASI-1			CIMPASI-2			CIMPACT			
	PBO	CZP 200	CZP 400	PBO	CZP 200	CZP 400	PBO	ETN	CZP 200	CZP 400
N	51	95	88	49	90	87	57	170	165	167
DLQI										
N included in analysis	48	93	86	49	90	87	[redacted]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	13.9 (8.3)	13.3 (7.4)	13.1 (6.5)	12.9 (7.3)	15.2 (7.2)	14.2 (7.2)	13.2 (7.6)	14.1 (7.4)	12.8 (7.0)	15.3 (7.3)
Mean change from baseline, mean (SD)	−3.3 (6.9)	−8.9 (8.5)	−9.6 (6.5)	−2.9 (6.6)	−11.1 (7.8)	−10.0 (7.6)	[redacted]	[redacted]	[redacted]	[redacted]

	CIMPASI-1			CIMPASI-2			CIMPACT			
	PBO	CZP 200	CZP 400	PBO	CZP 200	CZP 400	PBO	ETN	CZP 200	CZP 400
Change from baseline to week 16, LS mean (SE)	−3.3 (0.80)	−9.3 (0.58)	−10.2 (0.60)	−3.8 (0.84)	−10.4 (0.62)	−10.0 (0.64)				
Adjusted mean treatment difference vs. PBO (97.5% CI)[a]		−6.00 (−8.18 to −3.81)	−6.84 (−9.05 to −4.62)		−6.62 (−8.88 to −4.36)	−6.19 (−8.46 to −3.93)		NR	−7.27 (−9.03 to −5.50)[b]	−8.46 (−10.22 to −6.7)[b]
P value		< 0.0001	< 0.0001		< 0.0001	< 0.0001		NR	< 0.0001[c]	< 0.0001[c]
Achieved DLQI ≥ 4-point change from baseline; n (%)	21 (41.2)	63 (66.3)	69 (78.4)	20 (40.8)	68 (74.7)	66 (75.9)				
Achieved DLQI absolute score of ≤ 1; n (%)	3 (5.9)	45 (47.4)	40 (45.5)	4 (8.2)	42 (46.2)	44 (50.6)				
HADS-A										
N included in analysis										
Baseline, mean (SD)										
Change from baseline to week 16, LS mean (SE)										
Adjusted mean treatment difference vs. PBO (95% CI)[a]										
P value										
HADS-D										
N included in analysis										
Baseline, mean (SD)										
Change from baseline to week 16, LS mean (SE)										
Adjusted mean treatment difference vs. PBO (95% CI)[a]										
P value										
SF-36 Physical Component Score										
N included in analysis										

	CIMPASI-1			CIMPASI-2			CIMPACT			
	PBO	CZP 200	CZP 400	PBO	CZP 200	CZP 400	PBO	ETN	CZP 200	CZP 400
Baseline (mean [SD])	[redacted]									
Change from baseline to week 16, LS mean (SE)	[redacted]									
Adjusted mean treatment difference vs. PBO (95% CI)[a]		[redacted]								
P value		[redacted]								
Achieved ≥ 2.5-point change from baseline; n (%)	[redacted]									
SF-36 Mental Component Score										
N included in analysis	[redacted]									
Baseline mean (SD)	[redacted]									
Change from baseline to week 16, LS mean (SE)	[redacted]									
Adjusted mean treatment difference vs. PBO (95% CI)[a]		[redacted]								
P value		[redacted]								
Achieved ≥ 2.5-point change from baseline; n (%)	[redacted]									

ANCOVA = analysis of covariance; CI = confidence interval; CSR = Clinical Study Report; CZP = certolizumab pegol; DLQI = Dermatology Life Quality Index; ETN = etanercept; HADS-A = Hospital Anxiety and Depression Scale for anxiety; HADS-D = Hospital Anxiety and Depression Scale for depression; HRQoL = health-related quality of life; LOCF = last observation carried forward; LS = least squares; PBO = placebo; SF-36 = Short Form (36) Health Survey; SD = standard deviation; SE = standard error; vs. = versus.

[a] ANCOVA model of change from baseline HRQoL score, with treatment group, region, and prior biologic exposure (yes/no) as factors and baseline HRQoL score as a covariate (LOCF) for the randomized set.

[b] Ninety-five per cent CI.

[c] Outside the statistical testing hierarchy.

Source: CIMPASI-1 CSR,[13] CIMPASI-2 CSR,[14] CIMPACT.[16]

Symptom-Related Outcomes

Psoriasis Area and Severity Index

Initial Treatment Period

Results for Efficacy End Points Based on Psoriasis Area and Severity Index 75

PASI 75 at week 16 was one of the co-primary efficacy outcomes in CIMPASI-1 and -2,

whereas PASI 75 at week 12 and week 16 was the primary outcome and one of the secondary outcomes, respectively, in CIMPACT. Overall, a statistically significant difference in PASI 75 responder rate was observed for CZP-treated patients compared with placebo-treated patients at week 16 (CIMPASI-1 and CIMPASI-2) or week 12 (CIMPACT). Additionally, the PASI 75 responder rate was greater with both CZP dosing regimens versus the active comparator, etanercept, in CIMPACT.

In CIMPASI-1, 66.5% and 75.8% of patients in the CZP 200 mg and 400 mg groups achieved PASI 75 at week 16, respectively, compared with 6.5% of patients in the placebo group, corresponding to a 60.0% and 69.3% difference in response rate versus placebo, respectively (Table 14). The odds ratios for achieving a PASI 75 response versus placebo were 28.962 (97.5% CI, 6.968 to 120.371) for the CZP 200 mg group and 45.660 (97.5% CI, 10.657 to 195.634) for the CZP 400 mg group ($P < 0.0001$ for both comparisons).

In CIMPASI-2, 81.4% and 82.6% of patients in the CZP 200 mg and 400 mg groups achieved PASI 75 at week 16, respectively, compared with 11.6% of patients in the placebo group, corresponding to a 69.7% and 71.0% difference in response rate versus placebo, respectively (Table 14). The odds ratios for achieving a PASI 75 response versus placebo were 33.405 (97.5% CI, 9.965 to 111.983) for the CZP 200 mg every two weeks group and 36.212 (97.5% CI, 10.686 to 122.713) for the CZP 400 mg every two weeks group ($P < 0.0001$ for both comparisons).

In CIMPACT, 61.3% and 66.7% of patients in the CZP 200 mg and 400 mg groups achieved PASI 75 at week 12, respectively, compared with 5.0% of patients in the placebo group, corresponding to a 56.2% and 61.6% difference in response rate versus placebo, respectively (Table 15). The odds ratios for achieving a PASI 75 response versus placebo were 30.023 (95% CI, 8.971 to 100.481) for the CZP 200 mg every two weeks group and 37.988 (95% CI, 11.312 to 127.576) for the CZP 400 mg every two weeks group ($P < 0.0001$ for both comparisons). PASI 75 response rates were higher for both CZP doses (66.7% and 61.3% in the 400 mg and 200 mg groups, respectively) compared with etanercept (53.3%). CZP 400 mg was found to be superior to etanercept (odds ratio 1.756, 95% CI, 1.114 to 2.768, $P = 0.0152$) and CZP 200 mg was found to be noninferior to etanercept (odds ratio 1.388, 95% CI, 0.886 to 2.175, $P = 0.1523$). Since the P value for the CZP 400 mg superiority evaluation was below 0.05 and the lower bound of the 95% CI for the CZP 200 mg noninferiority evaluation did not go beyond the 10% margin (95% CI, −2.9, 18.9), both tests were significant based on a two-sided significance level of 0.05. Per the statistical testing hierarchy, the final step of the procedure was done, which was the CZP 200 mg every two weeks superiority evaluation versus etanercept; however, the P value for this comparison was greater than the two-sided 0.05 significance level, indicating that superiority of CZP 200 mg every two weeks to etanercept was not achieved.

At week 16, the PASI 75 responder rates improved in both CZP-treated groups (Table 14). Compared with placebo, the differences in PASI 75 responder rates were 64.4% and 70.9% for the CZP 200 mg and 400 mg group, respectively; which corresponded to an odds ratio of 55.413 (95% CI, 13.135 to 233.782) and 76.277 (95% CI, 17.952 to 324.094), respectively ($P < 0.0001$ for both comparisons).

The results of the primary analysis using the MCMC method for multiple imputation were supported by similar findings from sensitivity analyses using nonresponder imputation and model-based multiple imputation (data not presented).

Subgroups of Interest

Efficacy results based on previous biologic failure were not reported. Only PASI 75 responder rates were reported based on previous systemic treatment experience. In all three trials, CZP groups had numerically greater responder rates compared with placebo; however, no statistical testing was reported (Table 20).

Maintenance Treatment Period

Overall, PASI 75 responder rates were maintained or continued to increase through week 48 across trials. No statistical comparisons were made between the CZP groups to assess comparative response rate, and a negligible number of patients received placebo during the maintenance period to allow for meaningful comparisons to be made (Table 23).

Results for Efficacy End Points Based on Psoriasis Area and Severity Index 90

PASI 90 at week 16 and 12 was a secondary efficacy outcome in CIMPASI-1 and -2, and CIMPACT, respectively. Overall, a statistically significant difference in PASI 90 responder rate was observed for CZP-treated patients compared with placebo-treated patients at week 16 (CIMPASI-1 and -2) or week 12 (CIMPACT).

In CIMPASI-1, 35.8% and 43.6% of patients in the CZP 200 mg and 400 mg groups achieved PASI 90 at week 16, respectively, compared with 0.4% of patients in the placebo group, corresponding to a 35.4% and 43.1% difference in response rate versus placebo, respectively. The odds ratios for being a PASI 90 responder versus placebo were 36.668 (97.5% CI, 5.717 to 235.195) for the CZP 200 mg group and 50.606 (97.5% CI, 7.880 to 324.988) for the CZP 400 mg group ($P < 0.0001$ for both comparisons).

In CIMPASI-2, 52.6% and 55.4% of patients in the CZP 200 mg and 400 mg groups achieved PASI 90 at week 16, respectively, compared with 4.5% of patients in the placebo group, corresponding to a 48.1% and 51.0% difference in response rate versus placebo, respectively. The odds ratios for achieving a PASI 90 response versus placebo were 24.283 (97.5% CI, 4.386 to 134.432) for the CZP 200 mg every two weeks group and 27.204 (97.5% CI, 4.895 to 151.198) for the CZP 400 mg every two weeks group ($P < 0.0001$ for both comparisons).

In CIMPACT, 31.2% and 34.0% of patients in the CZP 200 mg and 400 mg groups achieved PASI 90 at week 12, respectively, compared with 0.2% of patients in the placebo group, corresponding to a 31.0% and 33.8% difference in response rate versus placebo, respectively. The odds ratios for achieving a PASI 90 response versus placebo were 35.084 (95% CI, 7.363 to 167.179) for the CZP 200 mg every two weeks group and 39.949 (95% CI, 8.407 to 189.828) for the CZP 400 mg every two weeks group ($P < 0.0001$ for both comparisons). PASI 90 response was achieved by 27.1% of patients in the etanercept group at week 12; however, the comparison between CZP and etanercept was a secondary end point, discussed subsequently. At week 16, the PASI 90 responder rates improved in both CZP-treated groups. Compared with placebo, the differences in PASI 90 responder rates were 39.5% and 48.8% for the CZP 200 mg and 400 mg groups, respectively; this corresponded to an odds ratio of 49.527 (95% CI, 10.002 to 245.256) and 72.278 (95% CI, 14.650 to 356.602), respectively ($P < 0.0001$ for both comparisons).

The results of the primary analysis using the MCMC method for multiple imputation were supported by similar findings from sensitivity analyses using nonresponder imputation and model-based multiple imputation (data not presented).

Maintenance Treatment Period
Overall, PASI 90 responder rates were maintained or continued to increase in all CZP-treated patients through week 48 in all three trials. No statistical comparisons were made between the CZP groups to assess comparative response rate, and the number of patients who received placebo during the maintenance period was too negligible to allow for meaningful comparisons to be made.

Results for Efficacy End Points Based on Psoriasis Area and Severity Index 100
PASI 100 at either time point was not a primary or secondary end point; however, the results were presented for both the initial treatment period and maintenance period. Overall, a statistically significant difference in PASI 100 responder rate was observed for CZP-treated patients compared with placebo-treated patients at week 12 (CIMPACT) or week 16 (CIMPASI-1 and -2).

In CIMPASI-1, 13.7% and 12.7% of patients in the CZP 200 mg and 400 mg groups achieved PASI 100 at week 16, respectively, compared with 0.2% of patients in the placebo group, corresponding to a 13.5% and 12.5% difference in response rate versus placebo, respectively (nominal *P* value 0.0043 and 0.0070, respectively).

In CIMPASI-2, 15.4% and 18.8% of patients in the CZP 200 mg and 400 mg groups achieved PASI 100 at week 16, respectively, compared with 1.8% of patients in the placebo group, corresponding to a 13.6% and 17.1% difference in response rate versus placebo, respectively (nominal *P* value 0.0251 and 0.0131, respectively).

In CIMPACT, 10.9% and 11.0% of patients in the CZP 200 mg and 400 mg groups achieved PASI 100 at week 12, respectively, compared with 0.1% of patients in the placebo group, corresponding to a 10.8% and 11.0% difference in response rate versus placebo, respectively (nominal *P* value 0.0053 and 0.0048, respectively). PASI 100 response was achieved by 6.1% of patients in the etanercept group at week 12; however, no comparison was made between CZP and etanercept. At week 16, the PASI 100 responder rates improved slightly in both CZP-treated groups. Compared with placebo, the differences in PASI 100 responder rates were 12.0% and 15.7% for the CZP 200 mg and 400 mg groups, respectively (nominal *P* value 0.0043 and 0.0011, respectively).

Maintenance Treatment Period
Overall, PASI 100 responder rates were maintained or continued to increase in all CZP-treated patients through week 48 in all three trials. No statistical comparisons were made between the CZP groups to assess comparative response rate, and the number of patients who received placebo during the maintenance period was too negligible to allow for meaningful comparisons to be made.

Static Physician's Global Assessment

Initial Treatment Period

Results for Efficacy End Points Based on an Improvement in Physician's Global Assessment of at Least Two Categories

PGA response (defined as having a PGA score of clear or almost clear [with at least a two-category improvement]) at week 16 was a co-primary efficacy end point in CIMPASI-1 and -2, and a secondary efficacy end point at week 12 and week 16 in CIMPACT. Overall, a statistically significant difference in PGA responder rate was observed for CZP-treated patients compared with placebo-treated patients in all trials (Table 14).

In CIMPASI-1, 47.0% and 57.9% of patients in the CZP 200 mg and 400 mg groups, respectively, achieved a PGA response at week 16 compared with 4.2% of patients in the placebo group, corresponding to a 42.8% and 53.6% difference in response rate versus placebo, respectively. The odds ratios for being a PGA responder versus placebo were 20.116 (97.5% CI, 3.699 to 109.399) for the CZP 200 mg group and 31.143 (97.5% CI, 5.687 to 170.548) for the CZP 400 mg group ($P < 0.0001$ for both comparisons).

In CIMPASI-2, 66.8% and 71.6% of patients in the CZP 200 mg and 400 mg groups, respectively, achieved a PGA response at week 16 compared with 2.0% of patients in the placebo group, corresponding to a 64.8% and 69.6% difference in response rate versus placebo, respectively. The odds ratios for achieving a PGA response versus placebo were 106.225 (97.5% CI, 9.572 to 1,178.843) for the CZP 200 mg group and 133.163 (97.5% CI, 11.904 to 1,489.578) for the CZP 400 mg group ($P < 0.0001$ for both comparisons).

In CIMPACT, 39.8% and 50.3% of patients in the CZP 200 mg and 400 mg groups, respectively, achieved a PGA response at week 12 compared with 1.9% of patients in the placebo group, corresponding to a 37.9% and 48.5% difference in response rate versus placebo, respectively. The odds ratios for achieving a PGA response versus placebo were 36.566 (95% CI, 5.061 to 264.196) for the CZP 200 mg group and 56.129 (95% CI, 7.787 to 404.555) for the CZP 400 mg group ($P = 0.0004$ and $P < 0.0001$, respectively). PGA response was achieved by 39.2% of patients in the etanercept group at week 12; however, no statistical comparison was made between CZP and etanercept or between etanercept and placebo. At week 16, the PGA responder rates improved in both CZP-treated groups. Compared with placebo, the differences in PGA responder rates were 44.9% and 55.0% for the CZP 200 mg and 400 mg groups, respectively, which corresponded to an odds ratio of 27.165 (95% CI, 6.504 to 113.453) and 40.717 (95% CI, 9.741 to 170.198), respectively ($P < 0.0001$ for both comparisons).

The results of the primary analysis using the MCMC method for multiple imputation were supported by similar findings from sensitivity analyses using nonresponder imputation and model-based multiple imputation (data not presented).

Subgroups of Interest

Efficacy results based on previous biologic failure were not reported. Subgroup analyses based on body weight were reported; however, because the subgroups were based on quintiles of body weight at baseline, those results are not reported here. PGA responder rates were analyzed based on previous systemic treatment experience. In all three trials, CZP groups had numerically greater responder rates compared with placebo; however, no statistical testing was reported (Table 14).

Maintenance Treatment Period

Overall, PGA responder rates were maintained or improved through week 48 in CIMPASI-1 and -2. In CIMPACT, PGA response rates fluctuated through week 48 and generally decreased slightly among CZP-treated patients from the week 16 response rates, with the exception of the CZP 400 mg every two weeks group, where the response rate increased slightly. No statistical comparisons were made between the CZP groups to assess comparative response rate, and the number of patients who received placebo during the maintenance period was too negligible to allow for meaningful comparisons to be made (Table 23).

Table 14: Summary of Symptom-Related Outcomes During Initial Treatment Period (16 Weeks) (Randomized Set)

	CIMPASI-1			CIMPASI-2			CIMPACT			
	PBO	CZP 200	CZP 400	PBO	CZP 200	CZP 400	PBO	ETN	CZP 200	CZP 400
N	51	95	88	49	90	87	57	170	165	167
PASI 75 Responder Rate Versus Placebo										
Responder rate (%)	6.5	66.5	75.8	11.6	81.4	82.6	3.8	NA	68.2	74.7
Estimate (95% CI) for difference in proportion of responders vs. PBO		60.0 (47.92 to 72.17)	69.3 (57.65 to 80.99)		69.7 (57.12 to 82.36)	71.0 (58.47 to 83.43)			64.4 (55.12 to 73.63)	70.9 (62.15 to 79.59)
Odds ratio vs. PBO (97.5% CI)[a]		28.962 (6.968 to 120.371)	45.660 (10.657 to 195.634)		33.405 (9.965 to 111.983)	36.212 (10.686 to 122.713)			55.41 (13.14 to 233.78)[b]	79.28 (17.95 to 324.09)[b]
P value vs. PBO		< 0.0001	< 0.0001		< 0.0001	< 0.0001			< 0.0001	< 0.0001
PASI 90 Responder Rate										
Responder rate (%)	0.4	35.8	43.6	4.5	52.6	55.4	0.3	NA	39.8	49.1
Estimate (95% CI) for difference in proportion of responders vs. PBO		35.4 (20.85 to 49.87)	43.1 (27.56 to 58.71)		48.1 (35.04 to 61.26)	51.0 (37.75 to 64.19)			39.5 (25.58 to 53.38)	48.8 (34.22 to 63.41)
Odds ratio vs. PBO (97.5% CI)[a]		36.668 (5.717 to 235.195)	50.606 (7.880 to 324,988)		24.283 (4.386 to 134.432)	27.204 (4.895 to 151.198)			49.527 (10.002 to 245.256)[b]	72.278 (14.650 to 356.602)[b]
P value		< 0.0001	< 0.0001		< 0.0001	< 0.0001			< 0.0001	< 0.0001
PASI 100										
Responder rate (%)	0.2	13.7	12.7	1.8	20.4	20.7	[redacted]	[redacted]	[redacted]	[redacted]
Estimate (95% CI) for difference in proportion of responders vs. PBO		13.5 (3.71 to 23.29)	12.5 (2.99 to 22.04)		18.6 (8.88 to 28.22)	18.9 (8.97 to 28.79)			[redacted]	[redacted]
P value		0.0043[c]	0.0070[c]		0.0117[c]	0.0111[c]			[redacted]	[redacted]
PGA										
Responder rate (%)	4.2	47.0	57.9	2.0	66.8	71.6	3.4	NA	48.3	58.4
Estimate (95% CI) for difference in proportion of responders vs. PBO		42.8 (30.70 to 54.86)	53.6 (41.33 to 65.94)		64.8 (52.16 to 77.46)	69.6 (57.48 to 81.77)			44.9 (35.39 to 54.49)	55.0 (45.59 to 64.35)
Odds ratio vs. PBO (97.5% CI)[a]		20.116 (3.699 to 109.399)	31.143 (5.687 to 170.548)		106.225 (9.572 to 1,178.843)	133.163 (11.904 to 1,489.578)			27.165 (6.504 to 113.453)[b]	40.717 (9.741 to 170.198)[b]
P value[b]		< 0.0001	< 0.0001		< 0.0001	< 0.0001			< 0.0001	< 0.0001

	CIMPASI-1			CIMPASI-2			CIMPACT			
	PBO	CZP 200	CZP 400	PBO	CZP 200	CZP 400	PBO	ETN	CZP 200	CZP 400
PGA Responses for Subgroups of Interest										
Previous systemic therapy							[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				

CI = confidence interval; CSR = Clinical Study Report; CZP = certolizumab pegol; ETN = etanercept; LOCF = last observation carried forward; LS = least squares; MCMC = Markov chain Monte Carlo; NA = not applicable; PASI 75/90/100 = at least a 75%, 90%, or 100% reduction from baseline in Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; PBO = placebo; vs. = versus.

[a] Logistic regression model with treatment group, region, and prior biologic exposure (yes/no) as factors, with MCMC methods used to impute missing data.

[b] Ninety-five per cent CI.

[c] Outside the statistical testing hierarchy.

Source: CIMPASI-1 CSR,[13] CIMPASI-2 CSR,[14] CIMPACT.[16]

Table 15: Psoriasis Area and Severity Index 75 Response at Week 12 for CIMPACT Study (Randomized Set)

	CIMPACT			
	PBO	ETN	CZP 200	CZP 400
N	57	170	165	167
PASI 75 Responder Rate Versus Placebo (at Week 12)				
Responder rate (%)	5.0	53.3	61.3	66.7
Estimate (95% CI) for difference in proportion of responders vs. PBO			56.2 (46.4 to 66.0)	61.6 (52.1 to 71.2)
Odds ratio vs. PBO (95% CI)[a]			30.02 (8.97 to 100.48)	37.99 (11.31 to 127.58)
P value vs. PBO			< 0.0001	< 0.0001
PASI 75 Responder Rate Versus ETN (at Week 12)				
Responder rate (%)	5.0	53.3	61.3	66.7
Estimate (95% CI) for difference in proportion of responders vs. ETN			8.0 (−2.9 to 18.9) (noninferiority met)[b]	13.4 (2.7 to 24.1) (noninferiority met)[b]
Odds ratio vs. ETN (95% CI)[a]			1.388 (0.886 to 2.175)	1.756 (1.114 to 2.768)
P value vs. ETN			0.1523[c]	0.0152[c]

CI = confidence interval; CZP = certolizumab pegol; ETN = etanercept; PASI 75 = at least a 75% reduction from baseline in Psoriasis Area and Severity Index; PBO = placebo; vs. = versus.

[a] Logistic regression model with treatment group, region, and prior biologic exposure (yes/no) as factors, with MCMC methods used to impute missing data.

[b] Noninferiority was met, as the lower bound of the 95% CI was greater than −10% for the difference in proportions.

[c] CZP 400 mg was superior to ETN but not CZP 200 mg.

Source: CIMPACT Clinical Study Report.[16]

Harms

Harms data were reported for the initial treatment period (week 16 for CIMPASI-1 and -2, week 12 for CIMPACT) as well as for the combined initial and maintenance treatment periods (week 0 to 48 for all trials).

Adverse Events

Overall, the percentage of patients who experienced a treatment-emergent adverse event (TEAE) during the initial treatment period ranged from 54% to 69% between treatment groups across the CIMPASI trials, and between 46% and 57% in the CIMPACT trial. Results from week 48 data showed the CZP 400 mg dose was associated with more AEs compared with the 200 mg group. The most commonly reported TEAEs across the trials included general disorders, infections and infestations nasopharyngitis and upper respiratory infections), and pruritus.

Serious Adverse Events

With the exception of the placebo arm in CIMPACT, the incidence of SAEs was low (< 5%) during the initial treatment period. SAEs were reported more frequently in CZP 200 mg and CZP 400 mg groups than placebo in CIMPASI-1 and CIMPASI-2: 4% and 7.6% versus 2% in CIMPASI-1, and 7.4% and 5.4% versus 0% in CIMPASI-2. In CIMPACT, SAEs were more frequent in the placebo group than in the active treatment groups. Results from week 48 data showed a low incidence of SAE in both CZP groups.

Withdrawals Due to Adverse Events

None of the included studies reported withdrawals due to adverse events (WDAEs) in the placebo groups. WDAEs in the active treatment groups ranged from 0.6% to 8.4% during the initial treatment period. Results from week 48 data showed a relatively low incidence of WDAEs (< 10%) in both CZP groups.

Mortality

One mortality case was reported in the CZP 400 mg group from CIMPASI-1. The mortality was due to a traffic accident.

Notable Harms

Several harms outcomes of particular interest were identified in the study protocol.

Infections and infestations were reported more frequently in the CZP 200 mg and CZP 400 mg groups than in the placebo or etanercept groups: 50% and 52.8% versus 31.4% in CIMPASI-1, and 50.5% and 52.7% versus 30.6% in CIMPASI-2, and 40.8% and 37.3% versus 28.1% (placebo) and 23.2% (etanercept) in CIMPACT.

Injection-site reactions were more frequent in the CZP 200 mg and CZP 400 mg groups than in the placebo groups in the CIMPASI trials: 8% and 13.2% versus 3.9% in CIMPASI-1, and 8.4% and 14% versus 6.3% in CIMPASI-2. Reported incidence was similar across treatment groups in the CIMPACT trial.

The incidence of benign or malignant neoplasms was generally low (< 3.3%) and was homogenous across treatment groups. None of the included studies reported cases of inflammatory bowel disease, serious hypersensitivity reactions, or suicidal ideation.

Table 16: Overall Summary of Treatment-Emergent Adverse Events for Initial Treatment Period (Safety Set)

	CIMPASI-1 (16 Weeks)			CIMPASI-2 (16 Weeks)			CIMPACT (12 Weeks)			
	PBO	CZP 200	CZP 400	PBO	CZP 200	CZP 400	PBO	ETN	CZP 200	CZP 400
N	51	95	88	49	90	87	57	168	165	167
Harms Outcomes										
Any TEAEs	28 (54.9)	52 (54.7)	57 (64.8)	33 (67.3)	54 (60.0)	60 (69.0)	32 (56.1)	78 (46.4)	78 (47.3)	82 (49.1)
Discontinuation due to TEAEs	0	0	2 (2.3)	0	3 (3.3)	1 (1.1)	0	4 (2.4)	1 (0.6)	1 (0.6)
All deaths	0	0	0	0	0	0	0	0	0	0
Most Common AEs (Incidence ≥ 5%)										
Nasopharyngitis	7 (13.7)	18 (18.9)	18 (20.5)	5 (10.2)	8 (8.9)	6 (6.9)	5 (8.8)	11 (6.5)	14 (8.5)	12 (7.2)
URTI	3 (5.9)	7 (7.4)	8 (9.1)	2 (4.1)	4 (4.4)	5 (5.7)	6 (10.5)	11 (6.5)	6 (3.6)	8 (4.8)
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
Serious TEAEs	1 (2.0)	2 (2.1)	5 (5.7)	0	2 (2.2)	4 (4.6)	5 (8.8)	1 (0.6)	1 (0.6)	4 (2.4)
Most Common AEs by SOC (Incidence ≥ 2%)										
[redacted]										

AE = adverse event; CSR = Clinical Study Report; CZP = certolizumab pegol; ETN = etanercept; PBO = placebo; SOC = system organ class; TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection.

Source: CIMPASI-1 CSR,[13] CIMPASI-2 CSR,[14] CIMPACT.[16]

Table 17: Overall Summary of Treatment-Emergent Adverse Events (Week 0 to 48) (Treated With Certolizumab Pegol Set)

	CIMPASI-1		CIMPASI-2		CIMPACT	
	CZP 200	CZP 400	CZP 200	CZP 400	CZP 200	CZP 400
N	100	144	95	129	265	354
Any TEAEs	72 (72.0)	111 (77.1)	73 (76.8)	103 (79.8)	175 (66.0)	230 (65.0)
Patient discontinuations due to TEAEs	0	5 (3.5)	8 (8.4)	8 (6.2)	4 (1.5)	11 (3.1)
All deaths	0	1 (0.7)	0	0	0	0
Most Common AEs (Incidence ≥ 5%)						
Nasopharyngitis	28 (28.0)	40 (27.8)	17 (17.9)	25 (19.4)	35 (13.2)	44 (12.4)
URTI	12 (12.0)	13 (9.0)	11 (11.6)	13 (10.1)	16 (6.0)	29 (8.2)
[redacted]						
[redacted]						
[redacted]						
Serious TEAEs	4 (4.0)	11 (7.6)	7 (7.4)	7 (5.4)	12 (4.5)	23 (6.5)
Most Common AEs by SOC (Incidence ≥ 2)						
[redacted]						

	CIMPASI-1		CIMPASI-2		CIMPACT	
	CZP 200	CZP 400	CZP 200	CZP 400	CZP 200	CZP 400
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

AE = adverse event; CSR = Clinical Study Report; CZP = certolizumab pegol; PBO = placebo; SOC = system organ class; TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection.

Source: CIMPASI-1 CSR,[13] CIMPASI-2 CSR,[14] CIMPACT.[16]

Discussion

Summary of Available Evidence

Three phase III randomized trials (CIMPASI-1, CIMPASI-2, CIMPACT) were included in this review. Two were placebo-controlled (CIMPASI-1, CIMPASI-2), while one had an active comparator, etanercept (CIMPACT). The three trials evaluated the efficacy and safety of CZP 200 mg every two weeks and CZP 400 mg every two weeks; three loading doses of CZP 400 mg were used at weeks 0, 2, and 4 for patients randomized to CZP 200 mg every two weeks. The co-primary efficacy end points for CIMPASI-1 and CIMPASI-2 were PASI 75 and PGA clear or almost clear (with at least a two-category improvement) at week 16 comparing both CZP doses versus placebo. The primary efficacy end point for CIMPACT was PASI 75 at week 12, comparing both CZP doses versus placebo, whereas PASI 75 at week 16, comparing both CZP doses versus placebo, was evaluated as a secondary efficacy end point. In CIMPACT, comparisons of CZP with etanercept were made at week 12 because the approved duration of etanercept treatment at 50 mg twice weekly is 12 weeks. All three trials presented data through week 48 (limited long-term data beyond week 48 are available); however, much of the data from week 16 to week 48 did not provide useful comparative information for this review.

This systematic review identified and included one published trial comparing CZP and etanercept; however, no other published RCTs with direct comparisons of CZP and other biologics for the treatment of plaque psoriasis were identified. The manufacturer provided one indirect treatment comparison that compared CZP with other biologic treatments of moderate-to-severe plaque psoriasis, which is described in Appendix 7.

Notable limitations of the included trials included the following: potentially unblinded treatment administration and risk of disclosure of treatment allocation, unblinded comparison of CZP and etanercept, notable imbalances across treatment groups within trials for a number of variables, compromised original randomization in the maintenance period, a higher dropout rate during the maintenance period relative to the initial treatment period, and the use of an enriched sample in the maintenance period. The methodological strengths of the trials included the use of validated instruments to measure outcomes, an appropriate statistical analysis plan, and a trial population that reflected patient characteristics and treatments typical of the Canadian context.

Interpretation of Results

Efficacy

Results from CIMPASI-1 and -2 demonstrated that CZP 200 mg and 400 mg every two weeks were superior to placebo for the primary and secondary efficacy outcomes at week 16: achievement of PASI 75 response, PGA response (clear or almost clear, i.e., a score of 0 or 1), PASI 90 response, and improvements in DLQI score from baseline. Results from CIMPACT showed that both doses of CZP were superior to placebo for the primary and secondary efficacy outcomes at week 12 and week 16: achievement of PASI 75 response, PGA response, and PASI 90 response. Additionally, CZP 400 mg was superior to etanercept in achieving PASI 75 at week 12, whereas CZP 200 mg was noninferior to etanercept in achieving this outcome but not superior. These results were robust to a number of sensitivity analyses to account for missing data imputation. Improvement in symptoms and skin clearance as measured by the PASI and PGA are important goals of therapy based on CDA clinical practice guidelines, which indicate that the PASI and PGA are commonly used in clinical practice in Canada. Further, the observed differences in the co-primary and secondary outcomes represent a clinically meaningful improvement for psoriasis patients, according to the clinical expert consulted by CDR for this review. Assessment of other symptoms-related outcomes and HRQoL outcomes (e.g., PASI 90 and PASI 100, DLQI, HADS-A and HADS-D, EQ-5D-3L, and SF-36) were supportive of the findings for the previously mentioned efficacy outcomes and suggest a beneficial effect of CZP over placebo, but they were not adjusted for multiplicity.

In all three trials, data through week 48 suggest that patients who responded to CZP treatment (either dose) at week 12 or week 16 continued to have good response to treatment, as shown by PASI and PGA scores as well as a number of HRQoL measures. However, as noted, week 48 results may overstate the effect of CZP due to the focus on the enriched population of responders. In addition, no statistical comparisons between treatment arms were made for any post–week 16 (CIMPASI-1 and -2) or post–week 12 (CIMPACT) end points, therefore, results for the maintenance period should be interpreted descriptively.

Of the subgroups identified as relevant by the review team, data were available only for previous systemic treatment experience. Analysis of primary outcomes (PASI 75 and PGA responder rate) by previous systemic treatment experience showed no consistent pattern, although a statistical comparison was not done.

According to patient group input, the most significant physical symptoms of psoriasis include scales, flaking, itching, joint pain, cracking and bleeding, and pain. The input also suggests that lesions affect psychological well-being. Assessment of the disease-specific DLQI instrument and generic EQ-5D-3L, HADS-A and HADS-D, and SF-36 PCS and MCS suggest that improvements in the symptoms of plaque psoriasis (demonstrated by PASI and PGA) resulted in improvements in HRQoL for CZP-treated patients compared with placebo at week 12 or week 16. However, statistical comparisons for these outcomes were not adjusted for multiplicity, with the exception of DLQI score change from baseline in CIMPASI-1 and -2. No statistical comparisons for HRQoL measures were made between CZP and etanercept. As described previously, a number of biologics are currently available in the market to treat moderate-to-severe psoriasis, including anti-TNF drugs (adalimumab, etanercept, and infliximab), IL-12 and IL-23 inhibitors (ustekinumab, risankizumab), and the IL-17A inhibitors (brodalumab, secukinumab, and ixekizumab). The CIMPACT trial included

as a comparator only one of many options for plaque psoriasis: etanercept. To address the lack of direct comparative evidence from other drug treatments for psoriasis, CDR reviewed and critically appraised the manufacturer's submitted indirect treatment comparison.

[redacted]

Harms

Overall, the proportion of patients with an AE during the initial treatment period in the CZP group was comparable to the placebo and etanercept groups. During the maintenance period, a similar proportion of patients in the two CZP dose groups reported having an AE. The most common AEs in both phases of all three trials were nasopharyngitis, upper respiratory tract infection, headache, pruritus, and arthralgia. This indicates that the AE profile of CZP remained similar with longer exposure.

The overall frequency of SAEs and events leading to discontinuation of the study was low in both periods. This can be expected, given the relatively short follow-up duration of 48 weeks; the safety profile of CZP can be better assessed with long-term data. Finally, one death was reported in the three trials, which was not related to the treatment.

A number of AEs of particular interest were identified for this review, including infections and malignancy events, both of which are featured in the warnings and precautions section of the Health Canada–approved product monograph. The approved product monograph[11] contains a boxed warning stating that any new infection that develops while on CZP, or after recent treatment, should be closely monitored. Furthermore, the monograph highlights that lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers; therefore, CZP is not indicated for use in pediatric patients.

Potential Place in Therapy[2]

CZP is an anti-TNF biologic indicated for the treatment of moderate-to-severe psoriasis. Currently, there are 10 biologics (including CZP) approved for this indication. CZP is one of three anti-TNF drugs. Unlike other anti-TNFs, CZP is Fc-free and does not transfer across the placenta. Hence, it is believed to be safe in pregnancy.

There is a paucity of data on the transfer of biologics across the placenta and into breast milk. In clinical practice, it is generally accepted (based on clinical experience) that biologics are safe in the first two trimesters of pregnancy; their withdrawal is generally advisable in the third trimester. It is believed that the oral bioavailability of biologics is minimal and mothers can breastfeed while on biologics. CZP is the only anti-TNF with formal pharmacokinetic studies on placental and breast-milk transfer. These studies provide more reassuring data to clinicians and pregnant and nursing women that CZP is safe in pregnancy and lactation.

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

CZP provides another biologic choice for patients and physicians. The currently available biologics, especially the newer drugs (anti-IL-17 and anti-IL-23), provide good efficacy and a durable response. Less than 10% to 20% of patients fail to respond to one of the biologics or lose efficacy or have a contraindication. CZP may be tried when another drug fails or is not appropriate.

Biologics are currently used as continuous therapy. When a patient is started on a biologic, the treatment is expected to be continuous and lifelong. A major unmet need is a treatment that is remittive or would work well on an intermittent "as-needed" basis. So far, neither CZP nor any of the biologics are able to fulfill this need.

Conclusions

Based on the results of three phase III RCTs in adults with moderate-to-severe plaque psoriasis, compared with placebo and etanercept, CZP 200 mg and CZP 400 mg resulted in statistically significant and clinically important improvements in skin clearance and dermatological symptoms over the short-term initiation phase, as measured by the PASI and PGA. [redacted]. Long-term comparative efficacy data from RCTs is lacking, as results beyond week 16 had limited interpretability. The safety profile of CZP in patients with psoriasis is consistent with its other indications.

Appendix 1: Patient Input Summary

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

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

Two patient input submissions were provided for this review. One submission was from the Psoriasis Society of Canada (PSC), the other submission was jointly provided by the Canadian Skin Patient Alliance (CSPA), the Canadian Association of Psoriasis Patients (CAPP), and the Canadian Psoriasis Network (CPN).

PSC is a national non-profit organization that is managed by volunteers. The organization aims to provide programs and services to those with psoriasis. PSC publishes a national psoriasis newsletter twice a year, hosts psoriasis meetings across Canada, and has psoriasis support groups across Canada (www.psoriasissociety.org).

CSPA is a national non-profit organization for Canadians living with skin diseases, conditions, and traumas. It is dedicated to advocating for, educating, supporting, promoting the skin health of, and improving the quality of life of these individuals. CSPA advocates for best treatment options for patients with skins conditions, provides education on a variety of issues affecting these patients, and supports the members of their affiliated organizations who work specifically on their disease areas, such as acne, scleroderma, melanoma, and psoriasis (www.canadianskin.ca).

CAPP is a national, non-profit organization that aims to better serve the needs of and improve the quality of life of all Canadian patients with psoriasis. CAPP strives to be a resource and advocate for patients with psoriasis and their families, and aims to improve patient care and quality of life (www.canadianpsoriasis.ca).

CPN is a national, non-profit organization dedicated to improving the quality of life of all Canadians who are living with psoriasis and psoriatic arthritis while vigorously pursuing a cure. CPN aims to provide current information on research and treatment options to build awareness and advocacy about the complexities of psoriasis and psoriatic arthritis (www.canadianpsoriasisnetwork.com).

PSC declared receiving funding (in the amount of $0 to $5,000) from three organizations, including UCB, United Way, and Dermtek Pharma. CSPA declared receiving funding (in the amount of $5,001 to $10,000) from Janssen Canada and Novartis. CSPA also received funding (in the amount of $10,001 to $50,000) from Celgene and Pfizer Canada. Additionally, CSPA received funding (in excess of $50,000) from AbbVie Canada. CAPP declared receiving funding (in the amount of $0 to $5,000) from Novartis. CAPP also received funding (in the amount of $10,001 to $50,000) from AbbVie Canada, Eli Lilly Canada, Celgene, UCB, Bausch Health, and Leo Pharma. Additionally, CAPP received funding (in excess of $50,000) from Janssen Canada. CPN declared receiving funding (in the amount of $10,001 to $50,000) from Eli Lilly, Celgene, Novartis, Amgen, and Pfizer Canada). Additionally, CPN received funding (in excess of $50,000) from Janssen Canada and AbbVie Canada.

2. Condition Related Information

The information for the PSC submission was gathered through phone calls from patients who shared their experiences of living with psoriasis. For the combined submission from CSPA, CAPP, and PSC, the information was gathered from a previous submission for risankizumab.

The majority of the survey respondents (74%) identified as individuals with psoriasis that they feel is uncontrolled. Findings from a recent questionnaire conducted by CPN and

CAPP regarding stability found that more than 38% of survey respondents have lived for 10 or more years feeling that their condition was not satisfactorily controlled. The length of time these respondents have lived with psoriasis ranged from two to 55 years. The majority of respondents (87.5%) said they experience psoriasis on their legs/knees, 75% they experience it on their arms/elbows, and 75% said they experience it on their scalp. Others indicated involvement of their back (56%), face (50%), feet (31%), or palms (25%).

Respondents identified the following as having an impact on them when they are not being treated or when treatment is not working: feelings of embarrassment, loss of sleep, problems with intimacy, and negative effects on self-confidence. A total of 47% of respondents indicated that their concentration at work is affected frequently, and more than half (53%) indicated that they frequently experience feelings of depression. Some respondents reported discrimination in the workplace, with co-workers believing they could "catch" the skin condition; others reported hairstylists refusing service because of psoriasis on the scalp. While shopping, it has been reported that cashiers do not want to come in contact with their hands, and will place products and/or money on the counter and slide it over to them, instead of directly passing it. When asked about the impact of psoriasis on daily life, 81% indicated they do not wear certain types of clothing, 50% indicated they have trouble sleeping, and 31% had to miss social events.

The family members and caregivers of those with psoriasis indicated the following challenges: emotional challenges (just more than 66%); costs (associated with travel to appointments, medications, other) (55%); lack of support or information about psoriasis (44%); missing school or work (33%), difficulties with intimacy (33%), and missing social events (33%).

3. Current Therapy Related Information

People who responded to the survey indicated experience with a range of different therapies, including topical treatments, phototherapy, oral systemic drugs, and biologics. A total of 58% said their current medications were "very convenient" to use. For those who have experienced side effects (approximately 50%), tiredness, dry face, dry lips, redness, soreness, thinning skin, painful burns, hair loss, and weight gain were reported. Respondents using treatment stated they still had outbreaks and felt like there was no long-term solution and only temporary fixes. Many respondents said their treatments eventually stopped working, were too inconvenient, or had too many side effects.

4. Expectations About the Drug Being Reviewed

The importance of access to new medication was highlighted in both submissions; what works for one patient may not work for another, even if symptoms are very similar. Patients are often waiting for the next treatment option in hopes that it will work well for them and achieve 100% effectiveness with limited side effects. Female patients indicated a need for new treatments that are safe to use during pregnancy. When respondents were asked, "What aspects of psoriasis are the most important to control, in your opinion," the majority (73%) selected "itching," just more than 53% indicated "pain," and about one-third selected all of the following: bleeding, related conditions (e.g., diabetes, heart disease), depression, and social stigma.

Below are a few examples of quotes from the patients regarding their experience and expectations for new treatments:

In general ... it's isolated my life to the extend [sic] I am depressed, how can one not be with this "disease." The worst part is the itch, pain, and the bleeding.... and it is so hard to control!"

"Life is difficult with this disease... it's so painful... some of these questions just don't answer half of the pain that anyone goes through with this skin condition!"

"I was unable to participate in any social activity, could not walk downstairs and did not feel like socializing due to the pain and discomfort from my psoriasis on my feet. When I have experienced a flare-up, I stay at home, in my bedroom."

"My well-being is just... well... just not well... you isolate because of the pain or the embarrassment! Try vacuuming your bed daily from all the shredding skin …that in itself is painful!"

"Topical treatments and light therapy worked many years ago for psoriasis on my body, but did not work for the soles of my feet or hands. Oral meds had no effect at all. Stelara [sic] did not work at all, the only thing that has given me my life back is Humira."

"Humira made me ill, made the psoriasis worse than it ever was. Methotrexate affected the organs 1 month after starting the treatment, cyclosporine affected organs after 1 year [sic]."

"Does anyone know when Cimzia will be approved for use? I'm eagerly waiting. Stelara only works ok for me, but doesn't come close to clearing me. It just prevents me from getting back to 60% covered, but I stay about 15% to 20% covered with the max dose of Stelara. I switched to Cosentyx, but I was one of the lucky ones that got awful diarrhea from it and stopped."

Appendix 2: Literature Search Strategy

June 11, 2019, Embase, Ovid, MEDLINE

Search History Sorted by Search Number, Ascending			
#	**Searches**	**Results**	**Type**
1	certolizumab pegol/	6,329	Advanced
2	(cimzia* or certolizumab* or CDP 870 or CDP870 or CZP or HSDB 7848 or HSDB7848 or PHA 738144 or PHA738144 or G6ADW90R16 or UMD07X179E).ti,ab,ot,rn,nm,kf.	8,008	Advanced
3	exp psoriasis/	117,818	Advanced
4	psoria*.ti,ab,kf.	113,132	Advanced
5	1 or 2	8,008	Advanced
6	3 or 4	138,189	Advanced
7	5 and 6	1,738	Advanced
8	7 use medall	236	Advanced
9	*certolizumab pegol/	1,375	Advanced
10	(cimzia* or certolizumab* or CDP 870 or CDP870 or CZP or HSDB 7848 or HSDB7848 or PHA 738144 or PHA738144).ti,ab,kw,dq.	4,586	Advanced
11	psoriasis vulgaris/	9,399	Advanced
12	psoria*.ti,ab,kw,dq.	114,224	Advanced
13	9 or 10	4,756	Advanced
14	11 or 12	115,303	Advanced
15	13 and 14	854	Advanced
16	15 use oemezd	645	Advanced
17	8 or 16	881	Advanced
18	conference abstract.pt.	3,427,021	Advanced
19	17 not 18	490	Advanced
20	remove duplicates from 19	302	Advanced

Appendix 3: Excluded Studies

Table 18: Excluded Studies

Reference	Reason for Exclusion
Papp KA, Blauvelt A, Bukhalo M, et al. Risankizumab versus Ustekinumab for Moderate to Severe Plaque Psoriasis. N Engl J Med. 2017;376(16):1551-1560	Phase II trial
Krueger JG, Ferris LK, Menter A, et al. Anti-IL-23A mAb BI 655066 for treatment of moderate to severe psoriasis: Safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol. 2015;136(1):116-124.e117	Phase I trial
Kolli SS, Gabros SD, Pona A, Cline A, Feldman SR. Tildrakizumab: A Review of Phase II and III Clinical Trials. Ann Pharmacother. 2018:1060028018809522.	Systematic review

Appendix 4: Detailed Outcome Data

Table 19: Change in Psoriasis Area and Severity Index Score to Week 16 (Randomized Set)

	CIMPASI-1			CIMPASI-2			CIMPACT			
	PBO	CZP 200	CZP 400	PBO	CZP 200	CZP 400	PBO	ETN	CZP 200	CZP 400
N	[redacted]									
Baseline mean (SD)	[redacted]									
Initial Treatment Period										
Mean change from baseline (SD)	[redacted]									
Percentage change from baseline, mean (SD)	[redacted]									

CSR = Clinical Study Report; CZP = certolizumab pegol; ETN = etanercept; PBO = placebo; SD = standard deviation.

Source: CIMPASI-1 CSR,[13] CIMPASI-2 CSR,[14] CIMPACT CSR.[16]

Table 20: Subgroup Analysis for Psoriasis Area and Severity Index 75 Responder Rate (Initial Treatment Period)

	CIMPASI-1			CIMPASI-2			CIMPACT			
	PBO	CZP 200	CZP 400	PBO	CZP 200	CZP 400	PBO	ETN	CZP 200	CZP 400
N	[redacted]									
PASI 75 Responder Rate at Week 16										
Subgroups of Interest										
Previous Systemic Therapy (Any)										
Yes, n (%)	[redacted]									
No, n (%)	[redacted]									

CSR = Clinical Study Report; CZP = certolizumab pegol; ETN = etanercept; PASI 75 = at least a 75% reduction from baseline in Psoriasis Area and Severity Index; PBO = placebo.

Source: CIMPASI-1 CSR,[13] CIMPASI-2 CSR,[14] CIMPACT CSR.[16]

Summary of the Maintenance Phase of the Three Included Studies

Table 21: Dermatology Life Quality Index Results for Maintenance Phase (Week 16 to 48) in CIMPACT (Maintenance Set)

	Blinded Groups (N = 310)									Escape Groups (N = 223)			
Initial Treatment	**PBO**	**ETN**		**CZP 200 mg q.2.w.**			**CZP 400 mg q.2.w.**			**PBO**	**ETN**	**CZP 200 mg q.2.w.**	**CZP 400 mg q.2.w.**
Maintenance Treatment	**PBO**	**PBO**	**CZP 200 mg q.2.w.**	**PBO**	**CZP 200 mg q.2.w.**	**CZP 400 mg q.4.w.**	**PBO**	**CZP 200 mg q.2.w.**	**CZP 400 mg q.2.w.**	**Escaped to CZP 400 mg q.2.w.**			
N	[redacted]												
Baseline mean (SD)	[redacted]												
Mean change from baseline (SD)[a]	[redacted]												
Achieved ≥ 4-point change from baseline in DLQI; n (%)[b]	[redacted]												
Achieved DLQI score ≤ 1; n (%)[b]	[redacted]												

CZP = certolizumab pegol; DLQI = Dermatology Life Quality Index; ETN = etanercept; PBO = placebo; q.2.w. = every two weeks; q.4.w. = every four weeks; SD = standard deviation.

[a] [redacted]

[b] [redacted]

Source: CIMPACT Clinical Study Report.[16]

Table 22: Change in Psoriasis Area and Severity Index Score for Maintenance Period (Randomized Set)

	CIMPASI-1			CIMPASI-2		
	PBO	CZP 200	CZP 400	PBO	CZP 200	CZP 400
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance Treatment Period (Week 16 to 48)						
Mean change from baseline (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage change from baseline, mean (SD)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CZP = certolizumab pegol; CSR = Clinical Study Report; PASI = Psoriasis Area and Severity Index; PBO = placebo; SD = standard deviation.

[a] [redacted]

Source: CIMPASI-1 CSR,[13] CIMPASI-2 CSR.[14]

Table 23: Psoriasis Area and Severity Index and Physician's Global Assessment Response for Maintenance Period (Randomized Set)

	CIMPASI-1[a]			CIMPASI-2[a]		
	PBO	CZP 200	CZP 400	PBO	CZP 200	CZP 400
N	NA	95	88	NA	91	87
PASI 75 Responder Rate						
Percentage of responders (95% CI)		67.2 (57.09 to 77.39)	87.1 (79.81 to 94.45)		78.7 (68.93 to 88.45)	81.3 (71.90 to 90.67)
PASI 90 Responder Rate						
Percentage of responders (95% CI)		42.8 (32.17 to 53.41)	60.2 (49.23 to 71.09)		59.6 (47.94 to 71.28)	62.0 (50.23 to 73.78)
PASI 100 Responder Rate						
Percentage of responders (95% CI)		21.8 (13.00 to 30.59)	23.6 (14.23 to 33.07)		31.4 (19.77 to 43.01)	38.3 (26.06 to 50.45)
PGA Responder Rate						
Percentage of responders (95% CI)		52.7 (41.99 to 63.32)	69.5 (59.24 to 79.77)		72.6 (61.22 to 83.92)	66.6 (54.35 to 78.86)

CI = confidence interval; CSR = Clinical Study Report; CZP = certolizumab pegol; MMRM = mixed-effect model repeated measure; NA = not applicable; PASI 75/90/100 = at least a 75%, 90% or 100% reduction from baseline in Psoriasis Area and Severity Index; PBO = placebo; PGA = Physician's Global Assessment.

[a] Based on randomized set with MMRM for missing data. For patients who met the escape criterion (i.e., did not achieve PASI 50 at week 16), their week 16 value was carried forward through all remaining time points up to week 48, and those that met withdrawal criteria (due to not achieving a PASI 50 response at week 32 or later) were analyzed as nonresponders for subsequent time points.

Source: CIMPASI-1 CSR,[13] CIMPASI-2 CSR,[14] CIMPACT CSR.[16]

Table 24: Psoriasis Area and Severity Index and Physician's Global Assessment Response for Maintenance Phase in CIMPACT (Maintenance Set)

	Blinded Groups (N = 310)[a]									Escape Groups (N = 223)			
Initial Treatment	**PBO**	**ETN**		**CZP 200 mg q.2.w.**			**CZP 400 mg q.2.w.**			**PBO**	**ETN**	**CZP 200 mg q.2.w.**	**CZP 400 mg q.2.w.**
Maintenance Treatment	**PBO**	**PBO**	**CZP 200 mg q.2.w.**	**PBO**	**CZP 200 mg q.2.w.**	**CZP 400 mg q.4.w.**	**PBO**	**CZP 200 mg q.2.w.**	**CZP 400 mg q.2.w.**	**Escaped to CZP 400 mg q.2.w.**			
N	2	24	50	22	44	44	25	50	49	53	85	49	36
PASI 75 Responder Rate													
Percentage of responders (95% CI)	100 (100 to 100)	8.3 (0 to 19.39)	82.0 (71.35 to 92.65)	45.5 (24.65 to 66.26)	79.5 (67.63 to 91.46)	88.6 (79.26 to 98.01)	36.0 (17.18, 54.82)	80.0 (68.91 to 91.09)	98.0 (94.0 to 100)	75.5 (63.9 to 87.1)	76.5 (67.5 to 85.5)	61.2 (47.6 to 74.9)	80.6 (67.6 to 93.5)
PASI 90 Responder Rate													
Percentage of responders (95% CI)	50.0 (0.0 0, 100)	4.2 (0.00, 12.16)	78.0 (66.52, 89.48)	18.2 (2.06, 34.30)	61.4 (46.98, 75.75)	68.2 (54.42, 81.94)	12.0 (0.00, 24.74)	60.0 (46.42, 73.58)	87.8 (78.58, 96.93)	60.4 (47.2, 73.6)	57.6 (47.1, 68.2)	36.7 (23.2, 50.2)	44.4 (28.2, 60.7)
PASI 100 Responder Rate													
Percentage of responders (95% CI)	[redacted]												
PGA Responder Rate													
Percentage of responders (95% CI)	50.0 (0.0 0 to 100)	4.2 (0.00 to 12.16)	72.0 (59.55 to 84.45)	13.6 (0.00 to 27.98)	61.4 (46.98 to 75.75)	70.5 (56.97 to 83.94)	12.0 (0.00 to 24.74)	64.0 (50.70 to 77.30)	87.8 (78.58 to 96.93)	66.0 (53.3 to 78.8)	69.4 (59.6 to 79.2)	46.9 (33.0 to 60.9)	55.6 (39.3 to 71.8)

CZP = certolizumab pegol; ETN = etanercept; MS = Maintenance Set; NRI = nonresponder imputation; PASI 75/90/100 = at least a 75%, 90% or 100% reduction from baseline in Psoriasis Area and Severity Index; PBO = placebo; PGA = Physician's Global Assessment; q.2.w. = every two weeks; q.4.w. = every four weeks.

[a] Based on maintenance set with nonresponder imputation for missing data.

Source: CIMPACT Clinical Study Report.[16]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Psoriasis Area and Severity Index (PASI)
- Physician's Global Assessment (PGA), static version (sPGA)
- Dermatology Life Quality Index (DLQI)
- Hospital Anxiety and Depression Scale (HADS)

Findings

Evidence from validation studies is summarized for all instruments according to the following metrics and depending on information availability: comprehensiveness, feasibility, validity (i.e., content, construct [convergent, discriminant], and criterion [concurrent, predictive] validity), reliability (internal consistency; i.e., inter-item correlations), reproducibility (i.e., test–retest [inter/intra-rater] reliability); responsiveness, floor and ceiling effects, and scaling assumptions. Of the four patient-reported outcomes / health-related quality-of-life (HRQoL) measures, PASI and PGA are described in greater detail since these were the primary end points in the CIMPASI and CIMPACT trials.

Interpretation of the reliability and validity metrics were based on the following criteria:

- Inter/intra-rater reliability/agreement (kappa statistics or interclass coefficient [ICC]): < 0 to 0.2 = poor, 0.21 to 0.4 = fair, 0.41 to 0.6 = moderate, 0.61 to 0.8 = substantial, 0.81 to 1.00 = almost perfect agreement.[51]
- Internal consistency (Cronbach's alpha) and test–retest reliability (≥ 0.7 is considered acceptable).[52]
- Validity, i.e., between-scale comparison (correlation coefficient, r): ≤ 0.3 = weak, 0.3 to ≤ 0.5 = moderate, > 0.5 = strong).[53]

Table 25: Brief Descriptions of Instruments Used in the Trials

Instrument	Type	Evidence of Validity	MCID/Benchmark	References
PASI	A single estimate of a patient's disease severity at a given time based on induration, erythema, and scaling.	Yes	PASI 90 and PASI 100 are the updated treatment goals in clinical practice. PASI 75 is a traditional outcome, although it may still be clinically meaningful to patients. MCIDs for PASI scores were not identified.	Ashcroft et al. (1999)[54] Carlin et al. (2004)[55] Feldman et al. (2004)[56] Gourraud et al. (2012)[57] Mattei et al. (2014)[58]
sPGA	The sPGA is used to determine a single estimate of the patient's overall severity of disease at a given point in time. Psoriatic lesions are graded for induration, erythema, and scaling based on scales	Yes	Not identified.	Weisman et al. (2003)[59] Cappelleri et al. (2013)[60] Chow et al. (2015)[38]

Instrument	Type	Evidence of Validity	MCID/Benchmark	References
	of 0 to 5 that are then averaged over all lesions.			Simpson et al. (2015)[39]
DLQI	A 10-item, dermatology-specific quality-of-life questionnaire.	Yes	Range: 2.2 to 6.9.	Finlay et al. (1994)[40] Shikiar et al. (2003)[61] Mazzotti et al. (2003)[62] Shikiar et al. (2006)[63] Basra et al. (2008)[64]
HADS	A 14-item self-administered questionnaire to detect the presence and severity of mood and anxiety disorders.	No	Not identified.	N/A
SF-36	The SF-36 consists of eight health domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) for which individual domain scores can be calculated. It also provides two component summary scores: PCS and MCS. Scores range from 0 to 100, with higher scores indicating better health.	Yes	Ranges: 2.57 to 3.91 points for PCS and 3.89 to 6.05 points for the MCS.	Frendl and Ware (2014)[45] Mease et al. (2006)[46] Shikiar et al. (2006)[61]

MCID = minimal clinically important difference; MCS = mental component summary; PASI = Psoriasis Area and Severity Index; DLQI = Dermatology Life Quality Index; HADS = Hospital Anxiety and Depression Scale; PSC = physical component summary; SF-36 = Short Form (36) Health Survey; sPGA = static Physician's Global Assessment.

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. A PASI score of less than 10 is considered mild disease and a score of 10 or greater is considered moderate-to-severe disease.[65] A 75% reduction in the PASI score (PASI 75) was the traditional benchmark for clinical trials in psoriasis and is the criterion for the efficacy of new psoriasis treatments approved by the FDA.[55] However, according to the clinical expert consulted for this review, in current clinical practice, the treatment goal is achievement of PASI 90 or PASI 100. PASI 90 and PASI 100 are scored using a dichotomous scale (yes/no: patient achieved ≥ 90% or 100% improvement from baseline PASI score).

The PASI is calculated 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.[56] Each of these areas is assessed separately for erythema, induration, and scaling, and rated on a scale of 0 (none) to four (very severe). The extent of psoriatic involvement for each region 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%

- 6 = 90% to 100%

The following formula is used to calculate the PASI score:[56]

PASI = 0.1 $(Eh + Ih + Sh)\ Ah$ + 0.2 $(Eu + Iu + Su)\ Au$ + 0.3 $(Et + It + St)\ At$ + 0.4 $(El + Il + Sl)\ Al$

(Where E = erythema, I = induration, S = scaling, A = area, h = head score, t = trunk score, u = upper extremities score, and l = lower extremities score.)

Validity

One study by Simpson et al.[39] used data from a phase III clinical trial (N = 445) to validate three systems of physician-determined psoriasis severity, PASI being one of them. Construct validity was assessed by evaluating the correlation between PASI scores and skin-related quality of life (QoL) (DLQI and a DLQI item about psoriasis symptoms) in grading psoriasis severity. PASI showed moderate positive correlations with both DLQI overall and a single item of DLQI related to psoriasis ($0.36 \leq r \leq 0.54$). The study also investigated the content validity of PASI by assessing the relative impact of each individual component of PASI on QoL using multiple regression analysis. It was found that the attribute of psoriasis that most consistently associated with DLQI scores was BSA, followed by, in the order of consistency, plaque elevation, erythema, and scale. While PASI calculation incorporates BSA, it gives equal weights to elevation, erythema, and scale. The authors reported that a scoring system for the PASI that weights psoriasis symptoms equally would not capture the varying degrees to which these factors affect the patient's rating of QoL.

One study by Bożek et al.[66] assessed the correlations of PASI with other commonly used instruments in psoriasis, including BSA and PGA, and found a strong correlation with both PGA (Pearson correlation coefficient r > 0.6) and BSA (r > 0.75).

Reliability

The reliability of PASI was assessed in a number of studies. One study by Bożek et al.[66] assessed the intra-rater and inter-rater reliability of PASI. In total, 10 practising dermatologists evaluated nine adult patients with plaque-type psoriasis (varying extent) twice on the same day. The interclass correlations (ICCs) for all components of PASI were > 0.75, indicating very good intra-rater reliability, except for the ICC for scaling (0.72), indicating good intra-rater reliability. The coefficient of variation (CV) for PASI was 36.9 overall, indicating moderate inter-rater reliability. The highest variability was found for the head and neck (117.8) and the lowest variability was for the area score (26.8).

The systematic review by Puzenat et al.[67] reported good internal consistency, limited intra-observer variation, and moderate inter-observer variation for PASI.

Responsiveness

The systematic review by Puzenat et al.[67] reported moderate sensitivity to change for PASI. PASI has a low response distribution since only about half of the scale is used in practice.[68] The responsiveness is particularly low if < 10% BSA is affected, because changes in PASI score entirely depend on plaque severity score improvement and may therefore underestimate the general degree of improvement.[68]

MCID

A systematic review by Mattei et al.[58] (including 13 randomized controlled trials) reported that a ≥ 75% reduction in PASI translated to clinically significant QoL improvement in patients assessed using the DLQI. The clinical expert consulted for this review indicated that PASI 90 or even PASI 100 is increasingly being used in clinical settings.

Physician's Global Assessment

The PGA is a frequently used end point in psoriasis clinical trials that provides a simple subjective measurement of the clinical signs of psoriasis. Various PGAs have been used in psoriasis with different descriptions and scores, with the most common PGA versions using five- to six-point scales.[69] The are two primary forms of PGA: a static form that measures the physician's impression of the disease at a single point, and a dynamic form in which the physician evaluates global improvement from a baseline.[66] The trials in this review used the static form of PGA. Psoriatic lesions are graded for induration, erythema, and scaling based on scales ranging from 0 to 4 that are then averaged over all lesions to obtain a single estimate of the patient's overall severity of disease at a given point in time.[60] All three items are given an equal weighting.[70] The following table highlights the scoring for induration, erythema, and scaling.

Table 26: Physician's Global Assessment Scoring

Score	Induration	Erythema	Scaling
0	No evidence	No evidence of erythema, although hyperpigmentation may be present	No evidence of scaling
1	Minimal	Faint erythema	Minimal: occasional fine scale
2	Mild or slight	Light red coloration	Fine scale dominates
3	Elevated	Red coloration	Moderate: coarse scale predominates
4	Marked	Dark- to deep-red coloration	Marked: thick, non-tenacious scale dominates

Source: Cappelleri et al.[60]

The sum of the three scales are added and then divided by three ([I + E + S] ÷ 3) to obtain a final PGA score as follows:

- 0 = cleared, except for residual discoloration
- 1 = minimal; majority of lesions have individual scores that average 1
- 2 = mild; majority of lesions have individual scores that average 2
- 3 = moderate; majority of lesions have individual scores that average 3
- 4 = severe; majority of lesions have individual scores that average 4.

Validity

A recent study by Duffin et al.[70] assessed the validity and reliability of PGA using data from four phase III clinical studies of tofacitinib in patients with psoriasis (N = 3,641 total). The confirmatory factor analysis that was used to test the fit of the PGA measurement model showed that equal weighting of the three items (erythema, induration, and scaling) was appropriate, as indicated by the Bentler comparative fit index (CFI) values > 0.98 (acceptable fit defined as a CFI > 0.9) and standardized path coefficients all above the threshold of 0.4. Construct validity was assessed using a known-group approach by measuring the relationship between PGA and PASI. A "robust monotonic functional

relationship" between PASI and PGA was observed, indicating the PGA scale can discriminate between different degrees of psoriasis severity. Convergent and divergent validity were assessed by determining the correlation of the PGA with three scales: patient global assessment (PtGA), PASI, and DLQI. The Pearson correlation coefficients between PGA and the three scales were 0.4 to 0.79, indicating moderate-to-strong correlation, with the strongest correlation found with PASI. These findings were consistent with a previous psychometric study by Cappelleri et al.[60] that used data from one of the four clinical trials used in Duffin et al.

The study by Simpson et al.[39] described previously assessed the construct and content validity of sPGA by assessing its association with DLQI. The correlation between sPGA and DLQI was moderately positive ($0.29 \leq r \leq 0.43$). However, its content validity is uncertain due to the following reasons: not incorporating any assessment of BSA, an important component of patients' well-being; and not appropriate weighting psoriasis plaque components (e.g., elevation, erythema, and scale) that are known to disproportionally impact QoL.

The study by Bożek et al.[66] described previously assessed correlations between PGA and two other scales (PASI, BSA) and found strong correlations with these parameters ($0.56 \leq r \leq 0.85$).

The systematic review by Puzenat et al.[67] described previously assessed the relative content validity of PGA using PASI as the gold standard, and a strong correlation was found (two studies, N = 51 for PGA).

Reliability

The recent study by Duffin et al.[70] described previously reported acceptable test–retest reliability of PGA measurements, with an ICC value of 0.7, indicating consistency of PGA scoring. Additionally, internal consistency was found to be acceptable, with a Cronbach's coefficient alpha of > 0.9 post-baseline. The test–retest reliability (ICC > 0.7) and internal consistency reliability (a Cronbach's alpha of 0.8) were similar in a previous psychometric study by Cappelleri et al.[60] This study used data from one of the four clinical trials used in Duffin et al.

The study by Bożek et al.[66] described previously assessed the reliability of PGA and found very good intra-rater reliability (ICC, 0.87) but moderate inter-rater variability (CV, 29.3).

A systematic review by Puzenat et al.[67] reported low intra-observer variability but moderate inter-observer variability for PGA.

Responsiveness

No evidence regarding the responsiveness of PGA was identified from the literature.

Minimal Clinically Important Difference

Many studies now employ only the final value of clear or almost clear (0 or 1) in the sPGA as treatment success. Different studies have used different definitions of clear or almost clear, making comparisons between studies difficult.[59] The study by Duffin et al.[70] described previously assessed the minimal clinically important difference (MCID) for dynamic PGA by using PtGA as a continuous anchor. The estimated MCID from the study was 0.55 (95% CI, 0.54 to 0.56). The estimate from the Cappelleri et al.[60] study was similar, 0.52 (95 % CI, 0.47 to 0.56).

Dermatology Life Quality Index

The DLQI is a widely used dermatology-specific health-related quality-of-life (HRQoL) instrument that is simple and easy to use in a busy clinical setting. This scale has been used for at least 36 different skin conditions in 20 countries and has been translated into at least 21 different languages.[71] It is a 10-item questionnaire that measures the effect of having skin disease on six different aspects relating to quality of life: symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment.[40,63] Each of the 10 questions is given a score of 0, 1, 2, or 3 based on the following responses, respectively: "not at all," "a little," "a lot," or "very much." The maximum score per aspect is either 3 (with a single question) or 6 (with two questions) and the scores for each can be expressed as a percentage of either 3 or 6. The overall DLQI is calculated by summing the score of each question, resulting in a numeric score of between 0 and 30 (or a percentage of 30).[40,63] The higher the score, the greater the degree of quality-of-life impairment. The meanings of the DLQI scores in terms of the effect on a patient's life are as follows:[64,51]

- 0 to 1 = no effect
- 2 to 5 = small effect
- 6 to 10 = moderate effect
- 11 to 20 = very large effect
- 21 to 30 = extremely large effect.

Reliability and Validity

The DLQI has shown good test–retest reliability based on reassessment seven to 10 days after the initial assessment (the correlation between overall DLQI scores was 0.99, $P < 0.0001$; for individual question scores, the correlation was 0.95 to 0.98, $P < 0.001$).[40] The DLQI has also shown good internal consistency reliability (Cronbach's alpha coefficients ranged from 0.75 to 0.92 when assessed in 12 international studies),[64] construct validity (37 separate studies have mentioned the DLQI correlates with either generic or dermatology-specific and disease-specific measures),[64] and responsiveness (the DLQI is reportedly able to detect changes over time, according to 17 different studies).[64] Similar measures of the validity, reliability, and responsiveness of DLQI have also been shown in evaluations of the use of the instrument specifically for adult patients with moderate-to-severe psoriasis.[61-63,71]

The DLQI can be completed within a few minutes, making it a very time-efficient scoring system for use in clinical settings.[71]

Minimal Clinically Important Difference

Estimates of the MCID for DLQI have ranged from 2.2 to 6.9 in patients with psoriasis.[63,64] It should be noted that some of the anchors that were used to obtain the DLQI MCID were not patient-based (i.e., Basra et al.[64] derived estimates from PASI and PGA anchors and also used a distribution-based approach); therefore, they do not necessarily identify the smallest difference that patients would consider important.

Hospital Anxiety and Depression

The HADS is a widely used generic patient-reported questionnaire designed to identify anxiety disorders and depression in patients at non-psychiatric medical institutions.[41] It includes 14 questions, each of which was answered by patients using a four-point scale (0

to 3: 0 indicating absence, 3 indicating extreme presence; and higher scores indicating more severe anxiety or depression symptoms). An anxiety subscale score (HADS-A) (possible score of 0 to 21) was calculated by combining seven items from the HADS, and a depression subscale score (HADS-D) (possible score of 0 to 21) was calculated by combining the remaining seven items.[42] For both subscales, scores of less than 7 indicate healthy state, 8 to 10 indicate borderline case, and 11 to 21 indicate diseased case. The HADS is useful for initial diagnosis and to track progression (or resolution) of psychological symptoms.

Reliability and Validity

The psychometric properties of HADS have been assessed in various conditions; however, evidence for the validity of this scale in psoriasis was not found.[72] A number of clinical trials used HADS to evaluate the psychological impact of drugs in patients with psoriasis or mental conditions secondary to psoriasis, but these were not designed to assess the validity or reliability.[42,73,74]

Minimal Clinically Important Difference

An MCID for HADS in patients with psoriasis was not identified from the literature. However, the trials used a HADS-A and HADS-D score of < 8 as MCID.

Short Form (36) Health Survey

The 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.[45] The SF-36 consists of eight health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.[45] For each of the eight domains, 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 and eight dimensions are each measured on a scale of 0 to 100, which are t scores (mean of 50 and standard deviation of 10) that have been standardized to the US general population. Thus, a score of 50 on any scale would be at the average or norm of the general US population, while a score 10 points lower (i.e., 40) would be one standard deviation below the norm. On any of the scales, an increase in score indicates improvement in health status.[45]

A systematic review by Frendl and Ware[45] examined SF-36 concordance and its MCID across many different indications in studies evaluating drug therapy effectiveness. The SF-36 was observed to be responsive (when compared with primary clinical measures) in patients with psoriasis in these studies. In addition, a PCS or MCS improvement of at least three points versus placebo was observed in seven of the 10 psoriasis studies identified.

Based on anchor data, the developer of the SF-36 proposed the following minimal mean group differences for the individual domain scores: physical functioning, 3; role physical, 3; bodily pain, 3; general health, 2; vitality, 2; social functioning, 3; role emotional, 4; and mental health, 3. It should be noted that these MCID values were determined to be appropriate for groups with mean t score ranges of 30 to 40; for higher t score ranges, MCID values may be higher.[46] As these MCID values were based on clinical and other non–patient-reported outcomes, they do not necessarily identify the smallest difference that patients would consider important.

The MCID of the PCS and MCS was also estimated in a study involving patients with moderate-to-severe plaque psoriasis. This study provided results for an estimated MCID for patient-reported SF-36 scores. The estimated MCID was based on PASI and PGA anchor data: MCID-1 (PASI 25 to PASI 49), MCID-2 (PASI 50 to PASI 74), and MCID-3 (difference between nonresponders and minimal responders on PGA), and supported by two distribution-based approaches that use the standard error of measurement and one-half of the standard deviation as an upper limit for the MCID.[61] The estimated MCID for PCS ranged from 2.57 to 3.91, which was consistent with previous research.[61] The most reasonable estimates of the MCID for the MCS ranged from 3.89 to 6.05. The use of non–patient-based anchor data to estimate the MCIDs in this study should be noted as a limitation. Further, the PGA anchor produced results that were inconsistent with the two other anchors, two distributional based approaches, and previous estimates of the MCID for the PCS reported in the literature.[61] As such, the results from the PGA anchor are not reported in this appendix.

Appendix 6: Summary of Other Studies

Summary of the Pharmacokinetic Studies

This section summarizes two pharmacokinetic (PK) studies that were aimed primarily at evaluating the safety of certolizumab pegol (CZP) use in pregnant women and the resulting exposure in newborns through placental transfer or breast milk. The studies did not meet the inclusion criteria for the systematic review component of this report; however, these studies were included to provide information on the impact of CZP in pregnant and lactating women and their infants.

Study Design

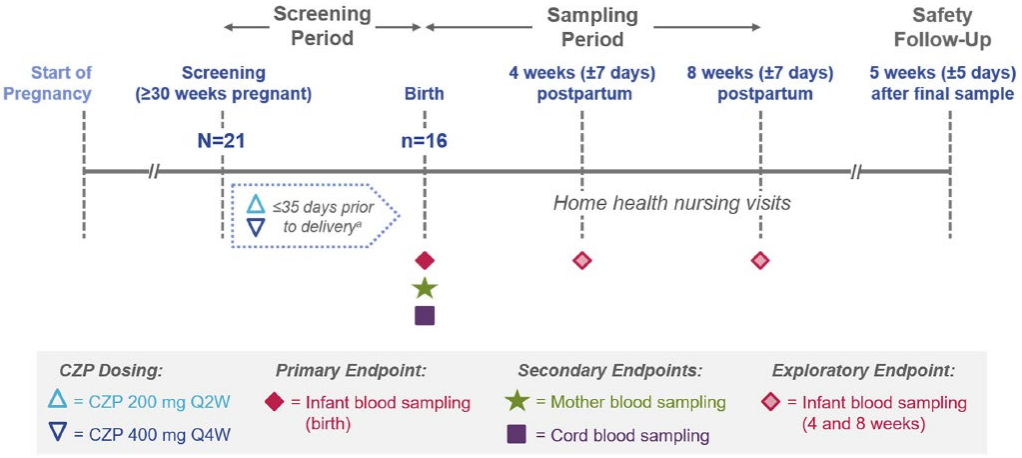
Both CRIB[75] and CRADLE[76] were prospective, post-marketing, multi-centre, PK trials in which mothers received commercial CZP at the 200 mg every two weeks dose or 400 mg every four weeks dose. CRIB was designed to evaluate the transfer of CZP from pregnant women to the fetus in utero, whereas CRADLE was aimed to measure the CZP concentration in breast milk. CRIB was conducted in 11 sites in France, Netherlands, Switzerland, and the US; CRADLE was conducted by six investigators, three in the US, one in Switzerland, and two in the Netherlands. Figure 5 and Figure 6 show the design of the two trials.

Both trials consisted of three distinct periods: screening, sampling, and safety follow-up. In the CRIB trial, following the screening period, an eight-week sampling period ensued, during which maternal blood samples were collected within 24 hours before or after delivery, umbilical cord samples were collected within one hour of birth, and infant blood samples were collected within 24 hours after birth and at weeks 4 and 8 post-partum. Plasma CZP concentration, anti-CZP antibodies, and total polyethylene glycol (PEG) levels were measured using laboratory assays.

In the CRADLE trial, mothers received at least three CZP doses during the screening period to bring their plasma CZP concentration to a steady state. Following the screening period, mature breast milk samples were collected across a single dosing period (every two weeks or every four weeks). For mothers on CZP 200 mg every two weeks, samples were collected every two days over a two-week period; for mothers on CZP 400 mg every four weeks, an additional sample was collected on day 28. The dosing and first sample collection were done on the same day and at approximately the same time of day. Samples were collected through in-home nursing visits, which minimized the burden on mothers. Samples collected were subsequently analyzed for CZP concentration and total PEG using laboratory assays.

Both trials included a safety follow-up period, consisting of five weeks ± 5 days, in which adverse events (AEs) in all mothers who received at least one dose of CZP, and their infants were measured. All participating mothers who entered the sampling period completed the study.

Figure 5: CRIB Study Design

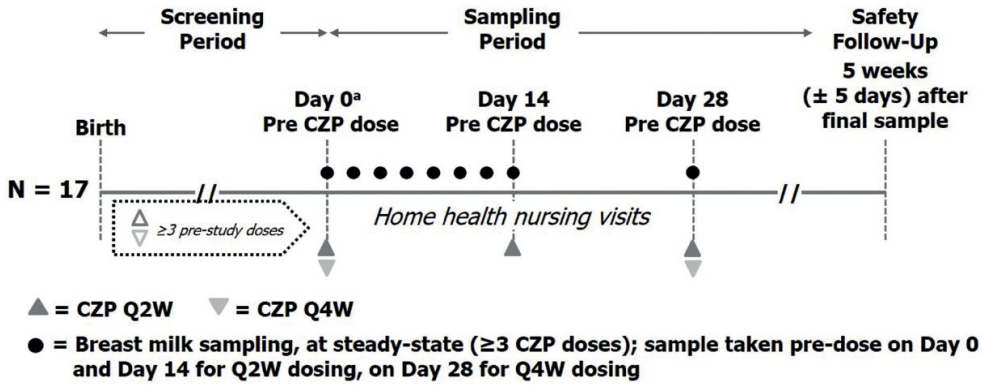


CZP = certolizumab pegol; Q2W = every two weeks; Q4W = every four weeks.

[a] Last CZP dose given within 35 days prior to delivery.

Source: Mariette et al.[75]

Figure 6: CRADLE Study Design



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

[a] Day 0 of the sampling period was ≥ 6 weeks post-delivery and when the patient was on an established CZP dose regimen (at least the third dose, regardless of CZP dosing schedule, but no maximum limit).

Source: Clowse et al.[76]

Populations

Inclusion and Exclusion Criteria

Women eligible for the CRIB trial were ≥ 30 weeks pregnant at the time of enrolment and being treated with commercial CZP for a locally approved indication (rheumatoid arthritis, Crohn's disease, psoriatic arthritis, or axial spondyloarthritis or ankylosing spondylitis). Patients received a CZP dose within 35 days prior to delivery; further CZP treatment during pregnancy was continued at the physician's discretion. The following exclusion criteria were in place: having any pregnancy-related abnormalities, significant clinical or laboratory

abnormalities, chronic or acute uteroplacental insufficiency, receiving any biologics or anti–tumour necrosis factor drugs (anti-TNFs) other than CZP, medications with a strong risk of human fetal teratogenicity, and those with a positive or indeterminate tuberculosis test at screening, with active or latent tuberculosis infection, or at high risk for tuberculosis infection.

The CRADLE trial enrolled lactating mothers who were ≥ 6 weeks post-partum and receiving CZP for any of the aforementioned indications. Women were excluded from the trial if they were pregnant or planning to become pregnant, had positive or indeterminate tuberculosis testing, active or latent tuberculosis infection or at high risk of tuberculosis infection, received any recent biologics, anti-TNFs, or biological disease-modifying drugs other than CZP, had a premature delivery (< 37 weeks' gestation), and mothers with active mastitis. No restrictions were made regarding an upper age limit for infants or multiple births.

Baseline Characteristics

The demographic and baseline characteristics of all participating mothers and their infants are given in Table 27. None of the participating mothers received CZP for psoriasis. Overall, the gestational age and weight at birth were within the range that is considered healthy for all infants, according to the clinical expert consulted for this review. Additionally, a normal appearance, pulse, grimace, activity, respiration (APGAR) score was found for all 16 infants in the CRIB trial; these data were not available for CRADLE.

Table 27: Baseline Characteristics of Mothers and Infants

	CRIB[a]	CRADLE[a]
Mothers, median (minimum, maximum), unless stated otherwise	N = 16[b]	N = 18[b]
Age, years	31 (18 to 40)	33.7 (4.2)
Weight, kg	–	68.9 (9.6)[c]
BMI, kg/m²	–	23.6 (3.0)[c]
Mother's indication for CZP treatment, n		
Rheumatoid arthritis	11	7
Crohn's disease	3	5
Psoriatic arthritis	1	3
Axial spondyloarthritis / ankylosing spondylitis	1	2
Delivery type, n		
Vaginal	14	–
Caesarean section	2	–
Infants, median (minimum, maximum), unless stated otherwise	N = 16	N = 17
Female, n (%)	10 (62.5)	11 (64.7)
Gestational age at birth, weeks	39.9 (37.7 to 41.7)	40.0 (39.0 to 41.7)
Weight at birth, kg	3.3 (2.6 to 4.0)	3.5 (2.6 to 4.1)
Length at birth,[d] cm	49.5 (46.0 to 55.9)	50.7 (48.0 to 57.0)
Head circumference at birth,[d] cm	34.5 (32.5 to 37.0)	
Normal APGAR score (7 to 10),[e] n		
At 1 minute	16	
At 5 minutes	16	

	CRIB[a]	CRADLE[a]
Age at time of mother's first sample, months	–	2.8 (1.6 to 16.8)
Age at time of mother's first sample, n (%)		
≤ 6 months	–	13 (76.5)
> 6 months to ≤ 12 months	–	2 (11.8)
≥ 12 months to ≤ 18 months	–	2 (11.8)

APGAR = appearance, pulse, grimace, activity, respiration; BMI = body mass index; CZP = certolizumab pegol; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation.

[a] In CRIB, data are "median (minimum to maximum)" values unless otherwise stated. In CRADLE, values for mothers are "mean (SD);" values for infants are "median (minimum to maximum)."

[b] Mothers who entered the sampling period in CRIB; includes one screen failure in CRADLE.

[c] N = 17.

[d] n = 15 (1 infant with missing data) in CRIB.

[e] APGAR scores range from 0 to 10; scores of 7 to 10 are considered normal.

Source: Mariette et al.[75] and Clowse et al.[76]

Interventions

In both trials, mothers received commercial CZP 200 mg every two weeks or 400 mg every four weeks subcutaneously. With the exception of one mother in each trial, all patients received CZP 200 mg every two weeks.

Outcomes

The primary end point in the CRIB trial was CZP concentration in the infants' plasma at birth. Secondary end points included CZP and anti–CZP antibody levels in the mothers' plasma and in the umbilical cords. The following exploratory end points were assessed: CZP levels in the infants' plasma at weeks 4 and 8, anti–CZP antibody levels in the infants' plasma at birth and weeks 4 and 8, and PEG concentrations in the plasma of mothers, cords, and infants.

In CRADLE, the primary end points were average CZP concentrations in breast milk (C_{ave}) and the average daily infant dose (ADID) of maternal CZP. The concentration of total PEG in breast milk and the relative infant dose (RID) were assessed as an exploratory end point and a post hoc outcome, respectively. C_{ave} was measured by plotting concentration versus time profile over the dosing period. ADID was a function of the amount of CZP ingested by a child (estimate from C_{ave}) and the estimated daily volume of milk ingested. (The estimated standardized milk consumption of a fully breastfed two-month-old infant was 150 mL/kg/day, obtained from the 2005 FDA draft guidance.) RID was a function of ADID relative to maternal dose, presented as a percentage.

In addition to the PK end points, both studies analyzed AEs occurring from the time of informed consent through safety follow-up in all participating mothers and their infants. The concentration of total PEG in breast milk and the RID were assessed as an exploratory objective and post hoc variable, respectively.

Results

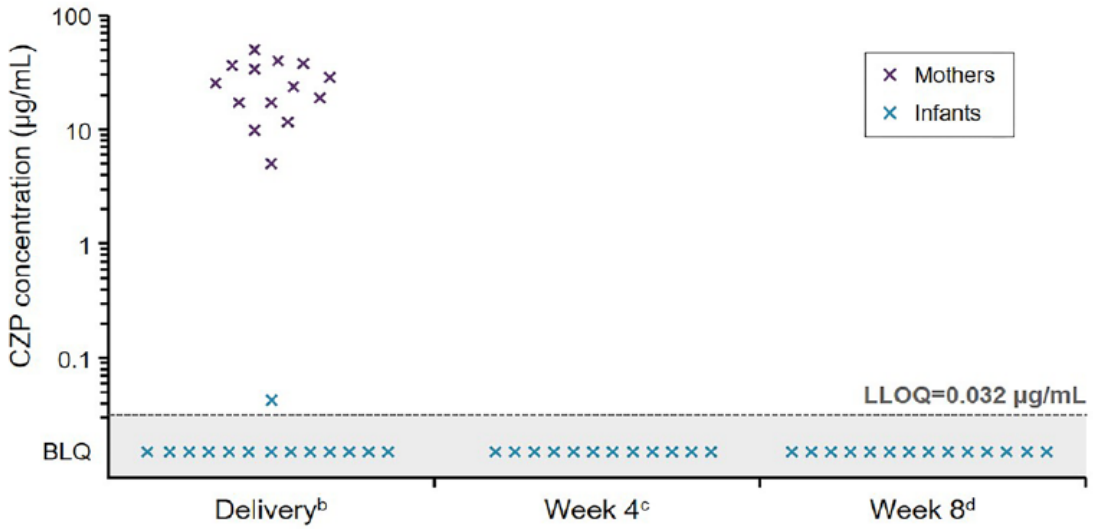
Pharmacokinetic Results

Certolizumab Pegol Plasma Concentrations

In the CRIB trial, the median CZP plasma level at delivery for all participating mothers (n = 16) was 24.4 mcg/mL (range 5.0 mcg/mL to 49.4 mcg/mL). Umbilical cord samples

collected (n = 15) showed quantifiable CZP levels in three samples (lower limit of quantification [LLOQ] = 0.032 mcg/mL), with the maximum cord-to-mother plasma ratio for these three cords being 0.0025. Plasma samples from infants (n = 14) showed one infant with a minimal CZP level at birth that was above the LLOQ, infant-to-mother plasma ratio was 0.0009. All 14 infants with CZP plasma levels at week 4 and week 8 were below the LLOQ. Additionally, nine mothers continued CZP post-partum and breastfed their infants; none of these infants had quantifiable CZP plasma levels. Figure 7 shows the plasma CZP concentrations in mothers and infants who had their samples analyzed over the course of the study.

Figure 7: Plasma Certolizumab Pegol Concentrations in Mothers and Infants



BLQ = below the LLOQ; CZP = certolizumab pegol; LLOQ = lower limit of quantification.

Note: Two of 16 infants were excluded from the final per-protocol set: one due to missing data at birth and one due to implausible pharmacokinetic data (high plasma CZP concentration at birth [0.485 mcg/mL]).

[b] Infant samples were collected within 24 hours post-delivery, while mother samples could be collected within 24 hours before or after delivery.

[c] Data are ± 7 days (two samples missing).

[d] Data are ± 7 days.

Source: Mariette et al.[75]

In the CRADLE trial, a total of 137 breast milk samples were collected from 17 mothers. CZP concentrations were minimal or below LLOQ in all samples, including no measurable CZP in 77 of the 137 (56%) samples. Four of the 17 participating women did not have measurable CZP levels in their breast milk at any time point during the study. In the remaining 13 mothers with a measurable concentration during at least one time point, the highest CZP concentration was 0.076 mcg/mL. The estimated median ADID and C_{ave} among all mothers was 0.003503 mg/kg/day (range 0 to 0.0104 mg/kg/day) and 0.023 mcg/mL (range 0.007 to 0.07), respectively. The post hoc median RID was 0.15% (range 0.04% to 0.30%).

Safety Results

Results for the safety follow-up period included all CZP-exposed mothers who were screened and the infants of all participating mothers. Overall, 15 mothers and five infants in CRIB experienced 34 and 13 AEs, respectively, and 10 mothers and eight infants in CRADLE

experienced 14 and 11 AEs, respectively. Most AEs were mild to moderate in nature. A total of three serious AEs (SAEs) were reported: arrested labour and prolonged labour were reported in two mothers in CRIB, and one case of breast abscess was reported in CRADLE. All SAEs in the mothers were resolved, except for the delivery of a premature baby in CRIB. One infant in CRIB experienced an SAE, an unspecified infection characterized by elevated white blood cell count with no clinical signs, which was also resolved with medication.

Table 28: Safety Results in Mothers and Infants

	CRIB		CRADLE	
	Mothers (n = 21)[a]	**Infants (n = 16)**	**Mothers (n = 18)[a]**	**Infants (n = 17)**
Any TEAEs, n (%)[b]	15 (71.4)	5 (31.3)	10 (55.6)	8 (47.1%)
Mild	4 (19.0)	2 (12.5)	3 (16.7)	6 (35.3)
Moderate	9 (42.9)	2 (12.5)	6 (33.3)	2 (11.8)
Severe	2 (9.5)	1 (6.3)	1 (5.6)	0
Discontinuation due to TEAEs, n (%)[b]	2 (9.5)	0	1	–
Drug-related TEAEs, n (%)[b]	3 (14.3)	1 (6.3)	4	1
Serious TEAEs,[c] n (%)[b]	7 (33.3)	2 (12.5)	1 (5.6)	0
Deaths	0	0	–	–

AE = adverse event; TEAE = treatment-emergent adverse event.

[a] Safety set for mothers (includes five screen failures).

[b] Number of mothers or infants reporting at least one AE for the indicated category.

[c] Serious TEAEs were classified using the FDA regulatory definitions for serious AEs.

There were two incidences of screening failures in mothers, one in CRIB and one in the CRADLE trial.

Source: Mariette et al.[75] and Clowse et al.[76]

Conclusion

Results from the CRIB trial suggested no-to-minimal placental transfer of CZP during the third trimester. A quantifiable CZP level at birth was found in only one infant and was minimal (< 0.1% of the adult therapeutic level). No quantifiable CZP levels were found in subsequent weeks in any infants. Nine mothers continued CZP post-partum and breastfed their infants; none of these infants had quantifiable CZP plasma levels. Likewise, findings from the CRADLE trial showed minimal transfer of CZP from plasma to breast milk, with infants receiving 0.15% of the maternal dose, on average. No new safety issues were identified in either trial; AEs in mothers and infants appeared to be consistent with the known safety profile of CZP. Although the trial duration was relatively short, making longer-term exposure and the potential for toxicity difficult to assess, this was reasonable, according to the clinical expert, given the trials were primarily aimed at characterizing the PK profile of CZP. The trials used sensitive instruments and assays to detect CZP levels in plasma and breast milk. The authors of the CRIB trial highlighted the lack of data characterizing CZP concentrations earlier in pregnancy and lack of investigation of the potential impact of the loading dose (CZP 400 mg at weeks 1, 2, and 4) as notable limitations. In conclusion, the studies provided information on the impact of CZP in pregnant and lactating women and their infants. Evidence from the two trials suggests limited fetal exposure and limited exposure to the newborn with continued use of CZP.

Appendix 7: Summary of Indirect Comparisons

Introduction and Background

Given the limited evidence from head-to-head studies that have compared certolizumab pegol (CZP) against most of the other relevant biologics that are used to treat moderate-to-severe plaque psoriasis in adult patients, the objective of this appendix is to summarize and critically appraise the evidence available regarding the comparative efficacy and safety of CZP versus other treatments through indirect treatment comparison (ITC).

Methods

The manufacturer submitted [redacted],[77] which was reviewed, summarized, and critically appraised. CADTH Common Drug Review (CDR) conducted an independent literature search for published ITCs that compared CZP with other relevant comparators for the treatment of moderate-to-severe plaque psoriasis in adult patients; two additional publications were identified: Sbidian et al.[78] and Ungprasert et al.[79] However, these network meta-analyses (NMAs) are not summarized or critically appraised in this appendix because both used only data from one phase II trial evaluating CZP versus placebo and did not include the pivotal phase III data.[47]

Description of Indirect Treatment Comparisons Identified

Table 29 presents the population, interventions, comparisons, and outcomes for the included ITC.

Table 29: Population, Interventions, Comparators, Outcomes, and Study Design Criteria For Study Selection

	Manufacturer-Sponsored and -Submitted ITC 2018[77]
Population	[redacted]
Intervention	[redacted]
Comparators	[redacted]

	Manufacturer-Sponsored and -Submitted ITC 2018[77]
	[redacted]
Outcomes	[redacted]
Study Design	[redacted]

ITC = indirect treatment comparison

Source: Manufacturer-submitted ITC.[77]

Review and Appraisal of the Manufacturer-Sponsored Indirect Treatment Comparison[77]

Objectives and Rationale for the Indirect Treatment Comparison

[redacted]

Methods for the Indirect Treatment Comparison

Literature Search and Selection

[redacted]

Systematic searches were carried out in [redacted]

[redacted]

[redacted]

Data Extraction

[redacted]

Statistical Methods

[redacted]

[redacted]

[redacted]

[redacted]

Results of Indirect Treatment Comparison

[redacted]

[redacted]

[redacted]

Figure 8: [redacted]

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

Source: Manufacturer-submitted indirect treatment comparison.[77]

Figure 9: [redacted]

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

Source: Manufacturer-submitted indirect treatment comparison.[77]

Study and Patient Characteristics

[redacted]

Table 30: [redacted]

Study	Treatment				Age (Mean)	Male %	Psoriatic Arthritis %	Time Since Diagnosis (Years)	Biologic Exposed %	Baseline PASI Score (Mean)	Baseline DLQI Score (Mean)
	1	2	3	4							
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Study	Treatment				Age (Mean)	Male %	Psoriatic Arthritis %	Time Since Diagnosis (Years)	Biologic Exposed %	Baseline PASI Score (Mean)	Baseline DLQI Score (Mean)
	1	2	3	4							
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Study	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Age (Mean)	Male %	Psoriatic Arthritis %	Time Since Diagnosis (Years)	Biologic Exposed %	Baseline PASI Score (Mean)	Baseline DLQI Score (Mean)
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DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area and Severity Index.

[redacted]

Source: Manufacturer-submitted indirect treatment comparison.[77]

Comparators

[redacted]

[redacted]

Outcomes

[redacted]

Assessment of Risk of Bias for Included Studies

[redacted]

[redacted]

[redacted]

Figure 10: [redacted]

Figure 10 contained confidential information and was removed at the request of the manufacturer.

Source: Manufacturer-submitted indirect treatment comparison.[77]

Investigation of Heterogeneity

[redacted]

[redacted]

Results of Model Selection

[redacted]

Results

All Patients

[redacted]

Figure 11:

Figure 11 contained confidential information and was removed at the request of the manufacturer.

Source: Manufacturer-submitted indirect treatment comparison.[77]

Table 31: [redacted]

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[redacted]	[redacted]	[redacted]	[redacted]
Deviance information criterion	[redacted]	[redacted]	[redacted]
Total residual deviance	[redacted]	[redacted]	[redacted]
Study standard deviation	[redacted]	[redacted]	[redacted]
Beta coefficient	[redacted]	[redacted]	[redacted]

[redacted].

Source: Manufacturer-submitted indirect treatment comparison.[77]

Table 32: [redacted]

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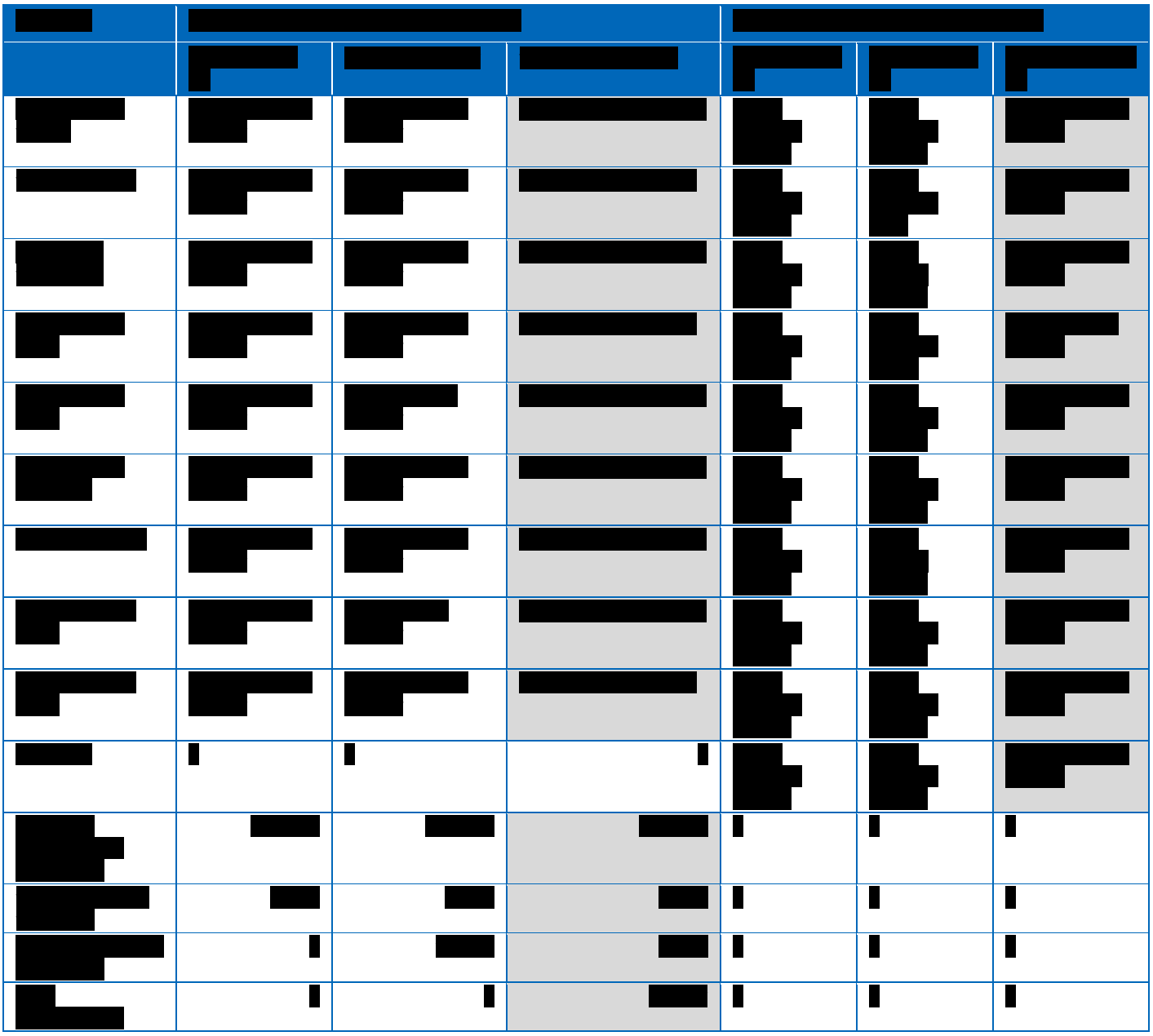

[redacted].

Source: Manufacturer-submitted indirect treatment comparison.[77]

Table 33:

Source: Manufacturer-submitted indirect treatment comparison.[77]

Table 34:

Deviance information criterion			
Total residual deviance			
Between standard deviation			
Beta coefficient			

Source: Manufacturer-submitted indirect treatment comparison.[77]

Table 35: [redacted]

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Source: Manufacturer-submitted indirect treatment comparison.[77]

Table 36:

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Source: Manufacturer-submitted indirect treatment comparison.[77]

Table 37: [redacted]

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Source: Manufacturer-submitted indirect treatment comparison.[77]

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Source: Manufacturer-submitted indirect treatment comparison.[77]

Subgroup Analysis: [redacted]

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Figure 12: [redacted]

Figure 12 contained confidential information and was removed at the request of the manufacturer.

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Source: Manufacturer-submitted indirect treatment comparison.[77]

Table 41: [redacted]

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Table 44:

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Source: Manufacturer-submitted indirect treatment comparison.[77]

Table 49:

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Table 50:

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Critical Appraisal

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Summary

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Conclusion

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