Assessment report

Cimzia

International non-proprietary name: certolizumab pegol

Procedure No. EMEA/H/C/001037/II/0065

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
ADAb	anti-drug antibodies
ANCOVA	analysis of covariance
BMI	body mass index
BSA	body surface area
CI	confidence interval
CIMPACT	Study PS0003
CIMPASI-1	Study PS0005
CIMPASI-2	Study PS0002
CRF	Case Report form
CSR	clinical study report
Ctrough	trough concentration
CZP	certolizumab pegol
DLQI	Dermatology Life Quality Index
ES	Efficacy Set
ETN	etanercept
HADS-A	Hospital Anxiety and Depression Scale for anxiety
HADS-D	Hospital Anxiety and Depression Scale for depression
IL	interleukin
ISAP	Integrated Statistical Analysis Plan
ITT	intent-to-treat
IVRS/IWRS	Interactive voice response system/ Interactive Web Response System
LOCF	last observation carried forward
LS	least squares
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mNAPSI	modified Nail Psoriasis Severity Index
MS	Maintenance Set
MTX	methotrexate
NRI	non-responder imputation
OC	observed case
PASI	Psoriasis Area and Severity Index
PASI50	at least 50% reduction from Baseline in PASI
PASI75	at least 75% reduction from Baseline in PASI
PASI90	at least 90% reduction from Baseline in PASI
PASI100	100% reduction from Baseline in PASI
PGA	Physician's Global Assessment
PopPK	population PK
PPS	Per Protocol Set
PK	Pharmacokinetics
PsA	psoriatic arthritis
PSO	psoriasis
PT	preferred term
Q2W	every 2 weeks
Q4W	every 4 weeks
RS	Randomized Set
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous
SCE	Summary of Clinical Efficacy
SD	standard deviation
SE	standard error
SF-36®	Short Form 36-Item Health Survey
SOC	System Organ Class
TNFα	tumor necrosis factor alpha
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire–Specific Health Problem

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, UCB Pharma S.A. submitted to the European Medicines Agency on 25 July 2017 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include plaque psoriasis in adult patients for Cimzia; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated.

The Package Leaflet is updated in accordance. The RMP version 13.2 has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0101/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (EMEA-C1-001071-PIP03-14) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH has received Scientific Advice from the CHMP for the development of CZP in psoriasis.

The first advice was received in December 2006 and concerned clinical aspects (dose selection, durability of treatment response, response to re-treatment, blinding vs. placebo, drug-drug-interactions, study design e.g. choice of comparator and non-inferiority margin, primary end-point, size of the safety database, etc.).

The second was a follow-up advice received in June 2014, which concerned the overall clinical study programme, the patient population (to support a first- or a second-line indication) the dose selection,

the primary end-points and their time points for assessment, the placebo-control up to Week 16, statistical analysis, the extent of safety data, etc.

Overall, the Applicant has taken the CHMP advice into consideration in the CZP psoriasis development. One comment in the most recent advice was that the restriction of previous exposure to not more than 2 biological response modifiers (including anti-TNF) for PsA or PSO and that subjects must not have been a primary failure to any prior biologic therapy (defined as no response within the first 12 weeks) may have consequences for the final indication wording, as there will be no data available on those with primary biologic failure.

Another issue concerned the size of the proposed safety database and whether it would be sufficient for MAA and could be supplemented with safety data in other licensed indications and from post marketing surveillance data. This approach was overall endorsed, however, since there are no approved indications with the 400mg Q2W maintenance dose within the EU, additional safety studies may be necessary to support this higher dose in PSO patients.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder

Timetable	Actual dates
Start of procedure:	12 August 2017
CHMP Rapporteur Assessment Report	6 October 2017
PRAC Rapporteur Assessment Report	13 October 2017
PRAC members comments	18 October 2017
Updated PRAC Rapporteur Assessment Report	19 October 2017
PRAC Outcome	26 October 2017
CHMP members comments	30 October 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	3 November 2017
Request for supplementary information (RSI)	9 November 2017
CHMP Rapporteur Assessment Report	20 February 2018
PRAC Rapporteur Assessment Report	23 February 2018
PRAC members comments	28 February 2018
Updated PRAC Rapporteur Assessment Report	1 March 2017
PRAC Outcome	8 March 2018
CHMP members comments	12 March 2018
Updated CHMP Rapporteur Assessment Report	15 March 2018
Request for Supplementary Information (RSI)	22 March 2018
Submission deadline	29 March 2018
Re-start of procedure:	30 March 2018
CHMP Rapporteur Assessment Report	11 April 2018
CHMP members comments	16 April 2018

Timetable	Actual dates
Opinion	26 April 2018

2. Scientific discussion

2.1. Introduction

This application refers to the Certolizumab pegol (CZP) is a recombinant, humanised antibody Fab' fragment against tumour necrosis factor alpha (TNFα) expressed in *Escherichia coli* and conjugated to polyethylene glycol (PEG). CZP (Cimzia) is currently approved in for the treatment of Rheumatoid arthritis (RA), Axial spondyloarthritis (AxPA) and Psoriatic arthritis (PsA).

The current variation application seeks to extend the approved indication also to include Plaque psoriasis. Cimzia is indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The proposed posology in psoriasis is 400 mg every 2 weeks, but a dose of 400 mg at Weeks 0, 2 and 4 followed by 200 mg every 2 weeks may be considered.

The clinical development for CZP in psoriasis consists of two phase 2 studies and three phase 3 studies which are discussed hereafter.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

An increase in environmental exposure is generally expected when a new indication is added and the patient population is increased and this potential impact should be evaluated by the applicant. The applicant has submitted an acceptable justification for not conducting further environmental risk assessment. Due to the nature of certolizumab pegol (polypeptide) and according to the current Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2), products containing peptides are unlikely to result in significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1–1: Phase 2 and 3 studies of CZP in adult subjects with moderate to severe chronic plaque PSO

Study number/ study design	Number of subjects		Maximum duration of treatment	Key efficacy variables
Phase 2				
C87040: multicenter, dose response, double-blind, placebo-controlled, randomized study	CZP 200mg Q2W[a]=59 CZP 400mg Q2W=58 PBO=59		12 weeks	• Percentage of subjects who achieved at least a PASI75 response at Week 12 • Percentage of subjects with a PGA rating of clear or almost clear at Week 12
C87044: multicenter, double-blind follow-up for C87040[b]	CZP 200mg Q2W=34 CZP 400mg Q2W=37 PBO=0		12 weeks	• Difference in PASI scores between Week 12 of C87040 and Week 12 of C87044
Phase 3				
CIMPASI-1: multicenter, randomized, double-blind, parallel-group study, followed by a double-blind Maintenance Period and open-label follow-up	Initial Treatment Period (Weeks 0 to 16)		144 weeks	• PASI75 at Week 16 • PGA Clear or Almost clear (with at least a 2-category improvement) at Week 16 • PASI90 at Week 16 • Change from Baseline in DLQI at Week 16 • PASI75 at Week 48 • PGA Clear or Almost clear (with at least a 2-category improvement) at Week 48
	CZP 200mg Q2W[c]=95 CZP 400mg Q2=88 PBO=51			
	Maintenance Treatment Period (Weeks 16 to 48)[d]			
	CZP 200mg Q2W[c]=79 CZP 400mg Q2W=141 PBO=3			
CIMPASI-2: multicenter, randomized, double-blind, parallel-group study, followed by a double-blind Maintenance Period and open-label follow-up	Initial Treatment Period (Weeks 0 to 16)		144 weeks	• PASI75 at Week 16 • PGA Clear or Almost clear (with at least a 2-category improvement) at Week 16 • PASI90 at Week 16 • Change from Baseline in DLQI at Week 16 • PASI75 at Week 48 • PGA Clear or Almost clear (with at least a 2-category improvement) at Week 48
	CZP 200mg Q2W[c]=91 CZP 400mg Q2W=87 PBO=49			
	Maintenance Treatment Period (Weeks 16 to 48)[d]			
	CZP 200mg Q2W[c]=81 CZP 400mg Q2W=123 PBO=6			

Table 1–1: Phase 2 and 3 studies of CZP in adult subjects with moderate to severe chronic plaque PSO, contin.

CIMPACT: multicenter, randomized, double-blind, parallel-group, placebo- and active-controlled study, followed by a placebo-controlled, double-blind Maintenance Period and open-label follow-up	Initial Treatment Period (Weeks 0 to 16)[e]	144 weeks	• PASI75 at Week 12[e] • PGA at Week 12[e] • PASI90 at Week 12 • PASI75 at Week 16 • PGA at Week 16 • PASI90 at Week 16
	CZP 200mg Q2W[c]=165 CZP 400mg Q2W=167 ETN=170 PBO=57		
	Maintenance Treatment Period (Weeks 16 to 48)[d]		
	CZP 200mg Q2W=144 CZP 400mg Q2W=272 CZP 400mg Q4W=44 PBO=73		

CZP=certolizumab pegol; ETN=etanercept; PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; PASI90=at least 90% reduction from Baseline in Psoriasis Area and Severity Index; PGA=Physician's Global Assessment; PBO=placebo; PSO=psoriasis; Q2W=every 2 weeks; Q4W=every 4 weeks

[a] Loading dose of CZP 400mg at Week 0

[b] In C87044, only subjects who responded after 12 weeks of treatment in C87040 (ie, showed an improvement ≥75% from Baseline PASI score in C87040) and who subsequently relapsed within the 24-week Follow-Up Period of C87040, were re-treated with the dose they were randomized to in C87040. Relapse was defined as a reduction by more than 50% of the maximal improvement in PASI score from Baseline during the Treatment Period.

[c] Loading dose of CZP 400mg at Weeks 0, 2, and 4. For the Maintenance Period of CIMPASI-1 and CIMPASI-2, subjects randomized initially to PBO received CZP 400mg Q2W at Weeks 16, 18, and 20 (loading doses) followed by CZP 200mg Q2W (starting at Week 22) if a PASI75 response was not achieved at Week 16 (but a PASI50 was achieved at Week 16.)

[d] The number of subjects specified for the Maintenance Treatment Period includes subjects who escaped to open-label CZP 400mg Q2W at Week 16.

[e] Measured at Week 12 because the approved duration of initial ETN treatment at 50mg twice weekly is 12 weeks.

2.3.2. Pharmacokinetics

The pharmacokinetics (PK) of certolizumab pegol (CZP) in patients with moderate to severe chronic plaque psoriasis (PSO) was investigated in two phase 2 studies (C87040 and C87044) and three phase 3 studies (CIMPASI-1 [PS0005], CIMPASI-2 [PS0002]), and CIMPACT [PS0003]).

Validated bioassays were used for determining the concentration of CZP in PK samples obtained in these studies. The occurrence of anti-drug antibodies (ADAb) was also determined using validated methods.

The phase 3 studies were analysed using population PK (PopPK) modelling. The phase 2 studies were not included in the PopPK analysis.

The PopPK analysis data set consisted of in total 820 subjects providing 4361 PK observations. Female subjects made up 35.9 % of the population. Almost all subjects, 94 %, were categorized as "Caucasian". The median (range) age was 46.0 years (18 to 80 years) and the median (range) disease duration was 15.7 years (0.3 to 63.7 years). The median (range) body weight of the subjects was 87.9 kg (42 to 198 kg).

A one compartment model with first-order absorption and first-order elimination from the central compartment was used to describe the data. ADAb status was seen to substantially increase CZP clearance, reducing the trough concentration (Ctrough) of CZP by about 85%. Clearance and volume of distribution was seen to increase with increasing body weight. The effect these two covariates on the trough concentration of CZP at week 16 of treatment is shown in the table below.

Table 1 Predicted CZP Ctrough at Week 16, based on the final PK model, stratified by WT category, by ADAb status and dose at randomization

Dose / Stratification	Median (μg/mL)	(5th to 95th) percentiles
ADAb negative		
CZP 200 mg Q2W / 41.8-74.5 kg	35.11	(20.6 to 59.3)
CZP 200 mg Q2W / 74.5-84.5 kg	28.05	(16.9 to 45.1)
CZP 200 mg Q2W / 84.5-94.3 kg	25.19	(15.1 to 40.5)
CZP 200 mg Q2W / 94.3-107.5 kg	21.96	(13.0 to 35.5)
CZP 200 mg Q2W / 107.5-198.5 kg	17.27	(9.39 to 29.4)
CZP 400 mg Q2W / 41.8-74.5 kg	69.59	(41.1 to 115)
CZP 400 mg Q2W / 74.5-84.5 kg	55.81	(33.8 to 88.0)
CZP 400 mg Q2W / 84.5-94.3 kg	50.07	(30.1 to 79.3)
CZP 400 mg Q2W / 94.3-107.5 kg	43.86	(26.1 to 69.8)
CZP 400 mg Q2W / 107.5-198.5 kg	34.39	(18.8 to 58.0)
ADAb positive		
CZP 200 mg Q2W / 41.8-74.5 kg	5.698	(2.68 to 11.4)
CZP 200 mg Q2W / 74.5-84.5 kg	4.334	(2.11 to 8.39)
CZP 200 mg Q2W / 84.5-94.3 kg	3.810	(1.85 to 7.41)
CZP 200 mg Q2W / 94.3-107.5 kg	3.222	(1.56 to 6.36)
CZP 200 mg Q2W / 107.5-198.5 kg	2.404	(1.09 to 5.06)
CZP 400 mg Q2W / 41.8-74.5 kg	11.40	(5.37 to 22.8)
CZP 400 mg Q2W / 74.5-84.5 kg	8.678	(4.23 to 16.8)
CZP 400 mg Q2W / 84.5-94.3 kg	7.599	(3.70 to 14.8)
CZP 400 mg Q2W / 94.3-107.5 kg	6.461	(3.13 to 12.7)
CZP 400 mg Q2W / 107.5-198.5 kg	4.796	(2.18 to 10.1)

WT: body weight; ADAb: anti-CZP antibodies; ADAb negative indicates subjects with no ADAb event (>2.4 U/mL) in the first 16 weeks; ADAb positive indicates subjects with ADAb >2.4 U/mL at all time points in the first 16 weeks; CZP: certolizumab pegol; Q2W: dosing every 2 weeks; C_{trough}: trough concentration

2.3.1. PK/PD modelling

A Population PK-PD analysis was performed using PASI and PGA data up to Week 16 from CIMPASI-1, CIMPASI-2, and CIMPACT. Data only up to 16 weeks were used to develop the models due to the response-driven change in treatment from Week 16 onwards. Therefore the analysis dataset included 4919 PASI observations from 849 subjects and 5760 PGA observation records for 835 subjects out of, in total, approximately 11000 PASI and PGA observations from 849 subjects.

Covariates that were tested in the modeling were: baseline PASI/PGA score, body size (eg. weight, BSA), age, occurrence of anti-drug antibodies (ADAb), sex, disease duration, geographical region and prior biologics therapy.

PASI

The PASI PKPD model included a component to describe the PASI baseline observations, a placebo effect component, a drug effect component, and a component describing the time-course of PASI response.

The PASI baseline observations were, due to the inclusion criterion in the study protocols, constrained between 11.5 and 72 by using a logit transformation of the PASI baseline parameter to make it possible for the parameter to obtain values of 12 and 72.

The treatment effect (Treatment) was defined as the sum of the placebo effect (Placebo) and the drug effect (Drug),

Treatment = Placebo + Drug,

where Drug was assumed to give an improvement in PASI (a reduction in PASI), while the placebo effect component could give both an improvement and/or worsening of the disease. The final PASI model used a sigmoidal maximum effect (Emax) model to describe the drug effect where the individual model predicted concentration was used as a predictor of the response.

An indirect effect model characterized the delay between the start of the treatment and the PASI response, where the treatment effect inhibited the zero-order production rate constant (Kin) parameter as shown in the equation below.

$$dPASI/dt = Kin \times (1 - Drugeffect - Placeboeffect) - Kout \times PASI$$

The covariate-parameter relationships included in the final PASI model were: prior treatment with biologics and region on PASI baseline; WT on Placeboeffect; modeled PASI baseline on Emax; WT and region on PASI t1/2; and at least one ADAb event >2.4 U/mL during the first 16 weeks on EC90.

PGA

A discrete Markov model was developed to describe the PGA observations. The treatment effect was characterized by an exposure-response relationship based on an Emax function driven by the individual model predicted concentration. Region was included as a covariate on Emax. Emax for Central/Eastern Europe and North America was estimated at 2.71 and Emax for Western Europe was estimated at 2.13. ADAb16 positive was a significant covariate on EC50, where subjects with at least one anti-CZP antibodies event (>2.4 U/mL) in the first 16 weeks had a 126% increase in EC50.

The PKPD modeling of PASI and PGA were carried out using adequate methods.
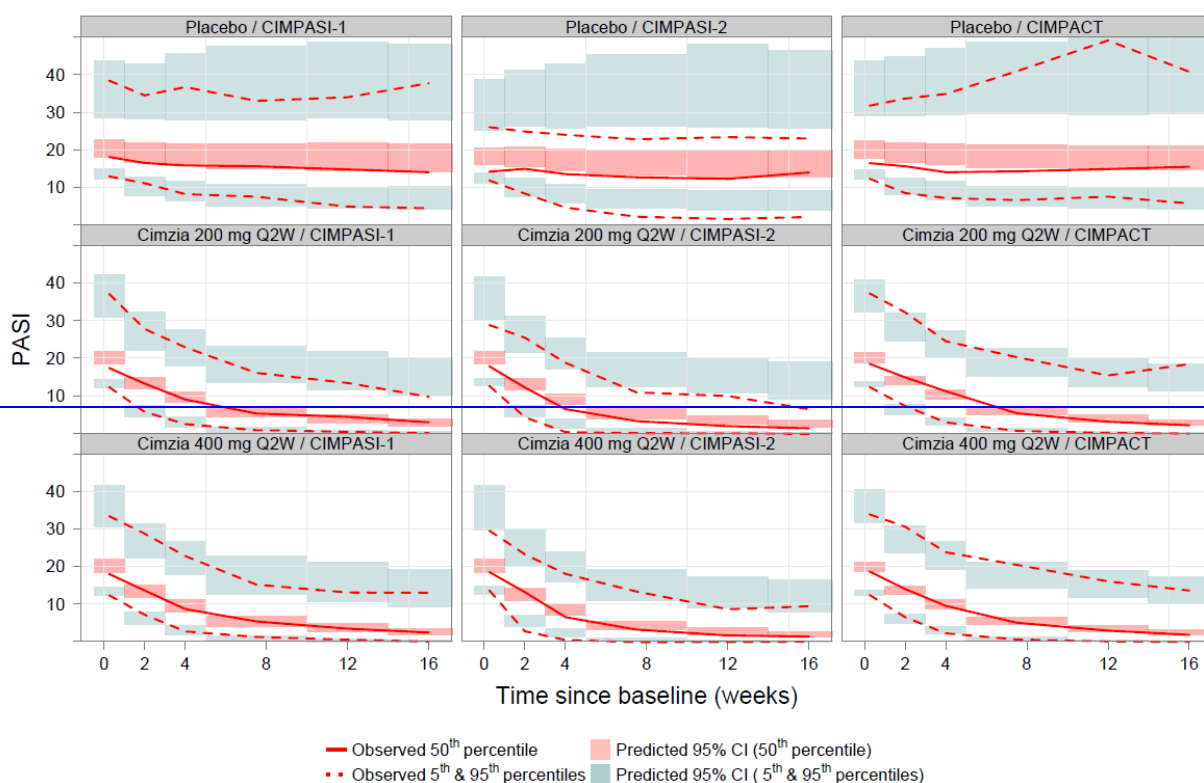
The Visual predictive checks for the PGA model appear to be sufficient.

2.3.2. Immunogenicity

As background information, anti-drug antibodies (ADAb) have been observed in approximately 5% to 15% of patients that are treated with Certolizumab pegol (CTZ) which has an impact on the clearance of CTZ and also on the effect.

A validated ELISA method was designed to detect the presence of ADAb in samples obtained from patients in the PSO studies.

The incidence of ADAb was consistently over 2-fold higher in the CZP 200mg Q2W group compared with the CZP 400mg Q2W group. In the Initial Treatment Period of the Phase 3 studies, the incidence of ADAb positivity in the CZP 200mg Q2W group (which includes both PASI75 responders and escapers) was 14.7% (51 of 347 subjects) compared with 5.3% (18 of 340 subjects) in the CZP 400mg Q2W group (ie, a 2.8-fold higher incidence). In the Combined Initial and Maintenance Treatment Period of the Phase 3 studies, the incidence of ADAb positivity in the CZP 200mg Q2W group was 19.2% (54 of 281 subjects) compared with 8.3% (22 of 265 subjects) in the CZP 400mg Q2W group (ie, a 2.3-fold higher incidence).

It was concluded from the population PK analysis that the presence of ADAb increased the CL/F of CZP by approximately 3-fold, resulting in a decrease of about 85% in the Ctrough.

Figure 1 Illustration of the predicted proportion of PASI75 responders versus time profiles, based on the final model, stratified by ADAb status.
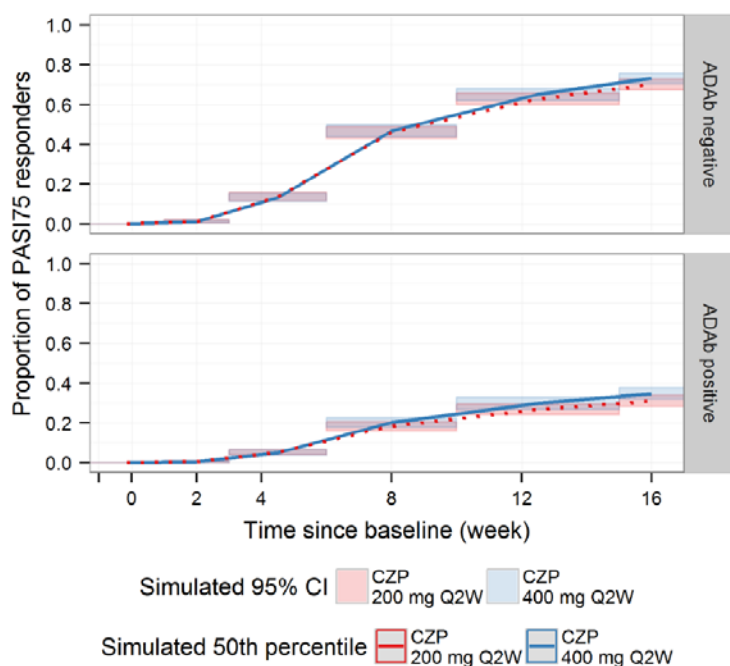
2.3.3. Discussion on clinical pharmacology

The pharmacokinetics of certolizumab pegol (CZP) was studied in >800 patients with moderate to severe chronic plaque psoriasis (PSO) in the CIMPASI-1, CIMPASI-2 and CIMPACT Phase 3 trials. The PK data were described by a one compartment model with first-order absorption and a first-order elimination from the central compartment. The typical value of CL/F was 0.338 L/day and V/F was 4.71 L and the variability between individuals was moderate. The presence of anti-drug antibodies (ADAb) increased CL/F 3-fold which led to an 85% reduction in Ctrough. CL/F and V/F increased with body size. To compare, a subject with a body weight of 150 kg would have >3-fold higher Ctrough compared to a subject with a body weight of 50 kg. PASI t1/2 appears to be longer as body weight increases, therefore it is predicted to take longer to achieve steady state exposure and clinical response in heavier subjects.

The relation between PASI score and CZP plasma concentration could be described by an indirect response with an Emax model. The model dictates that a plasma concentration of 11.1 µg/mL would achieve 90% of the maximal response. The median Ctrough associated with the dose level 200 mg Q2W is above this value and both the 200 mg Q2W and the 400mg Q2W doses are essentially on the upper flat part of the exposure-response curve. However, due to inter-individual variability in exposure to CZP (Ctrough) as well as in the sensitivity to CZP exposure (EC90), the higher dose level is expected to lead to a higher proportion of individuals obtaining PASI90 response.

Of note, due to the fact that both 200 mg Q2W and 400 mg Q2W are on the upper flat part of the exposure-response curve, the difference in PASI response is much smaller between the two dose levels as compared to the difference in plasma concentration. This is important for correct interpretation of the clinical relevance of differences in the PK of CZP.

2.3.4. Conclusions on clinical pharmacology

The clinical pharmacology data submitted in support of the application are acceptable. Pharmacokinetics and exposure-response of certolizumab pegol (CTZ) have been characterized in patients with moderate to severe chronic plaque psoriasis (PSO).

2.4. Clinical efficacy

The CZP development program in subjects with moderate to severe chronic plaque PSO consists of 5 clinical studies:

- Completed Phase 2 studies C87040 and C87044

- Phase 3 double-blind, placebo-controlled studies PS0005 and PS0002 (hereafter referred to as the CIMPASI studies, where PS0005 is CIMPASI-1 and PS0002 is CIMPASI-2). The Initial Treatment Period (Week 0 to Week 16) and the Maintenance Treatment Period (Week 16 to Week 48) have been completed. The Open-Label Extension (OLE) Treatment Period (Week 48 to Week 144) is ongoing.

- Phase 3 double-blind, placebo- and active-controlled study PS0003 (hereafter referred to as CIMPACT). The Initial Treatment Period (Week 0 to Week 16) and the Maintenance Treatment Period (Week 16 to Week 48) have been completed. The OLE Treatment Period (Week 48 to Week 144) is ongoing.

2.4.1. Dose response study(ies)

No conventional dose response study has been performed in the indication plaque psoriasis.

No formal dose ranging study with a wide range of dose levels was performed to support the posology of CZP in the indication plaque psoriasis however information from other indications is available. In the Phase 2 studies C87040 and C87044, two different dose levels were studied (CZP 200mg Q2W and CZP 400mg Q2W) and these two doses were also studied in phase 3, both for initial treatment and for maintenance treatment (including 400 mg Q4W) in study CIMPACT. As described above, a population PK-PD analysis was performed using PASI and PGA data up to Week 16 from the pivotal studies, CIMPASI-1, CIMPASI-2, and CIMPACT.

The dose ultimately proposed as the recommended dose (see further below) is a higher dose than recommended in the currently approved indications for Cimzia (RA, PsA, AS).

The phase 2 studies C87040 and C87044 are described below.

1) Study C87040

Methods

Study C87040 was a multicenter, dose-response, double-blind, parallel-design, placebo-controlled, 3-arm, randomized study in subjects with moderate to severe chronic plaque PSO.

Study participants

The key inclusion criteria were similar to those in the Phase 3 studies (as described later), with the exceptions that 18 year olds were not eligible, and the chronic plaque PSO had to be stable for at least 3 months and diagnosed as moderate to severe for at least 6 months.

Treatments

There was also no PGA requirement for entry into this study. In addition, subjects randomized to CZP 200mg Q2W only received 1 loading dose of CZP 400mg as opposed to the 3 loading doses that were administered in the Phase 3 studies in subjects who were randomized to CZP 200mg Q2W.

After a Screening Period of 1 week, subjects were randomized to 1 of 3 treatment groups:

- Placebo Q2W for 12 weeks

- CZP 400mg at Week 0, followed by CZP 200mg Q2W

- CZP 400mg Q2W

The Treatment Period lasted 12 weeks, with a Follow-Up Period of a maximum 24 weeks.

Treatment non-responders (subjects who did not achieve at least a PASI75 response at the end of the 12-week Treatment Period) were discontinued from the study after a 12-week, drug-free follow-up period for safety evaluation. Treatment responders (subjects who achieved a PASI75 response at the end of the 12-week Treatment Period) who relapsed during the 24-week Follow-Up Period were eligible to enter C87044 and to be retreated with their original treatment dose from C87040.

Outcomes/Endpoints

For PASI75 responders at Week 12, relapse was defined as a >50% decrease in the maximal improvement from Baseline in the PASI score achieved during the Treatment Period of C87040.

The primary efficacy endpoints were proportion of subjects with a PGA rating of 'clear' or 'almost clear' at Week 12 and the proportion of subjects (responders) achieving at least a 75% decrease from baseline in PASI score (PASI75) at Week 12.

Secondary efficacy parameters were time to treatment response, time to relapse, PASI50 and PASI90 responder rates, BSA affected by PSO, and time to withdrawal from treatment due to lack of efficacy.

Results

Numbers analysed
A total of 176 subjects were randomized to 3 treatment groups: placebo (59 subjects), CZP 200mg Q2W following a single loading dose of 400mg (59 subjects), and CZP 400mg Q2W (58 subjects). The 176 randomized subjects represented the intent-to-treat (ITT) population.

The majority of subjects in each group completed the 12-week treatment period: 40 (67.8%) placebo subjects, 54 (91.5%) CZP 200mg Q2W subjects and 54 (93.1%) CZP 400mg Q2W subjects. Twenty-eight subjects prematurely discontinued from the treatment period. The main reasons for discontinuation were lack or loss of efficacy (14 placebo subjects, 3 CZP 200mg Q2W subjects, and 1 CZP 400mg Q2W subject). Other reasons for discontinuing were AEs (3 placebo subjects, 2 CZP 200mg Q2W subjects, and 3 CZP 400mg Q2W subjects), and lost to follow-up (2 placebo subjects).

Subjects in the ITT Population entered a follow-up period lasting up to a maximum of 24 weeks after treatment. One hundred and twenty two (69.3%) subjects completed the follow-up period: 27 (45.8%) placebo subjects, 45 (76.3%) CZP 200mg Q2W subjects, and 50 (86.2%) CZP 400mg Q2W subjects; 54 subjects discontinued from the follow-up period. The main reasons for discontinuing from the follow-up period were lack or loss of efficacy (14 placebo subjects and 7 CZP 200mg Q2W subjects), and unknown reasons (13 placebo subjects, 4 CZP 200mg Q2W subjects, and 4 CZP 400mg Q2W subjects).

Demographic characteristics were similar for each treatment group. At randomization, the mean age of the ITT population was 43.4 (±11.8) years (range 18 to 73 years). The majority of subjects were white (97.7%), and more than two-thirds (70%) were male. Mean (±SD) weight of subjects was 82.2 (±19.6) kg. The mean (±SD) BMI of subjects was 27.1 (±5.5) kg/m2, and ranged between 16.7 and 55.8 kg/m2. The mean PASI score was 21.95 and mean BSA was 28.38.

The population included was as expected for a population with moderate to severe psoriasis. Study completion was >90% in the CZP groups and lower in the placebo group, mainly due to lack of efficacy.

Summary of main Efficacy results

Table: Results of primary efficacy endpoints in C87040 (ITT)

	PBO N=59	CZP 200mg Q2W N=59	CZP 400mg Q2W N=58
PASI75 response at Week 12 [a]			
Responder, n (%)	4 (6.8)	44 (74.6)	48 (82.8)
Odds ratio: CZP/PBO [b] estimate [95% CI]	NA	40.2 [13.7, 150.3]	73.4 [23.5, 292.6]
Treatment effect p-value vs PBO	NA	<0.001	<0.001
PGA response at Week 12 [c]			
Responder, n (%)	1 (1.7)	31 (52.5)	42 (72.4)
Odds ratio: CZP/PBO [b] estimate [95% CI]	NA	64.1 [12.7, 1169.1]	162.6 [31.4, 2999.2]
Treatment effect p-value vs PBO	NA	<0.001	<0.001

CI=confidence interval; CZP= certolizumab pegol; ITT=intent-to-treat; NA=not applicable; PASI=Psoriasis Area and Severity Index; PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; PBO=placebo; PGA=Physician's Global Assessment; Q2W=every 2 weeks
Note: Subjects with a missing PASI or PGA score at Week 12 (Visit 10) are considered as nonresponders for that parameter.
[a] PASI75 response was defined as a decrease in PASI score at Week 12 (Visit 10) from Baseline of at least 75%.
[b] Logistic regression with treatment and baseline severity of psoriasis as factors. Confidence limits were based on likelihood ratio statistics.
[c] PGA response was defined as a PGA rating at Week 12 (Visit 10) of clear or almost clear.

At Week 12, a PASI90 response was observed in 1 (1.7%) placebo subject, 23 (39.0%) CZP 200mg Q2W subjects, and 27 (46.6%) CZP 400mg Q2W subjects (p <0.001 for the comparison of each CZP dose versus placebo).

For subjects who were PASI75 responders at Week 12, the median time to relapse was 22 weeks (95% CI: 17, 26) for the CZP 200mg Q2W) group, and 20 weeks (95% CI: 17, 22) for the CZP 400mg Q2W group. In this subgroup, 30 out of 44 subjects (68%) and 38 out of 48 subjects (79%) in the CZP 200mg Q2W and CZP 400mg Q2W groups, respectively, relapsed. None of the 4 placebo responders relapsed.

Both CZP doses were statistically and clinically different from placebo for both co-primary efficacy endpoints, with fairly high PASI75 response rates at week 12. More than two thirds of the PASI75 responders relapsed after stopping treatment with a median time to relapse of about 20 weeks (5 months).

2) Study C87044

Methods

C87044 was a double-blind, multicenter follow-up study to C87040. Subjects received the same treatment regimens in C87044 as they had received in C87040: CZP 200 mg Q2W or CZP 400 mg Q2W or placebo.

Only subjects who achieved a PASI75 response at Week 12 in C87040 and subsequently relapsed within 24 weeks could be retreated in C87044. After a Screening Period of 1 week, subjects in C87044

entered the 12-week Retreatment Period. A Safety Visit occurred 12 weeks after the end of the Retreatment Period or 12 weeks after the Discontinuation Visit in case of withdrawal from C87044.

In order to preserve the double-blind nature of C87040 and C87044, double-blind procedures were followed in C87044 after the unblinding of C87040 until the database lock of C87044.

Results

Numbers analysed

In total, 71 subjects entered the follow-up study, C87044: 34 subjects received CZP 200 mg Q2W (following a single loading dose of 400 mg) and 37 subjects received CZP 400 mg Q2W. The 71 subjects represented the ITT population. No placebo treated subjects entered C87044 since no placebo responders in C87040 met the criteria for relapse.

The majority of subjects in each group completed the 12-week treatment period of C87044: 32 (94.1%) and 35 (94.6%) subjects receiving CZP 200 mg Q2W and CZP 400 mg Q2W, respectively. Four (5.6%) subjects prematurely discontinued from the treatment period, two subjects in each group.

Outcomes and estimation

The primary efficacy endpoint was the difference in PASI scores between first treatment Week 12 of C87040 and retreatment Week 12 of C87044. For subjects with a missing PASI score at Week 12, their last observed PASI score under retreatment was used (LOCF). Results for the primary endpoint are presented in the table below.

Table: PASI score after retreatment in C87044

	CZP 200mg Q2W	CZP 400mg Q2W
PASI score at initial Baseline (mean [SD]) (ITT)	21.89 (7.52)	22.99 (8.79)
PASI score at 12 weeks in Initial Treatment (median [95% CI]) (ITT)	1.60 (0.90, 2.70)	1.80 (1.20, 2.60)
PASI at 12 weeks in Retreatment (median [95% CI]) (ITT)	3.35 (1.40, 6.30)	2.00 (0.60, 3.30)
Median difference in PASI score at 12 weeks (Retreatment - Initial Treatment) [95% CI])		
ITT population (N=34; N=37)	1.25 (0.10, 4.40)	0.20 (0.00, 0.70)
PP population (N=23; N=25)	1.00 (-0.60, 5.80)	0.00 (-0.50, 0.70)

CI=confidence interval; CZP=certolizumab pegol; ITT=intent-to-treat; PASI=Psoriasis Area and Severity Index; PP=Per Protocol; Q2W=every 2 weeks; SD=standard deviation

Approximately 75% and 83% of subjects receiving CZP 200mg Q2W and CZP 400mg Q2W, respectively, achieved a PASI75 response with the initial 12-week treatment in C87040, and were thereby eligible to participate in C87044. The median time to a loss of response was 20 to 22 weeks, and those who relapsed within 24 weeks of discontinuation of treatment were eligible for retreatment. After 12 weeks of retreatment, reductions in median PASI scores were once again observed for both CZP dose groups. The study was not designed to test any hypothesis regarding retreatment effect.

The results of this study indicate that patients responding to CZP and who were off therapy for a period were able to respond again upon retreatment. However, as also pointed out by the Applicant, subjects from study C87040 were not re-randomized to enter study C87044. Therefore, the results for the two treatment groups (CZP 200mg Q2W and CZP 400mg Q2W) in C87044 are not comparable, and no inferential analysis to compare treatment groups was performed.

2.4.2. Main study(ies)

There were three main studies: CIMPASI-1 (PS0005) , CIMPASI-2 (PS0005) and CIMPACT (PS0003).

Studies **CIMPASI-1** and **CIMPASI-2** had identical design and will therefore be described together. Study **CIMPACT** had a somewhat different design and differences compared with the CIMPASI studies will therefore be highlighted and specific features of this study described separately.
The results of the three studies are however presented in the same section. (see section results)

1)_Studies CIMPASI-1 and CIMPASI-2_

Methods

Both studies CIMPASI-1 and CIMPASI-2 were randomized, double-blind, parallel-group, placebo-controlled, multicenter studies designed to demonstrate the efficacy and safety of CZP in subjects with moderate to severe chronic plaque psoriasis.

Study CIMPACT was also a randomized, double-blind, parallel-group, placebo-controlled, multicenter study that was also active-controlled (etanercept, ETN).

Study participants

Main inclusion criteria for study CIMPASI-1 and CIMPASI-2:

- Adult men and women ⩾18 years.
- Chronic plaque psoriasis for at least 6 months.
- Baseline PASI ⩾12 and BSA ⩾10% and Physician's Global Assessment (PGA) score ⩾3.
- Candidates for systemic PSO therapy and/or phototherapy and/or chemophototherapy.
- Female subjects must have been either postmenopausal for at least 1 year, surgically incapable of childbearing, or effectively practicing an acceptable method of contraception. Male subjects must have agreed to ensure they or their female partner(s) used adequate contraception during the study and for at least 10 weeks after the subject received his final dose of study medication.

Main exclusion criteria:

- Erythrodermic, guttate, generalized pustular form of PSO.
- Subjects with a history of chronic or recurrent infections (more than 3 episodes requiring antibiotics/antivirals during the preceding year), recent serious or life-threatening infection within the 6 months prior to the Baseline Visit (including herpes zoster), hospitalization for any infection in the last 6 months, or any current sign or symptom that may have indicated an infection.
- Subjects with concurrent acute or chronic viral hepatitis B or C, or with known HIV infection.
- Subjects with known history of or current clinically active infection with Histoplasma, Coccidiodes, Paracoccidioides, Pneumocystis, nontuberculous mycobacteria (NTMB), Blastomyces, or Aspergillus.
- Subjects with a history of an infected joint prosthesis at any time with that prosthesis still in situ.
- Subjects who received any live (includes attenuated) vaccination within the 8 weeks prior to Baseline
- Subjects with a high risk of infection (eg, subjects with leg ulcers, indwelling urinary catheter, persistent or recurrent chest infections, permanently bedridden or wheelchair bound subjects).
- Subjects with a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease.
- Subjects with concurrent malignancy or history of malignancy, except for the following specific exceptions, were excluded. Subjects who met the following criteria may have been included:

- – ⩽3 excised or ablated basal cell carcinomas of the skin
- – One squamous cell carcinoma (stage T1 maximum) of the skin successfully excised or ablated, with no signs of recurrence or metastases for more than 2 years prior to Screening
- – Actinic keratosis(-es)
- – Squamous cell carcinoma in situ of the skin successfully excised or ablated, more than 6 months prior to Screening
- – Uterine cervical carcinoma in situ successfully surgically treated with no signs of recurrence or metastases for more than 5 years prior to Screening

- Subjects with congestive heart failure.
- Subjects with a history of, or suspected, demyelinating disease of the central nervous system (eg, multiple sclerosis or optic neuritis).
- Subjects who had major surgery (including joint surgery) within the 8 weeks prior to Screening, or planned surgery within 6 months after entering the study.
- Subjects with a current or recent history of severe, progressive, and/or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac, or neurological disease.
- Subjects with clinically significant laboratory abnormalities (eg, aspartate aminotransferase [AST] and alanine aminotransferase [ALT] were >3x the upper limit of normal [ULN], total bilirubin >1.5xULN, creatinine >ULN, or white blood cell [WBC] <3.0x109/L).
- Subjects with any other condition which, in the Investigator's judgment, would make the subject unsuitable for inclusion in the study.
- Subjects must not have been exposed to more than 2 biological response modifiers (including anti-TNF) for PsA or PSO prior to the Baseline Visit (prior use must have been in accordance with the table below).
  - – Subjects must not have been a primary failure to any prior biologic therapy (primary failure defined as no response within the first 12 weeks of treatment with the biologic) and may have been a secondary failure (ie, subject initially responded to therapy and then stopped treatment due to loss of response after Week 12) to no more than 1. Subjects who stopped biologic therapy for intolerance or reasons unrelated to efficacy were not considered secondary failures.

- Subjects must not have used the other medications in the manner as detailed in the table below.
- Subjects with a diagnosis of inflammatory arthritis other than PsA (eg, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, fibromyalgia) or subjects who were taking PsA medications (except stable doses of NSAIDs; subjects were allowed as needed use of acetaminophen, paracetamol, or pain medications).
- Subjects with known TB infection, at high risk of acquiring TB infection, or latent TB infection (unless appropriate prophylaxis was initiated prior to study treatment and continued to completion of prophylaxis), according to certain definitions.
- Female subjects who were breastfeeding, pregnant, or planned to become pregnant during the study or within 5 months or 3 months (country-specific criteria). Male subjects who were planning a partner pregnancy during the study or within 10 weeks following the final dose of study medication.
- Subjects with a known hypersensitivity to any excipients of CZP or with a history of an adverse reaction to PEG.

Table: Exclusions for prior treatment

Drug class	Dose	Exclusion criteria
Systemic retinoids	Any dose	12 weeks prior to the Baseline Visit
Systemic treatment (nonbiological) Systemic immunosuppressants agents (eg, MTX, cyclosporine, azathioprine, thioguanine) Systemic fumarate Systemic corticosteroids Phototherapy or photochemotherapy	Any dose	Used within the 4 weeks prior to the Baseline Visit.
Anti-TNFs Infliximab, adalimumab, golimumab etanercept	Any dose	12 weeks prior to the Baseline Visit
Other biologics and other systemic therapies: Alefacept Efalizumab Ustekimumab Apremilast Secukinumab	Any dose	12 weeks prior to the Baseline Visit for alefacept, efalizumab, and apremilast 24 weeks prior to the Baseline Visit for ustekinumab and secukinumab
Any other antipsoriatic agent (systemic) under investigation (or approved after the protocol is approved)	Any dose	24 weeks
Rituximab	Any dose	2 years
Topical agents Any other antipsoriatic agent (topical) under investigation	Any dose	4 weeks
Topical corticosteroids for dermatological use Vitamin D analogues and topical retinoids Keratolytic agents and coal tar	Any dose	2 weeks

anti-TNF=anti-tumor necrosis factor; MTX=methotrexate

Concomitant medications
All medications (including over-the-counter drugs, vitamins, antacids) being taken at the time of Baseline or during study participation were collected and recorded on the eCRF.

The use of concomitant medications for medical conditions (eg, hypertension, diabetes, acute infections) or treatment of an AE was permitted during this study as long as medications were not explicitly prohibited by the protocol. NSAIDs, acetaminophen, paracetamol, and opioids for PsA were permitted during the study. During the OLE Treatment Period, some topical psoriasis medications were permitted (moderate potency class III to V topical corticosteroids, vitamin D analogues and topical retinoids and keratolytic and coal tar).

Prohibited concomitant treatments (medications and therapies) were largely the same as listed above in the table above for exclusions for prior treatment. Systemic retinoids were also prohibited during the studies.

Treatments

Each study included 5 periods: Screening, Initial Treatment (double-blind, placebo-controlled), Maintenance Treatment (dose-blind), Open-Label Treatment, and Safety Follow-up. They are described below.

The completed initial double-blind treatment periods of 16 weeks were used to demonstrate the efficacy of CZP over placebo. Further double-blind treatment from Weeks 16 to 48, which has also been completed, was intended to collect information on maintenance dosing. Open-label treatment periods for an additional 96 weeks are ongoing.

The CIMPASI-1 and CIMPASI-2 study design is presented in the figure 2 below.

Figure 2: CIMPASI-1 and CIMPASI-2 study design
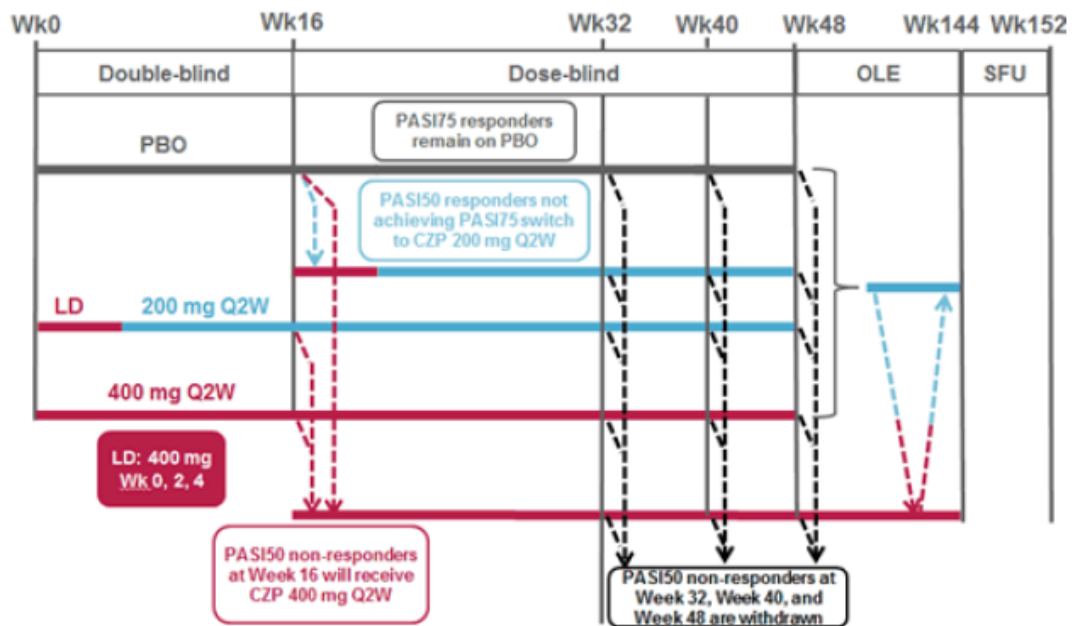
CZP=certolizumab pegol; LD=loading dose; OLE=open-label extension; PASI50=at least 50% reduction from Baseline in Psoriasis Area and Severity Index; PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; PBO=placebo; Q2W=every 2 weeks; SFU=Safety Follow-Up; Wk=week

Period 1 – Screening Period

The Screening Period lasted up to 5 weeks and had the purpose of determining the eligibility of subjects to enter the study, to perform assessments (e.g. degree of psoriasis severity and area of involvement), laboratory data and washout of any medications not permitted for use during the study.

Period 2 – Initial Treatment Period: Week 0 to Week 16

During the 16-week Initial Treatment Period, subjects were randomized in a 2:2:1 ratio to receive either:

- **CZP 200mg Q2W:** CZP administered sc at the dose of CZP 400mg at Weeks 0, 2, and 4, followed by CZP 200mg Q2W (starting at Week 6)

- **CZP 400mg Q2W:** CZP administered sc at the dose of CZP 400mg Q2W

- **Placebo:** placebo administered sc Q2W

Study treatments (including placebo) were administered by dedicated, trained site personnel at Baseline, and at Weeks 2, 4, 6, 8, 10, 12, and 14.

Period 3 – Maintenance Treatment Period: Week 16 to Week 48

The treatment received in Period 3 was based on the response to treatment at Week 16. All CZP and placebo treatments were administered by dedicated, unblinded, trained site staff in the clinic. Subjects who achieved at least a 50% reduction from Baseline in PASI response (PASI50) at Week 16 continued therapy as follows:

- Subjects randomized to CZP 200mg Q2W continued to receive CZP 200mg Q2W.

- Subjects randomized to CZP 400mg Q2W continued to receive CZP 400mg Q2W.

- Subjects randomized to placebo who achieved a PASI50 but not a 75% reduction from Baseline in PASI response (PASI75) at Week 16 received CZP 400 mg at Weeks 16, 18, and 20 (loading doses) followed by CZP 200mg Q2W (starting at Week 22).

- Subjects randomized to placebo who achieved a PASI75 response at Week 16 continued to receive placebo.

During the double-blind Maintenance Treatment Period, subjects continued to receive study medication in a double-blind fashion and were assessed at Weeks 32, 40, and 48 for continued PASI50 response. Subjects who did not achieve a PASI50 response at Week 32 or a later timepoint were withdrawn from the study.

Subjects who did not achieve a PASI50 response at Week 16 escaped from blinded treatment and received open-label CZP 400mg Q2W. Subjects who received unblinded CZP 400mg Q2W for 16 weeks in the escape arm and did not achieve a PASI50 response were withdrawn from the study.

Period 4 – Open-label Treatment Period: Week 48 to Week 144

All subjects who completed the Maintenance Treatment Period through Week 48 (with a PASI50 response at Week 48) will receive open-label treatment for up to an additional 96 weeks. During this period, subjects who completed the Week 48 Visit with a PASI50 response in a dose-blind group will receive CZP 200mg Q2W.

All subjects who completed the Week 48 Visit in the escape arm, will continue to receive CZP 400mg Q2W or may, at the discretion of the Investigator, have their dose decreased to CZP 200mg Q2W if they achieved a PASI75 response at Week 48.

Subjects who receive CZP 200mg Q2W and do not achieve a PASI50 response at Weeks 60, 72, 84, 96, 108, 120, or 132 will receive CZP 400mg Q2W for at least 12 weeks. Subjects who receive CZP 400mg Q2W for at least 12 weeks and do not achieve a PASI50 response will be withdrawn from the study.

Subjects who receive CZP 200mg Q2W and achieve a PASI50 response but not a PASI75 response at Weeks 60, 72, 84, 96, 108, 120, or 132 may have their CZP dose increased to 400mg Q2W, at the discretion of the Investigator.

Subjects who receive CZP 400mg Q2W for at least 12 weeks and achieve a PASI75 response at Weeks 48, 60, 72, 84, 96, 108, 120, or 132 may be switched to CZP 200mg Q2W, at the discretion of the Investigator.

During the Open-label Treatment Period, CZP will be self-administered by the subject after the subject has been trained by study staff.

Period 5 –Safety Follow-up Period: Week 144 to Week 152

All subjects, including those who withdrew from study treatment, will have a SFU Visit 10 weeks after the final dose of study medication. The SFU could occur prior to Week 144 for those subjects who prematurely withdrew from the study.

The treatments and study design for studies CIMPASI-1 and -2 are considered adequate. Those subjects who were randomized to placebo and achieved a PASI75 response at Week 16 continued to receive placebo. During the initial and maintenance study periods, study treatments were administered by dedicated, trained site personnel while in the the Open-label Treatment Period, CZP was self-administered by the subject after the subject has been trained by study staff.

Objectives

The primary objective in both CIMPASI-1 and CIMPASI-2 was to demonstrate the efficacy of CZP administered sc at the doses of CZP 400 mg every 2 weeks (Q2W) and CZP 200 mg Q2W after a loading dose of CZP 400 mg at Weeks 0, 2, and 4 in the treatment of moderate to severe chronic plaque PSO.

Secondary objectives were to assess the optimal initial treatment dose for the treatment of moderate to severe chronic plaque PSO; assess durability of the clinical response with continued treatment; assess the safety and tolerability of CZP and improvement of skin-related quality of life (DLQI).

Other objectives were to demonstrate the effects of CZP on various aspects of the disease, e.g. improvement of general Health Related Quality of Life (SF-36®), depression and anxiety, work productivity and activity impairment, subject's health status, psoriatic nail disease in subjects with nail disease at Baseline and to assess the safety and efficacy of long-term use of CZP.

Outcomes/endpoints

Co-primary efficacy variables:

- PASI75 at Week 16

- PGA Clear or Almost clear (with at least 2-category improvement) at Week 16

PASI (Psoriasis Area and Severity Index) is a well-known scoring system for psoriasis, which averages the redness, thickness, and scaliness of psoriatic lesions (graded on a 0 to 4 scale), and weighs the resulting score by the area of skin involved.

The PGA (Physician's Global Assessment) scale used was a static PGA for psoriasis to assess disease activity. The overall severity of psoriasis was graded on a 5-point scale, ranging from 0 (Clear; No signs of psoriasis; post-inflammatory hyperpigmentation may be present) to 4 (Severe; Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions).

Secondary efficacy variables:

- PASI90 at Week 16

- PGA Clear or Almost clear (with at least 2-category improvement) at Week 48

- PASI75 at Week 48

- Change from Baseline in DLQI at Week 16

Other efficacy variables were also evaluated at all scheduled visits:

- PASI50, PASI75, PASI90, and 100% reduction from Baseline in PASI (PASI100); absolute and percent change from Baseline in PASI score
- PGA Clear or Almost clear (with at least 2-category improvement) and PGA score distribution
- Time to onset of action, defined as the time to PASI50, PASI75 and PASI90, respectively
- Absolute and percent change from Baseline in the BSA affected by PSO
- Change from Baseline in modified Nail Psoriasis Severity Index (mNAPSI)
- Change from Baseline in SF-36 all domains, and physical and mental component summary scores, and percent of subjects achieving the minimal clinically important difference (MCID)
- Change from Baseline in DLQI, percent of subjects achieving MCID, and percent achieving DLQI Remission
- Change from Baseline in Hospital Anxiety and Depression Scale for anxiety (HADS-A) and Hospital Anxiety and Depression Scale for depression (HADS-D) scores, percent of subjects with scores below 8 in HADS-A and HADS-D (subjects with normal scores)
- Change from Baseline in Work Productivity and Activity Impairment Questionnaire–Specific Health Problem (WPAI-SHP) v2.0 adapted to PSO scores
- Responses to the European Quality of Life 5 dimensions, 3 levels (EQ-5D-3L™) questionnaire, absolute and changes from Baseline in EQ-5D-3L visual analogue scale (VAS) scores
- Direct medical resource use: number of concomitant medical procedures, number of health care provider consultations not foreseen by the protocol, number of hospitalizations, number of emergency room visits, and length of hospital stay
- Socio-professional status questionnaire (educational level, professional status, and assistance in the usual activities)

The co-primary efficacy end-points used in the CIMPASI studies, PASI 75 response and PGA response (clear/almost clear), are commonly used in plaque psoriasis trials and are relevant. The primary end-point was assessed at week 16. In psoriasis studies for several other monoclonal antibodies, the primary endpoint has been assessed at 12 weeks. However, 16 weeks is also deemed a reasonable time point for the primary efficacy assessment and no issue is raised. Other end-points addressed the effect at 48 weeks, other PASI response variables and effects on the scores over time, affected body surface area, nail engagement as well as patient reported outcomes.

Sample size

A total of 225 subjects were planned, and subjects were randomly assigned in a 2:2:1 ratio to the three treatment groups.

Both CZP doses were evaluated separately for superiority to placebo. To account for the testing of multiple doses, the significance level of 0.05 was split evenly between CZP 400mg Q2W and CZP 200mg Q2W such that each dose was evaluated at a significance level of 0.025. The assumed response rates for PGA at Week 16 were 70%, 50%, and 5% for CZP 400mg Q2W, CZP 200mg Q2W, and placebo, respectively. Additionally, the assumed response rates for PASI75 at Week 16 were 80%, 75%, and 10% for CZP 400mg Q2W, CZP 200mg Q2W, and placebo, respectively. For each dose, PGA response at Week 16 represented the smaller treatment difference between the 2 co-primary variables. The power to detect a statistically significant difference between CZP (either dose) and placebo based on PGA response, given the above assumptions and using a 2-sided test significance level of 0.025 was >99%.

Randomisation

An IVRS/IWRS was used to assign eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by the Sponsor. The randomization schedule was produced by an independent biostatistician otherwise not involved in the study. Subject treatment assignment was stratified by site. Approximately 225 eligible subjects were planned to be randomized to a 2:2:1 ratio:

- CZP 200mg Q2W: CZP administered sc at the dose of CZP 400mg at Baseline, and Weeks 2 and 4, followed by CZP 200mg Q2W (starting at Week 6)

- CZP 400mg Q2W: CZP administered sc at the dose of CZP 400mg Q2W

- Placebo: placebo administered sc Q2W

At the Baseline Visit, subjects were randomized into the study. The Investigator or designee used the IVRS/IWRS for randomization. The IVRS/IWRS automatically informed the Investigator or designee of the subject's randomization number and allocated kit numbers to the subject based on the subject number during the course of the study. Subject numbers and kit numbers were tracked via the IVRS/IWRS.

Blinding (masking)

All subject treatment details were allocated and maintained by the IVRS/IWRS. There is some difference in the presentation and viscosity between CZP and placebo, and therefore special precautions were taken to ensure the study blind was maintained for CZP/placebo administration during the Initial Treatment Period (Baseline to Week 16) and Maintenance Treatment Period (Week 16 to Week 48).

CZP and placebo were administered at the investigational sites by unblinded, dedicated study medication administration personnel. The unblinded personnel were not involved in the study in any way other than assuring study medication was taken from the correct kit and administered to the subjects. Study sites were required to have a written blinding plan in place, signed by the Principal Investigator, which detailed the site's steps for ensuring the double-blind nature of the study was maintained.

During the Initial Treatment Period and the Maintenance Treatment Period, the Sponsor provided blinded and unblinded site monitors for the purposes of verifying safety, efficacy, and study medication administration and documentation records until the last subject reached study Week 48 and the database was locked for the primary efficacy analysis. Unblinded study site personnel needed to be available through the Week 48 database lock in order to resolve queries. Study monitors and study site personnel, blinded to treatment assignment, did not discuss or have access to any study medication related information.

Pharmacokinetic (PK) and antibody data are not provided to the blinded study team until after the Maintenance Treatment Period database lock occurs for the study.

Study blinding was also maintained through the use of the IVRS/IWRS, if dose adjustments were required for lack of treatment response. Changes to the subject's dose were made automatically through the IVRS/IWRS.

Statistical methods

All efficacy analyses were performed using the Randomized Set (RS). The Per Protocol Set (PPS) was used for a sensitivity analysis on the primary endpoints only. The Enrolled Set (ES) consisted of all subjects who gave informed consent and the RS consisted of all subjects randomized into the study.

The PPS consisted of subjects in the RS who had been in the study up to the Week 16 Visit without any important protocol deviations that may have influenced the validity of the data for the co-primary efficacy variables. The PPS excluded subjects who were identified based on the review of important protocol deviations prior to database lock.

For statistical modeling purposes, a pooled center variable was used to account for the possibility of centers that enrolled a low number of subjects. A center pooling algorithm was used for each geographic region, North America and Europe.

For the analysis of the co-primary efficacy endpoints, both pooled center and prior biologic exposure (yes/no) will be included as factors in the statistical model. Study center is the only stratification variable used in the randomization. Because some centers may enroll a low number of subjects, pooled center will be used in the model to account for potential geographic variability. Prior biologic exposure is included as this may have an impact on the efficacy of treatment. The analysis of the secondary endpoint (DLQI score at Week 16) will include pooled center and prior biologic exposure as well as Baseline DLQI score as a covariate. Inclusion of the Baseline score will account for any potential Baseline imbalance.

The co-primary efficacy variables for this study were the PGA and PASI75 responses at Week 16. As both are binary variables, they were analyzed in a similar fashion. The primary analyses for these variables were based on logistic regression for the RS. The odds ratio of the responder rate at Week 16 was estimated and tested between randomized treatment groups using a logistic regression model with factors of treatment group, geographic region, and prior biologic exposure (yes/no). The odds ratio, associated CI, and p-value were presented.

Missing data for the co-primary variables and other key efficacy variables (eg, PASI50, PASI90, and PASI100) will be handled using the Markov Chain Monte Carlo (MCMC) method for multiple imputation. This is a commonly used method for handling intermittent or monotonic missing data under the assumption of a missing at random (MAR) pattern of missing reasonableness. 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 PASI75, the multiple imputation procedure was based on the actual PASI score. Sensitivity analyses which apply different methods of handling missing data for the co-primary endpoints are planned. Other binary efficacy variables that are summarized without statistical modelling will use nonresponse imputation (NRI) as the method for handling missing data. For missing continuous efficacy variables, the last observation carried forward (LOCF) approach will be used.

The statistical analysis of the co-primary efficacy variables and selected secondary efficacy variables will account for multiplicity and control the familywise type I error rate at a 2-sided alpha level of 0.05 by using a fixed sequence testing procedure. The hypotheses are mapped into 2 sets (H1, H3, H5, and H7) and (H2, H4, H6, and H8) so that hypotheses within each set correspond to the same CZP dose. The type I error will be split equally between CZP 400mg Q2W and CZP 200mg Q2W, so that each dose will be tested at a 2- sided alpha level of 0.025.

The first 2 hypotheses for each dose (H1 and H3 for CZP 400mg Q2W; H2 and H4 for CZP 200mg Q2W) test whether the given CZP dose is superior to placebo for PASI75 response and PGA response at Week 16. These are the hypothesis tests corresponding to the co-primary endpoints. If both are rejected at a 2-sided alpha level of 0.025, that alpha will be passed to the next test in the sequence, allowing the testing procedure to proceed. The hypotheses associated with the subsequent tests are for secondary efficacy endpoints and are based on testing for superiority relative to placebo. See Figure 3 for details on this procedure.

If all hypotheses within one set of hypotheses (either CZP 400mg Q2W or CZP 200mg Q2W) have been rejected, the corresponding type I error probability can be passed on to the other set of hypotheses and that set can be retested if necessary at a 2-sided alpha level of 0.05 (Bretz et al, 2009).

Figure 3: Fixed sequence testing procedure
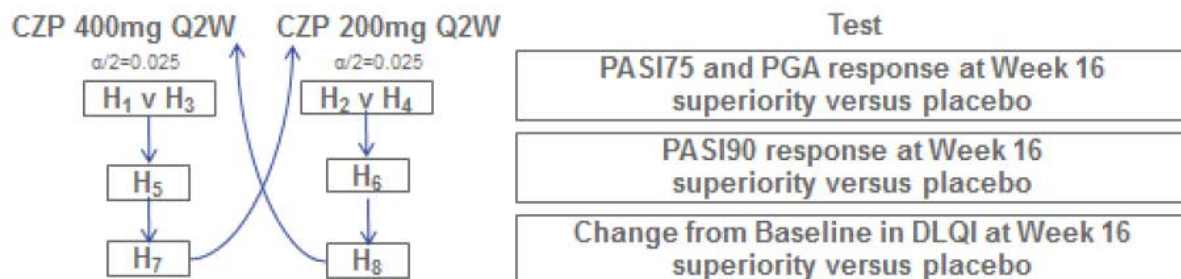
Subgroup analyses by randomized treatment group were performed for age, gender, race, ethnicity, duration of disease, geographic region, BMI, weight, prior systemic chemophototherapy or phototherapy, prior systemic therapy (nonbiologic), prior biologic exposure, prior anti-TNF exposure, any prior systemic therapy for PSO, previous exposure to at least 2 systemic treatments out of phototherapy, MTX, 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 coprimary efficacy variables using both OC and NRI and presented only descriptive statistics for Week 16 using the RS.

Sensitivity analyses which applied different methods of handling missing data for the coprimary endpoints were also performed. The following sensitivity analyses were performed on each of the coprimary efficacy variables:

1. Nonresponder imputation was used to impute missing values. Specifically, any subject with a missing PGA (or PASI75) value at Week 16 was treated as a nonresponder for analysis purposes.

2. A model-based multiple imputation method imputed missing data for the PGA (or PASI75) responder data.

2) Study CIMPACT

Study participants

Main inclusion and exclusion criteria
The inclusion and exclusion criteria were the same as in studies CIMPASI-1 and CIMPASI-2, with the following exceptions:

- Subjects with a known hypersensitivity to latex or any excipients of etanercept (ETN) were excluded.
- With respect to Prior medications exclusions, subjects must not have received any previous treatment with ETN for the treatment of PSO.

The inclusion and exclusion criteria are adequate for CIMPASI -1 and CIMPASI-2. A PASI score of at least 12, PGA of at least 3 and a total body surface area (BSA) of minimally 10% is adequate to define patients with moderate to severe plaque psoriasis and is in accordance with the CHMP guideline. The

patients should be candidates for systemic psoriasis therapy and/or phototherapy and/or chemophototherapy.

The inclusion and exclusion criteria are adequate also for study CIMPACT. It is agreed to exclude previous use of ETN. Previous use of other biologics targeting TNF-α was allowed after a washout of 12 weeks.

The list of prohibited medications and respective wash-out periods are deemed adequate.

Treatments

The study included 5 periods; a Screening Period, an Initial Treatment Period (double-blind, placebo- and active-controlled), a Maintenance Treatment Period (double-blind, placebo-controlled), an Open-label Extension (OLE) Treatment Period, and a Safety Follow-up (SFU) Period.

The completed initial double-blind treatment period of 16 weeks was used to demonstrate the efficacy of CZP over placebo and to compare the efficacy of CZP to ETN. Further re-randomized, double-blind treatment from Weeks 16 to 48, which has also been completed, was intended to collect information on dosing beyond initial treatment. An ongoing OLE treatment period for an additional 96 weeks will provide additional long term safety data on the use of CZP for moderate to severe chronic plaque PSO.

The CIMPACT study design is presented in the figure 4 below.

Figure 4: CIMPACT study design
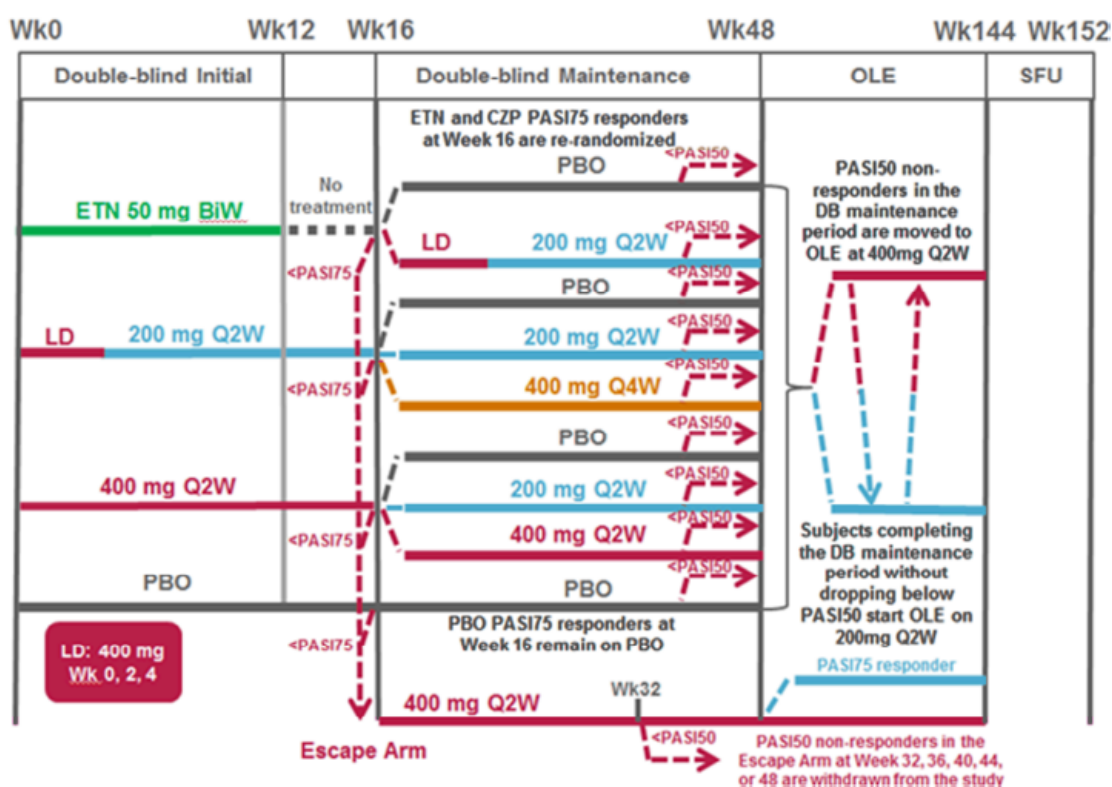
BiW=twice weekly; CZP=certolizumab pegol; DB=double-blind; ETN=etanercept; LD=loading dose; PASI50=at least 50% reduction from Baseline in Psoriasis Area and Severity Index; PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; PBO=placebo; OLE=Open-Label Extension; Q2W=every 2 weeks; Q4W=every 4 weeks; SFU=Safety Follow-Up; Wk=week

Period 1 - Screening Period

There was a Screening Period of up to 5 weeks with the purpose of determining the eligibility of subjects to enter the study, to obtain laboratory data, to verify that the doses of NSAIDs and other

pain relievers, if used to treat PsA, were stable, and to enable washout of any non-permitted medications.

Period 2 - Initial Treatment Period: Week 0-16 (double-blind, placebo- and active-controlled)

Eligible subjects were randomized to the following study treatments in a 3:3:3:1 ratio:

- **CZP 200 mg:** CZP administered sc at the dose of CZP 400 mg Q2W at Weeks 0, 2, and 4 (loading dose) followed by CZP 200 mg Q2W sc (starting at Week 6) through Week 14

- **CZP 400 mg:** CZP administered sc at the dose of CZP 400 mg Q2W through Week 14

- **Etanercept:** ETN administered sc at 50 mg twice weekly through Week 11.5

- **Placebo:** placebo administered sc Q2W through Week 14

Placebo, CZP 200 mg, and CZP 400 mg were given as 2 blinded injections Q2W. Etanercept was administered to subjects randomized to ETN twice weekly.

All CZP and placebo treatments were administered by dedicated unblinded site personnel at Weeks 0, 2, 4, 6, 8, 10, 12, and 14.

Etanercept treatments were administered by unblinded, trained study staff on site or by unblinded trained study staff outside of the study center, or self-administered by the subject after the subject had been trained from Weeks 0 to Week 11.5. The last ETN treatment occurred at Week 11.5 and no treatment was administered to subjects randomized to ETN during Weeks 12 through 14.

The Initial Treatment Period concluded with completion of the safety and efficacy assessments performed at Week 16.

Period 3 - Maintenance Treatment Period: Week 16-48

The treatment received in Period 3 was based on initial treatment and response to treatment at Week 16. All CZP and placebo treatments were administered by dedicated, unblinded, trained site staff in the clinic.

All subjects who did not achieve a PASI75 response at Week 16 were removed from blinded study medication and escaped to CZP 400mg Q2W. If a subject in this escape arm did not achieve at least a PASI50 response at Week 32, the subject was withdrawn from the study. A subject who achieved a PASI50 at Week 32 but did not achieve a PASI50 at a later visit was withdrawn from the study at that time.

For subjects who did achieve a PASI75 response at Week 16:

- Subjects initially randomized to placebo continued to receive blinded placebo

- Subjects initially randomized to ETN were re-randomized (2:1) to either CZP (loading dose of 400 mg at Weeks 16, 18, and 20 followed by 200 mg Q2W) or placebo

- Subjects initially randomized to CZP 200 mg Q2W were re-randomized (2:2:1) to receive either CZP 200 mg Q2W or CZP 400 mg every 4 weeks (Q4W; with placebo administered on alternate dosing weeks to maintain the blind) or placebo

- Subjects initially randomized to CZP 400mg Q2W were re-randomized (2:2:1) to CZP 200 mg Q2W or CZP 400 mg Q2W or placebo

Placebo, CZP 200 mg, and CZP 400 mg were given as 2 blinded injections Q2W.

If subjects relapsed, defined as a timepoint where the subject did not achieve a PASI50 response, the subject was removed from the double-blind, placebo-controlled Maintenance Treatment Period and entered into the OLE Treatment Period of the study.

Subjects who completed the Maintenance Treatment Period through Week 48 were entered into the OLE Treatment Period of the study.

Period 4 - Open-label Extension Treatment Period

Subjects may enter the 96-week OLE Treatment Period if:

- A subject in the double-blind, placebo-controlled Maintenance Treatment Period demonstrates a relapse (does not achieve a PASI50 response); subjects will initiate open-label CZP 400 mg Q2W at the visit where relapse criterion is met.

- A subject in the double-blind, placebo-controlled Maintenance Treatment Period completes the Week 48 visit without a relapse; subjects will initiate open-label CZP 200 mg Q2W.

- A subject completes the Week 48 Visit in the escape arm of the Initial Treatment Period; subjects will continue open-label CZP at 400 mg Q2W. If at Week 48, the subject achieves a PASI75 response, the subject may reduce the dose to 200 mg Q2W at the discretion of the Investigator.

The OLE Baseline will be the timepoint of the subject's last visit in Period 3 (Maintenance Treatment Period). Subject visits will occur at the following timepoints in the OLE Treatment Period: 4 weeks (OLE 4), 12 weeks (OLE 12), 24 weeks (OLE 24), 36 weeks (OLE 36), 48 weeks (OLE 48), 60 weeks (OLE 60), 72 weeks (OLE 72), 84 weeks (OLE 84), and 96 weeks (OLE 96 or OLE end-of-study, EOS).

Subjects receiving CZP 200 mg Q2W and not achieving a PASI50 response at OLE 12, OLE 24, OLE 36, OLE 48, OLE 60, OLE 72, or OLE 84 will receive CZP 400 mg Q2W for at least 12 weeks.

Subjects receiving CZP 200 mg Q2W and achieving a PASI50 response, but not a PASI75 response, at OLE 12, OLE 24, OLE 36, OLE 48, OLE 60, OLE 72, or OLE 84 may increase their dose of CZP to 400 mg Q2W at the discretion of the Investigator.

Subjects receiving CZP 400mg Q2W for at least 12 weeks and achieving a PASI75 response at OLE 12, OLE 24, OLE 36, OLE 48, OLE 60, OLE 72, or OLE 84 may be switched to CZP 200 mg Q2W treatment, at the discretion of the Investigator.

Subjects receiving CZP 400 mg Q2W for at least 12 weeks and not achieving a PASI50 response will be withdrawn from the study.

During the OLE Treatment Period, CZP will be self-administered by the subject after the subject has been trained by study staff. Study medication administration at OLE study visits will be administered by study staff or self-administered in the presence of study staff.

Period 5 - Safety Follow-up
All subjects, including those withdrawn from the study treatment, will have an SFU Visit10 weeks after their final dose of study medication.

The treatments and study design for study CIMPACT is also considered adequate. In this study, all subjects who did not achieve a PASI75 response at Week 16 were removed from blinded study medication and escaped to CZP 400 mg Q2W. For subjects who achieved a PASI75 response at Week 16, those initially randomized to placebo continued to receive blinded placebo. PASI75 responders in the CZP arms were re-randomised to different CZP regimens or placebo. In this study also another CZP regimen was tested, namely CZP 400 mg <u>every 4 weeks</u> (Q4W). Subjects (PASI75 responders) in the ETN arm were re-randomized (2:1) to either CZP (three loading doses of 400 mg followed by 200 mg Q2W) or placebo. Thus, in the maintenance part of the study there was large number (nine) of different arms defined based on their initial and subsequent treatments. In addition, there were four escape arm groups.

The rationale for using etanercept as the active comparator was that it is the first TNF inhibitor approved for the treatment of PSO and is part of the standard armamentarium. The approved initial dose is 50 mg twice weekly. It is agreed that ETN is an acceptable active comparator. However, its efficacy in plaque psoriasis seems to be in the lower range when compared with other biologics approved in this indication.

Objectives

The primary objective of the study was to compare the efficacy of CZP administered sc at the doses of CZP 400 mg every 2 weeks (Q2W) and CZP 200 mg Q2W after a loading dose of CZP 400 mg Q2W at Weeks 0, 2, and 4 to placebo in the treatment of moderate to severe chronic plaque PSO.

Secondary objectives were to compare the efficacy of CZP at two dose levels to ETN at a weekly dose of 100 mg in the treatment of moderate to severe chronic plaque PSO; to assess the optimal initial treatment dose and maintenance dose for the treatment of PSO and to assess the safety and tolerability of CZP. Other objectives were similar to those in the CIMPASI studies, with the addition of assessment of fatigue, as measured by the Fatigue Assessment Scale (FASca).

Outcomes/endpoints

Primary efficacy variable:

- PASI75 at Week 12

Secondary efficacy variables:

- PASI75 at Week 16
- PASI90 at Week 12 and Week 16
- PGA Clear or Almost Clear (with at least 2 category improvement) at Week 12
- PGA Clear or Almost Clear (with at least 2 category improvement) at Week 16
- PASI75 at Week 48 for those achieving PASI75 at Week 16

Other efficacy variables were also evaluated at all scheduled visits:
- PASI50, PASI75, PASI90, and 100% reduction from Baseline in PASI (PASI100); absolute and percent change from Baseline in PASI score
- Time to onset of action, defined as the time to PASI50, PASI75 and PASI90, respectively
- Time to relapse (not achieving PASI50 response) for those achieving PASI75 at Week 16
- PGA Clear or Almost clear (with at least 2-category improvement) and PGA score distribution

- Absolute BSA affected by PSO and absolute and percent change from Baseline in the BSA affected by PSO
- Change from Baseline in DLQI mean scores, percent of subjects achieving minimally clinical important difference (MCID), and percent achieving DLQI Remission
- Change from Baseline in WPAI-SHP v2.0 adapted to PSO scores
- Health status assess by EQ-5D-3L and EQ-5D-3L VAS
- Change from Baseline in FASca
- Change from Baseline in mNAPSI
- Direct medical resource use

In study CIMPACT, PASI 75 response at week 12 was the primary endpoint. Thus, another time point was used compared with the CIMPASI studies. Comparison of CZP over ETN was measured at Week 12 because the approved duration of initial ETN treatment at 50 mg twice weekly is 12 weeks. In the plaque psoriasis studies performed with ETN, the primary endpoint was assessed at week 12.

Sample size

A total of approximately 540 subjects were planned, and subjects were randomly assigned in a 3:3:3:1 ratio to the following treatment groups:

- CZP 200mg Q2W (with CZP 400mg loading dose at Weeks 0, 2, and 4) (162 subjects)

- CZP 400mg Q2W (162 subjects)

- ETN 50mg twice a week (162 subjects)

- Placebo (54 subjects)

The primary efficacy analysis was based on the comparison of both CZP doses to placebo for PASI75 response at Week 12. However, Week 12 comparisons of both CZP doses against ETN for PASI75 was also part of a fixed-sequence testing procedure to control for multiplicity. The assumed response rates for PASI75 at Week 12 were 80%, 75%, 57%, and 5% for CZP 400mg Q2W, CZP 200mg Q2W, ETN, and placebo, respectively. Using these assumed response rates, the overall sample size was based on the comparison with the smallest assumed treatment difference, which was the comparison between CZP 200mg Q2W and ETN. The power to detect a statistically significant difference between these 2 treatment groups given the above assumptions and using a 2-sided significance level of 0.05 was 91%.

The studies were adequately powered with >90% power for the smallest assumed treatment difference in the confirmatory testing procedure.

Randomisation

Similar procedures were used as in the CIMPASI studies. Study center was the only stratification variable used in the randomization. Approximately 540 eligible subjects were to be randomized to the following study treatments in a 3:3:3:1 ratio:

- CZP 200mg : CZP administered sc at the dose of CZP 400mg Q2W at Weeks 0, 2, and 4 (loading dose) followed by CZP 200mg Q2W sc (starting at Week 6) through Week 14

- CZP 400mg: CZP administered sc at the dose of CZP 400mg Q2W through Week 14

- ETN: ETN administered sc at 50mg twice weekly through Week 11.5

- Placebo: placebo administered sc Q2W through Week 14

Site was the only stratification factor performed in these studies. Other stratification factors that could have been considered are baseline body weight and previous psoriasis therapy. However, the baseline

demographic and disease characteristic data as presented below did not reveal any large imbalances between the different treatment groups in the different studies.

Blinding (masking)

Due to differences in presentation between ETN, CZP, and placebo treatments, special precautions were taken to ensure study blinding. Study sites were required to have blinded and unblinded study site personnel to handle efficacy assessments and treatment administration during the blinded periods of this study. Study sites were required to have a written blinding plan in place, signed by the Principal Investigator and appropriate study site personnel, which detailed the site's steps for ensuring that the study blind was maintained.

Etanercept can only be procured in a commercial presentation, which posed challenges for study blinding. Subjects randomized to ETN during the Initial Treatment Period received unblinded study medication.

Etanercept subjects received ETN injections at the investigational site, by unblinded study staff once Q2W. Etanercept administration on non-study visit days was administered by trained staff either on site, or outside of the study site or was self-administered by the subject after the subject had been trained. All sites used a dedicated, blinded assessor for the primary efficacy assessments, who performed the PASI, PGA, and BSA assessments at each designated visit. The blinded assessor had no other involvement with the subjects until completion of the Week 48 Visits, and lock of the interim clinical database. The unblinded study site staff needed to be available through this interim lock in order to help resolve queries.

As there are slight differences in the presentation and viscosity between CZP and placebo, special precautions were also taken in order to ensure the study blind was maintained for CZP/placebo. This procedures were similar to those in the CIMPASI studies.

Differences in presentation and viscosity between active treatment (CZP) and placebo may result in a risk for unblinding. However, appropriate measures seem to have been taken to preserve blinding.

With respect to the active comparator etanercept in study CIMPACT, differences in treatment regimens, drug presentation and viscosity vs. CZP and placebo led to blinding difficulties. A double-dummy technique may have been used, however, since ETN is administered as twice weekly injections and CZP every two weeks, achieving double-blinding would have increased the burden of additional injections for the subjects. Therefore, ETN treatments were administered in a single-blind fashion, meaning that the sponsor and the blinded site staff remained blinded, but the subject and unblinded study staff knew their treatment assignment during the first 16 weeks of the study.

Statistical methods

Efficacy analyses during the 16-week double-blind, placebo- and active-controlled, initial treatment period (Initial Treatment Period) were performed using the Randomized Set (RS). The RS consisted of all subjects randomized into the study.

Efficacy analyses during double-blind, placebo-controlled, maintenance treatment period (Maintenance Treatment Period) were performed using the Week 16 RS (WK16RS) or the Maintenance set (MS). The WK16RS consisted of all subjects who achieved a PASI75 response at Week 16 and were re-randomized into the double-blind, placebo-controlled Maintenance Treatment Period and the MS consisted of all subjects who completed the Week 16 Visit and had at least 1 efficacy assessment in the Maintenance Treatment Period. The Per Protocol Set (PPS) was used for a sensitivity analysis on the primary endpoint only. The PPS consisted of subjects in the RS who had been on the study up to

the Week 12 Visit without any important protocol deviations that may have influenced the validity of the data for the primary efficacy variable. The PPS excluded subjects who were identified based on the review of the important protocol deviations prior to database lock.

During the 32-week double-blind, placebo-controlled Maintenance Treatment Period, subjects were allocated to dose groups based on their original randomization and Week 16 PASI response. Specifically, those subjects who achieved a PASI75 response at Week 16 remained blinded to their treatment and were rerandomized (with the exception of placebo subjects who remained on placebo) in the placebo-controlled blinded Maintenance Treatment Period, while subjects who did not achieve a PASI75 response escaped to open-label CZP 400mg treatment in the escape arm. For efficacy, data were summarized separately for those subjects who remained in the blinded portion of the study and those subjects who switched to the escape arm. For those who remained in the blinded portion of the study, data were summarized based upon their original and rerandomized treatment groups, using the following blinded maintenance treatment groups (initial dose/maintenance dose):

- Placebo/placebo

- ETN/placebo

- ETN/CZP 200mg Q2W

- CZP 200mg Q2W/placebo

- CZP 200mg Q2W/CZP 200mg Q2W

- CZP 200mg Q2W/CZP 400mg Q4W

- CZP 400mg Q2W/placebo

- CZP 400mg Q2W/CZP 200mg Q2W

- CZP 400mg Q2W/CZP 400mg Q2W

For those subjects who moved to the escape arm, data were summarized based upon the treatment group assigned at randomization, using the following escape maintenance treatment groups (baseline/escape):

- Placebo/Escape CZP 400mg Q2W

- ETN/Escape CZP 400mg Q2W

- CZP 200mg Q2W/Escape CZP 400mg Q2W

- CZP 400mg Q2W/Escape CZP 400mg Q2W

For statistical modeling purposes, a pooled center variable was used to account for the possibility of centers that enrolled a low number of subjects. In order to obtain reasonable estimates of variability for a treatment arm at a given center, a minimum of 30 subjects were considered acceptable for a center to be included in the model without pooling. Geographic regions were defined as US, Western Europe, and Central/East Europe, there were no pooling across regions.

For the analysis of the primary efficacy endpoint, pooled center and prior biologic exposure (yes/no) were included as factors in the statistical model. Study center was the only stratification variable used in the randomization. Because some centers may have enrolled a low number of subjects, pooled center was used in the model to account for potential geographic variability. . Prior biologic exposure was included as this may have had an impact on the efficacy of treatment. The analysis of other efficacy endpoints (DLQI, WPAI, and FASca) included pooled center and prior biologic exposure as well

as Baseline score as a covariate. Inclusion of the Baseline score accounted for any potential Baseline imbalance.

As the primary efficacy variable was a binary variable, the primary analysis for it was based on logistic regression for the RS. The odds ratio of the responder rates at Week 12 was estimated and tested between treatment groups based on a logistic regression model with factors of treatment group, pooled center and prior biologic exposure (yes/no). The odds ratio, associated CI, and p-value were presented.

Missing data for the primary (PASI75 at Week 12) and secondary endpoints and selected additional efficacy variables (eg, PASI50, PASI90, PASI100, PGA) were handled using the Markov Chain Monte Carlo (MCMC) method for multiple imputation. As the blinded maintenance groups were re-randomized, the Maintenance Treatment Period was analyzed separately from the Initial Treatment Period (with the exception that the Baseline data [Week 0] were still considered Baseline for this period). Analyses were performed with imputation of missing data using the non-responder imputation (NRI) method and without imputation using observed case (OC) only. Other binary efficacy variables that were summarized without statistical modeling used NRI as the method for handling missing data.

The statistical analyses of the primary efficacy variable and selected secondary efficacy variables accounted for multiplicity by using a fixed-sequence testing procedure that controlled the overall Type 1 error. The sequential procedure is described below and began with the primary efficacy variable.

1. Tested CZP 400mg Q2W vs placebo for PASI75 at Week 12 at a 2-sided alpha level of 0.05. If the value was significant in favor of CZP, then the testing procedure proceeded to step 2. Otherwise, the testing procedure was concluded.

2. Tested CZP 200mg Q2W vs placebo for PASI75 at Week 12 at a 2-sided alpha level of 0.05. If the value was significant in favor of CZP, then the testing procedure proceeded to step 3. Otherwise, the testing procedure was concluded.

3. Tested CZP 400mg Q2W vs placebo for PGA at Week 12 at a 2-sided alpha level of 0.05. If the value was significant in favor of CZP, then the testing procedure proceeded to step 4. Otherwise, the testing procedure was concluded.

4. Tested CZP 200mg Q2W vs placebo for PGA at Week 12 at a 2-sided alpha level of 0.05. If the value was significant in favor of CZP, then the testing procedure proceeded to step 5. Otherwise, the testing procedure was concluded.

5. Tested CZP 400mg Q2W vs placebo for PASI90 at Week 12 at a 2-sided alpha level of 0.05. If the value was significant in favor of CZP, then the testing procedure proceeded to step 6. Otherwise, the testing procedure was concluded.

6. Tested CZP 200mg Q2W vs placebo for PASI90 at Week 12 at a 2-sided alpha level of 0.05. If the value was significant in favor of CZP, then the testing procedure proceeded to step 7. Otherwise, the testing procedure was concluded.

7. Tested CZP 400mg Q2W vs placebo for PASI75 at Week 16 at a 2-sided alpha level of 0.05. If significant in favor of CZP, then the testing procedure proceeded to step 8. Otherwise, the testing procedure was concluded.

8. Tested CZP 200mg Q2W vs placebo for PASI75 at Week 16 at a 2-sided alpha level of 0.05. If significant in favor of CZP, then the testing procedure proceeded to step 9. Otherwise, the testing procedure was concluded.

9. Tested CZP 400mg Q2W vs placebo for PGA at Week 16 at a 2-sided alpha level of 0.05. If significant in favor of CZP, then the testing procedure proceeded to step 10. Otherwise, the testing procedure was concluded.

10. Tested CZP 200mg Q2W vs placebo for PGA at Week 16 at a 2-sided alpha level of 0.05. If significant in favor of CZP, then the testing procedure proceeded to step 11. Otherwise, the testing procedure was concluded.

11. Tested CZP 400mg Q2W vs placebo for PASI90 at Week 16 at a 2-sided alpha level of 0.05. If significant in favor of CZP, then the testing procedure proceeded to step 12. Otherwise, the testing procedure was concluded.

12. Tested CZP 200mg Q2W vs placebo for PASI90 at Week 16 at a 2-sided alpha level of 0.05. If significant in favor of CZP, then the testing procedure proceeded to step 13. Otherwise, the testing procedure was concluded.

13. Tested CZP 400mg Q2W vs ETN for PASI75 at Week 12 to evaluate noninferiority based on the lower bound of a 2-sided 95% CI. If the value was significant in demonstrating noninferiority of CZP to ETN, then the testing procedure proceeded to step 14. Otherwise, the testing procedure was concluded.

14. Tested the following:

    a. CZP 400mg Q2W vs ETN for PASI75 at Week 12 to evaluate superiority of CZP to ETN.

    b. CZP 200mg Q2W vs ETN for PASI75 at Week 12 to evaluate noninferiority.

    Evaluation of statistical significance used the Hochberg method.

15. Tested CZP 200mg Q2W vs ETN for PASI75 at Week 12 at a 2-sided alpha level of 0.05 to evaluate superiority of CZP to ETN.

Subgroup analyses were conducted for age; gender; race; duration of disease; geographic region; BMI; weight; prior systemic photochemotherapy and/or phototherapy; prior systemic therapy (nonbiologic); prior biologic exposure; prior anti-TNF exposure; any prior systemic treatment for PSO; previous exposure to at least 2 systemic treatments out of phototherapy, MTX, and cyclosporine (with no previous biologic exposure); PASI score at Baseline; BSA at Baseline; and overall anti-CZP antibody status. These subgroup analyses were performed on the primary efficacy variable (PASI75 responder rate at Week 12) using both observed data and NRI and contained only descriptive statistics for Week 12 using the RS.

The same sensitivity analyses were performed as for the CIMPASI-1 and CIMPASI-2 studies.

3) Results of CIMPASI-1, CIMPASI-2 and CIMPACT

Participant flow

Study CIMPASI-1

Initial Treatment Period
A total of 286 subjects were screened for the study, 52 of whom were screen failures; the most common reason for being a screen failure was ineligibility (34 subjects, 11.9%).

A total of 234 randomized subjects started the Initial Treatment Period. Overall, 225 subjects (96.2%) completed the Initial Treatment Period. A total of 9 subjects (3.8%) discontinued during the Initial Treatment Period (prior to Week 16); overall, the most frequently reported primary reasons for discontinuation were consent withdrawn (5 subjects, 2.1%) and lost to follow-up (2 subjects, 0.9%).

Figure 5: Disposition of subjects by randomized treatment group – Initial Treatment Period (Weeks 0 to 16) (RS) (CIMPASI-1)
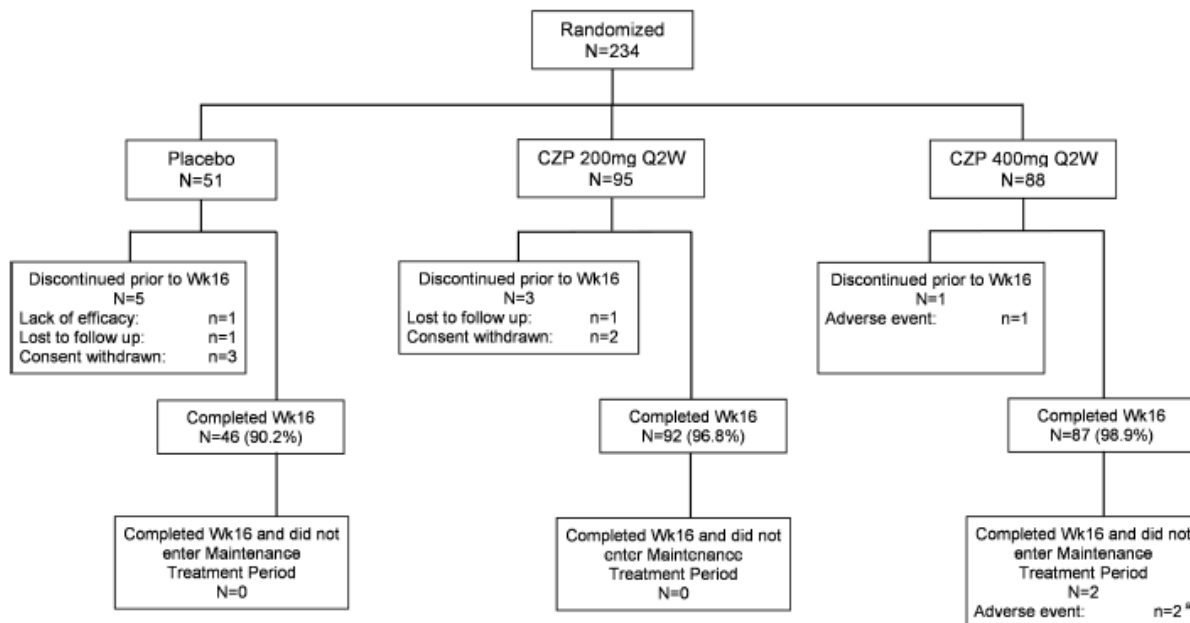
CZP=certolizumab pegol; Q2W=every 2 weeks; RS=Randomized Set; Wk=Week
[a] One of the 2 patients completed the Week 16 visit and was dosed at Week 16, but subsequently died due to a motor vehicle accident (see Section 11.3).

Maintenance Treatment Period

A total of 223 subjects started the Maintenance Treatment Period, and 202 subjects (90.6%) completed Week 48. A total of 21 subjects (9.4%) discontinued during the Maintenance Treatment Period (prior to Week 48; 10 of the 159 subjects who were in the Blinded Maintenance group and 11 of the 64 subjects who were in the Escape Maintenance group). Overall, the most frequently reported primary reasons for discontinuation were consent withdrawn and other: mandatory withdrawal due to not achieving a PASI50 response (7 subjects each, 3.1%). One subject discontinued the Maintenance Treatment Period due to an AE that was a non-serious and non-fatal AE.

Table: Disposition and discontinuation reasons by maintenance treatment group - Maintenance Treatment Period (Weeks 16 to 48) (MS) (CIMPASI-1)

Disposition	Blinded maintenance group				Escape maintenance group			
	PBO/ PBO N=3 n (%)	PBO/ CZP 200mg Q2W N=5 n (%)	CZP 200mg Q2W/ CZP 200mg Q2W N=74 n (%)	CZP 400mg Q2W/ CZP 400mg Q2W N=77 n (%)	PBO/Esc CZP 400mg Q2W N=38 n (%)	CZP 200mg Q2W/Esc CZP 400mg Q2W N=18 n (%)	CZP 400mg Q2W/Esc CZP 400mg Q2W N=8 n (%)	All subjects N=223 n (%)
Started Maintenance Treatment Period (Wks 16 to 48)	3 (100)	5 (100)	74 (100)	77 (100)	38 (100)	18 (100)	8 (100)	223 (100)
Completed Wk 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 Wk 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 PASI50 response	0	0	1 (1.4)	2 (2.6)	0	4 (22.2)	0	7 (3.1)

CZP=certolizumab pegol; Esc=escape; MS=Maintenance Set; PASI50=at least 50% reduction from Baseline in Psoriasis Area and Severity Index; PBO=placebo; Q2W=every 2 weeks; Wk=Week
Note: Rows with all zeros are not included in the in-text table.

Study CIMPASI-2

Initial Treatment Period
A total of 301 subjects were screened for the study, 74 of whom were screen failures; most commonly due to ineligibility (59 subjects, 19.6%).

A total of 227 randomized subjects started the Initial Treatment Period. Overall, 212 subjects (93.4%) completed the Initial Treatment Period; with similar completion rates across the three groups.

A total of 15 subjects (6.6%) discontinued during the Initial Treatment Period (prior to Week 16); the most frequently reported primary reasons for discontinuation were consent withdrawn (6 subjects, 2.6%) and AE (4 subjects, 1.8%; all AEs reported as primary reason for discontinuation were non-serious).
Of the 212 subjects who completed the Initial Treatment Period, 2 subjects (0.9%) did not enter the Maintenance Treatment Period.

Figure 6: Disposition of subjects by randomized treatment group – Initial Treatment Period (Weeks 0 to 16) (RS) (CIMPASI-2)
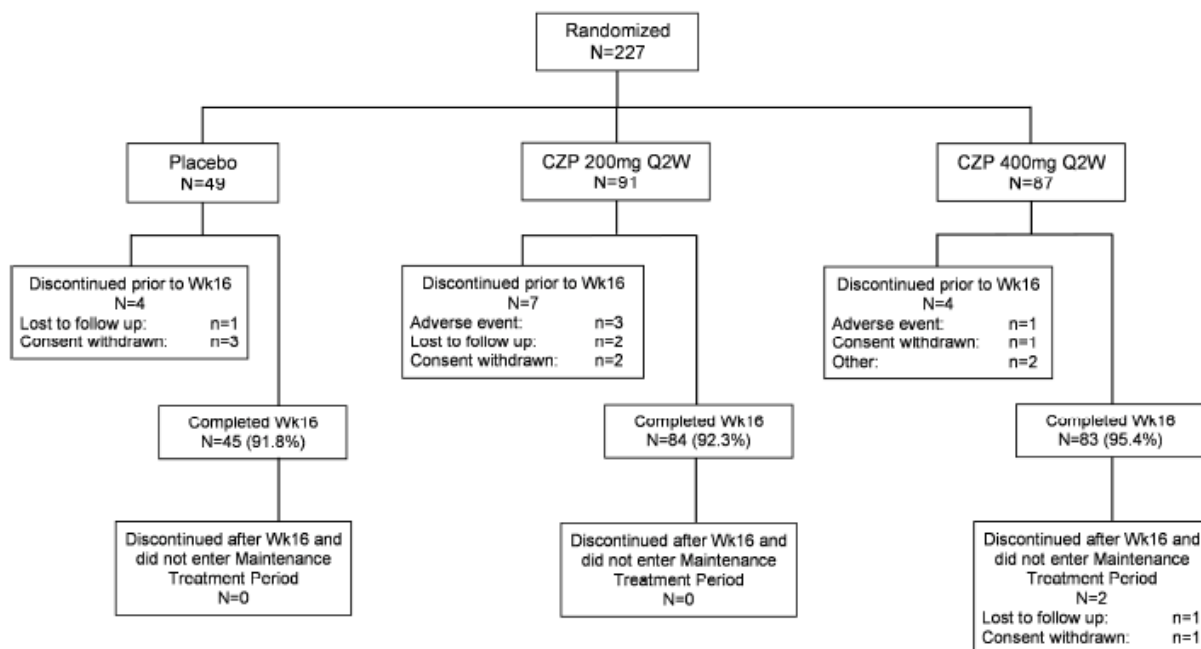
CZP=certolizumab pegol; Q2W=every 2 weeks; RS=Randomized Set; Wk=Week

Maintenance Treatment Period

A total of 210 subjects started the Maintenance Treatment Period, and 173 subjects (82.4%) completed Week 48. A total of 37 subjects (17.6%) discontinued during the Maintenance Treatment Period (prior to Week 48); the most frequently reported primary reasons for discontinuation were AE (12 subjects, 5.7%) and consent withdrawn and other: mandatory withdrawal due to not achieving a PASI50 response (7 subjects each, 3.3%).

Table: Disposition and discontinuation reasons by maintenance treatment group - Maintenance Treatment Period (Weeks 16 to 48) (MS) (CIMPASI-2)

Disposition	Blinded maintenance group				Escape maintenance group			
	PBO/ PBO N=6 n (%)	PBO/ CZP 200mg Q2W N=5 n (%)	CZP 200mg Q2W/ CZP 200mg Q2W N=76 n (%)	CZP 400mg Q2W/ CZP 400mg Q2W N=69 n (%)	PBO/Esc CZP 400mg Q2W N=34 n (%)	CZP 200mg Q2W/Esc CZP 400mg Q2W N=8 n (%)	CZP 400mg Q2W/Esc CZP 400mg Q2W N=12 n (%)	All subjects N=210 n (%)
Started Maintenance Treatment Period (Wks 16 to 48)	6 (100)	5 (100)	76 (100)	69 (100)	34 (100)	8 (100)	12 (100)	210 (100)
Completed Wk 48	5 (83.3)	3 (60.0)	64 (84.2) [a]	61 (88.4)	27 (79.4)	3 (37.5)	10 (83.3)	173 (82.4)
Discontinued prior to Wk 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)
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 PASI50 response	0	0	2 (2.6)	1 (1.4)	1 (2.9)	2 (25.0)	0	6 (2.9)

CZP=certolizumab pegol; Esc=escape; MS=Maintenance Set; PASI50=at least 50% reduction from Baseline in Psoriasis Area and Severity Index; PBO=placebo; Q2W=every 2 weeks; Wk=Week
Note: One of the 8 subjects in the CZP 200mg Q2W/Esc CZP 400mg Q2W and 2 of the 12 subjects in the CZP 400mg Q2W/Esc CZP 400mg Q2W group were PASI50 responders at Week 16, but were put into the escape group because their Week 16 visit occurred outside of the protocol-specified window.
Note: Rows with all zeros are not included in the in-text table.

[a] Subject 223-22325 (CZP 200mg Q2W) is counted as completing the Initial Treatment Period. The subject's study withdrawal visit occurred in the Maintenance Treatment Period, but the subject reported an adverse event which led to withdrawal that emerged during the Initial Treatment Period. Subject 232-23220 (CZP 200mg Q2W/CZP 200mg Q2W) is counted as completing the Maintenance Period. The subject's study withdrawal visit occurred in the Open-Label Extension, but the subject reported an adverse event which led to withdrawal that emerged during the Maintenance Period.

The number of patients completing the initial periods was high in both studies (>93%) and the most common reasons for discontinuation were consent withdrawn, lost to follow-up or AEs. The numbers of patients who completed the maintenance periods in the blinded maintenance groups were also fairly high.

The groups of patients continuing on placebo in the maintenance period (i.e. those who achieved PASI75 on placebo at week 16) were small, which is not unexpected.

CIMPACT study

Initial Treatment Period

A total of 731 subjects were screened for the study, 174 of whom were screen failures; the most common reason being ineligibility (136 subjects, 18.6%). A total of 559 randomized subjects started the Initial Treatment Period.

Overall, 535 subjects (95.7%) completed the Initial Treatment Period. The percentages of subjects who completed the Initial Treatment Period were similar across the CZP and placebo groups, and slightly lower in the ETN group (93.5%); mainly due to a higher percentage of subjects discontinuing due to an AE in the ETN group (2.4%) compared with the other groups (≤0.6% each). A total of 24

subjects (4.3%) discontinued during the Initial Treatment Period (prior to Week 16); the most frequently reported primary reasons for discontinuation were consent withdrawn, AE, and lost to follow up (around 1% each). Two of the 6 subjects who reported AE as the primary reason for discontinuation had serious, nonfatal events; one subject in the CZP 200mg Q2W group and one subject in the ETN group. Of the 535 subjects who completed the Initial Treatment Period, 2 subjects (0.4%) were not eligible for inclusion in the MS.

Figure 7: Disposition of subjects by randomized treatment group - Initial Treatment Period (Weeks 0 to 16) (RS) (CIMPACT)
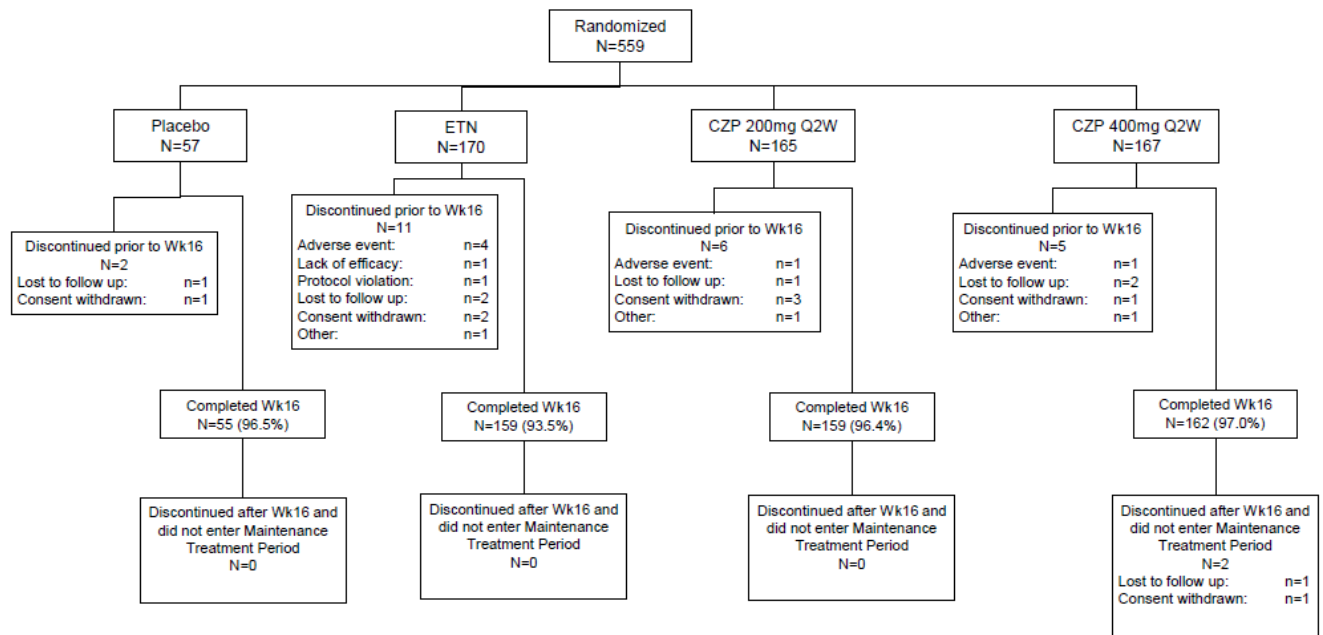
CZP=certolizumab pegol; ETN=etanercept; Q2W=every 2 weeks; RS=Randomized Set; Wk=Week
Note: Of the 2 subjects who completed the Week 16 Visit but are counted as not entering the Maintenance Treatment Period, 1 subject chose not to enter the Maintenance Treatment Period and another subject entered the Maintenance Period but was not eligible for inclusion in the Maintenance Set.

Maintenance Treatment Period

A total of 533 subjects started the Maintenance Treatment Period, and 478 subjects (89.7%) completed this period. A total of 55 subjects (10.3%) discontinued during the Maintenance Treatment Period (prior to Week 48); the most frequently reported primary reasons for discontinuation were other: mandatory withdrawal due to not achieving a PASI50 response (18 subjects, 3.4%), consent withdrawn (14 subjects, 2.6%), and AE (11 subjects, 2.1%).

Comparing the blinded groups (N=310 combined) and escape groups (N=223 combined), a higher percentage of subjects in the combined escape groups (40 of 223 subjects, 17.9%) discontinued prior to Week 48 than the combined blinded groups (15 of 310 subjects, 4.8%); this difference was largely due to meeting mandatory withdrawal criteria (failed to achieve a PASI50 response), which did not apply to the blinded groups. The percentage of subjects discontinuing due to an AE was slightly greater in the combined escape groups (3.6%) compared with the combined blinded groups (1.0%). All other reasons for discontinuation were low and similar between the combined blinded and combined escape groups.

Among the *blinded* maintenance treatment groups, the majority of subjects in each group completed the Maintenance Treatment Period (>90%). Of those who completed the Maintenance Treatment Period, most subjects completed without relapse (245 of 295 completers, 83.1%). Fifty subjects (of 295 completers, 16.9%) completed with relapse (ie, did not achieve a PASI50 response at some

timepoint during the Maintenance Treatment Period) and were removed from the placebo-controlled Maintenance Treatment Period and entered into the OLE Treatment Period of the study. Most (34 of 50 subjects, 68%) of the subjects who relapsed had been receiving placebo during the Maintenance Treatment Period. Among the *escape* maintenance treatment groups, the majority of subjects in each group completed the Maintenance Treatment Period (≥73.5%); a higher percentage of subjects discontinued prior to Week 48 in the CZP 200mg Q2W/Esc CZP 400mg Q2W group (26.5%) compared with the other escape groups (range: 13.2% to 16.7%). This difference was largely due to a higher percentage of subjects discontinuing due to a primary reason of lack of efficacy or mandatory withdrawal (failed to achieve a PASI50 response) versus the other groups.

Table: Disposition and discontinuation reasons by maintenance treatment group — Maintenance Treatment Period (Weeks 16 to 48) (MS) (CIMPACT)

	Blinded groups (N=310)									Escape groups (N=223)				
Initial treatment	PBO	ETN		CZP 200mg Q2W			CZP 400mg Q2W			PBO	ETN	CZP 200mg Q2W	CZP 400mg Q2W	All subjects
Maintenance treatment	PBO	PBO	CZP 200mg Q2W	PBO	CZP 200mg Q2W	CZP 400mg Q4W	PBO	CZP 200mg Q2W	CZP 400mg Q2W	Esc CZP 400mg Q2W				
Disposition	N=2 n (%)	N=24 n (%)	N=50 n (%)	N=22 n (%)	N=44 n (%)	N=44 n (%)	N=25 n (%)	N=50 n (%)	N=49 n (%)	N=53 n (%)	N=85 n (%)	N=49 n (%)	N=36 n (%)	N=533 n (%)
Started Maintenance Treatment Period (Wks 16 to 48)	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)
Completed Maintenance Treatment Period	2 (100)	23 (95.8)	48 (96.0)	20 (90.9)	40 (90.9)	43 (97.7)	23 (92.0)	47 (94.0)	49 (100)	46 (86.8)	71 (83.5)	36 (73.5)	30 (83.3)	478 (89.7)
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 Wk 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)
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 PASI50 response (applies only to escapers)	NA	NA	NA	NA	NA	NA	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; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; Wk=Week
[a] Relapse was defined as not achieving a PASI50 response at some timepoint during the Maintenance Treatment Period. Subjects 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 subject in an escape group did not achieve a PASI50 response at Week 32, the subject was withdrawn from the study. A subject in an escape arm who achieved a PASI50 response at Week 32 but did not achieve a PASI50 response at a later visit was withdrawn from the study at that time.

As in the CIMPASI studies, the number of patients completing the initial period was also high (>95%) and the most common reasons for discontinuation were consent withdrawn, lost to follow-up or AEs.

The numbers of patients who completed the maintenance periods in the blinded groups were also high (>90%). Only two patients continued on placebo in the maintenance period (i.e. those who achieved PASI75 on placebo at week 16).

Recruitment

Study CIMPASI-1 was conducted at 30 sites in North America (Canada, USA) and Europe (Czech Republic, Germany, Hungary). The study was conducted between December 2014 and October 2016 (first subject enrolled 16 Dec 2014; last subject completed 20 Oct 2016, based on an interim cut for the interim CSR).

Study CIMPASI-2 was conducted at 23 sites in North America (USA and Canada) and Europe (Austria and Poland). The study was conducted between December 2014 and August 2016 (first subject enrolled 15 Dec 2014; last subject completed 16 Aug 2016 based on an interim cut for the interim study report).

Study CIMPACT was conducted at 70 sites located in the USA, Western Europe, and Central/East Europe. The study was conducted between February 2015 and December 2016 (first subject enrolled 11 Feb 2015; last subject completed 05 Dec 2016.

Conduct of the studies

CIMPASI-1

Protocol amendments

The original protocol (dated 17 Jul 2014) underwent 3 local (country-specific) protocol amendments and 1 global protocol amendment. The local amendments concerned added HIV testing at Screening and the time period for use of adequate contraception during the study and after the last dose of study treatment.

The Global Protocol Amendment (24 Nov 2015) concerned administrative changes, addition of PASI90 as a secondary efficacy variable, clarification the responsibilities of the unblinded and blinded study personnel, allowed flexibility of self-administration of CZP during the Open-label Treatment Period, etc.

Protocol deviations

During the Initial Treatment Period, 30 subjects (13%) had at least 1 important protocol deviation; with somewhat higher incidences in the CZP groups compared with the placebo group. Overall, the most frequently reported important protocol deviations were related to procedures/tests (7.7%) and IP administration/study treatment (3.0%). A total of 6 subjects (2.6%) were excluded from the PPS due to important protocol deviations (related to IP administration/study treatment and use of disallowed medications; 3 subjects each, 1.3%).

During the Maintenance Treatment Period, 3 subjects (1.3%) had at least 1 important protocol deviation (2 subjects due to the use of disallowed medications and 1 due to IP administration/study treatment).

Compliance

During the Initial Treatment Period, the mean overall compliance in the SS was 98.8%; nearly all subjects (99.1%) had ≥ 80% compliance. Two subjects had <80% compliance (who each had 75% compliance and received 12 of 16 injections).

During the Maintenance Treatment Period, the mean overall compliance in the MS was 98.9% and nearly all subjects (98.7%) had ≥ 80% compliance. Overall, 3 subjects had <80% compliance.

CIMPASI-2

Protocol amendments

The original protocol (dated 17 Jul 2014) underwent 2 local (country-specific) protocol amendments and 1 global protocol amendment. These were overall similar to those in the CIMPASI-1 (PS0005) protocol.

Protocol deviations

During the Initial Treatment Period, 14 subjects (6.2%) had at least 1 important protocol deviation; with a higher incidence in the placebo group compared with the CZP groups.The most frequently reported important protocol deviations were related to IP administration/study treatment (2.6%) and

use of disallowed medications (1.8%). A total of 7 subjects (3.1%) were excluded from the PPS due to important protocol deviations, mainly due to IP administration/study treatment (1.8%).

During the Maintenance Treatment Period, 10 subjects (4.8%) had at least 1 important protocol deviation, mainly related to procedures/tests and IP administration/study treatment (3 subjects each).

Compliance

During the Initial Treatment Period, the mean overall compliance was 98.8%; nearly all subjects (98.7%) had ≥ 80% compliance. Three subjects had <80% compliance; all in the CZP 200mg Q2W group.

CIMPACT

Protocol amendments

The original protocol (dated 25 Jul 2014) underwent 7 local (country-specific) protocol amendments and 3 global protocol amendments. The local amendments concerned added HIV testing at Screening and the contraception duration.

The Global Protocol Amendment 1 (20 Apr 2015) concerned administrative changes, revisions related to treatment received in Period 3 being based on initial treatment and response to treatment at Week 16, ETN treatments allowed to be administered by trained study staff on site or outside of the study center to allow flexibility around self-administration (with compliance to be recorded), increase in number of planned sites, stratification across sites based on prior biologic use was eliminated, etc.

Global Protocol Amendment 2 (23 Dec 2015) included addition of PASI90 as a secondary efficacy variable (at Weeks 12 and 16 with PASI90 at Week 12 included in the sequential testing procedure), etc.

Global Protocol Amendment 3 (28 Oct 2016) concerned inclusion of the previously prespecified PASI75, PASI90, and PGA variables at Week 16 for CZP 400 mg Q2W and CZP 200 mg Q2W vs. placebo in the statistical hierarchical testing, etc.

Protocol deviations

During the Initial Treatment Period, 22 of 559 subjects (3.9%) had at least 1 important protocol deviation, with a similar incidence across groups. The most frequently reported important protocol deviations were related to IP administration/study treatment (2.1%). The incidence for this category was slightly higher in the ETN group (3.5%) compared with the CZP and placebo groups (≤ 1.8% for each), which may be due in part to the injection schedule for ETN (twice weekly).

A total of 11 subjects (2.0%) were excluded from the PPS due to important protocol deviations, most frequently related to IP administration/study treatment (5 subjects, 0.9%).

During the Maintenance Treatment Period, the incidence of important protocol deviations was low overall (13 subjects, 2.4%) with no apparent trend across groups.

Compliance

During the Initial Treatment Period, the mean overall compliance was 98.5%; nearly all subjects (98.2%) had ≥ 80% compliance.

During the 32-week Maintenance Treatment Period, the mean overall compliance was 98.4%); nearly all subjects (98.5%) had ≥ 80% compliance. Overall, 8 subjects (1.5%) had <80% compliance.

Amendments to the study protocols were performed in all three studies, but the amendments are not considered to have major impact on the interpretation of study results.

The incidence of protocol deviations was generally low and did not lead to any concerns. The compliance was high in all three studies.

Baseline data

For simplicity, a summary of demographic characteristics for subjects enrolled in all pivotal studies (CIMPASI-1, CIMPASI-2, CIMPACT), is provided in the table below. This is also referred to as Pool E1.

Table: Demographic characteristics in CIMPASI-1, CIMPASI-2, CIMPACT, and Pool E1

Characteristic	CIMPASI-1 All subjects N=234 n (%)	CIMPASI-2 All subjects N=227 n (%)	CIMPACT[a] All subjects N=559 n (%)	Pool E1 PBO N=157 n (%)	CZP 200mg Q2W N=351 n (%)	CZP 400mg Q2W N=342 n (%)	All Subjects N=850 n (%)
Age (years)							
n	234	227	559	157	351	342	850
Mean (SD)	44.9 (12.7)	45.9 (13.7)	45.7 (13.3)	46.0 (13.3)	46.1 (13.4)	45.2 (12.6)	45.7 (13.0)
Median	45.0	46.0	46.0	47.0	47.0	45.0	46.0
Min, max	21, 76	20, 75	18, 80	20, 73	19, 80	18, 75	18, 80
Age (years)							
<40	84 (35.9)	77 (33.9)	187 (33.5)	44 (28.0)	118 (33.6)	118 (34.5)	280 (32.9)
≥40 to <64	137 (58.5)	129 (56.8)	332 (59.4)	100 (63.7)	209 (59.5)	200 (58.5)	509 (59.9)
≥65	13 (5.6)	21 (9.3)	40 (7.2)	13 (8.3)	24 (6.8)	24 (7.0)	61 (7.2)
Gender, n (%)							
Male	162 (69.2)	127 (55.9)	381 (68.2)	95 (60.5)	238 (67.8)	210 (61.4)	543 (63.9)
Female	72 (30.8)	100 (44.1)	178 (31.8)	62 (39.5)	113 (32.2)	132 (38.6)	307 (36.1)
Racial group, n (%)							
Asian	NA	NA	7 (1.3)	NA	NA	NA	NA
White	211 (90.2)	211 (93.0)	540 (96.6)	146 (93.0)	331 (94.3)	322 (94.2)	799 (94.0)
Black	8 (3.4)	7 (3.1)	7 (1.3)	4 (2.5)	7 (2.0)	8 (2.3)	19 (2.2)
Other	15 (6.4)	9 (4.0)	5 (0.9)	7 (4.5)	13 (3.7)	12 (3.5)	32 (3.8)
Ethnicity, n (%)							
Hispanic or Latino	28 (12.0)	31 (5.5)	11 (6.5)	13 (8.3)	22 (6.3)	30 (8.8)	65 (7.6)
Not Hispanic or Latino	206 (88.0)	528 (94.5)	159 (93.5)	144 (91.7)	329 (93.7)	312 (91.2)	785 (92.4)
Weight (kg)							
n	234	227	558	157	351	342	850
Mean (SD)	93.03 (20.88)	93.18 (26.80)	88.77 (21.61)	92.15 (25.78)	92.58 (22.28)	89.17 (22.74)	91.13 (23.18)
Median	90.60	87.20	85.35	88.10	90.00	85.40	87.20
Min, max	48.0, 168.2	45.3, 197.5	41.8, 198.5	47.0, 198.5	48.0, 174.5	41.8, 197.5	41.8, 198.5
Height (cm)							
n	234	227	559	157	351	342	850
Mean (SD)	172.88 (10.78)	171.01 (9.69)	172.96 (9.95)	171.63 (9.37)	172.95 (10.04)	172.12 (10.48)	172.37 (10.10)
Median	173.00	171.00	174.00	170.20	173.00	173.00	173.00
Min, max	144.8, 199.0	146.0, 199.0	135.5, 200.7	151.1, 196.0	140.0, 199.0	144.8, 199.0	140.0, 199.0
BMI (kg/m²)							
n	234	227	558	157	351	342	850
Mean (SD)	31.195 (6.945)	31.788 (8.493)	29.589 (6.402)	31.18 (7.83)	30.95 (7.11)	30.06 (7.06)	30.63 (7.24)
Median	29.920	30.440	28.720	29.86	29.67	28.90	29.41
Min, max	18.83, 59.37	15.78, 66.08	15.42, 64.60	17.7, 57.4	15.8, 59.7	15.4, 66.1	15.4, 66.1

BMI=body mass index; cm=centimeter; CZP=certolizumab pegol; ETN=etanercept; kg=kilogram; m=meter; max=maximum; min=minimum; PBO=placebo; Q2W=every 2 weeks; SD=standard deviation

Demographic characteristics were generally well balanced across groups and across studies. One exception was that there were fewer males overall in CIMPASI-2 (56%) compared with CIMPASI-1 (69%) or CIMPACT (68%).

In Pool E1, the mean age of subjects was 45.7 years (range: 18 to 80 years), with more than half (60%) of the subjects in the age category ⩾40 to <64 years; a lower percentage of subjects in the placebo group were <40 years of age (28%) compared with the CZP 200 mg Q2W and 400 mg Q2W groups (33.6% and 34.5%, respectively). The majority of subjects were male (63.9%). Most subjects were White (94.0%) and not of Hispanic or Latino ethnicity (92.4%).

Overall, the mean BMI was 30.63 kg/m^2 and mean body weight was 91.1 kg; mean and median body weight and BMI were overall similar across treatment groups.

A summary of baseline disease characteristics for subjects enrolled in CIMPASI-1, CIMPASI-2, CIMPACT, and Pool E1 is provided in the table below.

Table: Baseline disease characteristics in CIMPASI-1, CIMPASI-2, CIMPACT, and Pool E1

Characteristic	CIMPASI-1 All subjects N=234 n (%)	CIMPASI-2 All subjects N=227 n (%)	CIMPACT [a] All subjects N=559 n (%)	Pool E1 PBO N=157 n (%)	Pool E1 CZP 200mg Q2W N=351 n (%)	Pool E1 CZP 400mg Q2W N=342 n (%)	Pool E1 All Subjects N=850 n (%)
PSO disease duration (years)							
n	234	227	559	157	351	342	850
Mean (SD)	17.69 (12.60)	17.96 (12.82)	18.293 (12.317)	17.67 (12.68)	18.52 (13.06)	18.16 (12.04)	18.22 (12.58)
Median	14.65	15.51	15.943	15.59	15.52	15.95	15.63
Min, max	0.5, 56.9	0.5, 54.3	0.51, 63.76	0.5, 54.6	0.5, 63.7	0.5, 56.9	0.5, 63.7
PSO disease duration (years), n (%)							
⩽Median	117 (50.0)	114 (50.2)	280 (50.1)	79 (50.3)	176 (50.1)	170 (49.7)	425 (50.0)
>Median	117 (50.0)	113 (49.8)	279 (49.9)	78 (49.7)	175 (49.9)	172 (50.3)	425 (50.0)
Previous biologic therapy used, n (%)							
Never used	160 (68.4)	151 (66.5)	405 (72.5)	117 (74.5)	245 (69.8)	235 (68.7)	597 (70.2)
1 therapy	57 (24.4)	54 (23.8)	120 (21.5)	31 (19.7)	82 (23.4)	80 (23.4)	193 (22.7)
2 therapies	17 (7.3)	21 (9.3)	34 (6.1)	9 (5.7)	24 (6.8)	26 (7.6)	59 (6.9)
⩾3 therapies	0	1 (0.4)	0	0	0	1 (0.3)	1 (0.1)
Prior anti-TNF therapy used, n (%)							
Yes	46 (19.7)	53 (23.3)	21 (3.8)	24 (15.3)	49 (14.0)	43 (12.6)	116 (13.6)
No	188 (80.3)	174 (76.7)	538 (96.2)	133 (84.7)	302 (86.0)	299 (87.4)	734 (86.4)
Previous systemic nonbiologic therapy used, n (%)							
Never used	144 (61.5)	134 (59.0)	338 (60.5)	98 (62.4)	210 (59.8)	199 (58.2)	507 (59.6)
1 therapy	68 (29.1)	67 (29.5)	164 (29.3)	43 (27.4)	106 (30.2)	105 (30.7)	254 (29.9)
2 therapies	16 (6.8)	21 (9.3)	47 (8.4)	13 (8.3)	28 (8.0)	29 (8.5)	70 (8.2)
⩾3 therapies	6 (2.6)	5 (2.2)	10 (1.8)	3 (1.9)	7 (2.0)	9 (2.6)	19 (2.2)
Prior chemophototherapy or phototherapy, n (%)							
Yes	102 (43.6)	94 (41.4)	289 (51.7)	70 (44.6)	164 (46.7)	162 (47.4)	396 (46.6)
No	132 (56.4)	133 (58.6)	270 (48.3)	87 (55.4)	187 (53.3)	180 (52.6)	454 (53.4)
Previous exposure to at least 2 systemic treatments out of phototherapy, MTX, and cyclosporine (with no previous biologic exposure), n (%)							
Yes	62 (26.5)	67 (29.5)	176 (31.5)	18 (11.5)	36 (10.3)	31 (9.1)	85 (10.0)
No	172 (73.5)	160 (70.5)	383 (68.5)	139 (88.5)	315 (89.7)	311 (90.9)	765 (90.0)
Any prior systemic therapy used for PSO, n (%)							
Yes	163 (69.7)	164 (72.2)	403 (72.1)	111 (70.7)	249 (70.9)	247 (72.2)	607 (71.4)
No	71 (30.3)	63 (27.8)	156 (27.9)	46 (29.3)	102 (29.1)	95 (27.8)	243 (28.6)

Previous exposure to anti-IL-17							
Yes	ND	ND	ND	13 (8.3)	54 (15.4)	43 (12.6)	110 (12.9)
No	ND	ND	ND	144 (91.7)	297 (84.6)	299 (87.4)	740 (87.1)
PSO BSA (%)							
n	234	227	559	157	351	342	850
Mean (SD)	25.1 (16.6)	21.7 (11.5)	27.4 (15.6)	23.5 (13.6)	25.6 (15.9)	25.5 (14.9)	25.2 (15.1)
Median	19.0	19.0	23.0	19.0	20.0	21.0	20.0
Min, max	10, 96	10, 81	10, 89	10, 85	10, 84	10, 96	10, 96
PSO BSA (%)							
≤Median	120 (51.3)	118 (52.0)	290 (51.9)	89 (56.7)	180 (51.3)	169 (49.4)	438 (51.5)
>Median	114 (48.7)	109 (48.0)	269 (48.1)	68 (43.3)	171 (48.7)	173 (50.6)	412 (48.5)
PASI score							
n	234	227	559	157	351	342	850
Mean (SD)	19.82 (7.94)	18.60 (6.15)	20.89 (8.14)	18.79 (6.87)	20.27 (8.07)	20.16 (7.52)	19.95 (7.64)
Median	17.40	16.60	18.40	16.60	17.60	18.40	17.60
Min, max	11.6, 68.6	11.7, 56.0	11.2, 58.5	12.0, 44.9	11.7, 55.5	11.6, 68.6	11.6, 68.6
PGA score [b], n (%)							
3 (moderate)	162 (69.2)	164 (72.2)	382 (68.3)	112 (71.3)	242 (68.9)	239 (69.9)	593 (69.8)
4 (severe)	71 (30.8)	63 (27.8)	177 (31.7)	45 (28.7)	109 (31.1)	103 (30.1)	257 (30.2)
DLQI total score							
n	227	226	558	154	346	340	840
Mean (SD)	13.4 (7.3)	14.4 (7.3)	14.0 (7.3)	13.4 (7.7)	13.6 (7.2)	14.5 (7.1)	13.9 (7.3)
Median	13.0	14.0	13.0	12.0	13.0	14.0	13.0
Min, max	0, 30	1, 30	0, 30	0, 30	0, 30	1, 30	0, 30
Concomitant PSA, n (%)							
Yes	29 (12.4)	57 (25.1)	90 (16.1)	25 (15.9)	59 (16.8)	65 (19.0)	149 (17.5)
No	205 (87.6)	170 (74.9)	469 (83.9)	132 (84.1)	292 (83.2)	277 (81.0)	701 (82.5)
Geographical region, n (%)							
Central/Eastern Europe	37 (15.8)	63 (27.8)	363 (64.9)	57 (36.3)	150 (42.7)	145 (42.4)	352 (41.4)
North America	120 (51.3)	157 (69.2)	92 (16.5)	71 (45.2)	136 (38.7)	133 (38.9)	340 (40.0)
Western Europe	77 (32.9)	7 (3.1)	104 (18.6)	29 (18.5)	65 (18.5)	64 (18.7)	158 (18.6)

BSA=body surface area; CZP=certolizumab pegol; DLQI=Dermatology Life Quality Index; ETN=etanercept; max=maximum; min=minimum;
MTX=methotrexate; ND=not done; PASI=Psoriasis Area and Severity Index; PBO=placebo; PGA=Physician's Global Assessment; PSA=psoriatic arthritis,
PSO=psoriasis; Q2W=every 2 weeks; SD=standard deviation; TNF=tumor necrosis factor
a Subjects receiving ETN are included in the CIMPACT "All subjects" column; however, these subjects are not included in the Pool E1 "All subjects" column.
b PGA score of at least 3 was required per Inclusion Criterion #5 in CIMPASI-1, CIMPASI-2, and CIMPACT.
Note: For the categorical summary of BSA, PASI, and PSO disease duration, the median of subjects included in Pool E1 was used to determine the cutpoints.

Baseline disease characteristics were generally well balanced across studies and reflected a population with moderate to severe PSO. Differences between the studies were observed for prior anti-TNF therapy, prior chemotherapy or phototherapy use, and geographical region. A lower percentage of subjects used prior anti-TNF therapy in CIMPACT (21 subjects, 3.8%) compared with CIMPASI-1 (46 subjects, 19.7%) and CIMPASI-2 (53 subjects, 23.3%). This difference in prior anti-TNF therapy is likely due to the fact that prior ETN use was not permitted in CIMPACT.

A higher percentage of subjects used chemotherapy or phototherapy in CIMPACT (289 subjects, 51.7%) compared with CIMPASI-1 (102 subjects, 43.6%), and CIMPASI-2 (94 subjects, 41.4%). Additionally, a higher percentage of subjects were from Europe in CIMPACT (approximately 83.5%) compared with CIMPASI-1 (48.7%) and CIMPASI-2 (30.8%).

In Pool E1, baseline disease characteristics were generally well balanced across treatment groups. The only notable exception was a slight imbalance in previous exposure to IL-17, with fewer subjects in the

placebo group (13 subjects, 8.3%) previously exposed to IL-17 compared with subjects in the CZP 200mg Q2W (54 subjects, 15.4%) and CZP 400mg Q2W (43 subjects, 12.6%) groups. The mean BSA was 25.2%, the mean PASI score was 19.95, the majority (69.8%) of subjects had a PGA score of 3, and the mean DLQI total score was 13.9.

The mean duration of disease was 18.2 years (range: 0.5 to 64 years), and the majority of subjects had never used a biologic therapy in the past (70.2%), had not used systemic non-biologic therapy in the past (59.6%), had not used chemophototherapy or phototherapy in the past (53.4%), and had not used anti-TNF therapy in the past (86.4%).

The majority (90.0%) of subjects did not have prior exposure to at least 2 systemic treatments out of phototherapy, MTX, and cyclosporine (with no previous biologic exposure). The majority of subjects had used systemic treatment for PSO (71.4%), and did not report a history of concomitant PsA (82.5%). A lower percentage of subjects were enrolled at sites in North America (40.0%) compared with sites in Europe (60.0%).

Prior and concomitant diseases and medications

CIMPASI-1

The majority (87%) of subjects reported a previous or ongoing medical condition/disease at baseline, well balanced across treatment groups. The most frequently reported conditions/diseases at Baseline were in the SOCs of Surgical and medical procedures (36%); Metabolism and nutrition disorders (35%); Musculoskeletal and connective tissue disorders (34%); Vascular disorders (30%); GI disorders (22%); and Immune system disorders (20%). The most frequently reported conditions/diseases at Baseline were hypertension (29%), psoriatic arthropathy (12%), and obesity (11%).

The majority (96%) of subjects reported prior PSO medication use; the incidence of prior use was generally well balanced across treatment groups. Prior use of any systemic therapy (defined as any treatment in the nonbiologic systemic agents, biologic agents, or phototherapy or photochemotherapy categories) was reported by 70% of subjects overall. The most frequently reported categories were topical prescription therapy (85% of subjects overall), phototherapy or photochemotherapy (44%), nonbiologic systemic agents (39%), and biologic agents (32%). The most frequently reported specific prior treatments were UVB (26% of subjects overall) and MTX (25%).

More than half (58%) of subjects reported prior non-PSO related medication use; the incidence of prior non-PSO medication use was well balanced across treatment groups (most frequently lipid-modifying agents, anti-inflammatory and antirheumatic products, blood glucose lowering drugs, drugs for peptic ulcer and gastroesophageal reflux, ACE inhibitors, other analgesics and antipyretics, beta-blocking agents and antithrombotic agents).

CIMPASI-2

Similar to CIMPASI-1, the majority (89%) of subjects reported a medical history condition or concomitant disease at Baseline that was balanced across treatment groups. The most frequently reported conditions/diseases at Baseline were in the same SOCs as in CIMPASI-1, but also in the; Infections and infestations (25%) and Psychiatric disorders (21%). The most frequently reported conditions/diseases at Baseline by PT were hypertension (31%), psoriatic arthropathy (25%), drug hypersensitivity (13%), obesity (13%), hyperlipidemia (11%), cholestectomy (11%), depression (11%), and gastro-oesophageal reflux disease (10%).

The majority (95%) of subjects reported prior PSO medication use; the incidence of prior medication

use was well balanced across treatment groups. Prior use of any systemic therapy was reported by 72% of subjects overall. The most frequently reported categories were topical prescription therapy (77%), phototherapy or photochemotherapy (41%), nonbiologic systemic agents (41%), and biologic agents (34%). The most frequently reported prior treatments were UVB (33%) and MTX (28%).

Slightly more than half (53.5%) of subjects reported prior non-PSO related medication use, most frequently ACE inhibitors, lipid-modifying agents, anti-inflammatory and anti-rheumatic products, antithrombotic agents and beta-blocking agents.

CIMPACT

The majority (83%) of subjects reported a medical history condition or concomitant disease at Baseline, the incidence of which was well balanced across treatment groups. The most frequently reported conditions/diseases at Baseline Musculoskeletal and connective tissue disorders (33%), largely due to psoriatic arthropathy; Metabolism and nutrition disorders (30%); Vascular disorders (29%); and Surgical and medical procedures (24%). The most frequently reported conditions/diseases at Baseline by PT were hypertension (26%), psoriatic arthropathy (16%), and obesity (11%).

Nearly all subjects (99.1%) reported prior PSO medication use, well balanced across treatment groups. Prior use of any systemic therapy (defined as any treatment in the non-biologic systemic agents, biologic agents, or phototherapy or photochemotherapy categories) was reported by 72% of subjects overall.

The most frequently reported categories of PSO medication were topical prescription therapy (89%), phototherapy or photochemotherapy (52%), and non-biologic systemic agents (40%). The most frequently reported prior treatments were UVB (33%), other biologic agents (24%), MTX (23%), and Psoralen and UVA (18%). The majority of subjects (107 of 132 subjects) in the other biologic agents reported prior treatment with the investigational drug brodalumab.
Overall, approximately half (47.8%) of subjects reported prior non-PSO related medication use (largely similar types of medication as in the CIMPASI studies).

Maintenance
In the CIMPASI studies, the demographic and Baseline characteristics of subjects in the Maintenance Set were similar to the Randomized Set. In general, the treatment groups were well balanced with respect to demographic characteristics, although some variability was noted due to the small sample sizes of some treatment groups. The same applied to the CIMPACT study.

Pool E4
In Pool E4 (the subset of subjects from CIMPASI-1, CIMPASI-2, and CIMPACT who were PASI50 non-responders at Week 16 and subsequently escaped to CZP 400 mg Q2W), demographic characteristics in the escape treatment groups were generally similar to all subjects in the overall study population. One exception was that subjects in Pool E4 had slightly higher mean BMI and mean body weight compared with Pool E1 (BMI 32.1 kg/m^2 vs. 30.6 kg/m^2, respectively; body weight 95 kg vs. 91 kg, respectively).

Numbers analysed

CIMPASI-1

Table: Analysis sets by randomized treatment group - Initial Treatment Period (Weeks 0 to 16) (ES) (CIMPASI-1)

Analysis set	PBO N	CZP 200mg Q2W N	CZP 400mg Q2W N	All subjects N
Randomized Set	51	95	88	234
Safety Set	51	95	88	234
Per Protocol Set	45	90	84	219

CZP=certolizumab pegol; ES=Enrolled Set; PBO=placebo; Q2W=every 2 weeks

Table: Analysis sets by maintenance treatment group - Maintenance Treatment Period (Weeks 16 to 48) (ES) (CIMPASI-1)

Analysis set	Blinded maintenance group				Escape maintenance group			All subjects N
	PBO/ PBO N	PBO/ CZP 200mg Q2W N	CZP 200mg Q2W/ CZP 200mg Q2W N	CZP 400mg Q2W/ CZP 400mg Q2W N	PBO/Esc CZP 400mg Q2W N	CZP 200mg Q2W/Esc CZP 400mg Q2W N	CZP 400mg Q2W/Esc CZP 400mg Q2W N	
Randomized Set	3	5	74	78	38	18	8	234
Safety Set	3	5	74	78	38	18	8	234
Treated with CZP Set	0	5	74	78	38	18	8	226
Maintenance Safety Set	3	5	74	78	38	18	8	224
Maintenance Set	3	5	74	77	38	18	8	223
Treated with Blinded CZP Set	0	5	74	78	0	18	8	188

CZP=certolizumab pegol; ES=Enrolled Set; Esc=escaped to; PBO=placebo; Q2W=every 2 weeks

CIMPASI-2

Table: Analysis sets by randomized treatment group - Initial Treatment Period (Weeks 0 to 16) (ES) CIMPASI-2

Analysis set	PBO N	CZP 200mg Q2W N	CZP 400mg Q2W N	All subjects N
Randomized Set	49	91	87	227
Safety Set	49	90	87	226
Per Protocol Set	43	81	81	205

CZP=certolizumab pegol; ES=Enrolled Set; PBO=placebo; Q2W=every 2 weeks

Table: Analysis sets by maintenance treatment group - Maintenance Treatment Period (Weeks 16 to 48) (ES) CIMPASI-2

Analysis set	Blinded maintenance group				Escape maintenance group			All subjects N
	PBO/ PBO N	PBO/ CZP 200mg Q2W N	CZP 200mg Q2W/ CZP 200mg Q2W N	CZP 400mg Q2W/ CZP 400mg Q2W N	PBO/Esc CZP 400mg Q2W N	CZP 200mg Q2W/Esc CZP 400mg Q2W N	CZP 400mg Q2W/Esc CZP 400mg Q2W N	
Randomized Set	6	5	76	71	34	8	12	227
Safety Set	6	5	76	71	34	8	12	226
Treated with CZP Set	0	5	76	71	34	8	12	216
Maintenance Safety Set	6	5	76	71	34	8	12	212
Maintenance Set	6	5	76	69	34	8	12	210
Treated with Blinded CZP Set	0	5	76	71	0	8	12	182

CZP=certolizumab pegol; ES=Enrolled Set; Esc=escaped to; PBO=placebo; Q2W=every 2 weeks

CIMPACT

Table: Analysis sets by randomized treatment group - Initial Treatment Period (Weeks 0 to 16) (ES) (CIMPACT)

Analysis set	PBO N	ETN N	CZP 200mg Q2W N	CZP 400mg Q2W N	All subjects N
Randomized Set	57	170	165	167	559
Per Protocol Set	55	154	155	160	524
Safety Set	57	168	165	167	557

CZP=certolizumab pegol; ES=Enrolled Set; ETN=etanercept; PBO=placebo; Q2W=every 2 weeks

Table: Analysis sets by maintenance treatment group - Maintenance Treatment Period (Weeks 16 to 48) (ES) (CIMPACT)

	Blinded groups									Escape groups				
Initial treatment	PBO	ETN			CZP 200mg Q2W			CZP 400mg Q2W		PBO	ETN	CZP 200mg Q2W	CZP 400mg Q2W	All subjects
Maintenance treatment	PBO	PBO	CZP 200mg Q2W	PBO	CZP 200mg Q2W	CZP 400mg Q4W	PBO	CZP 200mg Q2W	CZP 400mg Q2W	Esc CZP 400mg Q2W				
Analysis set	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Randomized Set	2	24	50	22	44	44	25	50	49	53	85	49	37	559
Maintenance Set	2	24	50	22	44	44	25	50	49	53	85	49	36	533
Maintenance Safety Set	2	24	50	22	44	44	25	50	49	53	85	49	37	534
Treated with CZP Set	0	0	50	22	44	44	25	50	49	53	85	49	37	520
Week 16 Randomized Set	2	24	50	22	44	44	25	50	49	0	0	0	0	310

CZP=certolizumab pegol; ES=Enrolled Set; Esc=escaped to; ETN=etanercept; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks

In the CIMPASI studies, it is noted that some of the groups in the maintenance period were very small, e.g. the PBO/PBO and PBO/CZP 200 mg Q2W, reflecting that the PASI75 response was low for placebo.

Outcomes and estimation

Note : The primary efficacy end-points are all presented below per study. For secondary endpoints, results are mainly presented for studies combined. An overview of the efficacy pools as defined by the Applicant is presented in the table below.

Table: Overview of efficacy pools

Pool name	Studies included in pool	Treatment groups included in pool	Treatment Periods included in pool	Purpose of pool
E1	CIMPASI-1, CIMPASI-2, CIMPACT	Subjects randomized to: CZP 400mg Q2W CZP 200mg Q2W PBO	Initial Treatment Period (Weeks 0 to 16)	Investigate subgroups; add precision to treatment effect through Week 16 in all Phase 3 studies
E2	CIMPASI-1, CIMPASI-2	Subjects randomized to: CZP 400mg Q2W CZP 200mg Q2W PBO	Initial Treatment Period (Weeks 0 to 16)	Add precision to treatment effect through Week 16 in the CIMPASI studies
E3	CIMPASI-1, CIMPASI-2	Subjects randomized to: CZP 400mg Q2W CZP 200mg Q2W PBO	Initial and Maintenance Treatment Periods (Weeks 0 to 48)	Add precision to treatment effect through Week 48 in the CIMPASI studies
E4	CIMPASI-1, CIMPASI-2, CIMPACT	Subjects randomized to: CZP 400mg Q2W CZP 200mg Q2W PBO	Maintenance Treatment Period (Weeks 16 to 48)	To investigate treatment effect through Week 48 in the subset of subjects who were PASI50 nonresponders at Week 16 and subsequently escaped to CZP 400mg Q2W

Primary efficacy end-points

<u>CIMPASI-1 and CIMPASI-2</u>

The co-primary efficacy variables were PASI75 at Week 16 and PGA (Clear or Almost clear, with at least a 2-category improvement) at Week 16.

Table: PASI75 responder rate at Week 16 by randomized treatment group (RS) (CIMPASI-1)

	PBO N=51	CZP 200mg Q2W N=95	CZP 400mg Q2W N=88
Primary analysis: MCMC method for multiple imputation [a]			
Responder rate (%)	6.5	66.5	75.8
Estimate (95% CI) for difference in proportion of responders vs PBO		60.0 (47.92, 72.17)	69.3 (57.65, 80.99)
Odds ratio vs PBO		28.962	45.660
97.5% CI for odds ratio		6.968, 120.371	10.657, 195.634
P-value [b]		<0.0001	<0.0001
Sensitivity analysis: NRI [c]			
Responder rate (%)	5.9	66.5	75.2
Odds ratio vs PBO		31.675	48.262
97.5% CI for odds ratio		7.586, 132.257	11.274, 206.606
P-value		<0.0001	<0.0001
Sensitivity analysis: model-based multiple imputation [d]			
Responder rate (%)	6.3	67.2	75.7
Odds ratio vs PBO		30.845	46.883
97.5% CI for odds ratio		7.297, 130.388	10.870, 202.200
P-value		<0.0001	<0.0001
Observed results			
PASI75 responder, n/Nobs (%)	3/46 (6.5)	62/92 (67.4)	65/87 (74.7)

CI=confidence interval; CZP=certolizumab pegol; MCMC=Markov Chain Monte Carlo; Nobs=number of subjects with a nonmissing result; NRI=nonresponder imputation; PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; PBO=placebo; Q2W=every 2 weeks; RS=Randomized Set

Note: Estimates of responder rate, odds ratios, CIs, and p-values were based on a logistic regression model with factors for treatment, region, and prior biologic exposure (yes/no).

[a] Missing data were imputed using multiple imputation based on the MCMC method.
[b] The p-value for the primary analysis was evaluated at a 2-sided significance level of 0.025 for each CZP dose vs PBO.
[c] Subjects with a missing PASI75 response at Week 16 were considered nonresponders.
[d] Missing data were imputed using multiple imputation based on the same logistic regression model as used for the analysis.

Table: PGA responder rate at Week 16 by randomized treatment group (RS) (CIMPASI-1)

	PBO N=51	CZP 200mg Q2W N=95	CZP 400mg Q2W N=88
Primary analysis: MCMC method for multiple imputation [a]			
Responder rate (%)	4.2	47.0	57.9
Estimate (95% CI) for difference in proportion of responders vs PBO		42.8 (30.70, 54.86)	53.6 (41.33, 65.94)
Odds ratio vs PBO		20.116	31.143
97.5% CI for odds ratio		3.699, 109.399	5.687, 170.548
P-value [b]		<0.0001	<0.0001
Sensitivity analysis: NRI [c]			
Responder rate (%)	4.1	46.8	57.4
Odds ratio vs PBO		20.321	31.082
97.5% CI for odds ratio		3.744, 110.301	5.686, 169.899
P-value		<0.0001	<0.0001
Sensitivity analysis: model-based multiple imputation [d]			
Responder rate (%)	4.4	47.2	57.8
Odds ratio vs PBO		19.819	30.336
97.5% CI for odds ratio		3.626, 108.331	5.517, 166.789
P-value		<0.0001	<0.0001
Observed results			
Responder, n/Nobs (%)	2/46 (4.3)	42/92 (45.7)	48/87 (55.2)

CI=confidence interval; CZP=certolizumab pegol; MCMC=Markov Chain Monte Carlo; Nobs=number of subjects with a nonmissing result; NRI=nonresponder imputation; PBO=placebo; PGA=Physician's Global Assessment; Q2W=every 2 weeks; RS=Randomized Set

Note: PGA responders=Clear or Almost clear (with at least a 2-category improvement) at Week 16.

Note: Estimates of responder rates, odds ratios, CIs, and p-values were based on a logistic regression model with factors for treatment, region, and prior biologic exposure (yes/no).

[a] Missing data were imputed using multiple imputation based on the MCMC method.

[b] The p-value for the primary analysis was evaluated at a 2-sided significance level of 0.025 for each CZP dose vs PBO.

[c] Subjects with a missing PGA response at Week 16 were considered nonresponders.

[d] Missing data were imputed using multiple imputation based on the same logistic regression model as used for the analysis.

Table: PASI75 responder rate at Week 16 by randomized treatment group (RS) (CIMPASI-2)

	PBO N=49	CZP 200mg Q2W N=91	CZP 400mg Q2W N=87
Primary analysis: MCMC method for multiple imputation [a]			
Responder rate (%)	11.6	81.4	82.6
Estimate (95% CI) for difference in proportion of responders vs PBO		69.7 (57.12, 82.36)	71.0 (58.47, 83.43)
Odds ratio vs PBO		33.405	36.212
97.5% CI for odds ratio		9.965, 111.983	10.686, 122.713
P-value [b]		<0.0001	<0.0001
Sensitivity analysis: NRI [c]			
Responder rate (%)	10.9	77.6	80.3
Odds ratio vs PBO		28.445	33.328
97.5% CI for odds ratio		8.862, 91.304	10.162, 109.299
P-value		<0.0001	<0.0001
Sensitivity analysis: model-based multiple imputation [d]			
Responder rate (%)	12.3	82.9	82.4
Odds ratio vs PBO		34.873	33.668
97.5% CI for odds ratio		10.604, 114.686	10.236, 110.737
P-value		<0.0001	<0.0001
Observed results			
PASI75 responder, n/Nobs (%)	6/45 (13.3)	70/85 (82.4)	69/84 (82.1)

CI=confidence interval; CZP=certolizumab pegol; MCMC=Markov Chain Monte Carlo; Nobs=number of subjects with a nonmissing result; NRI=nonresponder imputation; PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; PBO=placebo; Q2W=every 2 weeks; RS=Randomized Set

Note: Estimates of responder rate, odds ratios, CIs, and p-values were based on a logistic regression model with factors for treatment, region, and prior biologic exposure (yes/no).

[a] Missing data were imputed using multiple imputation based on the MCMC method.

[b] The p-value for the primary analysis was evaluated at a 2-sided significance level of 0.025 for each CZP dose vs PBO.

[c] Subjects with a missing PASI75 response at Week 16 were considered nonresponders.

[d] Missing data were imputed using multiple imputation based on the same logistic regression model as used for the analysis.

Table: PGA responder rate at Week 16 by randomized treatment group (RS) (CIMPASI-2)

	PBO N=49	CZP 200mg Q2W N=91	CZP 400mg Q2W N=87
Primary analysis: MCMC method for multiple imputation [a]			
Responder rate (%)	2.0	66.8	71.6
Estimate (95% CI) for difference in proportion of responders vs PBO		64.8 (52.16, 77.46)	69.6 (57.48, 81.77)
Odds ratio vs PBO		106.225	133.163
97.5% CI for odds ratio		9.572, 1178.843	11.904, 1489.578
P-value [b]		<0.0001	<0.0001
Sensitivity analysis: NRI [c]			
Responder rate (%)	1.6	62.9	69.3
Odds ratio vs PBO		101.800	135.334
97.5% CI for odds ratio		9.459, 1095.639`	12.404, 1476.549
P-value		<0.0001	<0.0001
Sensitivity analysis: model-based multiple imputation [d]			
Responder rate (%)	1.8	67.7	71.6
Odds ratio vs PBO		117.191	141.014
97.5% CI for odds ratio		10.555, 1301.209	12.513, 1589.107
P-value		<0.0001	<0.0001
Observed results			
Responder, n/Nobs (%)	1/45 (2.2)	53/85 (62.4)	55/84 (65.5)

CI=confidence interval; CZP=certolizumab pegol; MCMC=Markov Chain Monte Carlo; Nobs=number of subjects with a nonmissing result; NRI=nonresponder imputation; PBO=placebo; PGA=Physician's Global Assessment; Q2W=every 2 weeks; RS=Randomized Set

Note: PGA responders=Clear or Almost clear (with at least a 2-category improvement) at Week 16.

Note: Estimates of responder rates, odds ratios, CIs, and p-values were based on a logistic regression model with factors for treatment, region, and prior biologic exposure (yes/no).

[a] Missing data were imputed using multiple imputation based on the MCMC method.

[b] The p-value for the primary analysis was evaluated at a 2-sided significance level of 0.025 for each CZP dose vs PBO.

[c] Subjects with a missing PGA response at Week 16 were considered nonresponders.

[d] Missing data were imputed using multiple imputation based on the same logistic regression model as used for the analysis.

Both CIMPASI studies met their co-primary end-points, i.e. to demonstrate superiority vs. placebo with respect to PASI 75 response and PGA response at week 16. This was observed for both CZP dose levels. Analyses using the Per Protocol set supported the above analyses.

The difference between the 200 mg and the 400 mg dose was larger in study CIMPASI-1 with about 10% difference in response rates for both PASI75 and PGA. In study CIMPASI-2 the dose differences in PASI75 and PGA response rates were much smaller.

CIMPACT

Primary efficacy end-points

The primary efficacy variable was PASI75 at Week 12.

Table: PASI75 responder rate at Week 12 by randomized treatment group (RS) (CIMPACT)

	PBO N=57	ETN N=170	CZP 200mg Q2W N=165	CZP 400mg Q2W N=167
Primary analysis: MCMC method for multiple imputation [a]				
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, 66.0)	61.6 (52.1, 71.2)
Odds ratio vs PBO			30.023	37.988
95% CI for odds ratio			8.971, 100.48	11.312, 127.576
P-value			<0.0001	<0.0001
Sensitivity analysis: NRI [b]				
Responder rate (%)	4.8	51.2	59.8	65.7
Odds ratio vs PBO			29.333	37.821
95% CI for odds ratio			8.786, 97.930	11.296, 126.633
P-value			<0.0001	<0.0001
Sensitivity analysis: model-based multiple imputation [c]				
Responder rate (%)	4.9	54.3	61.7	67.6
Odds ratio vs PBO			31.387	40.656
95% CI for odds ratio			9.376, 105.072	12.108, 136.514
P-value			<0.0001	<0.0001
Observed results				
Responders, n/Nobs (%)	3/54(5.6)	91/159 (57.2)	102/157 (65.0)	113/162 (69.8)

CI=confidence interval; CZP=certolizumab pegol; ETN=etanercept; MCMC=Markov Chain Monte Carlo; Nobs=number of subjects with a nonmissing result; NRI=nonresponder imputation; PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; PBO=placebo; Q2W=every 2 weeks; RS=Randomized Set

Note: Estimates of percentages of responders, odds ratios, CIs, and p-values were based on using a logistic regression model with factors for treatment, region, and prior biologic exposure (yes/no).

[a] Missing data were imputed using multiple imputation based on the MCMC method.
[b] Subjects with missing PASI75 response at Week 12 were considered to be nonresponders.
[c] Missing data were imputed using multiple imputation based on the same logistic regression model as used for the analysis.

Study CIMPACT also met its primary end-point, i.e. to demonstrate superiority vs. placebo with respect to PASI 75 response at week 12. Sensitivity analyses (NRI and model-based multiple imputation) overall showed similar results as the primary method used (MCMC). Both CZP doses were superior to placebo with a difference of approximately 5% in favour of the 400 mg arm.

The results are also graphically displayed (separate and as Pool E1) in the section *Analysis performed across trials.*

Secondary efficacy variables

For secondary efficacy end-point, the results are displayed in the tables below.

PASI90 at Week 16

Table: PASI90 responder rates at Week 16 by randomized treatment group in CIMPASI-1, CIMPASI-2, CIMPACT, Pool E1, and Pool E2 (RS [MCMC])

Study or Pool	Responder rate %	Odds ratio (CZP vs PBO)	97.5% CI	P-value vs PBO
CIMPASI-1 at Week 16 [a]				
PBO (N=51)	0.4	-	-	-
CZP 200mg Q2W (N=95)	35.8	36.668	5.717, 235.195	<0.0001
CZP 400mg Q2W (N=88)	43.6	50.606	7.880, 324.988	<0.0001
CIMPASI-2 at Week 16 [a]				
PBO (N=49)	4.5	-	-	-
CZP 200mg Q2W (N=91)	52.6	24.283	4.386, 134.432	<0.0001
CZP 400mg Q2W (N=87)	55.4	27.204	4.895, 151.198	<0.0001
CIMPACT at Week 16 [b]				
PBO (N=57)	0.3	-	-	-
CZP 200mg Q2W (N=165)	39.8	49.527	10.002, 245.256	<0.0001
CZP 400mg Q2W (N=167)	49.1	72.278	14.650, 356.602	<0.0001
Pool E1				
PBO (N=157)	1.6	-	-	-
CZP 200mg Q2W (N=351)	44.5	49.6	9.9, 249.6 [c]	<0.0001
CZP 400mg Q2W (N=342)	52.2	67.6	13.4, 340.8 [c]	<0.0001
Pool E2				
PBO (N=100)	2.5	-	-	-
CZP 200mg Q2W (N=186)	45.9	34.3	6.7, 175.7 [c]	<0.0001
CZP 400mg Q2W (N=175)	52.2	44.1	8.6, 226.5 [c]	<0.0001

CI=confidence interval; CZP=certolizumab pegol; MCMC=Markov Chain Monte Carlo; PASI90=at least 90% reduction from Baseline in Psoriasis Area and Severity Index; PBO=placebo; Q2W=every 2 weeks; RS=Randomized Set

Note: Estimates of the responder rate, odds ratios, CIs, and p-values were based on a logistic regression model with factors for treatment, region, prior biologic exposure (yes/no), study (pooled analyses only), study*region (pooled analyses only), and study*prior biologic exposure (yes/no; pooled analyses only) on the multiply-imputed data sets where missing data were imputed using the MCMC method. The responder rates were the adjusted predicted probabilities from the logistic regression model.

Note: If there were no responders in a single treatment group, then odds ratios (with corresponding CIs and p-values) were derived using exact logistic regression on the multiply-imputed data sets. For such cases, responder rates were based on the raw proportions from the multiply-imputed data sets.

[a] The p-value for the primary analysis for CIMPASI-1 and CIMPASI-2 was evaluated at a 2-sided significance level of 0.025 for each CZP dose vs PBO.

[b] The PASI90 responder rate at Week 16 was a secondary efficacy variable in CIMPACT. The p-value was evaluated at a 2-sided significance level of 0.05 for each CZP dose vs PBO. The CIs presented in the table are 95% CI for the odds ratio, not 97.5%.

[c] A 97.5% CI was used at Week 16 for Pool E1 and Pool E2 to facilitate comparisons with the CI for this timepoint in the individual studies where 97.5% was used instead of 95% due to the multiplicity adjustment for testing 2 doses.

Figure 8: PASI90 responder rates at Week 16 by randomized treatment group in CIMPASI-1, CIMPASI-2, CIMPACT, and Pool E1 (RS [MCMC])
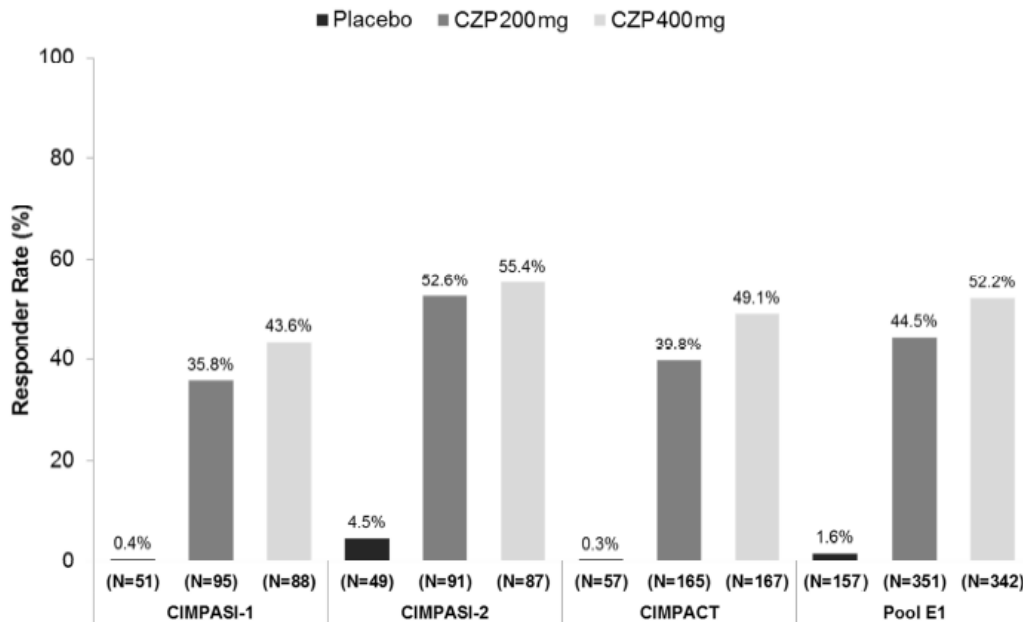
CZP=certolizumab pegol; MCMC=Markov Chain Monte Carlo; PASI90=at least 90% reduction from Baseline in Psoriasis Area and Severity Index; RS=Randomized Set

For all three studies (CIMPASI-1, CIMPASI-2 and CIMPACT), both CZP dose arms were statistically significantly superior to placebo for PASI90 response at week 16.

In both CIMPASI-1 and CIMPACT, PASI90 responder rates and odds ratios for being a PASI90 responder at Week 16 were numerically higher in the CZP 400mg Q2W group compared with the CZP 200mg Q2W group, whereas PASI90 responder rates were similar between the 2 CZP groups in CIMPASI-2. Similar results in relation to dose response were observed for the co-primary endpoints.

CIMPACT

Comparison vs. ETN

In study CIMPACT, etanercept (ETN) was included as active comparator, for comparison to CZP during the Initial Treatment Period. The comparison of CZP to ETN was made at the Week 12 time point since the initial treatment (induction) for Enbrel is 50 mg twice weekly for 12 weeks. Formal comparisons were made between CZP and ETN, testing for both non-inferiority and superiority, for PASI75 responder rate at Week 12. The results of this analysis are presented in the table below.

Table: PASI75 responder rate at Week 12 by randomized treatment group in CIMPACT — comparison to ETN (RS)

Responders	PBO N=57	ETN N=170	CZP 200mg Q2W N=165	CZP 400mg Q2W N=167
MCMC method for multiple imputation [a]				
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, 18.9)	13.4 (2.7, 24.1)
Odds ratio vs ETN			1.388	1.756
95% CI for odds ratio			0.886, 2.175	1.114, 2.768
P-value			0.1523	0.0152
Observed results				
Responders, n/Nobs (%)	3/54 (5.6)	91/159 (57.2)	102/157 (65.0)	113/162 (69.8)

CI=confidence interval; CZP=certolizumab pegol; ETN=etanercept; MCMC=Markov Chain Monte Carlo; Nobs=number of subjects with a nonmissing result; PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; PBO=placebo; Q2W=every 2 weeks; RS=Randomized Set
Note: Estimates of percentages of responders, odds ratios, CIs, and p-values were based on using a logistic regression model with factors for treatment, region, and prior biologic exposure (yes/no).
[a] Missing data were imputed using multiple imputation based on the MCMC method.

The CZP 400 mg Q2W dosing regimen demonstrated superiority over ETN for the PASI75 responder rate at Week 12 (66.7% vs. 53.3%; p=0.0152).

The CZP 200 mg Q2W dosing regimen was numerically greater although not statistically significantly different from ETN for PASI75 responder rate at Week 12 (61.3% and 53.3%, respectively; p=0.1523) and was determined to be statistically non-inferior (difference of 8%; 95% CI: -2.9, 18.9) to ETN based on a pre-specified 10% non-inferiority margin.

Somewhat greater numerical improvements over the ETN group in PASI75, PASI90 and PASI100 responder rates at Week 12 were demonstrated in the CZP 200mg Q2W group (in the range of approximately 4% to 8%) and in the CZP 400mg Q2W group (range 5% to 13%).

The testing for superiority of CZP vs. ETN was included as a rather late step in the sequential testing procedure and all tests previous in the sequence were concluded as being significant. Superiority could be concluded for PASI 75 at Week 12 for the higher 400 mg CZP dose and non-inferiority for the 200 mg dose, while superiority was not demonstrated for 200 mg. The applied non-inferiority margin of 10% was pre-specified with a justification that it represented a reasonable limit for establishing a similar skin efficacy response between active treatments and has been used also in other studies of moderate to severe chronic plaque psoriasis. This is endorsed and NI margin of 10% is deemed adequate. The resulting lower limit of the 95% CI for the PASI75 response for the 200 mg CZP dose vs. ETN was -2.9%.

PGA response at Week 12

The PGA Response at Week 12 was a secondary end-point in study CIMPACT.

At Week 12, the PGA responder rates were significantly greater in both the CZP 200 mg Q2W group (39.8%) and CZP 400 mg Q2W group (50.3%) as compared to the placebo group (1.9%). For ETN, the PGA response at Week 12 was 39.2%.

Both CZP dose groups showed significantly greater PGA response vs. placebo at Week 12 (Week 16 data are presented in the section *Analysis performed across trials (pooled analyses and meta-analysis*).
For PGA, the responder rate at Week 12 was similar between CZP 200 mg Q2W and ETN, whereas the responder rate was numerically higher (difference of 11%) in the CZP 400mg Q2W group compared with the ETN group.

Week 48 end-points (Maintenance period)

PASI75 at Week 48 (CIMPASI-1 and CIMPASI-2)

A summary of PASI75 responder rates at Week 48 for CIMPASI-1, CIMPASI-2, and Pool E3 is presented by randomized treatment group for the RS in the table below.

Table: PASI75 responder rates at Week 16 and Week 48 by randomized treatment group in CIMPASI-1, CIMPASI-2, and Pools E2 (Week 16)/E3 (Week 48) (RS [MCMC])

Study or Pool	Responder rate %	95% CI
CIMPASI-1		
Week 16		
CZP 200mg Q2W (N=95)	66.5	47.92, 72.17
CZP 400mg Q2W (N=88)	75.8	57.65, 80.99
Week 48		
CZP 200mg Q2W (N=95)	67.2	57.09, 77.39
CZP 400mg Q2W (N=88)	87.1	79.81, 94.45
CIMPASI-2		
Week 16		
CZP 200mg Q2W (N=91)	81.4	57.12, 82.36
CZP 400mg Q2W (N=87)	82.6	58.47, 83.43
Week 48		
CZP 200mg Q2W (N=91)	78.7	68.93, 88.45
CZP 400mg Q2W (N=87)	81.3	71.90, 90.67
Pooled		
Week 16 (Pool E2)		
CZP 200mg Q2W (N=186)	76.7	67.0, 86.4
CZP 400mg Q2W (N=175)	82.0	73.5, 90.5
Week 48 (Pool E3)		
CZP 200mg Q2W (N=186)	70.7	60.6, 80.7
CZP 400mg Q2W (N=175)	83.6	75.9, 91.3

CI=confidence interval; CZP=certolizumab pegol; MCMC=Markov Chain Monte Carlo; PASI75=at least 75%
  reduction from Baseline in Psoriasis Area and Severity Index; Q2W=every 2 weeks; RS=Randomized Set
Note: Subjects who met escape criteria at Week 16 (ie, did not achieve a PASI50) or who met criteria for mandatory
  withdrawal due to not achieving PASI50 response at Week 32 or Week 40 were treated as nonresponders at
  subsequent timepoints. For subjects who achieved a PASI50 response at Week 16 but were mistakenly put into the
  CZP 400mg Q2W escape arm, all visits after Week 16 were imputed with the value observed at Week 16 (ie,
  Week 16 carried forward). All other missing data were imputed using multiple imputation based on MCMC
  methodology.
Note: Estimates of responder rate and CIs were based on using a logistic regression model with factors for treatment,
  region, study (pooled analysis only), prior biologic exposure (yes/no), study*region, (pooled analysis only), and
  study*prior biologic exposure (yes/no; pooled analysis only) on the multiply-imputed data sets where missing data
  were imputed using the MCMC method. The responder rates were the adjusted predicted probabilities from the
  logistic regression model.

In both CIMPASI-1 and CIMPASI-2, PASI75 responder rates were maintained at Week 48 (67% and
79%, respectively) compared with Week 16 (67% and 81%) in the CZP 200 mg Q2W group.

PASI75 responder rates in the CZP 400 mg Q2W group were also maintained at Week 48 in CIMPASI-2
(Week 48: 81%; Week 16: 83%), while PASI75 responder rates continued to improve in CIMPASI-1
through Week 48 (87%) compared with Week 16 (76%).

PASI75 responder rates in the CZP 400 mg Q2W group at Week 48 were numerically higher compared
with the CZP 200 mg Q2W group in CIMPASI-1, while PASI75 responder rates were similar in the CZP
400 mg Q2W and CZP 200 mg Q2W groups in CIMPASI-2.

In Pool E2, PASI75 responder rates at Week 16 were 77% for the CZP 200 mg Q2W group and
82% for the CZP 400mg Q2W group. Compared with Week 16, the PASI75 responder rate in Pool E3 at
Week 48 was lower in the CZP 200 mg Q2W group (71%) and was maintained in the CZP 400 mg Q2W
group (84%). A greater numerical improvement was observed in the CZP 400 mg Q2W group
compared with the CZP 200 mg Q2W group in Pool E3 despite the fact that a dose response was not
observed in 1 of the 2 studies that comprise this pool (CIMPASI-2).

PGA Clear or Almost clear at Week 48 (CIMPASI-1 and 2)

A summary of PGA responder rates at Week 48 for CIMPASI-1, CIMPASI-2, and Pool E2/E3 is
presented by randomized treatment group for the RS in Table 3-12.

Table: PGA responder rates at Week 16 and Week 48 by randomized treatment group in CIMPASI-1, CIMPASI-2, and Pools E2 (Week 16)/E3 (Week 48) (RS [MCMC])

Study or Pool	Responder rate %	95% CI
CIMPASI-1		
Week 16		
CZP 200mg Q2W (N=95)	47.0	30.70, 54.86
CZP 400mg Q2W (N=88)	57.9	41.33, 65.94
Week 48		
CZP 200mg Q2W (N=95)	52.7	41.99, 63.32
CZP 400mg Q2W (N=88)	69.5	59.24, 79.77
CIMPASI-2		
Week 16		
CZP 200mg Q2W (N=91)	66.8	52.16, 77.46
CZP 400mg Q2W (N=87)	71.6	57.48, 81.77
Week 48		
CZP 200mg Q2W (N=91)	72.6	61.22, 83.92
CZP 400mg Q2W (N=87)	66.6	54.35, 78.86
Pools E2 and E3		
Week 16 (Pool E2)		
CZP 200mg Q2W (N=186)	56.8	46.5, 67.2
CZP 400mg Q2W (N=175)	65.3	55.1, 75.4
Week 48 (Pool E3)		
CZP 200mg Q2W (N=186)	61.0	50.3, 71.8
CZP 400mg Q2W (N=175)	68.9	58.7, 79.1

CI=confidence interval; CZP=certolizumab pegol; MCMC=Markov Chain Monte Carlo; PASI50=at least 50% reduction from Baseline in Psoriasis Area and Severity Index; PGA=Physician's Global Assessment; Q2W=every 2 weeks; RS=Randomized Set

Note: PGA responders=Clear or Almost clear (with at least 2-category improvement) at Week 48.

Note: Subjects who met escape criteria at Week 16 (ie, do not achieve a PASI50) or who met criteria for mandatory withdrawal due to not achieving PASI50 response at Week 32 or Week 40 were treated as nonresponders at subsequent timepoints. For subjects who achieved a PASI50 response at Week 16 but were mistakenly put into the CZP 400mg Q2W escape arm, all visits after Week 16 were imputed with the value observed at Week 16 (ie, Week 16 carried forward). All other missing data were imputed using multiple imputation based on MCMC methodology.

Note: Estimates of responder rate and CIs were based on using a logistic regression model with factors for treatment, region, study (pooled analysis only), prior biologic exposure (yes/no), study*region, (pooled analysis only), and study*prior biologic exposure (yes/no; pooled analysis only) on the multiply imputed data sets where missing data were imputed using the MCMC method. The responder rates were the adjusted predicted probabilities from the logistic regression model.

In both CIMPASI-1 and CIMPASI-2, PGA responder rates continued to slightly improve in the CZP 200 mg Q2W group through Week 48 (53% and 73%, respectively) compared with Week 16 (47% and 67%, respectively). While PGA responder rates in the CZP 400 mg Q2W group were maintained at Week 48 in CIMPASI-2 (Week 48: 67%; Week 16: 72%), PGA responder rates continued to improve in CIMPASI-1 through Week 48 (70%) compared with Week 16 (58%). At Week 48, PGA responder rates in the CZP 400 mg Q2W group were numerically higher compared with the CZP 200mg Q2W group in CIMPASI-1, while PGA responder rates were higher in the CZP 200 mg Q2W group versus the CZP 400 mg Q2W group in CIMPASI-2.

In Pool E2, PGA responder rates at Week 16 were 57% for the CZP 200 mg Q2W group and 65% for the CZP 400 mg Q2W group. Compared with Week 16, the PGA responder rate in Pool E3 was slightly improved in both the CZP 200 mg and 400 mg Q2W groups.

The PGA responder rate at Week 48 was higher in the CZP 400 mg Q2W group compared with the CZP 200 mg Q2W group in Pool E3 despite the fact the opposite trend was observed in 1 of the 2 studies that comprise this pool (CIMPASI-2).

PASI75 and PGA response rates at Week 48 overall generally showed maintained or increased response rates compared with Week 16, even if the pattern differed to some extent between doses and studies. The 400 mg Q2W dose tended to show higher response than 200 mg QW both at Week 16 and 48.

CIMPACT- Maintenance data

PASI75 at Week 48 (CIMPACT)

The secondary endpoint of PASI75 responder rate at Week 48 was only defined for subjects who achieved PASI75 at Week 16 in CIMPACT, not for subjects who escaped at Week 16. A summary of the PASI75 responder rate at Week 48 for PASI75 responders at Week 16 is presented by blinded maintenance treatment group for the WK16RS in the table below.

Table: PASI75 responder rate at Week 48 by re-randomized blinded treatment group in CIMPACT — Maintenance Treatment Period (WK16RS)

	CZP 200mg Q2W/ PBO N=22	CZP 200mg Q2W/ CZP 200mg Q2W N=44	CZP 200mg Q2W/ CZP 400mg Q4W N=44	CZP 400mg Q2W/ PBO N=25	CZP 400mg Q2W/ CZP 200mg Q2W N=50	CZP 400mg Q2W/ CZP 400mg Q2W N=49
Nonresponder imputation						
Responder rate, n (%)	10 (45.5)	35 (79.5)	39 (88.6)	9 (36.0)	40 (80.0)	48 (98.0)
Observed results						
Responders, n/Nobs (%)	10/12 (83.3)	35/36 (97.2)	39/41 (95.1)	9/15 (60.0)	40/42 (95.2)	48/48 (100)

CZP=certolizumab pegol; Nobs=number of subjects with a nonmissing result; PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; WK16RS=Week 16 Randomized Set
Note: For the analysis based on nonresponder imputation, subjects with missing data at Week 48 or who relapsed prior to Week 48 were treated as nonresponders.

In this analysis all subjects were PASI75 responders at Week 16 when entering the Maintenance Treatment Period. Therefore, the PASI75 responder rate at Week 48 could only be maintained or decreased. Subjects with missing data at Week 48 or subjects who relapsed (ie, no longer achieved a PASI50 response) prior to Week 48 were counted as non-responders based on NRI, as opposed to the multiple imputation method used in the CIMPASI studies.

A summary of the PASI75 responder rate at visits during the Maintenance Treatment Period by blinded maintenance treatment groups for subjects initially randomized to CZP is presented for the MS (NRI) in the figure 9 below.

Figure 9: PASI75 responder rates over time by re-randomized blinded maintenance treatment group for subjects initially randomized to CZP in CIMPACT - Maintenance Treatment Period (Weeks 16 to 48) (MS [NRI]).
Upper figure: CZP 200 mg Q2W in the initial period
Lower figure: CZP 400 mg Q2W in the initial period
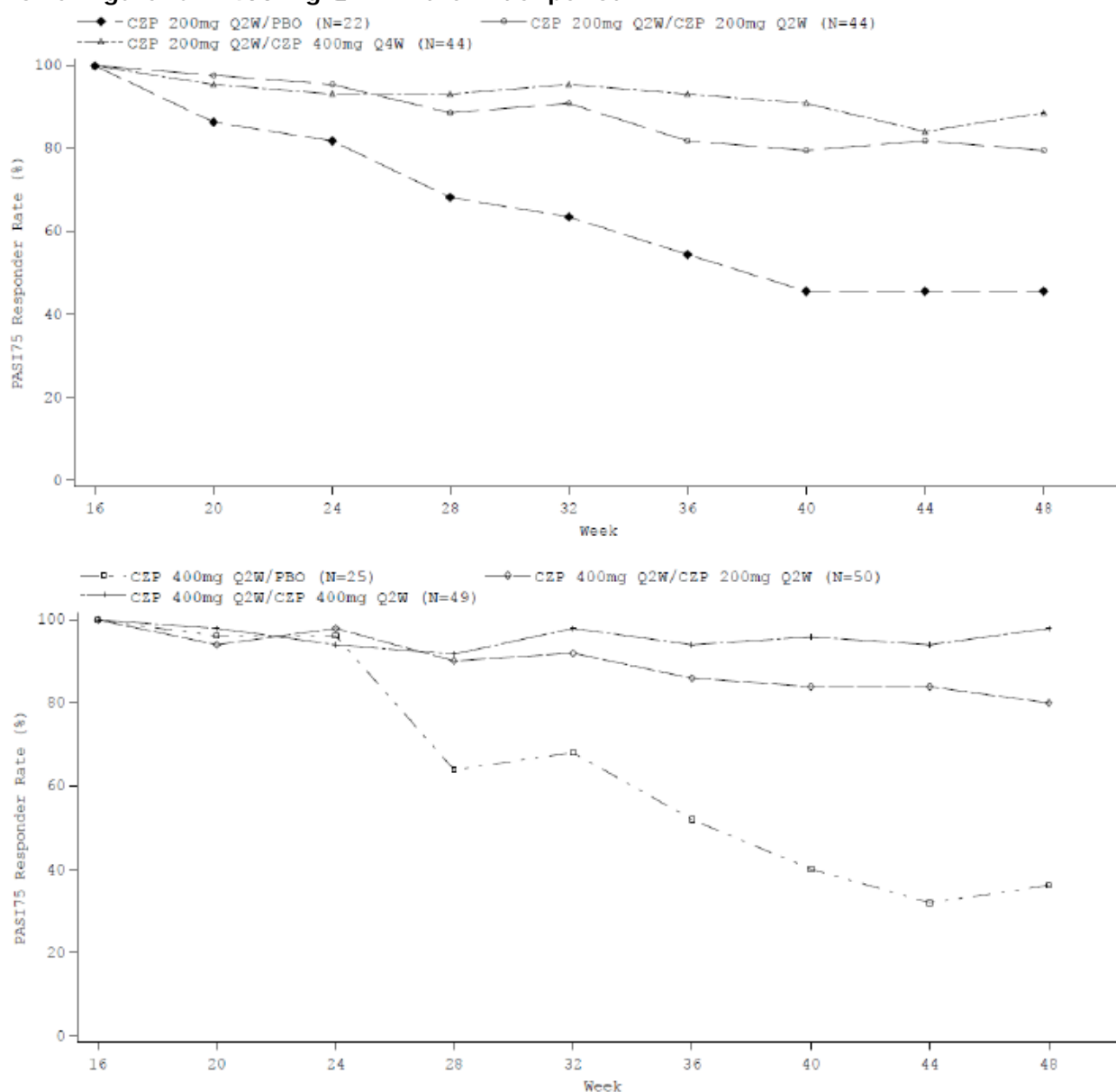
CZP=certolizumab pegol; MS=Maintenance Set; NRI=nonresponder imputation; PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks

In patients who were PASI75 responders at Week 16, for subjects initially randomized to CZP, the majority of subjects (>79%) in each group that received CZP treatment during the Maintenance Treatment Period continued to be PASI75 responders at Week 48. In the group that received CZP 400 mg Q2W in both the Initial and Maintenance Treatment Periods, 98% continued to be PASI75 responders at Week 48. For subjects initially randomized to CZP but who received placebo treatment during the Maintenance Treatment Period, the PASI75 responder rate decreased from Week 16 to Week 48.

For the blinded maintenance treatment groups initially randomized to CZP 200 mg Q2W, the PASI75 responder rate was numerically greater at Week 48 in the treatment group receiving CZP 400mg Q4W compared with the treatment group continuing on CZP 200mg Q2W during the Maintenance Treatment Period (88.6% vs 79.5%).

PGA at Week 48 (and week 16) (CIMPACT)

Table: PGA responder rates at Weeks 16 and 48 by re-randomized blinded maintenance treatment group for subjects initially randomized to CZP in CIMPACT - Maintenance Treatment Period (Weeks 16 to 48) (MS [NRI])

Visit Statistic	CZP 200mg Q2W/ PBO N=22	CZP 200mg Q2W/ CZP 200mg Q2W N=44	CZP 200mg Q2W/ CZP 400mg Q4W N=44	CZP 400mg Q2W/ PBO N=25	CZP 400mg Q2W/ CZP 200mg Q2W N=50	CZP 400mg Q2W/ CZP 400mg Q2W N=49
Week 16						
Responder rate (%)	72.7	68.2	81.8	72.0	84.0	81.6
95% CI	54.12, 91.34	54.42, 81.94	70.42, 93.21	54.40, 89.60	73.84, 94.16	70.79, 92.47
Week 48						
Responder rate (%)	13.6	61.4	70.5	12.0	64.0	87.8
95% CI	0.00, 27.98	46.98, 75.75	56.97, 83.94	0.00, 24.74	50.70, 77.30	78.58, 96.93

CI=confidence interval; CZP=certolizumab pegol; MS=Maintenance Set; NRI=nonresponder imputation;
PBO=placebo; PGA=Physician's Global Assessment; Q2W=every 2 weeks; Q4W=every 4 weeks
Note: PGA responders=Clear or Almost Clear (with ≥2-category improvement from Baseline) at each visit.

PGA responder rates during the Maintenance Treatment Period for subjects initially randomized to CZP are also presented in the figure 10 below.

Figure 10: PGA responder rates over time by re-randomized blinded maintenance treatment group for subjects initially randomized to CZP in CIMPACT - Maintenance Treatment Period (Weeks 16 to 48) (MS [NRI]).
Upper figure: CZP 200 mg Q2W in the initial period
Lower figure: CZP 400 mg Q2W in the initial period
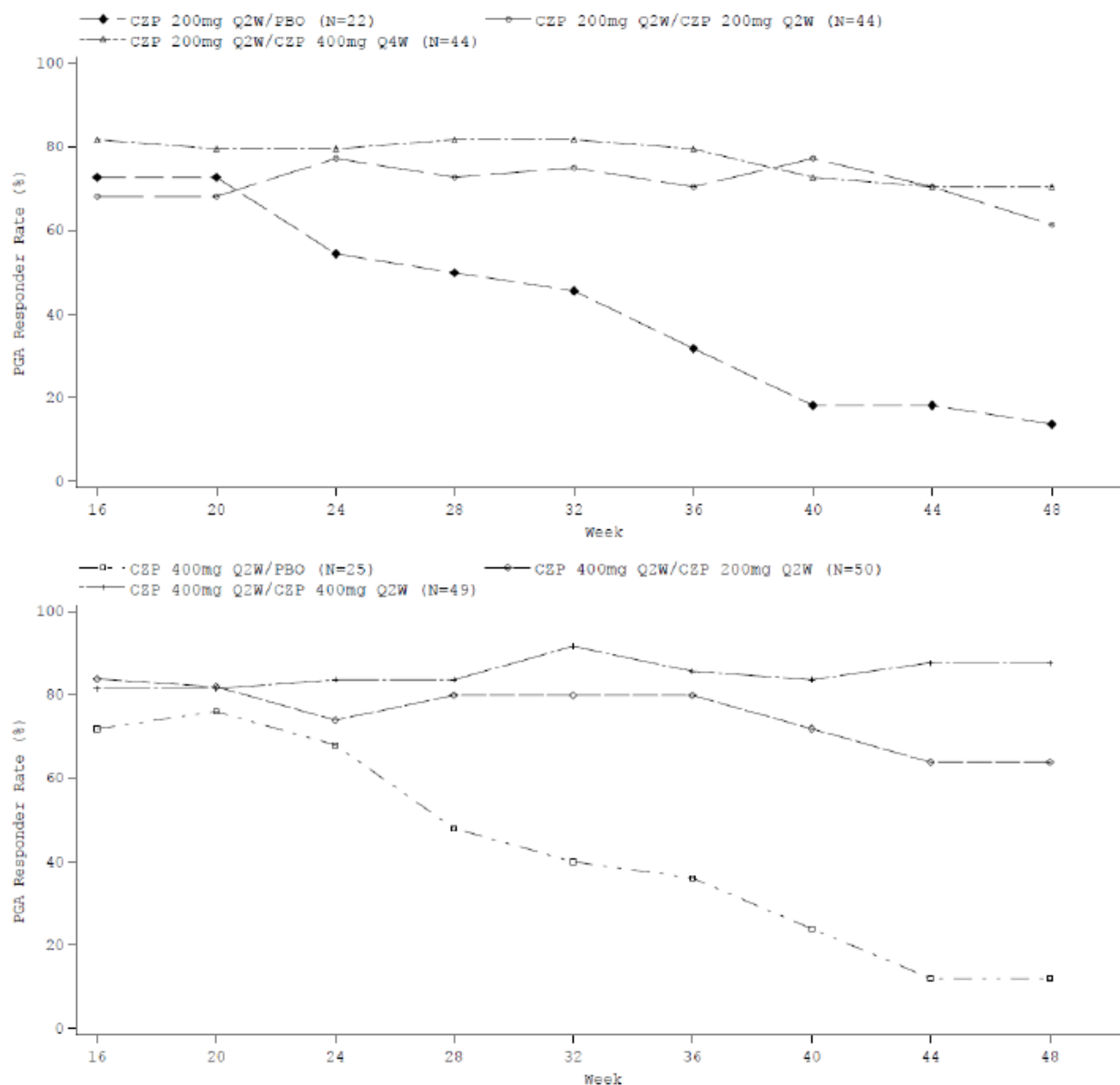
CZP=certolizumab pegol; MS=Maintenance Set; NRI=nonresponse imputation; PBO=placebo; PGA=Physician's
    Global Assessment; Q2W=every 2 weeks; Q4W=every 4 weeks
Note: PGA responders=Clear or Almost clear (with ≥2-category improvement) at each visit.
Note: Subjects who escaped at Week 16 were treated as nonresponders at all subsequent timepoints, and imputation
    using NRI methodology was used for all other missing data.

In the subjects who were PASI75 responders at Week 16, for subjects initially randomized to CZP, the majority of subjects (≥61%) in each group that received CZP treatment during the Maintenance Treatment Period achieved a PGA response at Week 48. For subjects initially randomized to CZP but who received placebo during the Maintenance Treatment Period, the PGA responder rate decreased from Week 16 to Week 48.

The blinded maintenance treatment group treated with CZP 400 mg Q2W through both the Initial and Maintenance Treatment Periods achieved the best response at Week 48, with a PGA responder rate of 87.8%, which was a 6.2% improvement from Week 16.

The group initially treated with CZP 400 mg Q2W that received a reduced dose during the Maintenance Treatment Period and the groups treated with CZP 200 mg Q2W (or the same cumulative monthly dose, 400 mg Q4W) throughout the study had an overall decrease in PGA responder rate (differences between Week 16 and Week 48 of -20%, -7%, and -11%, respectively).

Time to relapse

Time to relapse (i.e. not achieving a PASI50 response) was evaluated in CIMPACT for subjects achieving PASI75 at Week 16 using Kaplan-Meier estimation.

Time to relapse was longer for subjects who continued to receive CZP treatment in the Maintenance Treatment Period compared with subjects re-randomized to placebo (p≤0.0027 across all CZP maintenance groups vs. re-randomized to placebo).

No difference in time to relapse was observed for the CZP 200 mg Q2W/CZP 400 mg Q4W group vs. the CZP 200 mg Q2W/ CZP 200 mg Q2W group. A trend towards a difference in time to relapse was observed for the CZP 400mg Q2W/ CZP 400 mg Q2W group vs. the CZP 400 mg Q2W/CZP 200 mg Q2W group (p=0.0978).

Figure 11: Kaplan-Meier Plots of Time to Relapse (days) for those Achieving PASI75 at Week 16 by Blinded Maintenance Treatment Group - Maintenance Period Analysis Set: WK16RS (subjects initially randomized to CZP 200 mg Q2W).
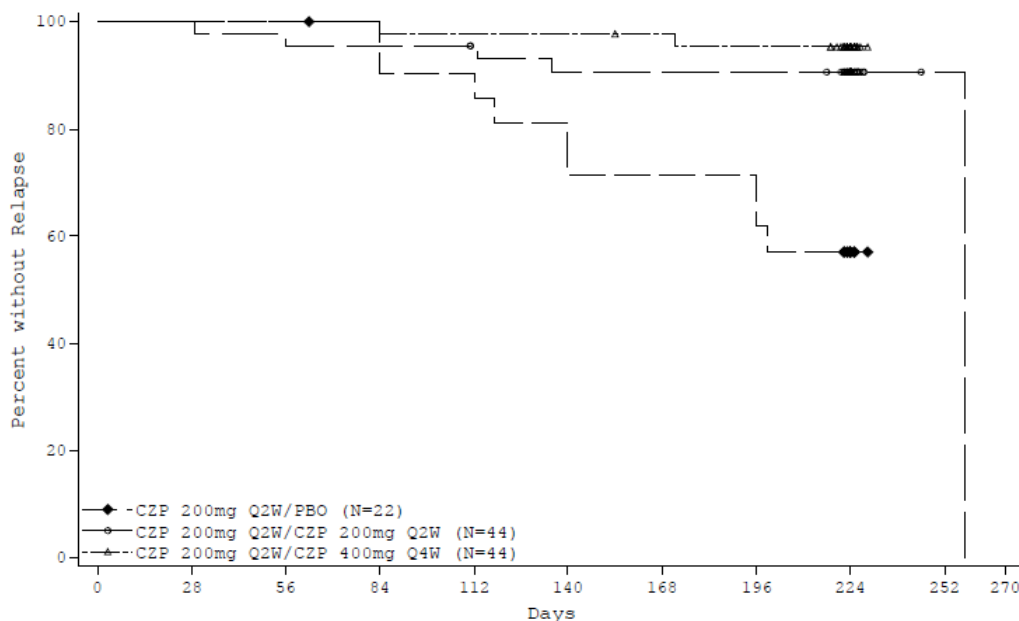
Figure 12: Kaplan-Meier Plots of Time to Relapse (days) for those Achieving PASI75 at Week 16 by Blinded Maintenance Treatment Group - Maintenance Period Analysis Set: WK16RS (subjects initially randomized to CZP 400 mg Q2W).
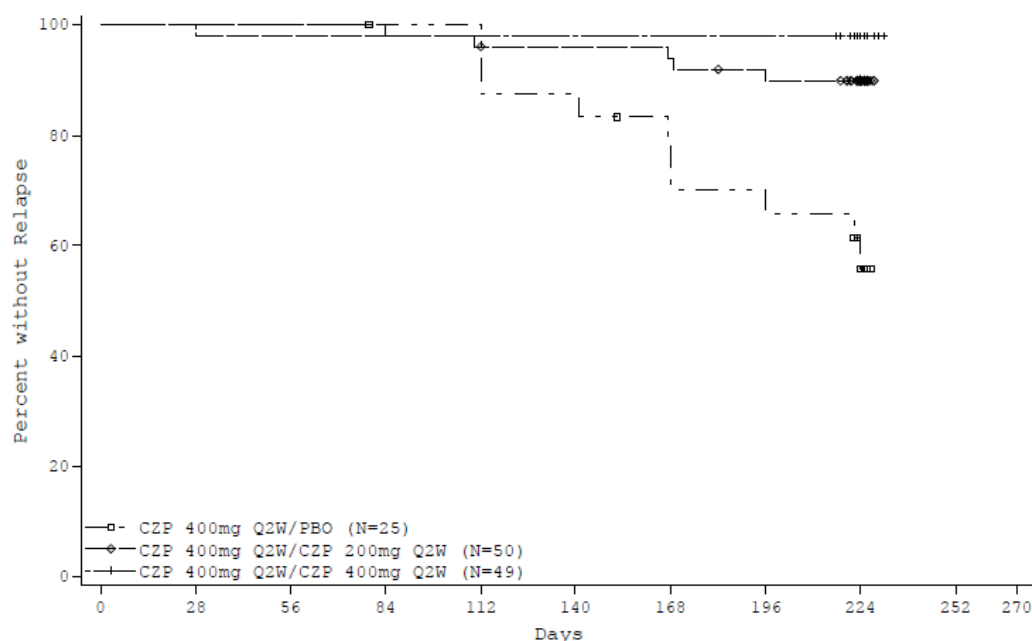
Rebound

The CIMPACT study design that included treatment groups that received CZP treatment during the Initial Treatment Period and switched to placebo at Week 16 for the Maintenance Treatment Period allowed for limited observations regarding a rebound effect.

A definition of rebound as a >125% increase from Baseline in PASI score within 14 weeks after the final dose of CZP treatment (i.e. by the Week 28 assessment) was applied. No subjects in the CZP 200 mg Q2W/PBO (N=22) or CZP 400 mg Q2W/PBO (N=25) groups met this definition. The maximum percent change from Baseline between Weeks 16 and 28 in both groups was -26.1%, which is still an improvement from Baseline.

Rebound was also addressed in the Phase 2 study, C87040, using a definition of >125% increase from Baseline in PASI score within 2 months of stopping CZP treatment. Among PASI75 responders, no subject met the definition of having a rebound effect.

Rebound was assessed in studies CIMPACT and the Phase 2 study, C87040, with a definition in accordance with the Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis (CHMP/EWP/2454/02, 2004). Although the number of patients available for assessment of rebound in Phase 3 is rather limited (e.g. 47 patients in CIMPACT), the data do not give cause for concern since no patients in either study met the definition of having a rebound effect.

Retreatment

Except for the Phase 2 study C87044, no information on retreatment of psoriasis patients with CZP after stopping treatment is available. Study C87044 was designed to address the question of response to retreatment after withdrawal of CZP among subjects who responded to the initial 12 weeks of treatment in C87040. Subjects who responded to treatment in C87040, and who relapsed within 24 weeks following treatment withdrawal, were retreated in C87044 for an additional 12 weeks with the same treatment they received in C87040. No inferential analyses were performed to compare treatment groups in C87044. The median differences in PASI scores between first treatment Week 12

and retreatment Week 12 were small both for CZP 200mg Q2W group (1.25 points; 95% CI: 0.10, 4.40) and the CZP 400mg Q2W (0.20 points; 95% CI: 0.00, 0.70).

Change from Baseline in DLQI at Week 16

Table: ANCOVA model for change from Baseline in DLQI at Week 16 by randomized treatment group in CIMPASI-1, CIMPASI-2, and CIMPACT (RS [LOCF])

	CIMPASI-1			CIMPASI-2			CIMPACT		
	PBO N=51	CZP 200mg Q2W N=95	CZP 400mg Q2W N=88	PBO N=49	CZP 200mg Q2W N=91	CZP 400mg Q2W N=87	PBO N=57	CZP 200mg Q2W N=165	CZP 400mg Q2W N=167
Baseline									
n	48	93	86	49	90	87	57	164	167
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)	12.8 (7.0)	15.3 (7.3)
Change from Baseline to Week 16									
n	48	93	86	49	90	87	57	164	167
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)	-1.1 (6.7)	-8.1 (7.5)	-11.0 (8.3)
Median	-3.5	-10.0	-10.0	-2.0	-11.5	-9.0	-1.0	-8.0	-10.0
Q1, Q3	-9.0, 0.0	-14.0, -3.0	-13.0, -5.0	-7.0, 2.0	-17.0, -6.0	-15.0, -5.0	-5.0, 4.0	-6.0, -3.0	-16.0, -5.0
Min, max	-14, 17	-30, 11	-27, 16	-22, 8	-27, 17	-29, 5	-14, 17	-29, 17	-30, 18
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)	-2.0 (0.81)	-9.2 (0.50)	-10.4 (0.50)
Comparison to PBO									
Adjusted mean treatment difference [a]		-6.00	-6.84		-6.62	-6.19		-7.27	-8.46
95% CI or 97.5% CI for difference [b]		-8.18, -3.81	-9.05, -4.62		-8.88, -4.36	-8.46, -3.93		-9.03, -5.50	-10.22, -6.70
P-value [c]		<0.0001 [c]	<0.0001 [c]		<0.0001 [c]	<0.0001 [c]		<0.0001 [d]	<0.0001 [d]

ANCOVA=analysis of covariance; CI=confidence interval; CZP=certolizumab pegol; DLQI=Dermatology Life Quality Index; LOCF=last observation carried forward; LS=least squares; max=maximum; min=minimum; PBO=placebo; Q2W=every 2 weeks; RS=Randomized Set; SD=standard deviation; SE=standard error

Note: Estimates of LS Means, SE, adjusted mean treatment differences, CIs, and p-values were based on an ANCOVA model of change from Baseline DLQI score with treatment group, region, and prior biologic exposure (yes/no) as factors and Baseline DLQI score as a covariate.

[a] Differences were based on (CZP 200mg Q2W-PBO) and (CZP 400mg Q2W-PBO).
[b] The CI for adjusted difference at Week 16 was 97.5% for CIMPASI-1 and CIMPASI-2 and 95% for CIMPACT.
[c] The p-value obtained for each treatment group comparison was tested at a significance level of 0.025 in the fixed-sequence testing procedure.
[d] P-value is nominal.

Change in DLQI (Dermatology Life Quality Index) was one of the secondary endpoints and was among the multiplicity-controlled end-points in the CIMPASI studies.
Improvement in health related quality of life, as measured by the mean change from Baseline in DLQI, was observed for CZP-treated subjects compared with placebo-treated subjects at Week 16 in all three studies.

Other end-points

PASI100 at Week 16

PASI100 at Week 16 was an "other" efficacy endpoint (not controlled for multiplicity) for CIMPASI-1, CIMPASI-2, CIMPACT, and the pooled analyses.

At Week 16, PASI100 responder rates were generally similar in both the CZP 200 mg Q2W (range of 12% to 15%) and CZP 400 mg Q2W groups (13% to 19%) across studies and greater than PASI100 responder rates observed in the placebo group (range of 0.2% to 1.8%) across all 3 studies, with no apparent dose response.

In Pool E1, differences in PASI100 responder rates were observed beginning at Week 4 in the CZP 200 mg Q2W group (p<0.05) and at Week 8 in the CZP 400 mg Q2W group (p<0.01). At Week 16, PASI100 responder rates were 12.7% in the CZP 200 mg Q2W group and 15.2% in the CZP 400 mg Q2W group compared with 0.7% in the placebo group. Efficacy results from Pool E2 were similar to those in Pool E1.

mNAPSI

mNAPSI was an "other" endpoint for CIMPASI-1 and CIMPASI-2 and the integrated analysis.

In the subgroup of subjects with psoriatic nail disease at Baseline (defined as a mNAPSI score >0 at Baseline), mean Baseline values in the CZP 200 mg Q2W and CZP 400 mg Q2W groups ranged from 4.6 to 6.0 in CIMPASI-1 and CIMPASI-2 and were 5.4 and 5.0, respectively, in Pool E3.

The results from both CIMPASI-1 and CIMPASI-2 provided similar results for both CZP treatment groups. In Pool E3, at Week 48, the mean mNAPSI scores for the groups receiving CZP 200mg Q2W or CZP 400 mg Q2W in both study periods were 1.0 and 0.9, respectively, representing a mean change from Baseline of -4.5 and -4.3, respectively. The majority of subjects with psoriatic nail disease at baseline had achieved an absence of nail disease (ie, mNAPSI score of 0) at Week 48 in the CZP 200 mg Q2W and CZP 400 mg Q2W groups (67.6% and 64.6%, respectively).

SF-36

In both CIMPASI-1 and CIMPASI-2, the mean Baseline PCS (Physical Component Summary) and MCS (Mental Component Summary) scores for both CZP dose groups were similar to the scores observed in the placebo group.

During the Initial Treatment Period, larger LS mean decreases from Baseline in both the PCS and MCS scores were observed at Weeks 8, 12, and 16 for both the CZP dose groups compared with placebo in CIMPASI-1 and CIMPASI-2.

For the MCS, LS mean changes from Baseline ranged from 4.44 to 5.53 in CIMPASI-1 and 4.00 to 4.91 in CIMPASI-2 for the CZP 200mg Q2W group; from 5.77 to 6.25 in CIMPASI-1 and 3.18 to 3.89 in CIMPASI-2 for the CZP 400mg Q2W group; and from -0.18 to 0.71 in CIMPASI-1 and -0.76 to 0.45 in CIMPASI-2 for the placebo group.

For the PCS, LS mean changes from Baseline ranged from 3.81 to 4.47 in CIMPASI-1 and from 3.97 to 4.92 in CIMPASI-2 for the CZP 200mg Q2W group; from 4.02 to 4.45 in CIMPASI-1 and 3.49 to 3.84 in CIMPASI-2 for the CZP 400mg Q2W group; and from 0.96 to 1.05 in CIMPASI-1 and 1.48 to 1.76 in CIMPASI-2 for the placebo group.

Least squares mean changes from Baseline for the MCS scores were generally larger than LS mean changes from Baseline for the PCS scores for both CZP groups in CIMPASI-1, likely since PSO has less effect on the physical attributes that are assessed by the SF-36.

SF-36 is a 36 item generic HRQoL instrument. This was also an "other" endpoint for CIMPASI-1 and CIMPASI-2. LS mean changes from Baseline for the Mental scores were generally larger than LS mean changes from Baseline for the Physical scores for both CZP.

HADS-A and HADS-D

The HADS-A and HADS-D scores for anxiety and depression, respectively, range from 0 to 21, with higher scores indicating a worse state. A score below 8 is considered to be normal (Snaith and Zigmond, 1994).

Table: ANCOVA model of change from Baseline in HADS-A and HADS-D over time by randomized treatment group in CIMPASI-1 and CIMPASI-2 (RS [LOCF])

	CIMPASI-1			CIMPASI-2		
	PBO N=51	CZP 200mg Q2W N=95	CZP 400mg Q2W N=88	PBO N=49	CZP 200mg Q2W N=91	CZP 400mg Q2W N=87
HADS-A, n	48	93	86	49	90	87
Baseline Mean (SD)	6.3 (4.0)	5.6 (3.8)	6.5 (3.7)	7.7 (4.6)	6.3 (4.1)	6.5 (3.9)
Change from baseline to Week 16						
LS mean (SE)	-0.2 (0.43)	-1.2 (0.31)	-1.1 (0.32)	-0.8 (0.44)	-1.4 (0.33)	-1.7 (0.34)
Adjusted mean treatment difference [a]		-1.00	-0.98		-0.55	-0.81
95% CI for difference [b]		-2.03, 0.02	-2.02, 0.06		-1.59, 0.49	-1.85, 0.24
P-value [c]		0.0556	0.0642		0.2979	0.1287
HADS-D, n	48	93	86	49	90	87
Baseline Mean (SD)	4.7 (4.2)	5.1 (3.7)	5.2 (3.6)	5.4 (3.8)	4.7 (3.8)	4.7 (4.0)
Change from baseline to Week 16						
LS mean (SE)	0.2 (0.44)	-1.6 (0.32)	-1.5 (0.33)	-0.1 (0.43)	-1.5 (0.31)	-0.9 (0.32)
Adjusted mean treatment difference [a]		-1.86	-1.68		-1.46	-0.86
95% CI for difference [b]		-2.92, -0.81	-2.75, -0.61		-2.46, -0.47	-1.86, 0.14
P-value [c]		0.0006	0.0023		0.0042	0.0918

ANCOVA=analysis of covariance; CI=confidence interval; CZP=certolizumab pegol; HADS-A=Hospital Anxiety and Depression Scale for anxiety; HADS-D=Hospital Anxiety and Depression Scale for depression; LOCF=last observation carried forward; LS=least squares; PBO=placebo; Q2W=every 2 weeks; RS=Randomized Set; SD=standard deviation; SE=standard error
Note: ANCOVA model of change from Baseline in HADS-A (or HADS-D) scores with treatment group, region, and prior biologic exposure (yes/no) as factors, and Baseline HADS-A (or HADS-D) score as a covariate.
[a] Differences were based on (CZP 200mg Q2W-PBO) and (CZP 400mg Q2W-PBO).
[b] 95% CI adjusted mean differences.
[c] P-values are nominal since comparisons were not controlled for multiplicity.

HADS-A and HADS-D are scores for anxiety and depression, where a score below 8 is considered to be normal. The majority of subjects had normal scores (<8) at baseline, but some decreases in HADS scores were generally observed and were overall larger for the CZP groups. HADS-A and HADS-D are scores for anxiety and depression, where a score below 8 is considered to be normal. The majority of subjects had normal scores (<8) at baseline, but some decreases in HADS scores were generally observed and were overall larger for the CZP groups. The results were rather inconsistent and mainly observed for the HADS-D scores.

In both CIMPASI-1 and CIMPASI-2, in those subjects who remained on their randomized treatment through Week 48, decreases from Baseline in the HADS-A and HADS-D scores were generally maintained at Week 48 relative to Week 16.

WPAI-SHP

The WPAI-SHP (v2.0) is a patient-reported questionnaire that assesses the subject's employment status, work absenteeism, work impairment presenteeism, overall work, and daily activity impairment

attributable to a specific health problem. The WPAI-SHP adapted to PSO was used.

Improvements were observed in some of the variables included in the WPAI-SHP questionnaire, with generally larger improvements for the CZP groups vs. placebo.
WPAI-SHP was another "other" endpoint. Some numerical differences in favour of the CZP groups vs. placebo were shown, however, these results do not warrant inclusion in section 5.1 of the SmPC.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Table 1. Summary of Efficacy for trial PS0005 (CIMPASI-1)

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group Study Followed by a Dose Blind Period and Open-Label Follow-Up to Evaluate the Efficacy and Safety of Certolizumab Pegol in Subjects with Moderate to Severe Chronic Plaque Psoriasis			
Study identifier	CIMPASI-1 (PS0005)		
Design	Phase 3, randomized, double-blind, placebo-controlled, multicenter study to demonstrate the efficacy and safety of CZP over placebo in adults with moderate to severe chronic plaque PSO		
	Duration of main phase:		16 weeks for the Initial Treatment Period and 32 weeks for the Maintenance Treatment Period (total of 48 weeks)
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		96 weeks
Hypothesis	Superiority		
Treatment groups	Placebo		Placebo, Duration: 16 weeks (Initial Treatment Period), 32 weeks (Maintenance Treatment Period). Number randomized: 51
	CZP 200mg Q2W		CZP 200mg Q2W (with 400mg at Weeks 0, 2 and 4), Duration: 16 weeks (Initial Treatment Period), 32 weeks (Maintenance Treatment Period). Number randomized: 95
	CZP 400mg Q2W		CZP 400mg Q2W, Duration: 16 weeks (Initial Treatment Period), 32 weeks (Maintenance Treatment Period). Number randomized: 88
Endpoints and definitions	Co-Primary endpoints	PASI75 and PGA Clear or almost clear (with at least 2-category improvement) at Week 16	To demonstrate the superiority of CZP in patients with moderate to severe chronic plaque PSO in PASI75 and PGA Clear or almost clear (with at least 2-category improvement) at Week 16, compared with placebo
	Secondary endpoint	PASI90 at Week 16	To demonstrate the superiority of CZP in patients with moderate to severe chronic plaque PSO in PASI90 at Week 16, compared with placebo
	Secondary endpoint	Change from Baseline in DLQI at Week 16	To demonstrate the superiority of CZP in patients with moderate to severe chronic plaque PSO in change from Baseline in DLQI at Week 16, compared with placebo
	Secondary endpoint	PASI75 at Week 48	To assess the efficacy of CZP in patients with moderate to severe chronic plaque PSO in PASI75 responder rate at Week 48

	Secondary endpoint	PGA Clear or almost clear (with at least 2-category improvement) at Week 48	To assess the efficacy of CZP in patients with moderate to severe chronic plaque PSO in PGA Clear or almost clear (with at least 2-category improvement) at Week 48
Database lock	20 Oct 2016 (last patient last visit for Week 48)		

Results and Analysis (MCMC imputation)

Analysis description	Co-Primary Analysis		
Analysis population and time point description	Randomized Set Week 16		

Descriptive statistics and estimate variability	Treatment group	Placebo	CZP 200mg Q2W	CZP 400mg Q2W
	Number of subjects	51	95	88
	PASI75	6.5%	66.5%	75.8%
	PGA Clear or almost clear (with at least 2-category improvement)	4.2%	47.0%	57.9%

Effect estimate per comparison	Co-Primary endpoint: PASI75 at Week 16	Comparison groups	CZP 200mg Q2W vs placebo
		Odds ratio	28.962
		97.5% CI for the odds ratio	6.968, 120.371
		P-value	<0.0001
		Comparison groups	CZP 400mg Q2W vs placebo
		Odds ratio	45.660
		97.5% CI for the odds ratio	10.657, 195.634
		P-value	<0.0001
	Co-Primary endpoint: PGA Clear or almost clear (with at least 2-category improvement)	Comparison groups	CZP 200mg Q2W vs placebo
		Odds ratio	20.116
		97.5% CI for the odds ratio	3.699, 109.399
		P-value	<0.0001
		Comparison groups	CZP 400mg Q2W vs placebo
		Odds ratio	31.143
		97.5% CI for the odds ratio	5.687, 170.548
		P-value	<0.0001

Analysis description	Key secondary analysis: PASI90 responder rate at Week 16		
Analysis population and time point description	Randomized Set Week 16		

Descriptive statistics and estimate variability	Treatment group	Placebo	CZP 200mg Q2W	CZP 400mg Q2W
	Number of subjects	51	95	88
	PASI90 at Week 16	0.4%	35.8%	43.6%

Effect estimate per comparison	Secondary endpoints: PASI90 at Week 16	Comparison groups	CZP 200mg Q2W vs placebo
		Odds ratio	36.668
		97.5% CI for the odds ratio	5.717, 235.193

		P-value	<0.0001
		Comparison groups	CZP 400mg Q2W vs placebo
		Odds ratio	50.606
		97.5% CI for the odds ratio	7.880, 324.988
		P-value	<0.0001

Analysis description	**Key secondary analysis: Change from Baseline in DLQI at Week 16**		
Analysis population and time point description	Randomized Set Week 16		

Descriptive statistics and estimate variability	Treatment group	Placebo	CZP 200mg Q2W	CZP 400mg Q2W
	Number of subjects	51	95	88
	LS mean change from Baseline in DLQI at Week 16	-3.3	-9.3	-10.2

Effect estimate per comparison	Secondary endpoints: Change from Baseline in DLQI at Week 16	Comparison groups	CZP 200mg Q2W vs placebo
		Adjusted mean treatment difference	-6.00
		97.5% CI for the difference	-8.18, -3.81
		P-value	<0.0001
		Comparison groups	CZP 400mg Q2W vs placebo
		Adjusted mean treatment difference	-6.84
		97.5% CI for the difference	-9.05, -4.62
		P-value	<0.0001

Analysis description	**Key secondary analysis: PASI75 at Week 48**	
Analysis population and time point description:	Randomized Set Week 48	

Descriptive statistics and estimate variability	Treatment group	CZP 200mg Q2W	CZP 400mg Q2W
	Number of subjects	95	88
	PASI75 at Week 48	67.2%	87.1%
	95% CI	57.09, 77.39	79.81, 94.45

Analysis description	**Key secondary analysis: PGA response at Week 48**	
Analysis population and time point description:	Randomized Set Week 48	

Descriptive statistics and estimate variability	Treatment group	CZP 200mg Q2W	CZP 400mg Q2W
	Number of subjects	95	88
	PGA Clear or almost clear (with at least 2-category improvement) at Week 48	52.7%	69.5%
	95% CI	41.99, 63.32	59.24, 79.77

Table 2. Summary of Efficacy for trial PS0002 (CIMPASI-2)

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group Study Followed by a Dose Blind Period and Open-Label Follow-Up to Evaluate the Efficacy and Safety of Certolizumab Pegol in Subjects with Moderate to Severe Chronic Plaque Psoriasis			
Study identifier	CIMPASI-2 (PS0002)		
Design	Phase 3, randomized, double-blind, placebo-controlled, multicenter study to demonstrate the efficacy and safety of CZP over placebo in adults with moderate to severe chronic plaque PSO		
	Duration of main phase:		16 weeks for the Initial Treatment Period and 32 weeks for the Maintenance Treatment Period (total of 48 weeks)
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		96 weeks
Hypothesis	Superiority		
Treatment groups	Placebo		Placebo, Duration: 16 weeks (Initial Treatment Period), 32 weeks (Maintenance Treatment Period). Number randomized: 49
	CZP 200mg Q2W		CZP 200mg Q2W with 400mg at Weeks 0, 2 and 4), Duration: 16 weeks (Initial Treatment Period), 32 weeks (Maintenance Treatment Period). Number randomized: 91
	CZP 400mg Q2W		CZP 400mg Q2W, Duration: 16 weeks (Initial Treatment Period), 32 weeks (Maintenance Treatment Period). Number randomized: 87
Endpoints and definitions	Co-Primary endpoints	PASI75 and PGA Clear or almost clear (with at least 2-category improvement) at Week 16	To demonstrate the superiority of CZP in patients with moderate to severe chronic plaque PSO in PASI75 and PGA Clear or Almost Clear (with at least 2-category improvement) at Week 16, compared with placebo
	Secondary endpoint	PASI90 at Week 16	To demonstrate the superiority of CZP in patients with moderate to severe chronic plaque PSO in PASI90 at Week 16, compared with placebo
	Secondary endpoint	Change from Baseline in DLQI at Week 16	To demonstrate the superiority of CZP in patients with moderate to severe chronic plaque PSO in change from Baseline in DLQI at Week 16, compared with placebo
	Secondary endpoint	PASI75 at Week 48	To assess the efficacy of CZP in patients with moderate to severe chronic plaque PSO in PASI75 responder rate at Week 48
	Secondary endpoint	PGA Clear or almost clear (with at least 2-category improvement) at Week 48	To assess the efficacy of CZP in patients with moderate to severe chronic plaque PSO in PGA Clear or almost clear (with at least 2-category improvement) at Week 48
Database lock	16 Aug 2016 (last patient last visit for Week 48)		
Results and Analysis (MCMC imputation)			
Analysis description	**Co-Primary Analysis**		
Analysis population and time point description	Randomized Set Week 16		

Descriptive statistics and estimate variability	Treatment group	Placebo	CZP 200mg Q2W	CZP 400mg Q2W
	Number of subjects	49	91	87

	PASI75	11.6%	81.4%	82.6%
	PGA Clear or almost clear (with at least 2-cateegory improvement)	2.0%	66.8%	71.6%

Effect estimate per comparison	Co-Primary endpoint: PASI75 at Week 16	Comparison groups	CZP 200mg Q2W vs placebo
		Odds ratio	33.405
		97.5% CI for the odds ratio	9.965, 111.983
		P-value	<0.0001
		Comparison groups	CZP 400mg Q2W vs placebo
		Odds ratio	36.212
		97.5% CI for the odds ratio	10.686, 122.713
		P-value	<0.0001
	Co-Primary endpoint: PGA Clear or almost clear (with at least 2-category improvement)	Comparison groups	CZP 200mg Q2W vs placebo
		Odds ratio	106.225
		97.5% CI for the odds ratio	9.572, 1178.843
		P-value	<0.0001
		Comparison groups	CZP 400mg Q2W vs placebo
		Odds ratio	133.163
		97.5% CI for the odds ratio	11.904, 1489.578
		P-value	<0.0001

Analysis description	**Key secondary analysis: PASI90 responder rate at Week 16**

Analysis population and time point description	Randomized Set Week 16		

Descriptive statistics and estimate variability	Treatment group	Placebo	CZP 200mg Q2W	CZP 400mg Q2W
	Number of subjects	49	91	87
	PASI90 at Week 16	4.5%	52.6%	55.4%

Effect estimate per comparison	Secondary endpoints: PASI90 at Week 16	Comparison groups	CZP 200mg Q2W vs placebo
		Odds ratio	24.283
		97.5% CI for the odds ratio	4.386, 134.432
		P-value	<0.0001
		Comparison groups	CZP 400mg Q2W vs placebo
		Odds ratio	27.204
		97.5% CI for the odds ratio	4.895, 151.198
		P-value	<0.0001

Analysis description	**Key secondary analysis: Change from Baseline in DLQI at Week 16**

Analysis population and time point description	Randomized Set Week 16

Descriptive statistics and estimate variability	Treatment group	Placebo	CZP 200mg Q2W	CZP 400mg Q2W
	Number of subjects	49	91	87
	LS mean change from Baseline in DLQI at Week 16	-3.8	-10.4	-10.0
Effect estimate per comparison	Secondary endpoints: Change from Baseline in DLQI at Week 16	Comparison groups	CZP 200mg Q2W vs placebo	
		Adjusted mean treatment difference	-6.62	
		97.5% CI for the difference	-8.88, -4.36	
		P-value	<0.0001	
		Comparison groups	CZP 400mg Q2W vs placebo	
		Adjusted mean treatment difference	-6.19	
		97.5% CI for the difference	-8.46, -3.93	
		P-value	<0.0001	

Analysis description	**Key secondary analysis: PASI75 at Week 48**	
Analysis population and time point description:	Randomized Set Week 48	
Descriptive statistics and estimate variability	Treatment group	CZP 200mg Q2W	CZP 400mg Q2W
	Number of subjects	91	87
	PASI75 at Week 48	78.7%	81.3%
	95% CI	68.93, 88.45	71.9, 90.67

Analysis description	**Key secondary analysis: PGA response at Week 48**	
Analysis population and time point description:	Randomized Set Week 48	
Descriptive statistics and estimate variability	Treatment group	CZP 200mg Q2W	CZP 400mg Q2W
	Number of subjects	91	87
	PGA Clear or almost clear (with at least 2-category improvement) at Week 48	72.6%	66.6%
	95% CI	61.22, 83.92	54.35, 78.86

Table 3. Summary of Efficacy for trial PS0003 (CIMPACT)

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo- and Active-Controlled Study Followed by a Placebo-Controlled Maintenance Period and Open-Label Follow-Up to Evaluate the Efficacy and Safety of Certolizumab Pegol in Subjects with Moderate to Severe Chronic Plaque Psoriasis
Study identifier	CIMPACT (PS0003)
Design	Phase 3, double-blind, parallel-group, randomized, placebo- and active-controlled, multicenter study with a double-blind, placebo-controlled maintenance period in adults with moderate to severe chronic plaque PSO

	Duration of main phase:	16 weeks for the Initial Treatment Period and 32 weeks for the Maintenance Treatment Period (total of 48 weeks)
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	96 weeks
Hypothesis	Fixed sequence testing procedure. Superiority to placebo. For etanercept, non-inferiority followed by superiority testing for each CZP dose.	
Treatment groups	Placebo	Placebo, Duration: 16 weeks (Initial Treatment Period), 32 weeks (Maintenance Treatment Period). Number randomized to Initial Treatment Period: 57
	CZP 200mg Q2W	CZP 200 mg Q2W (with 400mg at Weeks 0, 2 and 4). Duration: 16 weeks (Initial Treatment Period), 32 weeks (Maintenance Treatment Period). Number randomized to Initial Treatment Period: 165
	CZP 400mg Q2W	CZP 400 mg Q2W. Duration: 16 weeks (Initial Treatment Period), 32 weeks (Maintenance Treatment Period). Number randomized to Initial Treatment Period: 167
	Etanercept 50mg twice weekly	Etanercept 50mg twice weekly Duration: Through Week 12 (last injection at Week 11.5). Number randomized to Initial Treatment Period: 170

Endpoints and definitions	Primary endpoint	PASI75 at Week 12	To demonstrate the superiority of CZP in patients with moderate to severe chronic plaque PSO at Week 12, compared with placebo
	Secondary endpoint	PGA at Week 12	To demonstrate the superiority of CZP in patients with moderate to severe chronic plaque PSO in PGA at Week 12, compared with placebo
	Secondary endpoint	PASI90 at Week 12	To demonstrate the superiority of CZP in patients with moderate to severe chronic plaque PSO in PASI90 at Week 12, compared with placebo
	Secondary endpoint	PASI75 at Week 16	To assess the efficacy of CZP in patients with moderate to severe chronic plaque PSO in PASI75 responder rate at Week 16, compared with placebo
	Secondary endpoint	PGA Clear or almost clear (with at least 2-category improvement) at Week 16	To assess the efficacy of CZP in patients with moderate to severe chronic plaque PSO in PGA Clear or almost clear (with at least 2-category improvement) at Week 16, compared with placebo
	Secondary endpoint	PASI90 at Week 16	To demonstrate the superiority of CZP in patients with moderate to severe chronic plaque PSO in PASI90 at Week 16, compared with placebo
	Secondary endpoint	PASI75 at Week 12	To demonstrate non-inferiority/superiority of CZP in patients with moderate to severe chronic plaque PSO in PASI75 at Week 12, compared with etanercept
	Secondary endpoint	PASI75 at Week 48	To assess the efficacy of CZP in patients with moderate to severe chronic plaque PSO in PASI75 responder rate at Week 48 for those achieving PASI75 at Week 16

Database lock	05 Dec 2016 (last patient last visit for Week 48)

Results and Analysis (MCMC imputation)	
Analysis description	**Primary Analysis**

Analysis population and time point description	Randomized Set at Week 12			
Descriptive statistics and estimate variability	Treatment group	Placebo	CZP 200mg Q2W	CZP 400mg Q2W
	Number of subjects	57	165	167
	PASI75	5.0%	61.3%	66.7%
Effect estimate per comparison	Primary endpoint: PASI75 at Week 12	Comparison groups	CZP 200mg Q2W vs placebo	
		Odds ratio	30.023	
		95% CI for the odds ratio	8.971, 100.481	
		P-value	<0.0001	
		Comparison groups	CZP 400mg Q2W vs placebo	
		Odds ratio	37.988	
		95% CI for the odds ratio	11.312, 127.576	
		P-value	<0.0001	

Analysis description	**Key secondary analysis: PASI75 at Week 16**			
Analysis population and time point description	Randomized Set Week 16			
Descriptive statistics and estimate variability	Treatment group	Placebo	CZP 200mg Q2W	CZP 400mg Q2W
	Number of subjects	57	165	167
	PASI75 at Week 16	3.8%	68.2%	74.7%
Effect estimate per comparison	PASI75 at Week 16	Comparison groups	CZP 200mg Q2W vs placebo	
		Odds ratio	55.413	
		95% CI for the odds ratio	13.135, 233.782	
		P-value	<0.0001	
		Comparison groups	CZP 400mg Q2W vs placebo	
		Odds ratio	76.277	
		95% CI for the odds ratio	17.952, 324.094	
		P-value	<0.0001	

Analysis description	**Key secondary analysis: PGA Clear or almost clear (with at least 2-category improvement) at Week 12 and Week 16**			
Analysis population and time point description	Randomized Set Week 12 and Week 16			
Descriptive statistics and estimate variability	Treatment group	Placebo	CZP 200mg Q2W	CZP 400mg Q2W
	Number of subjects	57	165	167
	PGA Clear or almost clear (with at least 2-category improvement) at Week 12	1.9%	39.8%	50.3%
	Number of subjects	57	165	167
	PGA Clear or almost clear (with at least 2-category improvement) at Week 16	3.4%	48.3%	58.4%

Effect estimate per comparison	PGA Clear or almost clear (with at least 2-category improvement) at Week 12	Comparison groups	CZP 200mg Q2W vs placebo
		Odds ratio	36.566
		95% CI for the odds ratio	5.061, 264.196
		P-value	0.0004
		Comparison groups	CZP 400mg Q2W vs placebo
		Odds ratio	56.129
		95% CI for the odds ratio	7.787, 404.555
		P-value	<0.0001
	PGA Clear or almost clear (with at least 2-category improvement) at Week 16	Comparison groups	CZP 200mg Q2W vs placebo
		Odds ratio	27.165
		95% CI for the odds ratio	6.504, 113.453
		P-value	<0.0001
		Comparison groups	CZP 400mg Q2W vs placebo
		Odds ratio	40.717
		95% CI for the odds ratio	9.741, 170.198
		P-value	<0.0001

Analysis description	Key secondary analysis: PASI90 responder rate at Week 12 and Week 16			
Analysis population and time point description	Randomized Set Week 12 and Week 16			
Descriptive statistics and estimate variability	Treatment group	Placebo	CZP 200mg Q2W	CZP 400mg Q2W
	Number of subjects	57	165	167
	PASI90 at Week 12	0.2%	31.2%	34.0%
	Number of subjects	57	165	167
	PASI90 at Week 16	0.3%	39.8%	49.1%

Effect estimate per comparison	Secondary endpoints: PASI90 at Week 12	Comparison groups	CZP 200mg Q2W vs placebo
		Odds ratio	35.084
		95% CI for the odds ratio	7.363, 167.179
		P-value	<0.0001
		Comparison groups	CZP 400mg Q2W vs placebo
		Odds ratio	39.949
		95% CI for the odds ratio	8.407, 189.828
		P-value	<0.0001
	Secondary endpoints: PASI90 at Week 16	Comparison groups	CZP 200mg Q2W vs placebo
		Odds ratio	49.527
		95% CI for the odds ratio	10.002, 245.256
		P-value	<0.0001
		Comparison groups	CZP 400mg Q2W vs placebo
		Odds ratio	72.278
		95% CI for the odds ratio	14.650, 356.602
		P-value	<0.0001

Analysis description	**Key secondary analysis: PASI75 at Week 12: comparison to etanercept**			
Analysis population and time point description:	Randomized Set Week 12			
Descriptive statistics and estimate variability	Treatment group	Etanercept	CZP 200mg Q2W	CZP 400mg Q2W
	Number of subjects	170	165	167
	PASI75 at Week 16	53.3%	61.3%	66.7%

Effect estimate per comparison	Secondary endpoints: PASI75 at Week 16	Comparison groups	CZP 200mg Q2W vs etanercept
		Odds ratio	1.388
		95% CI for the odds ratio	0.886, 2.175
		P-value	0.1523
		Comparison groups	CZP 400mg Q2W vs etanercept
		Odds ratio	1.756
		95% CI for the odds ratio	1.114, 2.768
		P-value	0.0152

Notes	Non-inferiority to etanercept demonstrated for the 2 CZP doses. Superiority to etanercept demonstrated with CZP 400mg Q2W.		
Analysis description	**Key secondary analysis: PASI75 responder rate at Week 48 for those achieving PASI75 at Week 16 (NRI)**		
Analysis population and time point description:	Week 16 Randomized Set Week 48		

Descriptive statistics and estimate variability	Treatment sequence group	Number of subjects	PASI75 responder rate at Week 48
	Placebo/Placebo	2	100%
	Etanercept/Placebo	24	8.3%
	Etanercept/CZP 200mg Q2W	50	82.0%
	CZP 200mg Q2W/Placebo	22	45.5%
	CZP 200mg Q2W/CZP 200mg Q2W	44	79.5%
	CZP 200mg Q2W/CZP 400mg Q4W	44	88.6%
	CZP 400mg Q2W/Placebo	25	36.0%
	CZP 400mg Q2W/CZP 200mg Q2W	50	80.0%
	CZP 400mg Q2W/CZP 400mg Q2W	49	98.0%

Analysis performed across trials (pooled analyses and meta-analysis)

PASI 75 response at Week 16

Table: PASI75 responder rates at Week 16 by randomized treatment group in CIMPASI-1, CIMPASI-2, CIMPACT, Pool E1, and Pool E2 (RS)

Study or Pool	Responder rate %	Odds ratio (CZP vs PBO)	97.5% CI	P-value vs PBO
Primary analysis: MCMC method for multiple imputation				
CIMPASI-1 at Week 16 [a]				
PBO (N=51)	6.5	-	-	-
CZP 200mg Q2W (N=95)	66.5	28.962	6.968, 120.371	<0.0001
CZP 400mg Q2W (N=88)	75.8	45.660	10.657, 195.634	<0.0001
CIMPASI-2 at Week 16 [a]				
PBO (N=49)	11.6	-	-	-
CZP 200mg Q2W (N=91)	81.4	33.405	9.965, 111.983	<0.0001
CZP 400mg Q2W (N=87)	82.6	36.212	10.686, 122.713	<0.0001
CIMPACT at Week 16 [b]				
PBO (N=57)	3.8	-	-	-
CZP 200mg Q2W (N=165)	68.2	55.413	13.135, 233.782	<0.0001
CZP 400mg Q2W (N=167)	74.7	76.277	17.952, 324.094	<0.0001
Pool E1 at Week 16				
PBO (N=157)	7.5	-	-	-
CZP 200mg Q2W (N=351)	74.5	36.0	16.4, 79.0 [c]	<0.0001
CZP 400mg Q2W (N=342)	80.1	49.7	22.4, 109.9 [c]	<0.0001
Pool E2 at Week 16				
PBO (N=100)	9.9	-	-	-
CZP 200mg Q2W (N=186)	76.7	30.0	12.0, 74.9 [c]	<0.0001
CZP 400mg Q2W (N=175)	82.0	41.5	16.3, 105.7 [c]	<0.0001
Sensitivity analysis: NRI				
CIMPASI-1 at Week 16				
PBO (N=51)	5.9			
CZP 200mg Q2W (N=95)	66.5	31.675	7.586, 132.257 [c]	<0.0001
CZP 400mg Q2W (N=88)	75.2	48.262	11.274, 206.606 [c]	<0.0001
CIMPASI-2 at Week 16				
PBO (N=49)	10.9			
CZP 200mg Q2W (N=91)	77.6	28.445	8.862, 91.304 [c]	<0.0001
CZP 400mg Q2W (N=87)	80.3	33.328	10.162, 109.299 [c]	<0.0001

CIMPACT at Week 16				
PBO (N=57)	ND	ND	ND	ND
CZP 200mg Q2W (N=165)	ND	ND	ND	ND
CZP 400mg Q2W (N=167)	ND	ND	ND	ND
Pool E1 at Week 16				
PBO (N=157)	7.2			
CZP 200mg Q2W (N=351)	73.1	34.8	16.1, 75.3	<0.0001
CZP 400mg Q2W (N=342)	79.1	48.4	22.1, 106.0	<0.0001
Pool E2 at Week 16				
PBO (N=100)	9.6			
CZP 200mg Q2W (N=186)	75.5	29.2	11.9, 71.5	<0.0001
CZP 400mg Q2W (N=175)	81.0	40.3	16.1, 101.0	<0.0001

CI=confidence interval; CZP=certolizumab pegol; MCMC=Markov Chain Monte Carlo; NRI=nonresponder imputation; PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; PBO=placebo; Q2W=every 2 weeks; RS=Randomized Set

Note: Estimates of the responder rate, odds ratios, CIs, and p-values were based on a logistic regression model with factors for treatment, region, prior biologic exposure (yes/no), study (pooled analyses only), study*region (pooled analyses only), and study*prior biologic exposure (yes/no; pooled analyses only) on the multiply-imputed data sets where missing data were imputed using the MCMC method and separately using the NRI method (where subjects missing PASI75 response were considered to be nonresponders). The responder rates were the adjusted predicted probabilities from the logistic regression model.

[a] The p-value for the primary analysis for CIMPASI-1 and CIMPASI-2 was evaluated at a 2-sided significance level of 0.025 for each CZP dose vs PBO.

[b] The PASI75 responder rate at Week 16 was a secondary efficacy variable in CIMPACT. The p-value was evaluated at a 2-sided significance level of 0.05 for each CZP dose vs PBO. The CIs presented in the table are 95% CI for the odds ratio, not 97.5%.

[c] A 97.5% CI was used at Week 16 for Pool E1 and Pool E2 to facilitate comparisons with the CI for this timepoint in the individual studies where 97.5% was used instead of 95% due to the multiplicity adjustment for testing 2 doses.

Figure 13: PASI75 responder rates at Week 16 by randomized treatment group in CIMPASI-1, CIMPASI-2, CIMPACT, and Pool E1 (RS [MCMC])

CZP=certolizumab pegol; MCMC=Markov Chain Monte Carlo; PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; RS=Randomized Set

PASI results over time

Figure 14: PASI75 responder rates over time during the Initial Treatment Period by randomized treatment group in Pool E1 (RS [MCMC])

Note: Estimates of responder rate were based on using a logistic regression model with factors for treatment, region, study, prior biologic exposure (yes/no), study*region, and study*prior biologic exposure on the multiply imputed data sets where missing data were imputed using the MCMC method. The responder rates were the adjusted predicted probabilities from the logistic regression model.

Note: Exact statistics were used for Week 2.

CZP=certolizumab pegol; MCMC=Markov Chain Monte Carlo; PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; Q2W=every 2 weeks; RS=Randomized Set

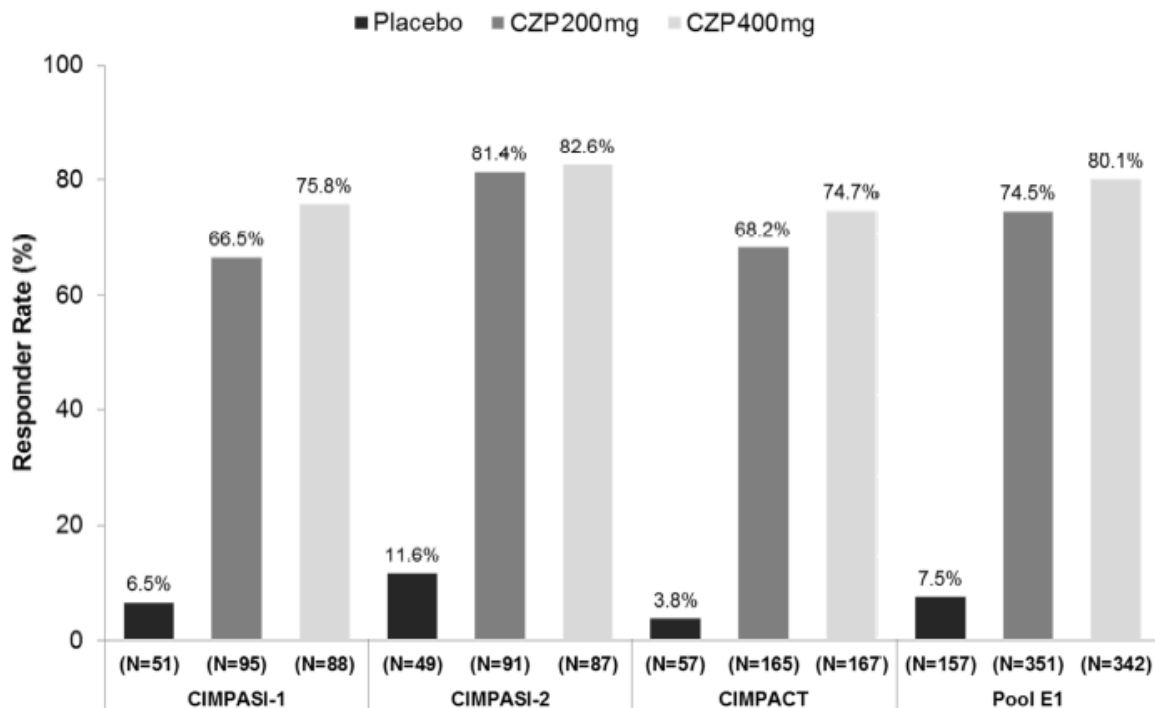**Figure 15: PASI75 responder rate during the combined Initial and Maintenance Treatment Period (Weeks 0 to 48) (Pool E2 and Pool E3 [MCMC])**
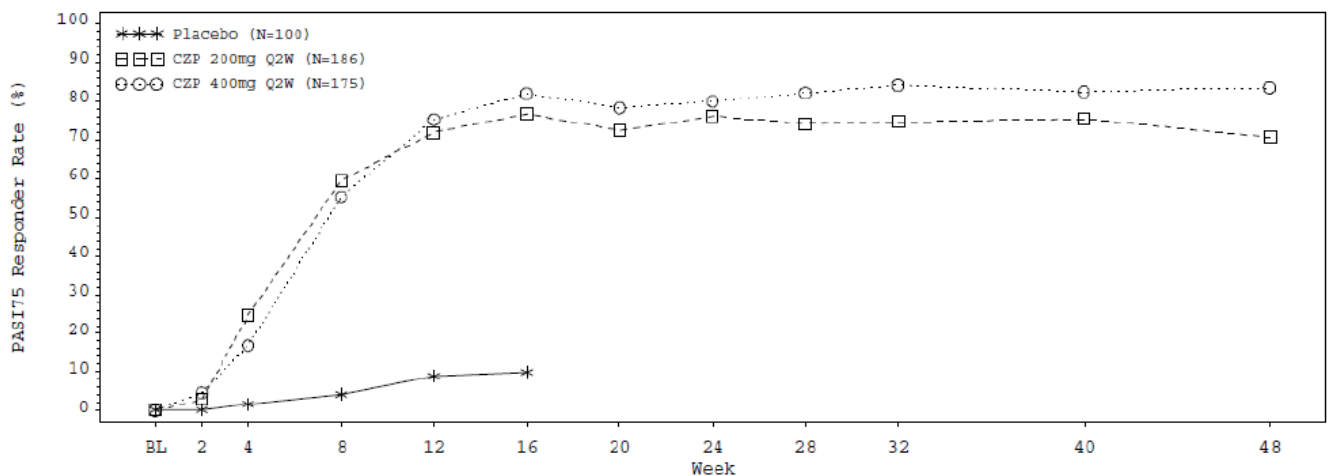
BL=baseline, CZP=certolizumab pegol, MCMC=Markov Chain Monte Carlo, PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; Q2W=every two weeks.

Note: Estimates of responder rates were based on a using a logistic regression model with factors for treatment, region, study, prior biologic exposure (yes/no), study*region, and study*prior biologic exposure on the multiply-imputed data sets where missing data were imputed using the MCMC method. The responder rates were the adjusted predicted probabilities from the logistic regression model.

Note: Exact statistics used for Week 2.

Note: Subjects who met escape criteria at Week 16 (ie, did not achieve a PASI50) or who met criteria for mandatory withdrawal due to not achieving PASI50 response at Week 32 or Week 40 were treated as nonresponders at subsequent timepoints. For subjects who achieved a PASI50 response at Week 16, but were mistakenly put into the CZP 400mg Q2W escape arm, all visits after Week 16 were imputed with the value observed at Week 16 (ie, Week 16 was carried forward). All other missing data were imputed using multiple imputation based on MCMC methodology.

Note: From Week 0 through Week 16, this figure was based on Pool E2 (excluding subjects randomized to placebo) which is the same set of subjects included in Pool E3.

Overall the PASI75 at Week 16 results tended to be more similar when studies CIMPASI-1 and CIMPACT were compared, with somewhat higher response rates in the CIMPASI-2 study.

Onset of effect started at about 4 weeks where a separation from placebo could be observed for both dose groups. Due to the initial loading dose scheme, both dose groups received the same treatment for the first weeks of the initial period.

The figure 15 on PASI75 response in pools E2 and E3 (the CIMPASI studies, 0-48 weeks) showed that the response remained at a stable level with slightly more responders on the 400 mg dose vs. the 200 mg dose.

PGA response at Week 16

Table: PGA responder rates at Week 16 by randomized treatment group in CIMPASI-1, CIMPASI-2, CIMPACT, Pool E1, and Pool E2 (RS)

Study or Pool	Responder rate %	Odds ratio (CZP vs PBO)	97.5% CI	P-value vs PBO
Primary analysis: MCMC method for multiple imputation				
CIMPASI-1 at Week 16 [a]				
PBO (N=51)	4.2	-	-	-
CZP 200mg Q2W (N=95)	47.0	20.116	3.699, 109.399	<0.0001
CZP 400mg Q2W (N=88)	57.9	31.143	5.687, 170.548	<0.0001
CIMPASI-2 at Week 16 [a]				
PBO (N=49)	2.0	-	-	-
CZP 200mg Q2W (N=91)	66.8	106.225	9.572, 1178.843	<0.0001
CZP 400mg Q2W (N=87)	71.6	133.163	11.904, 1489.578	<0.0001
CIMPACT at Week 16 [b]				
PBO (N=57)	3.4	-	-	-
CZP 200mg Q2W (N=165)	48.3	27.165	6.504, 113.453	<0.0001
CZP 400mg Q2W (N=167)	58.4	40.717	9.741, 170.198	<0.0001
Pool E1 at Week 16				
PBO (N=157)	2.8	-	-	-
CZP 200mg Q2W (N=351)	54.6	41.5	13.9, 123.6 [c]	<0.0001
CZP 400mg Q2W (N=342)	63.7	60.7	20.3, 181.4 [c]	<0.0001
Pool E2 at Week 16				
PBO (N=100)	2.7	-	-	-
CZP 200mg Q2W (N=186)	56.8	48.7	11.7, 203.3 [c]	<0.0001
CZP 400mg Q2W (N=175)	65.3	69.5	16.5, 292.0 [c]	<0.0001
Sensitivity analysis: NRI				
CIMPASI-1 at Week 16				
PBO (N=51)	4.1			
CZP 200mg Q2W (N=95)	46.8	20.321	3.744, 110.301	<0.0001
CZP 400mg Q2W (N=88)	57.4	31.082	5.686, 169.899	<0.0001

CIMPASI-2 at Week 16				
PBO (N=49)	1.6			
CZP 200mg Q2W (N=91)	62.9	101.800	9.459, 1095.639	<0.0001
CZP 400mg Q2W (N=87)	69.3	135.334	12.404, 1476.549	<0.0001
CIMPACT at Week 16				
PBO (N=57)	ND	ND	ND	ND
CZP 200mg Q2W (N=165)	ND	ND	ND	ND
CZP 400mg Q2W (N=167)	ND	ND	ND	ND
Pool E1 at Week 16				
PBO (N=157)	2.8			
CZP 200mg Q2W (N=351)	52.9	38.7	13.2, 113.5 [c]	<0.0001
CZP 400mg Q2W (N=342)	62.5	57.4	19.5, 169.3 [c]	<0.0001
Pool E2 at Week 16				
PBO (N=100)	2.6			
CZP 200mg Q2W (N=186)	55.1	46.0	11.3, 187.6 [c]	<0.0001
CZP 400mg Q2W (N=175)	64.2	67.1	16.3, 276.2 [c]	<0.0001

CI=confidence interval; CZP=certolizumab pegol; MCMC=Markov Chain Monte Carlo; ND=not done; NRI=nonresponder imputation; PGA=Physician's Global Assessment; PBO=placebo; Q2W=every 2 weeks; RS=Randomized Set

Note: PGA responders=Clear or Almost clear (with at least a 2-category improvement from Baseline) at Week 16.

Note: Estimates of the responder rate, odds ratios, CIs, and p-values were based on a logistic regression model with factors for treatment, region, prior biologic exposure (yes/no), study (pooled analyses only), study*region (pooled analyses only), and study*prior biologic exposure (yes/no; pooled analyses only) on the multiply-imputed data sets where missing data were imputed using the MCMC method and separately using the NRI method (where subjects missing PGA response were considered to be nonresponders). The responder rates were the adjusted predicted probabilities from the logistic regression model.

[a] The p-value for the primary analysis for CIMPASI-1 and CIMPASI-2 was evaluated at a 2-sided significance level of 0.025 for each CZP dose vs PBO.

[b] The PGA responder rate at Week 16 was a secondary efficacy variable in CIMPACT. The p-value was evaluated at a 2-sided significance level of 0.05 for each CZP dose vs PBO. The CIs presented in the table are 95% CI for the odds ratio, not 97.5%.

[c] A 97.5% CI was used at Week 16 for Pool E1 and Pool E2 to facilitate comparisons with the CI for this timepoint in the individual studies where 97.5% was used instead of 95% due to the multiplicity adjustment for testing 2 doses.

Figure 16: PGA responder rates at Week 16 by randomized treatment group in CIMPASI-1, CIMPASI-2, CIMPACT, and Pool E1 (RS [MCMC])
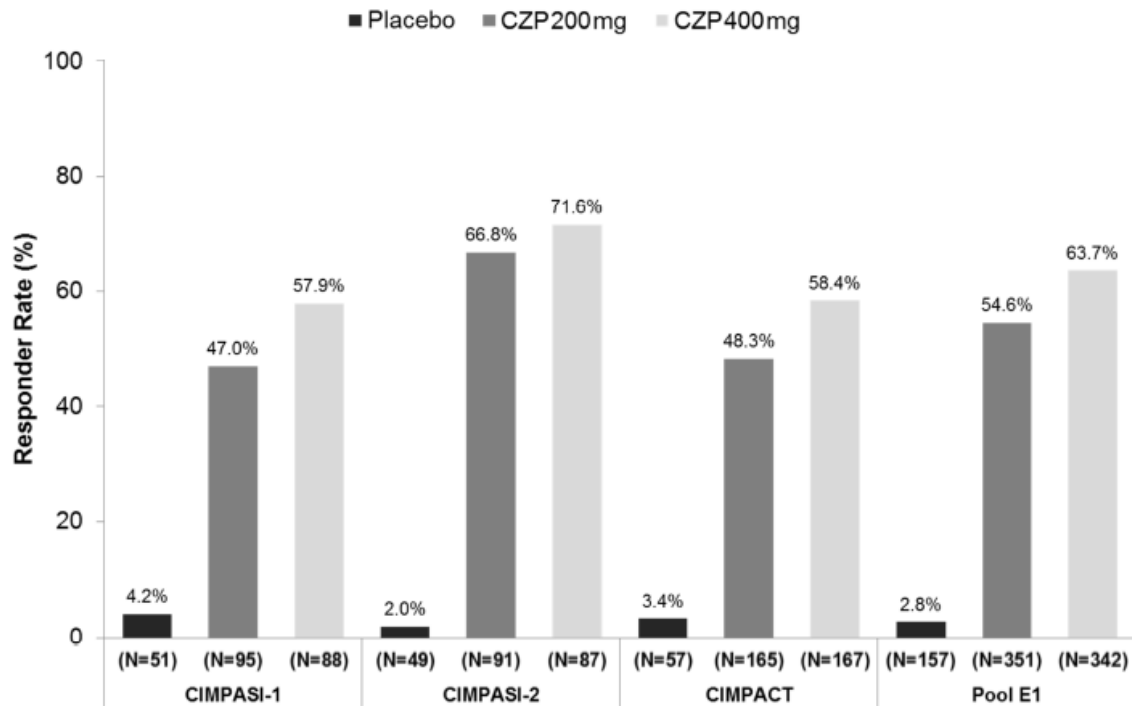
CZP=certolizumab pegol; MCMC=Markov Chain Monte Carlo; PGA=Physician's Global Assessment; RS=Randomized Set

PGA results over time

The PGA responder rates over time during the Initial Treatment Period of 16 weeks in Pool E1 (CIMPASI-1 and -2 and CIMPACT) are shown below. Results for PGA responder rate during the combined Initial and Maintenance Treatment Period (Weeks 0-48) in Pool E2 and Pool E3 (the CIMPASI studies) is shown in the figure 17 below.

Figure 17: PGA responder rates over time during the Initial Treatment Period by randomized treatment group in Pool E1 (RS [MCMC])

CZP=certolizumab pegol; MCMC=Markov Chain Monte Carlo; PGA=Physician's Global Assessment; Q2W=every 2 weeks; RS=Randomized Set

Note: Estimates of responder rate were based on using a logistic regression model with factors for treatment, region, study, prior biologic exposure (yes/no), study*region, and study*prior biologic exposure on the multiply imputed data sets where missing data were imputed using the MCMC method. The responder rates were the adjusted predicted probabilities from the logistic regression model.

Note: Factors excluded from Week 2: region, study*region, and study*prior biologic exposure.

Note: PGA responders=Clear or Almost Clear (with at least 2 category improvement from Baseline) at each visit.

Figure 18: PGA responder rate during the combined Initial and Maintenance Treatment Period (Weeks 0 to 48 in Pool E2 and Pool E3 (MCMC)
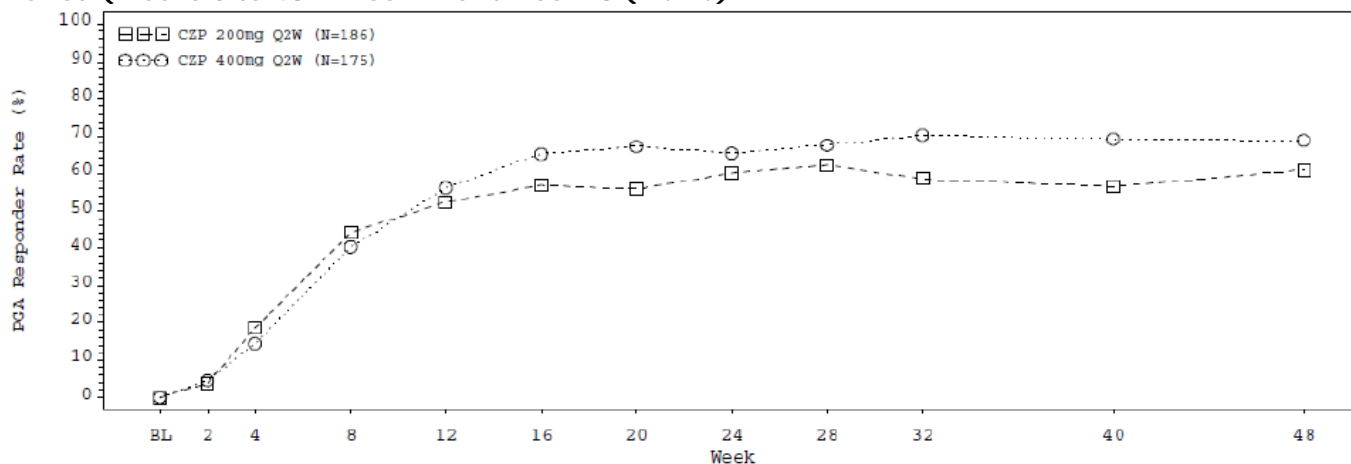
BL=baseline, CZP=certolizumab pegol, MCMC=Markov Chain Monte Carlo, PGA=Physician's Global Assessment, Q2W=every two weeks.

Note: Estimates of responder rates were based on a using a logistic regression model with factors for treatment, region, study, prior biologic exposure (yes/no), study*region, and study*prior biologic exposure on the multiply-imputed data sets where missing data were imputed using the MCMC method. The responder rates were the adjusted predicted probabilities from the logistic regression model.

Note: Exact statistics used for Week 2.

Note: PGA responders=Clear or almost clear (with at least 2 category improvement from Baseline) at each visit.

Note: Subjects who met escape criteria at Week 16 (ie, did not achieve a PASI50) or who met criteria for mandatory withdrawal due to not achieving PASI50 response at Week 32 or Week 40 were treated as nonresponders at subsequent timepoints. For subjects who achieved a PASI50 response at Week 16, but were mistakenly put into the CZP 400mg Q2W escape arm, all visits after Week 16 were imputed with the value observed at Week 16 (ie, Week 16 was carried forward). All other missing data were imputed using multiple imputation based on MCMC methodology.

Note: From Week 0 through Week 16, this figure was based on Pool E2 (excluding subjects randomized to placebo) which is the same set of subjects included in Pool E3.

The pattern for the PGA response showed a similar pattern across studies and over time as the PASI75 response.

Sub-group analyses

Consistency of treatment effect for the co-primary efficacy endpoints (PASI75 at Week 16 and PGA clear or almost clear at Week 16, with at least 2-category improvement from Baseline]) as well as for the secondary efficacy endpoint PASI90 at Week 16 within individual subgroups of subjects was evaluated based on the pooled data using Pool E1, where missing data were imputed using NRI. Any subject with a missing PASI75, PASI90, or PGA response at Week 16 was treated as a non-responder. Descriptive statistics were tabulated by treatment group for each of the following subgroups and categories:

- Geographic region (Central/Eastern Europe, North America, Western Europe)
- Demographic factors at Baseline:
  - Age group (years) (<40, ⩾40 to 64, ⩾65)
  - Gender (male, female)
  - Racial group (White, Black, Other)
  - Ethnic origin (Hispanic or Latino, not Hispanic or Latino)
- Baseline weight (kg) categories (per quintiles)
- BMI (kg/m^2) categories (per quintiles)
- PSO disease duration (years) (⩽median, >median)
- Exposure to at least 2 of the following systemic treatments: phototherapy, MTX, and cyclosporine (with no previous biologic exposure)
- Prior biologic exposure (yes/no)
- Disease severity at study Baseline as measured by PASI (⩽median, >median)
- Disease severity at study Baseline as measured by BSA (⩽median, >median)
- Anti-CZP antibody (ADAb) status (positive, negative)
- Any prior systemic therapy for PSO (yes/no)
- Prior anti-TNF therapy (Yes/No)
- Prior exposure to anti-IL-17 therapy (Yes/No)
- Concomitant PSA (Yes/No)

Figure 19: Forest Plot of PASI75 Responder Rate at Week 16 by Subgroup Analysis Set: Pool E1 (NRI)

Panel 1:

```
                                            CZP 200mg Q2W ■        CZP 400mg Q2W ●

Subgroup (interaction p-value)  CZP Dose    N       OR  (90% CI)        Resp.(%)
                                          CZP/PBO                        CZP/PBO
Geographical Region (p-value=0.5940)
  Central/Eastern Europe        200mg     150/ 57   45.5 ( 16.0, 129.5) 68/ 5
                                400mg     145/ 57   83.5 ( 28.8, 241.7) 79/ 5
  North America                 200mg     136/ 71   34.9 ( 15.9,  76.5) 74/ 8
                                400mg     133/ 71   36.2 ( 16.5,  79.7) 75/ 8
  Western Europe                200mg      65/ 29   23.8 (  6.2,  91.5) 62/ 7
                                400mg      64/ 29   32.5 (  8.4, 126.6) 67/ 7
Baseline BMI (kg/m2) (p-value=0.3384)
  <=1st (24.96)                 200mg #    65/ 30  168.6 ( 26.1,>999.9) 82/ 3
                                400mg #    75/ 30  190.8 ( 28.8,>999.9) 81/ 3
  >1st (24.96) - <=2nd (27.78)  200mg #    69/ 28   19.8 (  6.6,  59.5) 72/18
                                400mg #    74/ 28   43.3 ( 13.3, 140.7) 86/18
  >2nd (27.78) - <=3rd (30.93)  200mg #    62/ 32   81.6 ( 12.6, 529.6) 63/ 3
                                400mg #    75/ 32   85.1 ( 15.0, 482.5) 73/ 3
  >3rd (30.93) - <=4th (35.81)  200mg #    82/ 34   32.8 (  9.2, 117.2) 66/ 6
                                400mg #    54/ 34   47.9 ( 12.8, 179.4) 74/ 6
  >4th (35.81)                  200mg #    73/ 33   35.6 (  9.4, 134.6) 64/ 6
                                400mg #    64/ 33   23.9 (  6.6,  87.2) 59/ 6
Baseline Weight (kg) * (p-value=0.5782)
  <=1st (73.10)                 200mg #    62/ 33   55.6 ( 14.6, 211.2) 81/12
                                400mg #    75/ 33   53.7 ( 16.6, 173.6) 84/12
  >1st (73.10) - <=2nd (83.20)  200mg #    64/ 30   18.2 (  5.8,  57.3) 69/10
                                400mg #    77/ 30   32.6 ( 10.1, 104.7) 78/10
  >2nd (83.20) - <=3rd (92.60)  200mg #*   72/ 29  266.0 ( 22.5,>999.9) 75/ 0
                                400mg #    68/ 29  193.5 ( 18.0,>999.9) 76/ 0
  >3rd (92.60) - <=4th (107.35) 200mg #    74/ 33   12.8 (  4.4,  37.6) 57/ 9
                                400mg #    63/ 33   33.7 ( 10.2, 111.7) 71/ 9
  >4th (107.35)                 200mg #    79/ 32   65.8 ( 11.7, 370.6) 67/ 3
                                400mg #    59/ 32   54.1 (  9.5, 307.2) 64/ 3
```

```
     0.1                1                10        100        1000
       Favoring Placebo    Favoring CZP
              Odds ratio (90% CI) CZP vs Placebo
```

Panel 2:

```
                                            CZP 200mg Q2W ■        CZP 400mg Q2W ●

Subgroup (interaction p-value)  CZP Dose    N       OR  (90% CI)        Resp.(%)
                                          CZP/PBO                        CZP/PBO
Baseline PASI Score (p-value=0.5961)
  <=Median (17.60)              200mg     176/ 94   36.8 ( 17.9,  76.0) 71/ 7
                                400mg     157/ 94   42.6 ( 20.4,  89.0) 73/ 7
  >Median (17.60)               200mg     175/ 63   32.7 ( 13.3,  80.6) 67/ 6
                                400mg     185/ 63   53.8 ( 21.7, 133.5) 77/ 6
Baseline BSA (%) (p-value=0.3418)
  <=Median (20.0)               200mg     180/ 89   39.4 ( 18.4,  84.4) 72/ 7
                                400mg     169/ 89   42.6 ( 19.8,  91.9) 72/ 7
  >Median (20.0)                200mg     171/ 68   30.2 ( 13.1,  70.0) 67/ 7
                                400mg     173/ 68   54.6 ( 23.2, 128.1) 79/ 7
Prior exp to >=2 systemic tx (p-value=0.1511)
  Yes                           200mg      36/ 18   11.9 (  2.9,  48.3) 56/11
                                400mg      31/ 18   41.8 (  9.3, 187.7) 81/11
  No                            200mg     315/139   40.8 ( 22.0,  75.9) 71/ 6
                                400mg     311/139   51.3 ( 27.4,  95.9) 75/ 6
Prior biologic exposure (p-value=0.2557)
  Yes                           200mg #   106/ 40   98.5 ( 17.9, 542.4) 72/ 3
                                400mg #   107/ 40  100.9 ( 18.3, 557.2) 72/ 3
  No                            200mg #   245/117   26.8 ( 14.5,  49.6) 68/ 9
                                400mg #   235/117   41.2 ( 22.0,  77.3) 77/ 9
Any prior systemic tx for PSO (p-value=0.4784)
  Yes                           200mg     249/111   43.4 ( 20.5,  92.0) 67/ 5
                                400mg     247/111   65.0 ( 30.4, 138.9) 75/ 5
  No                            200mg     102/ 46   24.9 ( 10.4,  59.7) 74/11
                                400mg      95/ 46   28.7 ( 11.8,  69.4) 76/11
```

```
     0.1                1                10        100        1000
       Favoring Placebo    Favoring CZP
              Odds ratio (90% CI) CZP vs Placebo
```

Panel 3:

```
                                            CZP 200mg Q2W ■        CZP 400mg Q2W ●

Subgroup (interaction p-value)  CZP Dose    N       OR  (90% CI)        Resp.(%)
                                          CZP/PBO                        CZP/PBO
Anti-CZP Antibody Status * (p-value=0.5815)
  AB-                           200mg #   300/157   43.6 ( 24.5,  77.4) 75/ 7
                                400mg #   324/157   51.6 ( 29.0,  91.8) 78/ 7
  AB+                           200mg      51/  0    NA (   NA,   NA) 35/NA
                                400mg      18/  0    NA (   NA,   NA) 33/NA
Concomitant PSA (p-value=0.7878)
  Yes                           200mg #    59/ 25   68.2 ( 11.8, 394.7) 73/ 4
                                400mg #    65/ 25  127.6 ( 20.3, 803.5) 80/ 4
  No                            200mg #   292/132   29.7 ( 16.4,  53.9) 68/ 8
                                400mg #   277/132   40.2 ( 21.9,  73.9) 74/ 8
Previous Exposure to Anti-IL-17 Therapy * (p-value=0.5781)
  Yes                           200mg #*   54/ 13   60.9 (  5.4, 688.7) 72/ 0
                                400mg #*   43/ 13   49.8 (  4.5, 545.7) 70/ 0
  No                            200mg #   297/144   29.1 ( 16.5,  51.3) 69/ 8
                                400mg #   299/144   40.7 ( 23.0,  71.9) 76/ 8
Prior anti-TNF Therapy Used (p-value=0.6928)
  Yes                           200mg #    49/ 24   51.1 (  8.8, 297.6) 69/ 4
                                400mg #    43/ 24   55.2 (  9.2, 329.5) 70/ 4
  No                            200mg #   302/133   31.7 ( 17.4,  57.8) 69/ 8
                                400mg #   299/133   45.2 ( 24.6,  83.3) 76/ 8
```

```
     0.1                1                10        100        1000
       Favoring Placebo    Favoring CZP
              Odds ratio (90% CI) CZP vs Placebo
```
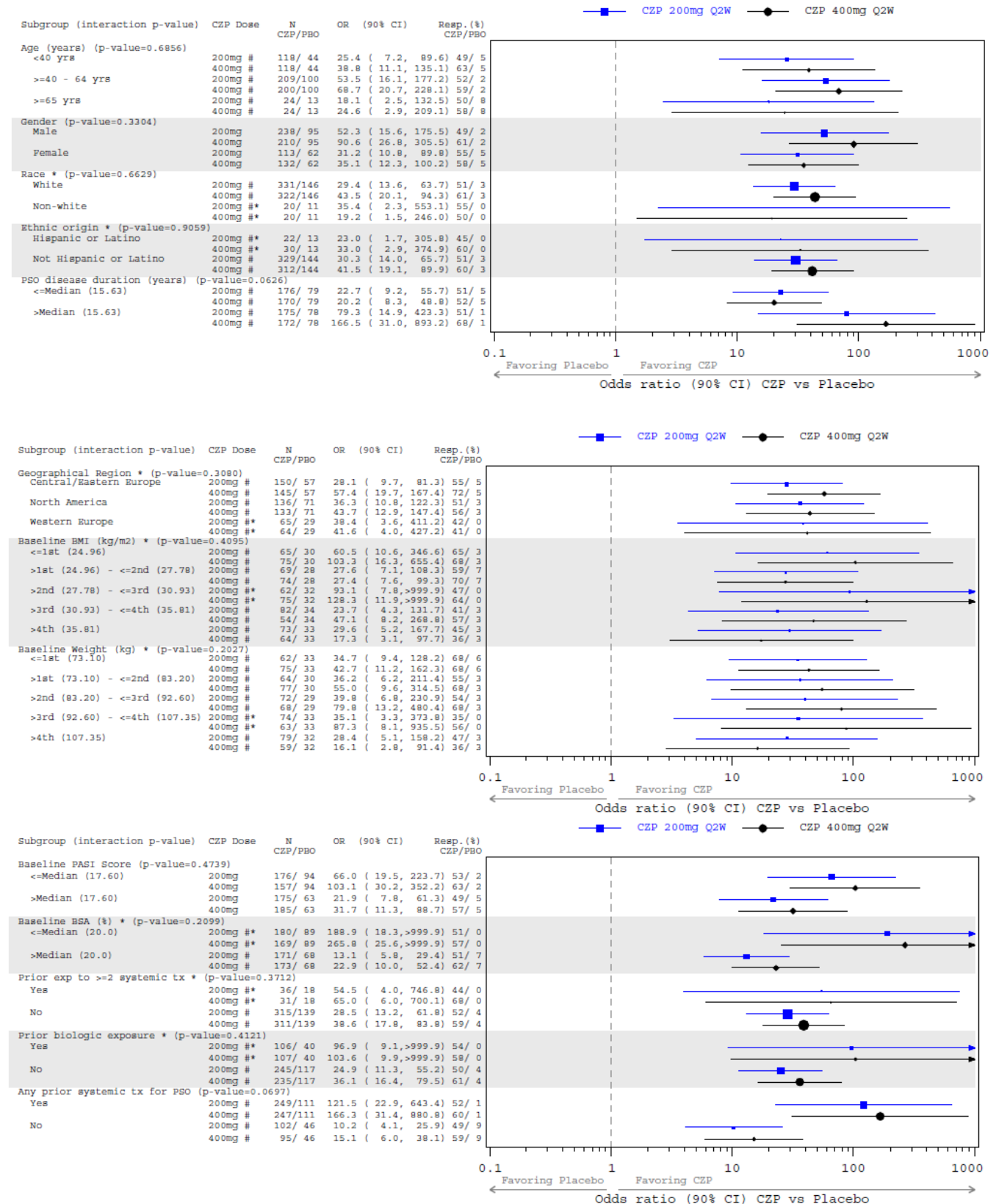
BMI=body mass index, CZP=certolizumab pegol, NRI=non-response imputation, PASI75=response is based on at least 75% improvement from Baseline in the PASI score, Q2W=every 2 weeks.
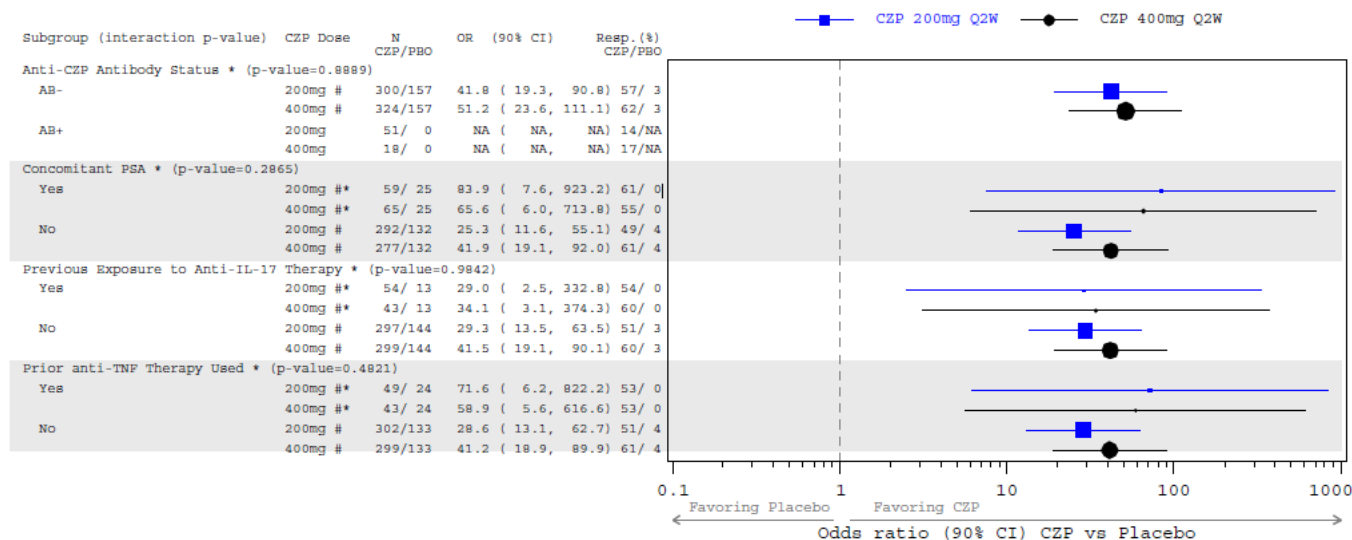Note: Treatment by subgroup interaction p-values are from a logistic regression model with factors for treatment group, region, prior biologic exposure (yes/no), study, study*region, study*prior biologic exposure (yes/no), subgroup, and the treatment by subgroup interaction term.
* Performed Firth's penalized maximum likelihood estimation to reduce bias in the parameter estimates.
# OR and CI are from a logistic regression model with factors for treatment group and study.

Figure 20: Forest Plot of PGA Responder Rate at Week 16 by Subgroup Analysis Set: Pool E1 (NRI)

Subgroup (interaction p-value)	CZP Dose	N CZP/PBO	OR (90% CI)	Resp.(%) CZP/PBO
Anti-CZP Antibody Status * (p-value=0.8889)				
AB-	200mg #	300/157	41.8 (19.3, 90.8)	57/ 3
	400mg #	324/157	51.2 (23.6, 111.1)	62/ 3
AB+	200mg	51/ 0	NA (NA, NA)	14/NA
	400mg	18/ 0	NA (NA, NA)	17/NA
Concomitant PSA * (p-value=0.2865)				
Yes	200mg #*	59/ 25	83.9 (7.6, 923.2)	61/ 0
	400mg #*	65/ 25	65.6 (6.0, 713.8)	55/ 0
No	200mg #	292/132	25.3 (11.6, 55.1)	49/ 4
	400mg #	277/132	41.9 (19.1, 92.0)	61/ 4
Previous Exposure to Anti-IL-17 Therapy * (p-value=0.9842)				
Yes	200mg #*	54/ 13	29.0 (2.5, 332.8)	54/ 0
	400mg #*	43/ 13	34.1 (3.1, 374.3)	60/ 0
No	200mg #	297/144	29.3 (13.5, 63.5)	51/ 3
	400mg #	299/144	41.5 (19.1, 90.1)	60/ 3
Prior anti-TNF Therapy Used * (p-value=0.4821)				
Yes	200mg #*	49/ 24	71.6 (6.2, 822.2)	53/ 0
	400mg #*	43/ 24	58.9 (5.6, 616.6)	53/ 0
No	200mg #	302/133	28.6 (13.1, 62.7)	51/ 4
	400mg #	299/133	41.2 (18.9, 89.9)	61/ 4

BMI=body mass index, CZP=certolizumab pegol, NRI=non-response imputation, PGA=Physician's Global Assessment, Q2W=every two weeks.
Note: Treatment by subgroup interaction p-values are from a logistic regression model with factors for treatment group, region, prior biologic exposure (yes/no), study, study*region, study*prior biologic exposure (yes/no), subgroup, and the treatment by subgroup interaction term.
* Performed Firth's penalized maximum likelihood estimation to reduce bias in the parameter estimates.
# OR and CI are from a logistic regression model with factors for treatment group and study.
Note: PGA responders=Clear or Almost Clear (with at least 2 category improvement from Baseline).

The PASI75 and PGA response rates in different weight groups are also presented in the figures 21 and 22 below.

Figure 21: PASI75 Responder Rate at Week 16 by Baseline Weight Quintile Analysis, Pool E1, NRI
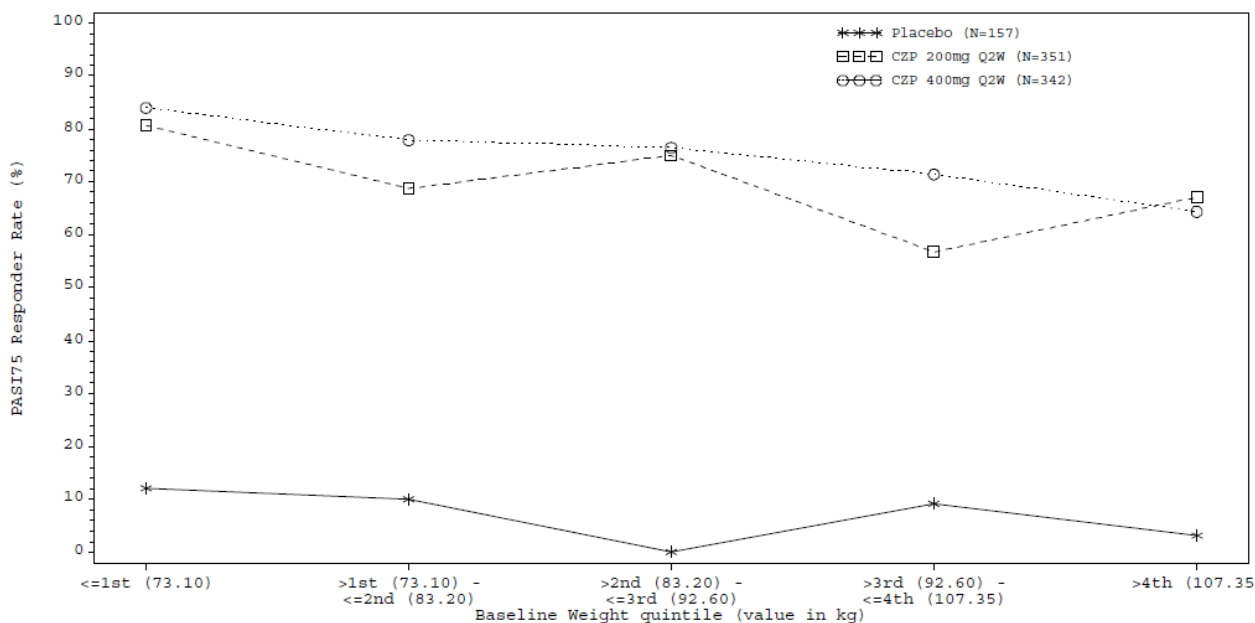
Figure 22: PGA Responder Rate at Week 16 by Baseline Weight Quintile Analysis, Pool E1, NRI
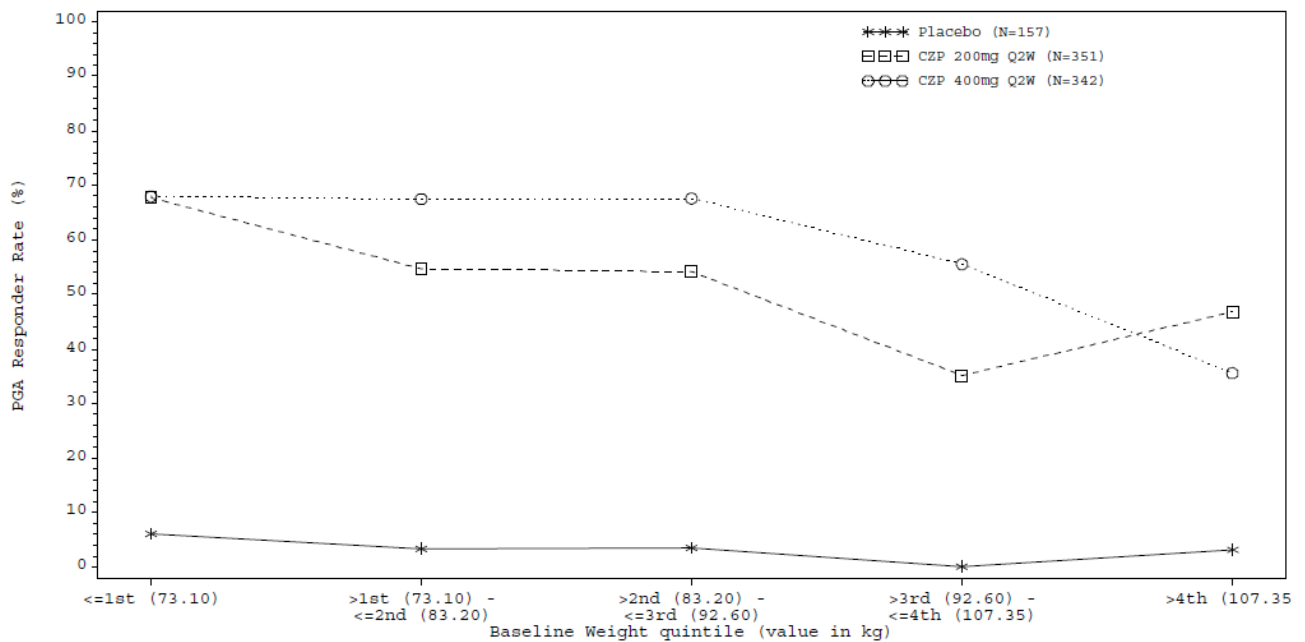
All subgroups showed difference from placebo in PGA, PASI75, and PASI90 responder rates at Week 16 for both CZP groups. Clinically meaningful efficacy based on PGA, PASI75, and PASI90 responder rates was observed both in subjects with or without a history of prior systemic treatment of psoriasis and is supportive of the proposed first line indication for treatment in patients who are candidates for systemic treatment or phototherapy.

At both Week 16 and Week 48, similar to the overall population, PGA, PASI75, and PASI90 responder rates in the CZP 400 mg Q2W group were numerically higher compared with the CZP 200 mg Q2W group across most subgroups.

Concerning baseline body weight, patients in the lower weight quintiles generally had somewhat higher PASI75 and PGA response rates compared with those in the higher weight quintiles. The differences were not consistent across dose regimens and did not warrant a body weight adjusted posology for Cimzia in psoriasis.

Immunogenicity

Table: Anti-CZP antibody subgroup analysis of PGA, PASI75, and PASI90 responder rates at Week 16 and Week 48 (Pool E1 and Pool E3 [NRI])

ADAb status	PBO n/Nsub (%) Responder Rate	CZP 200mg Q2W n/Nsub (%) Responder Rate	CZP 400mg Q2W n/Nsub (%) Responder Rate	Treatment by subgroup interaction p-value
PGA Responder Rates				
Week 16 (Pool E1), N [a]	157	351	342	
Antibody negative	5/157 (3.2)	172/300 (57.3)	202/324 (62.3)	0.8889
Antibody positive	0	7/51 (13.7)	3/18 (16.7)	
Week 48 (Pool E3), N	NA	186	175	
Antibody negative	NA	90/152 (59.2)	101/158 (63.9)	0.1068
Antibody positive	NA	8/34 (23.5)	1/17 (5.9)	
PASI75 Responder Rates				
Week 16 (Pool E1), N [a]	157	351	342	
Antibody negative	11/157 (7.0)	225/300 (75.0)	252/324 (77.8)	0.5815
Antibody positive	0	18/51 (35.3)	6/18 (33.3)	
Week 48 (Pool E3), N	NA	186	175	
Antibody negative	NA	107/152 (70.4)	123/158 (77.8)	0.5861
Antibody positive	NA	10/34 (29.4)	5/17 (29.4)	
PASI90 Responder Rates				
Week 16 (Pool E1), N [a]	157	351	342	
Antibody negative	2/157 (1.3)	138/300 (46.0)	160/324 (49.4)	0.4146
Antibody positive	0	4/51 (7.8)	3/18 (16.7)	
Week 48 (Pool E3), N	NA	186	175	
Antibody negative	NA	81/152 (53.3)	93/158 (58.9)	0.4066
Antibody positive	NA	4/34 (11.8)	4/17 (23.5)	

ADAb=anti-CZP antibody; CZP=certolizumab pegol; NA=not applicable; NRI=nonresponder imputation; Nsub=number of subjects in the given subgroup for that treatment group; PASI50=at least 50% reduction from Baseline in Psoriasis Area and Severity Index; PASI75=at least 75% reduction from Baseline in Psoriasis Area and Severity Index; PBO=placebo; Q2W=every 2 weeks

Note: A subject was counted as antibody positive if the subject was positive for ADAb while on treatment at any timepoint (excluding Baseline, Week 0, and Safety Follow-Up [For Pool E3]) up to and including Week 16 (Pool E1) or Week 48 (Pool E3). Otherwise, the subject was counted as antibody negative. Antibody negative was defined as having no values >2.4 units/mL in plasma samples taken while on treatment during the Initial Treatment Period (Pool E1) or the Initial and Maintenance Treatment Period (Pool E3). Antibody positive was defined as having a value >2.4 units/mL in plasma samples taken while on treatment during the Initial and/or Maintenance Treatment Period.

Note: Treatment by subgroup interaction p-values were from a logistic regression model with factors for treatment group, region, prior biologic exposure (yes/no), study, study*region, study*prior biologic exposure (yes/no), subgroup, and the treatment by subgroup interaction term.

Note: For Pool E3, subjects who met escape criteria at Week 16 (ie, did not achieve a PASI50) or who met criteria for mandatory withdrawal due to not achieving PASI50 response at Week 32 or Week 40 were treated as nonresponders at Week 48. For subjects who achieved a PASI50 response at Week 16 but were mistakenly put into the CZP 400mg Q2W escape arm, all visits after Week 16 were imputed with the value observed at Week 16 (ie, Week 16 carried forward). All other missing data were imputed using NRI methodology.

[a] Performed Firth's penalized maximum likelihood estimation to reduce bias in the parameter estimates.

The incidence of ADAb positivity was generally 2-fold higher in the CZP 200 mg Q2W group compared

with the CZP 400 mg Q2W group. Mean PGA, PASI75, and PASI90 responder rates were lower at Week 16 and Week 48 in ADAb positive subjects compared with ADAb negative subjects in both the CZP dose groups. Not all subjects who become ADAb positive experienced a reduction in their response to CZP treatment.

When comparing responder rates in ADAb negative subjects at Weeks 16 and 48 between CZP 400 mg Q2W and CZP 200mg Q2W, the responder rates in the CZP 400mg Q2W group were numerically higher than responder rates in the CZP 200 mg Q2W group. However, the dose response observed was smaller than the dose response seen in the overall population. This may be explained by the overall population including ADAb positive subjects, and the incidence of ADAb is higher among subjects in the CZP 200 mg Q2W group compared with the CZP 400 mg Q2W group, thus resulting in a greater decrease in efficacy in the CZP 200 mg Q2W group in the overall population.
The lower CZP dose of 200 mg showed a higher incidence of ADAb positivity compared with the CZP 400 mg group. The mean responder rates were lower at Week 16 and Week 48 in ADAb positive subjects compared with ADAb negative subjects in both the CZP dose groups, although not all ADAb positive subjects had a reduction in their CZP response.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development program for CZP in subjects with moderate to severe chronic plaque psoriasis consists of five clinical studies:

- The completed Phase 2 studies C87040 and C87044.
- The two identical Phase 3, double-blind, placebo-controlled studies CIMPASI-1 (PS0005) and CIMPASI-2 (PS0002). These studies had an initial treatment period (Week 0 to Week 16) followed by a maintenance treatment period (Week 16 to Week 48) that have both been completed.
- The Phase 3, double-blind, placebo- and active- (etanercept) controlled study CIMPACT (PS0003). This study also had an initial 16 week treatment period followed by a maintenance treatment period from Week 16 to 48.

All three pivotal studies have open-label extension (OLE) treatment periods (Week 48 to Week 144) that are still ongoing.

No formal dose ranging study with a wide range of dose levels was performed to support the posology of CZP in the indication plaque psoriasis however data are available in other indications. In the Phase 2 studies C87040 and C87044, two different dose levels were studied (CZP 200 mg Q2W and CZP 400 mg Q2W) and these two doses were also studied in phase 3, both for initial treatment and for maintenance treatment (including 400 mg Q4W) in study CIMPACT.
The inclusion and exclusion criteria were overall similar for the three pivotal studies and are adequate to define patients with moderate to severe plaque psoriasis (a PASI score of at least 12, PGA of at least 3 and a total body surface area of minimally 10%). The patients should be candidates for systemic psoriasis therapy and/or phototherapy and/or chemo-phototherapy. Subjects must not have been exposed to more than two biological response modifiers (including anti-TNF) for PsA or psoriasis and they should not have been a primary failure to any prior biologic therapy. They may have been a secondary failure (i.e. subject initially responded to therapy and then stopped treatment due to loss of response after Week 12), but not to more than one. In study CIMPACT, previous use of ETN was excluded, while previous use of other biologics targeting TNF α was allowed after a washout of 12 weeks.

There are some differences in presentation and viscosity between active treatment (CZP) and placebo, which may pose a risk for unblinding. Appropriate measures seem to have been taken to preserve

blinding and this approach has also been used other, prior CZP development programs. With respect to the active comparator etanercept in study CIMPACT, differences in treatment regimens, drug presentation and viscosity vs. CZP and placebo also led to blinding difficulties. Therefore, ETN treatments were administered in a single-blind fashion. A double-dummy technique may have been used in this situation, however, for different reasons (e.g. need for large number of injections, GMP issues), this approach was not taken, which is understood and accepted.The three studies had a similar initial treatment period, in which patients were randomized to CZP 200 mg Q2W (with initial CZP 400 mg doses at Weeks 0, 2, and 4, followed by CZP 200 mg Q2W starting at Week 6); CZP 400mg Q2W or placebo. In study CIMPACT there was also an etanercept treatment arm (ETN administered sc at 50 mg twice weekly through Week 11.5).

ETN is an acceptable active comparator even if its efficacy in plaque psoriasis seems to be in the lower range when compared with other biologics approved in this indication.

The studies differed in design during the maintenance treatment period. In the CIMPASI studies, subjects who achieved at least PASI50 at Week 16 continued therapy, i.e. subjects randomized to CZP 200 mg Q2W continued to receive CZP 200 mg Q2W, subjects randomized to CZP 400 mg Q2W continued to receive CZP 400mg Q2W, subjects randomized to placebo who achieved a PASI50 but not PASI75 at Week 16 received CZP 400 mg at Weeks 16, 18, and 20 (loading doses) followed by CZP 200 mg Q2W (starting at Week 22). Subjects randomized to placebo who achieved PASI75 at Week 16 continued to receive placebo. Subjects who did not achieve PASI50 at Week 16 escaped from blinded treatment and received open-label CZP 400 mg Q2W.

In study CIMPACT, all subjects who did not achieve PASI75 at Week 16 were removed from blinded study medication and escaped to CZP 400 mg Q2W. For PASI75 responders at Week 16, subjects initially randomized to placebo continued to receive blinded placebo; subjects initially randomized to ETN were re-randomized (2:1) to either CZP (400 mg at Weeks 16, 18, and 20 followed by 200 mg Q2W) or placebo; subjects initially randomized to CZP 200 mg Q2W were re-randomized (2:2:1) to receive either CZP 200 mg Q2W or CZP 400 mg every 4 weeks or placebo; subjects initially randomized to CZP 400 mg Q2W were re-randomized (2:2:1) to CZP 200 mg Q2W or CZP 400 mg Q2W or placebo.

In the randomization patients were stratified by site. Other stratification factors that could have been considered are baseline body weight and previous psoriasis therapy. However, the baseline demographic and disease characteristic data did not reveal any large imbalances between the different treatment groups in the different studies. Standard efficacy variables for plaque psoriasis have been used to assess efficacy of CZP in the phase II and III studies, in accordance with published guidelines, e.g. CHMP/EWP/2454/02, 2004. Both physician reported psoriasis efficacy evaluations (PASI and PGA) and patient reported psoriasis efficacy evaluations have been used (e.g. DLQI, SF-36, EQ-5D, HADS).

In the CIMPASI studies, the co-primary efficacy variables were PASI75 at Week 16 and PGA Clear or Almost clear (with at least 2-category improvement) at Week 16. For several other monoclonal antibodies, the primary endpoint has been assessed at 12 weeks. However, 16 weeks is also deemed a reasonable time point for the primary efficacy assessment and no issue is raised. In study CIMPACT, PASI 75 response at week 12 was the primary endpoint. Comparison of CZP over ETN was measured at Week 12 because the approved duration of initial ETN treatment at 50 mg twice weekly is 12 weeks and in the ETN plaque psoriasis studies, the primary endpoint was assessed at week 12.

Other end-points addressed the effect at 48 weeks, other PASI response variables and effects on the scores over time, affected body surface area, nail engagement as well as patient reported outcomes.

Efficacy data and additional analyses

In the phase 2 study C87040, both CZP doses (200 mg Q2W after one loading dose of 400 mg and 400 mg Q2W) were statistically and clinically different from placebo for both co-primary efficacy endpoints (PASI75 and PGA clear or almost clear), with fairly high PASI75 response rates at week 12 (75% for CZP 200 mg and 83% for CZP 400 mg). More than two thirds of the PASI75 responders relapsed after stopping treatment with a median time to relapse of about 20 weeks.

In the pivotal phase 3 studies, the number of patients completing the initial periods was high (>93%). The numbers of patients completing the maintenance periods in the blinded maintenance groups were also fairly high. The groups of patients continuing on placebo in the maintenance periods (i.e. those who achieved PASI75 on placebo at week 16) were small, which is not unexpected.

The treatment groups were overall quite well balanced with respect to baseline demographic and disease characteristics within studies and across studies, with a few differences noted, e.g. with respect to body weight and BMI.

The median PASI score at baseline was about 18 and around 70% of subjects had a PGA score of 3 (moderate), while 30% had a score of 4 (severe). Previous psoriasis therapies were also generally well balanced across arms within the different studies. About 70% of all subjects had never used biologic therapy before. Around 40-50% had used previous chemophototherapy or phototherapy and the majority of subjects (71%) had used any previous systemic treatment for psoriasis (which included phototherapies). A lower percentage of subjects used prior anti-TNF therapy in CIMPACT (3.8%) compared with CIMPASI-1 and CIMPASI-2 (20-23%), likely since prior ETN use was not permitted in CIMPACT.

Subjects who were considered primary failures to any prior biologic therapy (defined as no response within the first 12 weeks of treatment with the biologic) were excluded from CIMPASI-1, CIMPASI-2, and CIMPACT. In line with these exclusion criteria, the number of subjects being failures on a prior biologic agent was low, as expected (thus, meaning that exclusion criteria were not adhered to for these patients). In pool E1 (including all three studies), a total of 34 subjects (4%) were biologic failures. The PGA and PASI75 responder rates at Week 16 were numerically higher in the CZP subgroups compared with placebo, however, they were lower than observed in the overall population. This might be expected and this subgroup is too small to make firm conclusions.

The CIMPACT study included an ETN arm as active control, and all ETN-treated subjects who did not achieve a PASI75 response were switched to CZP 400 mg Q2W at Week 16. The Applicant considered that these subjects can be considered primary non-responders to anti-TNF, and that the Week 32 and 48 efficacy results in this population could provide relevant data on the benefit of CZP in primary non-responders. Even if this reasoning can be followed, this relates only to *one* other anti-TNF product and etanercept is generally one of the anti-TNF monoclonal antibodies with lowest response in plaque psoriasis (Reich et al., Br J Dermatol, 2012). Hence, the relevance of these data may be questioned, even if this group comprised 97 patients and the response rates seemed overall satisfactory at Weeks 32 and 48. In conclusion, the information in section 5.1 of the SmPC should adequately present the design of the pivotal studies. Hence, it is requested to include a sentence in this section to inform that patients who were 'primary' non-responders on any prior biologic therapy (defined as no response within the first 12 weeks of treatment) were excluded from the phase 3 studies.

Efficacy results for the initial treatment period

Both CIMPASI studies met their co-primary end-points, i.e. to demonstrate superiority vs. placebo with respect to PASI 75 response and PGA response at week 16. This was observed for both CZP dose levels. Sensitivity analyses (NRI and model-based multiple imputation) overall showed similar results

as the primary method used (MCMC), however, in CIMPASI-2 the response rates were generally lower using NRI.

Both CZP dose levels were superior to placebo in both studies. However, the difference between the 200 mg and the 400 mg dose was larger in study CIMPASI-1 with about 10% difference in response rates for both PASI75 and PGA. In study CIMPASI-2 the response rates were higher than in CIMPASI-1 but there were virtually no dose differences in PASI75 and PGA response rates. For the pooled CIMPASI studies (pool E2), PASI75 response for the placebo, CZP 200 mg and CZP 400 mg groups at Week 16 were 10%, 77% and 82%, respectively. Corresponding PGA responder rates were 3%, 57% and 65%, respectively.

Study CIMPACT also met its primary end-point, i.e. to demonstrate superiority vs. placebo with respect to PASI 75 response at week 12 (61.3% for CZP 200 mg; 66.7% for CZP 400 mg and 5% for placebo). Sensitivity analyses (NRI and model-based multiple imputation) overall showed similar results as the primary method used (MCMC). Both CZP doses were superior to placebo with a difference of approximately 5% in favour of the 400 mg arm.

Onset of effect started at about 4 weeks where a separation from placebo could be observed for both CZP groups. Due to the initial loading dose scheme, both CZP groups have received the same treatment for the first weeks of the initial period.

The testing for superiority of CZP vs. ETN was included as a rather late , the last step in the sequential testing procedure in study CIMPACT. Superiority could be concluded for PASI75 at Week 12 for the higher CZP 400 mg CZP dose and non-inferiority for the CZP 200 mg dose, while superiority was not demonstrated for 200 mg.

For the secondary end-point PASI90 response at week 16, both CZP dose arms were statistically significantly superior to placebo in all three studies. Similar to the co-primary endpoints, a dose difference was mainly observed in studies CIMPASI-1 and CIMPACT, while in study CIMPASI-2 the response rates were very similar for CZP 200 mg and 400 mg. The PASI90 responder rates were also higher in CIMPASI-2 compared with CIMPASI-1 and CIMPACT in both CZP groups. For the pooled studies (pool E1), PASI90 was 44.5% for the 200 mg dose, 52.2% for the 400 mg dose and 1.6% for placebo.

Change in DLQI (Dermatology Life Quality Index), a well-known and commonly used QoL scale in dermatology, was one of the secondary endpoints. Improvement in health related quality of life, as measured by the mean change from Baseline in DLQI, was observed for CZP-treated subjects compared with placebo-treated subjects at Week 16 in all three studies.

PASI100 at Week 16 was an "other" efficacy endpoint, not controlled for multiplicity. In Pool E1, the PASI100 responder rates at Week 16 were 12.7% in the CZP 200 mg Q2W group and 15.2% in the CZP 400 mg Q2W group compared with 0.7% in the placebo group.

Efficacy results for the maintenance treatment period

In the CIMPASI studies, PASI75 and PGA response rates at Week 48 overall showed maintained or increases response rates compared with Week 16, even if the pattern differed to some extent between doses and studies. The 400 mg Q2W dose tended to show higher response than 200 mg QW both at Week 16 and 48.

In study CIMPACT, in patients who were PASI75 responders at Week 16 for subjects initially randomized to CZP, the majority of subjects (>79%) in each group that received CZP treatment during the Maintenance Treatment Period continued to be PASI75 responders at Week 48. In the group that received CZP 400 mg Q2W in both the Initial and Maintenance Treatment Periods, 98% continued to

be PASI75 responders at Week 48. For subjects who received placebo, the PASI75 responder rate decreased from Week 16 to Week 48. For the blinded maintenance treatment groups initially treated with CZP 200 mg Q2W, the PASI75 responder rate was numerically greater at Week 48 in the treatment group receiving CZP 400mg Q4W compared with the treatment group continuing on CZP 200mg Q2W during the Maintenance Treatment Period (89% vs. 80%).

For PGA, in the subjects who were PASI75 responders at Week 16 for subjects initially randomized to CZP, the majority of subjects (≥61%) in each group that received CZP treatment during the Maintenance Treatment Period achieved a PGA response at Week 48. For subjects who received placebo, the PGA responder rate decreased from Week 16 to Week 48. The blinded maintenance treatment group treated with CZP 400 mg Q2W through both the Initial and Maintenance Treatment Periods achieved the best response at Week 48, with a PGA responder rate of 87.8%, which was a 6.2% improvement from Week 16. The group initially treated with CZP 400 mg Q2W that received a reduced dose during the Maintenance Treatment Period and the groups treated with CZP 200 mg Q2W (or the same cumulative monthly dose, 400 mg Q4W) throughout the study had an overall decrease in PGA responder rate (differences between Week 16 and Week 48 of -20%, -7%, and -11%, respectively).

Rebound was assessed in studies CIMPACT and the Phase 2 study, C87040, with a definition in accordance with the CHMP Psoriasis Guideline, i.e. a >125% increase from Baseline in PASI score occurring within 2 months of stopping therapy. Although the number of patients available for assessment of rebound was rather limited (e.g. 47 patients in CIMPACT), the data did not give cause for concern since no patients in either study met the definition of having a rebound effect.

Data on response to retreatment after withdrawal of CZP among responders is limited. Limited data from the phase 2 studies C87040/C87044 suggest that patients who responded to CZP may achieve similar PASI scores upon retreatment, although no inferential analyses were made. No specific claims about retreatment are given in the SmPC.

Nail involvement assessed via mNAPSI was an "other" endpoint for CIMPASI-1 and CIMPASI-2. Mean changes from Baseline at Week 48 in the mNAPSI score suggest that CZP treatment can improve psoriatic nail disease.

Sub-group analyses
Adequate sub-group analyses have been performed and the presented results did not give cause for concern. Concerning baseline body weight, patients in the lower weight quintiles generally had somewhat higher PASI75 and PGA response rates compared with those in the higher weight quintiles. The differences were not dramatic though a body weight adjusted posology is not proposed for Cimzia in psoriasis.

Concerning immunogenicity, the lower CZP dose of 200 mg showed a higher incidence of ADAb positivity compared with the CZP 400 mg group. The mean responder rates were lower at Week 16 and Week 48 in ADAb positive subjects compared with ADAb negative subjects in both the CZP dose groups, although not all ADAb positive subjects had a reduction in their CZP response.

2.4.4. Conclusions on the clinical efficacy

Three pivotal studies with adequate design have been performed to support the use of Cimzia (CZP) in patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Both CIMPASI studies met their co-primary end-points, i.e. to demonstrate superiority vs. placebo with respect to PASI 75 response and PGA response at week 16. This was observed for both CZP dose levels. For the pooled CIMPASI studies, PASI75 response for the placebo, CZP 200 mg and CZP 400

mg groups at Week 16 were 10%, 77% and 82%, respectively. Corresponding PGA responder rates were 3%, 57% and 65%, respectively. Study CIMPACT also met its primary end-point, to demonstrate superiority vs. placebo with respect to PASI 75 response at week 12 (61% for CZP 200 mg; 67% for CZP 400 mg and 5% for placebo). Both CZP doses were superior to placebo, with a difference of approximately 5%-10% in favour of the 400 mg arm. In CIMPACT, superiority vs. the active comparator etanercept could be concluded for PASI75 at Week 12 for the 400 mg CZP dose and non-inferiority for the 200 mg dose.

For the maintenance period, PASI75 and PGA response rates at Week 48 overall generally showed maintained or increased response rates compared with Week 16 in the CIMPASI studies, even if the pattern differed to some extent between doses and studies. The 400 mg Q2W dose tended to show higher response than 200 mg QW both at Week 16 and 48.

Study CIMPACT showed that in the group that received CZP 400 mg Q2W in both the Initial and Maintenance Treatment Periods, 98% continued to be PASI75 responders at Week 48. Also for the PGA, the blinded maintenance treatment group treated with CZP 400 mg Q2W through both the Initial and Maintenance Treatment Periods achieved the best response at Week 48, with a PGA responder rate of 88%, which was a 6% improvement from Week 16. Thus, maintaining the 400 mg Q2W regimen seems to provide a sustained response, even if many patients can maintain an adequate response also on 200 mg Q2W.

In conclusion, CZP has demonstrated clearly statistically significant and clinically relevant effects vs. placebo and etanercept in all three phase 3 studies.

In relation to the optimal posology, there was some discussion with the applicant and the CHMP. The Applicant initially proposed a posology for plaque psoriasis considering two options with no clear recommendation when to use a higher regimen or a lower regimen:
The recommended dose of Cimzia for adult patients with plaque psoriasis is 400 mg every 2 weeks. A dose of 400 mg at Weeks 0, 2 and 4 followed by 200 mg every 2 weeks may be considered (see section 5.1).

The CHMP did not agree with the initial proposal, considering also that based on the efficacy data, even if the difference in responder rates was not very large (5%-10%), there was virtually no dose difference observed in study CIMPASI-2 between the 400 mg and the 200 mg regimen. When comparing the outcome of the two dosage regimens used in the PSO population with the same two dosage regimens also used in the RA population, there were slightly more SAEs and AEs leading to withdrawal in the CZP 400mg Q2W group compared with the CZP 200mg Q2W group; there was no particular driver at SOC level for these differences. However, the dose proposed in psoriasis is higher compared with the other indications for Cimzia and the incidence of some adverse events was higher for the 400 mg dose compared with the 200 mg dose in some of the safety pool analyses.

Therefore the CHMP recommended that the 200mg regimen dose should be considered as the preferred maintenance dose with an option to increase to 400mg in case of insufficient response. The agreed posology for moderate to severe plaque psoriasis is presented below:

Loading dose : The recommended starting dose of Cimzia for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4.

Maintenance dose : After the starting dose, the maintenance dose of Cimzia for adult patients with plaque psoriasis is 200 mg every 2 weeks. A dose of 400 mg every 2 weeks can be considered in patients with insufficient response (see section 5.1).

One issue was raised on the wording of the indication, concerning the inclusion of "phototherapy", which was questioned. The indication initially proposed for Cimzia was "treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy". This

wording differed from recently approved monoclonal antibodies, e.g. secukinumab, ixekizumab and brodalumab targeting IL-17A, as well as for the anti TNF alfa antibody adalimumab (Humira), since these products do not include the part concerning phototherapy. There are no supportive data to support the use of Cimzia in psoriasis patients that could be candidate for phototherapy. The initially proposed indication would have placed Cimzia at an earlier treatment step in the treatment of psoriasis, i.e. a psoriasis patient that is a candidate for phototherapy could start Cimzia instead. This was questioned and during the procedure the indication was revised to "Cimzia is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy", which was endorsed by the CHMP.

2.5. Clinical safety

Introduction

The clinical data supporting efficacy and safety of certolizumab pegol (CZP) are 2 completed Phase 2 studies (C87040 and C87044) and 3 Phase 3 studies (PS0005, PS0002, and PS0003; also referred to as CIMPASI-1, CIMPASI-2, and CIMPACT, respectively) that have been completed through Week 48 in adult subjects with moderate to severe chronic plaque PSO. The 96-week open-label treatment periods of the Phase 3 studies are ongoing.

The initial marketing approval in the EU was on 01 Oct 2009. Presently Cimzia is approved for the treatment of rheumatoid arthritis, axial spondyloarthritis and psoriatic arthritis. As of 06 Mar 2017 (the most recent Periodic Safety Update Report [PSUR]), an estimated 12,364 subjects have been cumulatively exposed to CZP in completed and ongoing clinical studies. Overall, 1112 subjects have been exposed to CZP in the PSO clinical development program.

The proposed primary dosing schedule for Cimzia of moderate to severe plaque psoriasis of 400mg Q2W is somewhat different and on a long-term basis higher compared to the dosage regimen of i.e. psoriasis arthritis for which a maintenance dose of Cimzia 200 mg Q2W is recommended following a loading dose of 400mg at Weeks 0, 2, and 4. However, it is also stated in the posology section that a dosing schedule similar to the psoriasis arthritis may be considered. Based on the above the mean level of exposure to CZP of the plaque psoriasis population being treated following approval could be expected to be higher compared to the arthritis population. This is further discussed in relation to patient exposure below.

Patient exposure

Overall, 1112 subjects have been exposed to CZP in the PSO clinical development program. The clinical cut dates for each ongoing study are were: CIMPASI-2: 16 Aug 2016, CIMPASI-1: 20 Oct 2016, CIMPACT: 05 Dec 2016 and an additional safety cut was performed for all 3 studies on 06 Mar 2017 and provides additional safety data including deaths, serious adverse events (SAEs), adverse events (AEs) of interest, and pregnancies.

The primary study pool designed to support the safety of CZP for the proposed indication and population was safety pool 1 (Pool S1). Subject exposure for Pool S1, which includes subjects participating in the initial treatment period of the phase 3, placebo-controlled studies CIMPASI-1, CIMPASI-2, and CIMPACT, and receiving study drug (CZP or placebo) during the 16-week initial treatment period, and presented by randomized treatment group is revealed below.

Table 5–2: Study medication duration of exposure and subject exposure at risk during the Initial Treatment Period (Pool S1)

Variable	Statistic	PBO N=157	CZP 200mg Q2W N=350	CZP 400mg Q2W N=342	All CZP N=692
Duration of exposure (days)	n	157	350	342	692
	Mean (SD)	107.8 (17.8)	110.0 (14.0)	110.7 (12.2)	110.4 (13.2)
	Median	112.0	112.0	112.0	112.0
	Min, max	14, 140	14, 141	14, 132	14, 141
Subject exposure years at risk		46.9	106.5	104.5	211.0

CZP=certolizumab pegol; Max=maximum; Min=minimum; PBO=placebo; Q2W=every 2 weeks; SD=standard deviation

Supportive to Pool S1, there are 3 additional study pools: Pool S2, Pool S3, and Pool S4. Pool S2 consists of subjects who received study drug (CZP or placebo) during the placebo-controlled Initial Treatment Period in Phase 2 study C87040 and in the 3 placebo-controlled Phase 3 studies in subjects with chronic plaque PSO (CIMPASI-1, CIMPASI-2, and CIMPACT). Pool S3 consists of subjects who received CZP during the Initial, Maintenance, or OLE Treatment Periods in the Phase 2/3 studies (C87040, C87044, CIMPASI-1, CIMPASI-2, and CIMPACT). Pool S4 consists of subjects who received study drug (CZP or placebo) during the Maintenance Treatment Period (Weeks 16 to 48) in the Phase 3 studies (CIMPASI-1, CIMPASI-2, and CIMPACT). Please see table below:

Table 5–1: Overview of safety pools

Pool name	Studies included in pool	Treatment groups included in pool	Treatment Periods included in pool	Purpose of pool
S1	CIMPASI-1, CIMPASI-2, CIMPACT	Subjects exposed to: CZP 400mg Q2W, CZP 200mg Q2W, PBO	Initial Treatment Period (Weeks 0 to 16)	Primary safety pool; Investigate subgroups; summarize safety of CZP vs PBO through Week 16 in all Phase 3 PBO-controlled studies
S2	CIMPASI-1, CIMPASI-2, CIMPACT, C87040	Subjects exposed to: CZP 400mg Q2W, CZP 200mg Q2W, PBO	Initial Treatment Period (Weeks 0 to 12 for C87040; Weeks 0 to 16 for all other studies)	Summarize safety of CZP vs PBO through Week 16 in all Phase 2/3 PBO-controlled studies
S3	CIMPASI-1, CIMPASI-2, CIMPACT, C87040, C87044	Subjects exposed to: CZP 400mg Q2W, CZP 200mg Q2W, CZP 400mg Q4W	Initial Treatment Period, Maintenance Treatment Period, OLE Treatment Period (Weeks 0 to 144)	Summarize safety of CZP through Week 144 in all Phase 2/3 PSO studies
S4	CIMPASI-1, CIMPASI-2, CIMPACT	Subjects exposed to: CZP 400mg Q2W, CZP 200mg Q2W, CZP 400mg Q4W, PBO	Maintenance Treatment Period (Weeks 16 to 48)	Summarize safety of CZP vs PBO during Weeks 16 to 48 in all Phase 3 studies

CZP=certolizumab pegol; OLE=open-label extension; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks

In the initial application, safety was summarized primarily based on the Initial Treatment Period (Weeks 0 to 16, Pool S1) and the Maintenance Treatment Period (Weeks 16 to 48, Pool S4). Approximately 15% to 20% of the subjects included in the Pool S3 Phase 3 CZP 200mg Q2W treatment

group received their first CZP 200mg Q2W dose at start of OLE (Week 48) but were not assessed for labs or AEs prior to the clinical cut dates, thereby inflating the number of subjects who were exposed to CZP 200mg Q2W with no corresponding safety data assessed while on this dose. The incidence of AEs and lab shifts and markedly abnormal rates will be underestimated for this group, resulting in a potential bias for the comparison to the Phase 3 CZP 400mg Q2W group. The same applies for approximately 2% to 3% of the subjects included in the Pool S3 Phase 3 CZP 400mg Q2W treatment group who received their first CZP 400mg Q2W at some point during the OLE Treatment Period and were not assessed for labs or AEs prior to the clinical cut dates, thereby slightly inflating the number of subjects who were exposed to CZP 400mg Q2W with no corresponding safety data assessed while on this dose. The incidence of AEs as well as lab shifts and markedly abnormal rates are slightly underestimated for the CZP 400mg Q2W group. Overall, given the higher number of subjects impacted, the bias favors the CZP 200mg Q2W dose over the CZP 400mg Q2W dose. For this reason, safety was summarized primarily based on the Initial Treatment Period (Weeks 0 to 16, Pool S1) and the Maintenance Treatment Period (Weeks 16 to 48, Pool S4).

The applicant submitted a 120-Day Safety Update (featuring a new cut of the PSO data; 30 Jun 2017), amending the above incidence figures.

Overall study medication exposure in Pool S4, which includes subjects participating in the Maintenance Treatment Period of the Phase 3, placebo-controlled studies CIMPASI-1, CIMPASI-2, and CIMPACT, is presented by assigned treatment at Week 16 below.

Table 5–3: Study medication duration of exposure and subject exposure at risk during the Maintenance Treatment Period (Pool S4)

Variable	Statistic	PBO N=82	CZP 200mg Q2W N=348	CZP 400mg Q2W N=540	All CZP N=888
Duration of exposure (days)	n	82	348	540	888
	Mean (SD)	172.0 (66.8)	211.2 (41.4)	204.8 (49.2)	207.3 (46.4)
	Median	222.0	224.0	224.0	224.0
	Min, max	27, 234	14, 253	14, 279	14, 279
Subject exposure years at risk		39.1	203.6	312.4	516.0

CZP=certolizumab pegol; Max=maximum; Min=minimum; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SD=standard deviation
Note: Subjects were included in the treatment group based on the dose they were assigned to receive at Week 16, including subjects who escaped to CZP 400mg Q2W at Week 16.
Note: Data collected during treatment with the CZP 400mg Q4W dose in CIMPACT were summarized under the CZP 200mg Q2W treatment group as they are the same cumulative monthly dose.

Overall CZP exposure in Pool S3, the long-term safety pool, is summarized for each dose received.

Table 5–4: Study medication duration of exposure and subject exposure at risk as of the clinical cut dates (Pool S3)

Variable	Statistic	Phase 3 CZP 200mg Q2W N=703	Phase 3 CZP 400mg Q2W N=677	Phase 3 All CZP N=995	Phase 2/3 All CZP N=1112
Duration of exposure (days)	n	703	677	995	1112
	Mean (SD)	211.0 (154.8)	253.7 (108.1)	321.7 (119.2)	301.7 (127.7)
	Median	173.0	266.0	350.0	343.0
	Min, max	4, 648	3, 604	13, 662	13, 662
Subject exposure years at risk		404.9	478.3	883.2	951.7

CZP=certolizumab pegol; Max=maximum; Min=minimum; Q2W=every 2 weeks; Q4W=every 4 weeks; SD=standard deviation

Note: The clinical cut dates for each ongoing study are as follows: CIMPASI-2: 16 Aug 2016, CIMPASI-1: 20 Oct 2016, CIMPACT: 05 Dec 2016.

Note: Subjects who received both CZP 200mg Q2W and CZP 400mg Q2W are included in the population count for both treatment groups.

Note: Data collected during treatment with the CZP 400mg Q4W dose in CIMPACT has been summarized under the Phase 3 CZP 200mg Q2W treatment group as they are the same cumulative monthly dose.

In addition to the above, a specially designed pool of 4 studies (placebo-controlled and OLE) in rheumatoid arthritis provides additional supporting safety data for the PSO dose regimens used in the Phase 3 program and, specifically, longer term safety data for the 400mg Q2W dose. This includes a total of 1504 subjects exposed to 400mg Q2W and representing 2648.1 pt-yrs. The incidence and pattern of AEs, SAEs, AEs leading to withdrawal, and AEs of special interest observed in this RA pool of the 2 placebo-controlled studies and their open-label extension periods are consistent with those expected for subjects with RA on anti-TNFα therapy.

There is considerable experience from the use of CZP in other indications. However, it should be taken into account that the dosage is higher in plaque psoriasis compared with other indications. Of the 1112 subjects exposed to CZP in the PSO clinical development program, 540 patients were receiving the CZP 400mg Q2W dose for weeks 16 to weeks 48 with a mean exposure of 205 Days. If including the initial 16 week period and the OLE treatment period (pool S 3), 677 patients had a mean exposure of 254 days. The applicant states that in safety pool S3 a number of subjects who were exposed to either CZP 200mg Q2W or CZP 400 mg Q2W had, due to study designs and cut off dates, no corresponding safety data assessed while on the respective dose, thereby introducing possible bias. This safety pool, including patients for a long-term follow up, has therefore not been used in the analysis of adverse events. Finally the applicant makes a reference to RA studies performed with the 400mg Q2W dose with exposure of 1504 subjects. From the presentation it is somewhat unclear how many individuals that were actually exposed to the higher dose for ≥ 1year in the psoriasis population and the RA population respectively. The MAH has clarified that only 52 of 389 patients representing the number of subjects with a total cumulative exposure with CZP in PSO of at least 12 months actually were exposed to the higher dose of 400 mg Q2W for at least 12 months. This may be considered a rather limited number. However, as per the new cut of the PSO data that was performed (30 Jun 2017) the number of subjects with a cumulative duration of exposure for at least 12 months to the CZP 400mg Q2W dose increased to 273 subjects. This is considered acceptable to support the safety. In addition, there is some experience of 12 months exposure to the higher maintenance dose in the RA population.

Baseline demographics and disease characteristics

This has been presented in detail in the Efficacy section of this AR. Overall, 28.6% of the included study population with moderate to severe plaque psoriasis was systemic treatment naïve, 70.2% were

naïve to prior biologic therapies, 59.6% had never used a systemic non-biologic therapy, 53.4% had not used chemo-phototherapy or phototherapy, and 86.4% had not used anti-TNF therapy.

Adverse events

An overview of adverse events in Pool S1 is presented below.

Table 5–5: Overall summary of TEAEs (Pool S1)

Category	PBO N=157 100 subject-yrs=0.47		CZP 200mg Q2W N=350 100 subject-yrs=1.07		CZP 400mg Q2W N=342 100 subject-yrs=1.05		All CZP N=692 100 subject-yrs=2.11	
	n (%)	#	n (%)	#	n (%)	#	n (%)	#
Any TEAE	97 (61.8)	214	197 (56.3)	426	217 (63.5)	571	414 (59.8)	997
Serious TEAEs	7 (4.5)	7	5 (1.4)	9	16 (4.7)	20	21 (3.0)	29
Subject discontinuations due to TEAEs	0	0	4 (1.1)	5	4 (1.2)	7	8 (1.2)	12
Drug-related TEAEs	20 (12.7)	28	45 (12.9)	60	54 (15.8)	90	99 (14.3)	150
Severe TEAEs	8 (5.1)	8	8 (2.3)	10	13 (3.8)	16	21 (3.0)	26
All deaths (AEs leading to death)	0	0	0	0	0	0	0	0
Deaths (TEAEs leading to death)	0	0	0	0	0	0	0	0

CZP=certolizumab pegol; PBO=placebo; Q2W=every 2 weeks; TEAE=treatment-emergent adverse event
Note: n=number of subjects who reported at least 1 TEAE in the category. #=number of individual occurrences of the TEAE in that category.

In Pool S1, the incidence of TEAEs was higher in the CZP 400mg Q2W group (63.5%) compared with the CZP 200mg Q2W group (56.3%); however, the incidence in the CZP 400mg Q2W group was similar to placebo (61.8%). A similar trend was noted for serious TEAEs with a slightly higher incidence in the CZP 400mg Q2W group (4.7%) compared with the CZP 200mg Q2W group (1.4%) but similar to placebo (4.5%). Most TEAEs were considered mild or moderate in intensity and not related to study drug. Few subjects in the CZP dose groups discontinued due to TEAEs. No deaths were reported in Pool S1.

In Pool S4, there was a shorter duration of exposure in the placebo group that was driven by the subjects in this group who relapsed during the blinded Maintenance Treatment Period of CIMPACT and subsequently escaped to the OLE Treatment Period. Because the majority of the placebo subjects in Pool S4 were exposed to active study medication for 16 weeks prior to entering the Maintenance Treatment Period, the discussion will focus on the comparisons between the 2 CZP dose groups.

Table 5–6: Overall summary of TEAEs (Pool S4)

Category	CZP 200mg Q2W N=348 100 subject-yrs=2.0		CZP 400mg Q2W N=540 100 subject-yrs=3.1		All CZP N=888 100 subject-yrs=5.2	
	n (%)	#	n (%)	#	n (%)	#
Any TEAE	230 (66.1)	602	352 (65.2)	919	582 (65.5)	1521
Serious TEAEs	18 (5.2)	21	25 (4.6)	30	43 (4.8)	51
Subject discontinuations due to TEAEs	9 (2.6)	12	20 (3.7)	23	29 (3.3)	35
Drug-related TEAEs	48 (13.8)	88	73 (13.5)	120	121 (13.6)	208
Severe TEAEs	12 (3.4)	13	22 (4.1)	29	34 (3.8)	42
All deaths (AEs leading to death)	0	0	1 (0.2)	1	1 (0.1)	1
Deaths (TEAEs leading to death)	0	0	1 (0.2)	1	1 (0.1)	1

CZP=certolizumab pegol; PBO=placebo; Q2W=every 2 weeks; TEAE=treatment-emergent adverse event
Note: n=number of subjects who reported at least 1 TEAE in the category. #=number of individual occurrences of the TEAE in that category.

When evaluating safety pool S1 it is agreed that few subjects in the CZP dose groups discontinued due to TEAEs. This occurred in a similar degree in both CZP groups. It is also noted that there was no discontinuation in the placebo group. Drug related TEAEs seemed to be slightly more common in the patients receiving the highest dose with figures of 12.7%, 12.9% and 15.8% of the placebo, CZP 200 mg Q2W and CZP 400mg Q2W respectively. There was no difference of drug related TEAEs between CZP groups and only marginally higher percentage of severe TEAEs for 400 mg Q2W when evaluating pool S4.

Below is a summary of TEAEs in SOCs and PTs with an incidence greater than 5 % in Safety pool S1 and safety pool S4 respectively. In Pool S1, the incidence of TEAEs in the Initial Treatment Period was generally similar across all treatment groups. In some SOCs (Infections and infestations, Investigations, Nervous system disorders and Skin and subcutaneous tissue disorders), there was a lower incidence in the CZP 200mg Q2W group compared with the CZP 400mg Q2W and placebo groups, in which the incidences were similar. A small trend toward a dose response was observed in the SOCs of General disorders and administration site conditions and Respiratory, thoracic and mediastinal disorders. The driver for the difference in General disorders and administration site conditions was the injection site reactions high level term (HLT). For Respiratory, thoracic and mediastinal disorders, there was no particular driver for these differences. When adjusted for exposure, a similar trend across dose groups was generally noted. The most commonly reported TEAEs (by PT) in the CZP 400mg Q2W and CZP 200mg Q2W groups were nasopharyngitis (12.6% and 12.0%, respectively) and upper respiratory tract infection (6.7% and 4.9%, respectively). The incidence of nasopharyngitis in the placebo group (12.1%) was similar to the incidence in the 2 CZP dose groups. The incidence of upper respiratory tract infection in the placebo group (7.0%) was similar to the CZP 400mg Q2W group (6.7%) and slightly higher than in the CZP 200mg Q2W group (4.9%).

In Pool S4, the exposure-adjusted IRs in the 2 CZP dose groups were generally comparable, suggesting that the risks after long-term exposure under both CZP dose regimens are similar.

Table 5–7: Summary of TEAEs in SOCs and PTs with an incidence greater than 5% in any group (Pool S1)

System organ class Preferred term	PBO N=157 100 subject-yrs=0.47			CZP 200mg Q2W N=350 100 subject-yrs=1.07			CZP 400mg Q2W N=342 100 subject-yrs=1.05			All CZP N=692 100 subject-yrs=2.11		
	n (%)	#	IR	n (%)	#	IR	n (%)	#	IR	n (%)	#	IR
Any TEAE	97 (61.8)	214	342.58	197 (56.3)	426	292.12	217 (63.5)	571	348.30	414 (59.8)	997	319.10
Gastrointestinal disorders	12 (7.6)	18	26.95	28 (8.0)	36	27.55	33 (9.6)	47	33.39	61 (8.8)	83	30.43
General disorders and administration site conditions	9 (5.7)	10	19.87	21 (6.0)	28	20.66	30 (8.8)	41	30.64	51 (7.4)	69	25.56
Infections and infestations	53 (33.8)	63	136.19	108 (30.9)	140	121.61	124 (36.3)	164	146.59	232 (33.5)	304	133.80
Nasopharyngitis	19 (12.1)	21	43.10	42 (12.0)	47	42.20	43 (12.6)	50	44.08	85 (12.3)	97	43.13
Upper respiratory tract infection	11 (7.0)	12	24.26	17 (4.9)	17	16.40	23 (6.7)	26	22.91	40 (5.8)	43	19.60
Injury, poisoning, and procedural complications	7 (4.5)	8	15.35	18 (5.1)	20	17.38	19 (5.6)	25	18.83	37 (5.3)	45	18.10
Investigations	11 (7.0)	14	24.05	22 (6.3)	40	21.16	30 (8.8)	43	29.70	52 (7.5)	83	25.37
Musculoskeletal and connective tissue disorders	17 (10.8)	21	38.47	24 (6.9)	30	23.36	27 (7.9)	31	26.63	51 (7.4)	61	24.99
Nervous system disorders	13 (8.3)	16	29.01	18 (5.1)	21	17.56	32 (9.4)	52	32.29	50 (7.2)	73	24.80
Respiratory, thoracic, and mediastinal disorders	5 (3.2)	5	10.87	13 (3.7)	16	12.44	26 (7.6)	31	25.68	39 (5.6)	47	18.96
Skin and subcutaneous tissue disorders	22 (14.0)	25	52.42	34 (9.7)	39	33.83	43 (12.6)	55	44.77	77 (11.1)	94	39.18
Pruritus	9 (5.7)	10	20.19	5 (1.4)	5	4.75	12 (3.5)	13	11.77	17 (2.5)	18	8.20

CZP=certolizumab pegol; incl=including; IR=incidence rate; PBO=placebo; PT=preferred term; Q2W=every 2 weeks; SOC=system organ class; subject-yrs=subject-years; TEAE=treatment-emergent adverse event
Note: n=number of subjects who reported at least 1 TEAE in the SOC/PT. #=number of individual occurrences of the TEAE.
Note: IR=incidence of new cases per 100 subject-yrs.

Table 5–8: Summary of TEAEs in SOCs and PTs with an incidence greater than 5% in any group (Pool S4)

System organ class Preferred term	CZP 200mg Q2W N=348 100 subject-yrs=2.0			CZP 400mg Q2W N=540 100 subject-yrs=3.1			All CZP N=888 100 subject-yrs=5.2		
	n (%)	#	IR	n (%)	#	IR	n (%)	#	IR
Any TEAE	230 (66.1)	602	198.33	352 (65.2)	919	198.26	582 (65.5)	1521	198.29
Gastrointestinal disorders	27 (7.8)	35	13.89	45 (8.3)	62	15.09	72 (8.1)	97	14.62
General disorders and administration site conditions	16 (4.6)	17	8.06	37 (6.9)	45	12.33	53 (6.0)	62	10.63
Infections and infestations	138 (39.7)	224	89.53	203 (37.6)	314	84.02	341 (38.4)	538	86.17
Nasopharyngitis	49 (14.1)	62	26.48	82 (15.2)	101	29.15	131 (14.8)	163	28.09
Upper respiratory tract infection	25 (7.2)	28	12.86	36 (6.7)	45	11.92	61 (6.9)	73	12.29
Injury, poisoning and procedural complications	30 (8.6)	42	15.48	41 (7.6)	56	13.70	71 (8.0)	98	14.40
Investigations	26 (7.5)	45	13.12	45 (8.3)	75	14.95	71 (8.0)	120	14.22
Musculoskeletal and connective tissue disorders	46 (13.2)	58	24.36	58 (10.7)	74	19.94	104 (11.7)	132	21.68
Nervous system disorders	22 (6.3)	24	11.18	41 (7.6)	55	13.70	63 (7.1)	79	12.70
Respiratory, thoracic and mediastinal disorders	19 (5.5)	25	9.62	34 (6.3)	36	11.27	53 (6.0)	61	10.62
Skin and subcutaneous tissue disorders	31 (8.9)	38	15.87	50 (9.3)	61	16.76	81 (9.1)	99	16.41

CZP=certolizumab pegol; IR=incidence rate; PBO=placebo; PT=preferred term; Q2W=every 2 weeks; SOC=system organ class; subject-yrs=subject-years; TEAE=treatment-emergent adverse event
Note: n=number of subjects who reported at least 1 TEAE in the SOC/PT. #=number of individual occurrences of the TEAE.
Note: IR=incidence of new cases per 100 subject-yrs.

With respect to TEAEs there seem to be no new or unexpected findings of the overall observed in the psoriasis studies. From the presentation of safety pool S1 the most frequently reported SOC was Infections and infestations with 30.9% in the 200 mg Q2W group and 36.3 % in the 400 mg Q2W respectively with PTs nasopharyngitis and upper respiratory tract infections most commonly reported, followed by SOC Skin and subcutaneous tissues and SOC Musculoskeletal and connective tissue

disorders. The percentages of subjects reporting treatment emergent adverse events (TEAEs) were higher in the CZP 400mg Q2W group (63.5%) compared with the CZP 200mg Q2W group (56.3%) of pool S1; however, the incidence in the CZP 400mg Q2W group was similar to placebo (61.8%). As noted by the applicant a small trend toward a dose response was observed in the SOCs of General disorders and administration site conditions and Respiratory, thoracic and mediastinal disorders. The driver for the difference in General disorders and administration site conditions was the injection site reactions high level term (HLT). There is in addition a difference in the frequency of reports from SOC Nervous system (5.1% vs 9.4% for the CZP 200 mg Q2W vs the CZP 400 mg Q2W dose; 8.3% for placebo). It is agreed that from the presentation of safety data in Pool S4, these differences have decreased and the exposure-adjusted IRs in the 2 CZP dose groups were generally comparable though the SOC General disorders and administration site conditions with injection site reactions remain higher in the 400 mg Q2W group. However, the CHMP believes that there is still a possibility that a population exposed to a higher maintenance dose will be at higher risk of developing adverse drug reactions. This is further addressed below in the section on serious infections and selected adverse events of interest.

It is agreed that the incidence rate of the total number of TEAEs after an additional 32 weeks of exposure does not seem to increase. As for the risk of serious infections, this appears to be higher at the CZP 400mg Q2W dose during the first 16 weeks of treatment with a trend to be slightly higher also after longer exposure duration. But, it is difficult to draw firm conclusions given the low number of events overall. It is agreed that there seems to be no pattern in the type of infection observed between the 2 CZP dose regimens. The 120-Day Safety Update through a cut date of 30 Jun 2017 of Pool S3 (Initial, Maintenance and OLE) gives support to no difference in risk between the 2 CZP dose regimens regarding hepatobiliary disorders. Regarding malignancies, the number is too small to conclude that there is an increased risk for CZP 400mg Q2W.

When comparing the outcome of the two dosage regimens in the RA population there were slightly more SAEs and AEs leading to withdrawal in the CZP 400mg Q2W group compared with the CZP 200mg Q2W group; there was no particular driver at SOC level for these differences. Otherwise, in RA, there seemed to be consistency with what has been observed in the PSO safety pools.

In conclusion, based on the updated submitted data of safety and the fact that some of the events are too sparse to evaluate, there is no firm evidence that the safety profile of long term dosing with CZP 400mg Q2W significantly differ from CZP 200mg Q2W.

Serious adverse event/deaths/other significant events

Two treatment-emergent deaths occurred in subjects receiving CZP 400mg Q2W (1 subject during the Maintenance Treatment Period and 1 subject during the OLE Treatment Period); both were due to motor vehicle accidents. One additional death (exacerbation of chronic obstructive pulmonary disease [COPD]) was reported in the safety cut period in the CZP 200mg Q2W group. All 3 fatal events were considered not related to study medication.

Below is a summary of SOCs and PTs in at least 2 subjects of (1) the safety pool S1 and (2) the safety pool S4.

Table 5–9: Summary of SAEs in SOCs and PTs in at least 2 subjects in any group (Pool S1)

System organ class Preferred term	PBO N=157 100 subject-yrs=0.47			CZP 200mg Q2W N=350 100 subject-yrs=1.07			CZP 400mg Q2W N=342 100 subject-yrs=1.05			All CZP N=692 100 subject-yrs=2.11		
	n (%)	#	IR	n (%)	#	IR	n (%)	#	IR	n (%)	#	IR
Any serious TEAE	7 (4.5)	7	15.40	5 (1.4)	9	4.73	16 (4.7)	20	15.61	21 (3.0)	29	10.08
Blood and lymphatic system disorders	0	0	--	1 (0.3)	1	0.94	1 (0.3)	1	0.96	2 (0.3)	2	0.95
Gastrointestinal disorders	1 (0.6)	1	2.14	1 (0.3)	1	0.94	1 (0.3)	1	0.96	2 (0.3)	2	0.95
General disorders and administration site conditions	0	0	--	1 (0.3)	1	0.94	1 (0.3)	1	0.96	2 (0.3)	2	0.95
Infections and infestations	0	0	--	0	0	--	2 (0.6)	3	1.92	2 (0.3)	3	0.95
Injury, poisoning and procedural complications	1 (0.6)	1	2.13	1 (0.3)	1	0.94	3 (0.9)	3	2.88	4 (0.6)	4	1.90
Investigations	1 (0.6)	1	2.14	1 (0.3)	1	0.94	1 (0.3)	1	0.96	2 (0.3)	2	0.95
Musculoskeletal and connective tissue disorders	1 (0.6)	1	2.15	1 (0.3)	1	0.94	2 (0.6)	2	1.92	3 (0.4)	3	1.43
Osteoarthritis	0	0	--	0	0	--	2 (0.6)	2	1.92	2 (0.3)	2	0.95
Psychiatric disorders	0	0	--	2 (0.6)	2	1.88	1 (0.3)	1	0.96	3 (0.4)	3	1.42
Reproductive system and breast disorders	2 (1.3)	2	4.30	0	0	--	1 (0.3)	2	0.96	1 (0.1)	2	0.47

CZP=certolizumab pegol; incl=including; IR=incidence rate; PBO=placebo; PT=preferred term; Q2W=every 2 weeks; SAE=serious adverse event; SOC=system organ class; subject-yrs=subject-years; TEAE=treatment-emergent adverse event
Note: n=number of subjects who reported at least 1 serious TEAE in the category. #=number of individual occurrences.
Note: IR=incidence of new cases per 100 subject-yrs.

Table 5–10: Summary of SAEs in SOCs and PTs in at least 2 subjects in any group, during the Maintenance Treatment Period (Pool S4)

System organ class Preferred term	CZP 200mg Q2W N=348 100 subject-yrs=2.0			CZP 400mg Q2W N=540 100 subject-yrs=3.1			All CZP N=888 100 subject-yrs=5.2		
	n (%)	#	IR	n (%)	#	IR	n (%)	#	IR
Any serious TEAE	18 (5.2)	21	9.07	25 (4.6)	30	8.15	43 (4.8)	51	8.51
Cardiac disorders	0	0	--	2 (0.4)	2	0.64	2 (0.2)	2	0.39
Gastrointestinal disorders	1 (0.3)	1	0.49	1 (0.2)	1	0.32	2 (0.2)	2	0.39
Hepatobiliary disorders	2 (0.6)	2	0.99	1 (0.2)	1	0.32	3 (0.3)	3	0.58
Infections and infestations	3 (0.9)	3	1.48	6 (1.1)	7	1.93	9 (1.0)	10	1.75
Erysipelas	0	0	--	2 (0.4)	2	0.64	2 (0.2)	2	0.39
Injury, poisoning and procedural complications	3 (0.9)	5	1.48	6 (1.1)	8	1.93	9 (1.0)	13	1.75
Rib fracture	1 (0.3)	1	0.49	1 (0.2)	1	0.32	2 (0.2)	2	0.39
Musculoskeletal and connective tissue disorders	5 (1.4)	5	2.47	1 (0.2)	1	0.32	6 (0.7)	6	1.17
Psoriatic arthropathy	2 (0.6)	2	0.98	0	0	--	2 (0.2)	2	0.39
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	--	3 (0.6)	3	0.96	3 (0.3)	3	0.58
Nervous system disorders	2 (0.6)	2	0.99	2 (0.4)	2	0.64	4 (0.5)	4	0.78
Migraine	1 (0.3)	1	0.49	1 (0.2)	1	0.32	2 (0.2)	2	0.39
Skin and subcutaneous tissue disorders	0	0	--	2 (0.4)	2	0.64	2 (0.2)	2	0.39

CZP=certolizumab pegol; IR=incidence rate; PBO=placebo; PT=preferred term; Q2W=every 2 weeks; SAE=serious adverse event; SOC=system organ class; subject-yrs=subject-years; TEAE=treatment-emergent adverse event
Note: n=number of subjects who reported at least 1 serious TEAE in the category. #=number of individual occurrences.
Note: IR=incidence of new cases per 100 subject-yrs.

The most frequent SAEs reported in pool S4 were within SOCs Infections and Infestations and Injury, poisoning and procedural complications. When analysing all placebo-controlled PSO studies (pool S2) The incidence of SAEs was slightly lower in the CZP 200mg Q2W group compared with the placebo group (1.7% and 3.7%, respectively), and slightly higher in the CZP 400mg Q2W group (5.3%).When the incidence of SAEs was adjusted for duration of exposure, the IR was 11.98/100 subject-yrs in the

All CZP group (18.28/100 subject-yrs in the CZP 400mg Q2W group and 5.89/100 subject-yrs in the CZP 200mg Q2W group) and 13.97/100 subject-yrs in the placebo group.

Selected adverse events of interest

Serious infections, including opportunistic infections

In Pool S3, the incidence of SAEs of infections was low: 8 subjects (1.2%; IR 1.68/100 subject-yrs) in the Phase 3 CZP 400mg Q2W group and 4 subjects (0.6%; IR 0.99/100 subject-yrs) in the Phase 3 CZP 200mg Q2W group. In addition, 3 subjects reported serious infections in the Phase 2 studies. Two cases of tuberculosis (TB) were reported in the CZP 400mg Q2W group (1 each in Phase 2 and Phase 3); no other opportunistic infections were identified. In the pooled analyses, the IRs for serious infections including TB are in line with the IRs reported in the PSO population of 1.45 to 1.7/100 subject-yrs.

Certolizumab affects the immune system and it is well known that it causes an overall increased infection risk, similar to other anti-TNFs. It is noted that no (0 %) serious infections were reported for the lower dose 200 mg Q2W group during the first 16 week treatment period (pool S1) compared to two subjects (0.6%) with three individual occurrences of serious infections of the 400 mg Q2W group (IR=1.92 per 100 subject-yrs). During the maintenance period (pool S4) three subjects (0.9%) reported 3 occurrences of serious infections (IR=1.48 per 100 subject-yrs) in the 200 mg Q2W group compared to six subjects (1.1%) reporting 7 individual occurrences of serious infections (IR = 1.93 per 100 subject-yrs) in the 400 mg Q2W group. Infections are important adverse reactions of certolizumab pegol and most commonly lead to discontinuation of study medication during the performed studies (SOC of Infections and infestations). Although reported serious infections are only marginally increased in the group receiving the highest dose above, there is a possibility that a population exposed to a higher dose will be at higher risk of developing serious infections. Please refer to the discussion of TEAEs and SAEs above.

Malignancies

Anti-TNFα therapy has been associated with an increased risk of malignancies. In Pool S3, a total of 8 malignancies (including 3 non-melanoma skin cancers) were reported in 6 CZP-treated subjects (4 malignancies were reported in each treatment group). Two subjects reported 2 malignancies each; one on each dose. One event of laryngeal cancer was reported during the safety cut period. Non-skin malignancies were reported by 4 subjects: 1 subject with breast cancer, 1 subject with anaplastic oligodendroglioma and glioblastoma, 1 subject with neoplasm malignant (indicated as Hodgkin's lymphoma post-safety cut), and 1 subject with prostate cancer.

Malignant skin neoplasms were reported by 3 subjects: 2 subjects with basal cell carcinomas and 1 subject with keratoacanthoma (reported in the same subject as breast cancer). The exposure-adjusted IR for the Phase 3 All CZP subset of Pool S3 was 0.68/100 subject-yrs for any malignancy and 0.45/100 subject-yrs when excluding the nonmelanomic skin cancers HLT. The IR when excluding nonmelanoma skin cancers is similar to the IR of 0.6/100 pt-yrs reported with another anti-TNF in patients with PSO (Burmester and colleagues, 2013).

It is agreed that there are no significant findings concerning malignancies in general. However, studies with immunomodulatory agents have shown an increased risk for NMSC in patients with long standing psoriasis disease and a history of several previous therapies for the treatment of psoriasis and there is a possible association between NMSC risk and immunomodulatory therapy in psoriasis patients.

Congestive heart failure and MACE

Approximately 5% to 7% and 28% to 34% of subjects in Pool S1 had a history of cardiac disorders and vascular disorders, respectively. Overall, the incidence of congestive heart failure (CHF) and major cardiovascular events (MACE) was low. No events of CHF and 1 event of acute coronary syndrome were reported during the Initial Treatment Period of the Phase 3 studies in the active treatment groups; no events were reported in the placebo group. In the Maintenance Treatment Period, CHF and cardiac failure was reported in 1 subject each in the CZP 400mg Q2W group and transient ischaemic attack was reported in 1 subject in the CZP 200mg Q2W group (ISS Listing 1.2.3). A cerebrovascular accident was reported in 1 subject in the CZP 200mg Q2W group in the OLE Treatment Period. In the All CZP group in Pool S2, the IR was 0.42/100 subject-yrs and 0.53/100 subject-yrs in the Phase 2/3 All CZP group in Pool S3). No new concerns were identified in the psoriasis population, compared with previous indications for certolizumab pegol.

Demyelinating-like disorders

Use of TNFα inhibitors has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease, including multiple sclerosis. Two cases of multiple sclerosis were reported in the Phase 3 studies (Pool S3); one in each CZP dose group. In the 1 case of primary progressive multiple sclerosis in a subject receiving CZP 400mg Q2W, the diagnosis was an incidental finding during a neurologic evaluation for back pain. Review of symptoms revealed a gait disturbance and recurrent falls over the 2-year period predating entry into the clinical study (no new symptoms or physical findings occurred during the study). No new concerns concerning demyelating disorders were identified in the psoriasis population, compared with previous indications for CZP.

Lupus and lupus-like illness

No lupus or lupus-like events were reported for any of the Phase 2/3 studies.

Serious skin reactions

No serious skin reactions were reported for any of the Phase 2/3 studies.

Injection site reactions

In Pool S1, the incidence of injection site reactions (HLT) was 3.5% in the CZP 400mg Q2W group 1.7% in the CZP 200mg Q2W group; 0.6% of subjects in the placebo group reported an injection site reaction. One subject in CZP 400mg Q2W group reported injection site pain, and the majority of subjects had only 1 event of injection site reaction (18 subjects reporting 25 events). Even in the CZP 400mg Q2W group, where subjects received 2 active injections at each visit, the incidence and IR for injection site reactions was low (3.5%, IR 11.84/100 subject-yrs).

The table below presents incidences of different PTs of safety pool S3.

Table 5.3.11
Incidence of TEAEs by PT in the "Phase 3 All CZP" Group - Subjects Exposed to CZP
Analysis Set: Pool S3

MedDRA v18.1 Preferred Term	Phase 3 CZP 200mg Q2W N=703		Phase 3 CZP 400mg Q2W N=677		Phase 3 All CZP N=995		Phase 2/3 All CZP N=1112	
	n	(%)	n	(%)	n	(%)	n	(%)
Oropharyngeal pain	8	(1.1)	13	(1.9)	21	(2.1)	29	(2.6)
Pharyngitis	14	(2.0)	7	(1.0)	21	(2.1)	23	(2.1)
Fatigue	6	(0.9)	13	(1.9)	19	(1.9)	23	(2.1)
Rhinitis	7	(1.0)	11	(1.6)	18	(1.8)	22	(2.0)
Nausea	7	(1.0)	10	(1.5)	17	(1.7)	20	(1.8)
Oral herpes	10	(1.4)	7	(1.0)	17	(1.7)	20	(1.8)
Ligament sprain	9	(1.3)	7	(1.0)	16	(1.6)	17	(1.5)
Conjunctivitis	3	(0.4)	13	(1.9)	15	(1.5)	17	(1.5)
Contusion	4	(0.6)	11	(1.6)	15	(1.5)	16	(1.4)
Injection site reaction	5	(0.7)	10	(1.5)	15	(1.5)	16	(1.4)
Latent tuberculosis	9	(1.3)	6	(0.9)	15	(1.5)	15	(1.3)
Pyrexia	5	(0.7)	10	(1.5)	15	(1.5)	22	(2.0)
Vomiting	4	(0.6)	12	(1.8)	15	(1.5)	15	(1.3)
Folliculitis	7	(1.0)	7	(1.0)	14	(1.4)	15	(1.3)
Hepatic enzyme increased	8	(1.1)	6	(0.9)	14	(1.4)	14	(1.3)
Psoriatic arthropathy	7	(1.0)	7	(1.0)	14	(1.4)	15	(1.3)
Toothache	5	(0.7)	9	(1.3)	14	(1.4)	14	(1.3)
Abdominal pain	5	(0.7)	8	(1.2)	13	(1.3)	15	(1.3)
Influenza	4	(0.6)	8	(1.2)	12	(1.2)	16	(1.4)

CZP=certolizumab pegol, MedDRA=Medical Dictionary of Regulatory Activities, PT=Preferred Term, Q2W=every two weeks,
TEAE=Treatment-Emergent Adverse Event.
Note: n=number of subjects reporting at least one TEAE within Preferred Term.
Note: Table is ordered by descending frequency of PT in the "Phase 3 All CZP" group.
Note: Subjects who received both CZP 200mg Q2W and CZP 400mg Q2W are included in the population count for both treatment groups.

According to the table above the incidence of injection site reactions is doubled in the CZP 400 mg Q2W group compared to the CZP 200 mg Q2W group. Considering the fact that patients receive 2 active injections at each visit in the former group this is not unexpected.

Hypersensitivity reactions/anaphylactic reactions
There was one case of anaphylactoid reaction that occurred after the subject's first CZP injection (400mg). According to the submitted narratives this was a 44-year-old white male with a medical history of occasional migraines (2007-ongoing), psoriatic arthropathy (2005-ongoing), and per the CIOMS report no history of allergies or previous allergic reactions. The subject was first diagnosed with chronic plaque psoriasis in 1989, with approximate disease duration at the time of randomization of 25.8 years. The subject received first and only dose of the study drug on 04 Nov 2015. Maintenance Period assigned treatment (Weeks 16 to 46): The subject withdrew from the study after the first dose in Initial Period and thus did not enter Maintenance Period. The subject experienced an event of anaphylactoid reaction on 04 Nov 2015, during the Initial Period. The event occurred on the day of study drug initiation. The event was considered severe in intensity. Hypersensitivity reaction is an important identified risk of Cimzia already addressed in the SmPC and RMP. There is no need of amendments to the labelling based on the above case report.

Psoriasis and other subtypes of psoriasis
Psoriasis (PT): The IR in the Phase 3 All CZP group in Pool S3 was similar to IR in the All CZP group in Pool S1 (overall, 4.03/100 subject-yrs vs 4.77/100 subject-yrs, respectively; CZP 400mg Q2W: 4.90/100 subject-yrs vs 5.81/100 subject-yrs, respectively; CZP 200mg Q2W: 3.73/100 subjectyrs vs 3.76/100 subject-yrs, respectively)

No events of guttate, erythrodermic, or pustular psoriasis were reported during the Initial Treatment Period. In the Pool S3 Phase 3 studies, there were 3 events of guttate (1 subject in the CZP 200mg

Q2W group, 2 subjects in the CZP 400mg Q2W group), 1 event of erythrodermic (in the CZP 400mg Q2W group) and 1 event of pustular (in the CZP 400mg Q2W group) psoriasis.

The applicant has concluded that new or worsening psoriasis is a known effect of anti-TNFs in indications other than psoriasis. It is already included in the RMP of Cimzia as an important identified risk and in 4.8 of the SmPC-in line with the labelling for other anti-TNFs. There is no need of amendments to the labelling based on the outcome above.

Immunogenicity

In subjects who became anti-CZP antibody positive, the incidence of TEAEs was higher before the positive result (61.5%) compared with on or after the positive result (56.1%). In subjects who were always anti-CZP antibody negative, the percentage with TEAEs was 74.0%. The incidence of severe TEAEs (6.1%), drug-related TEAEs (13.5%), and serious TEAEs (2.7%) was lower in subjects on or after the positive result compared with before the positive result (8.8%, 22.3%, and 6.8%, respectively). The incidence of discontinuations was higher (4.7%) in subjects on or after the positive result compared with before the positive result (3.4%).

Hematopoietic cytopenia

One event of blood count abnormal was reported for 1 subject in the CZP 200mg Q2W group during the Maintenance Treatment Period. The event was considered not related to study medication.

Serious bleeding events

The incidence of serious bleeding events was low in CZP-treated subjects (0.5% [IR=0.57/100 subject-yrs]). In the Phase 3 studies (All CZP group) in Pool S3, 5 subjects experienced 7 serious bleeding events. One subject in the CZP 200mg Q2W group in the Phase 2 studies experienced a contusion and 1 event of rectal haemorrhage was reported during the safety cut period. None of the serious bleeding events were considered related to study medication.

Hepatic events (SMQ)

The incidence and exposure-adjusted IRs across the treatment groups in Phase 3 studies were similar (6.4% in the CZP 400mg Q2W group, and 4.6% in the CZP 200mg Q2W group). In Pool S3, the exposure-adjusted IRs were 9.30/100 subject-yrs for the Phase 3 CZP 400mg Q2W group and 8.17/100 subject-yrs for the Phase 3 CZP 200mg Q2W group. Incidence rates did not increase compared to Pool S1 (10.64/100 subject-yrs and 16.31/100 subject-yrs for the CZP 400mg Q2W and CZP 200mg Q2W groups, respectively). Although the incidence rates did not increase over time the exposure-adjusted IRs in Pool S3 were slightly higher for the phase 3 CZP 400mg Q2W group compared to the phase 3 CZP 200mg Q2W group. There is a possibility that a population exposed to a higher maintenance dose will be at higher risk of developing hepatobiliary reactions.

Laboratory findings

No notable emergent shift patterns, based on values at scheduled visits, were observed for any of the hematology or biochemistry parameters. The incidences of TEAEs (by PT) related to hematology and biochemistry values reported during the Initial Treatment Period (Pool S1) and Maintenance Treatment Period (Pool S4) were low, with no difference in incidences between the CZP 400mg Q2W and CZP 200mg Q2W groups.

Safety in special populations

Intrinsic (age, gender, and race) and extrinsic factors (region) did not appear to influence the safety of treatment with CZP. Table 2–3: Study drug duration by age group (by indication) of the updated RMP v.13 presents the age distribution of the included psoriasis patients in clinical trials of CZP:

Age group	Persons	Person time
Psoriasis[a]		
<40 years	380	325.3
40-<65	654	554.5
≥65	78	71.9
Total	1112	951.7

Seven pregnancies have occurred in 6 subjects (1 in CIMPASI-1, 2 in CIMPASI-2, 1 in CIMPACT, and 3 in C87040). Of the 3 pregnancies in C87040, 2 occurred in 1 subject (1 was treatment-emergent, and 1 was post-treatment). The outcomes of these pregnancies were: 1 healthy baby and 3 induced abortions (all in C87040); the remaining 3 pregnancy outcomes were pending at the data lock.

As requested in the PSUR 7 Assessment Report, a cumulative review of pregnancy cases has been provided in this PSUR and no safety signal was identified in this review. Use in pregnancy was assessed in depth within variation II-18 . In this variation a summary of cases reported up to Sept 2011 was included. In the PSUR 7 Assessment report, there are no new issues raised, beyond what was addressed in variation II-18 and monitoring within PSURs was recommended to continue. In addition, a cumulative review of all pregnancy cases was requested to be provided in the next PSUR.

Safety related to drug-drug interactions and other interactions

Drug interaction studies were described in detail in the original marketing application. Concomitant drug treatment with methotrexate, corticosteroids, nonsteroidal anti-inflammatory drugs, analgesics, 5-aminosalicylic acid analogues or anti-infectives had no effect on the PK of CZP. Drug-drug interactions have not been specifically addressed in the psoriasis clinical development program.

Discontinuation due to adverse events

In Pool S1, the incidence of any TEAE leading to discontinuation of study medication was low. The incidence was similar between the CZP 400mg Q2W and CZP 200mg Q2W groups (1.2% and 1.1%, respectively); no subject in the placebo group withdrew due to a TEAE. In Pool S4, the number of subjects who withdrew due to a TEAE was also low, and the incidence was similar between the CZP 400mg Q2W and the CZP 200mg Q2W groups (3.7% and 2.6%, respectively). In Pool S4, TEAEs leading to discontinuation of study medication were most commonly reported in the SOC of Infections and infestations (0.9% in the CZP 400mg Q2W group and 0.6% in the CZP 200mg Q2W group). No TEAE leading to discontinuation of study medication (by PT) was reported by 4 or more subjects in any treatment group.

Post marketing experience

An estimated 12,364 subjects have been cumulatively exposed to CZP in completed and ongoing clinical trials as of the PSUR data lock point of 06 Mar 2017. Based on the marketing experience across all indications, exposure to CZP has been estimated to reach 256,112 patient-years during the 3-year reporting interval of the PSUR and 420,451 patient-years cumulatively. During the reporting interval, 8 signals were evaluated.

A total of 7 signals were closed and refuted. These included mortality rate in RA, cervical cancer, long-term immunogenicity in RA and in CD patients, increased creatine phosphokinase (CPK) in axial spondyloarthritis patients, autoimmune hepatitis (2 additional addendums to this signal assessment

during the reporting period, both confirming the signal is refuted), and a nonclinical signal for PEG-induced vacuolation of the choroid plexus in monkeys. One signal (development of TB despite prior or concomitant prophylactic TB treatment) was closed and confirmed. In line with what has been previously documented for other TNF inhibitors, a review of the UCB Drug Safety database revealed that cases of TB have occurred in patients despite prior or concomitant TB prophylaxis. Four events (serious skin disorders, progressive multifocal leukoencephalopathy, deaths, and changes in blood glucose) were under close monitoring during the reporting interval. No new safety signals for CZP were identified from review of these 4 events. In addition, in the final Assessment Report of PSUR 7 (received on 09 Oct 2014), the EMA requested a cumulative analysis for dermatomyositis and glioblastoma in the next PSUR, as these safety issues have been assessed by the Pharmacovigilance Risk Assessment Committee for other anti-TNF agents. No new safety signals for CZP were identified from review of relevant safety data. No findings that have an impact on the favorable benefit-risk balance of CZP for each of the authorized indications have been identified from review of the information received during the 3-year reporting period. During the period covered by this report, the risk Hepatitis B reactivation was reclassified from important potential to an important identified risk. It has been added to "Hepatobiliary events including hepatitis, hepatic enzymes increased, and cholestasis."

There are several years of clinical experience from the use of certolizumab in different arthritis conditions. Class effects of anti-TNFs as wells as ADRs specifically reported for certolizumab are followed in the PSURs.

2.5.1. Discussion on clinical safety

Certolizumab pegol has been on the market for almost a decade. Its anti-TNF safety profile is considered well characterised. Special warning and precautions are in line with the class with an increased risk of serious infections including tuberculosis and opportunistic infections and hepatitis B virus reactivation; a potential role in the development of malignancies and lymphoproliferative disorders, contraindication in moderate to severe congestive heart failure, associated with haematological reactions, demyelinating disease, seizures and autoimmunity and immunosuppression. Following a review of the psoriasis safety data, the applicant has proposed no changes to the table of adverse reactions of section 4.8 of the approved SmPC.

The initially proposed posology in adult patients with plaque psoriasis was 400mg Q2W; a dose of 400mg at Weeks 0, 2, and 4 followed by 200mg Q2W may be considered. The dose 400mg Q2W is a higher dose compared with the approved posologies in rheumatoid arthritis and other arthritis conditions including psoriatic arthritis.

Regarding patient exposure, overall, 1112 subjects have been exposed to CZP in the PSO clinical development program. Four safety pools were used; one for subjects who received study drug (CZP or placebo) of the initial 16 weeks placebo controlled phase 3 studies (S1) , one for exposed subjects (CZP or placebo) during the placebo-controlled initial treatment period in Phase 2 study C87040 and in the 3 placebo-controlled Phase 3 studies in subjects with chronic plaque PSO (S2); one for CZP exposed subjects during the initial, maintenance, or OLE treatment periods in the phase 2/3 studies (S3) and finally one safety pool consisting of subjects who received study drug (CZP or placebo) during the maintenance treatment period (Weeks 16 to 48) in the Phase 3 studies(S4). Safety was summarized primarily based on the Pool S1 and the Pool S4 analysis sets. In addition, a specially designed pool of 4 studies (placebo-controlled and OLE) in rheumatoid arthritis provides additional supporting safety data for the PSO dose regimens used in the Phase 3 program and, specifically, longer term safety data for the 400mg Q2W dose. This includes a total of 1504 subjects exposed to 400mg Q2W and representing 2648.1 pt-yrs.

With respect to demographic characteristics less than a third of the included study population with moderate to severe plaque psoriasis was systemic treatment naïve but 86.4% had not used anti-TNF therapy previously.

The percentages of subjects reporting treatment emergent adverse events (TEAEs) were higher in the CZP 400mg Q2W group (63.5%) compared with the CZP 200mg Q2W group (56.3%) of pool S1; however, the incidence in the CZP 400mg Q2W group was similar to placebo (61.8%). A similar trend was noted for serious TEAEs with a slightly higher incidence in the CZP 400mg Q2W group (4.7%) compared with the CZP 200mg Q2W group (1.4%) but similar to placebo (4.5%). When analysing all placebo-controlled PSO studies (pool S2) the incidence of SAEs was higher in the CZP 400mg Q2W group (5.3%) compared to CZP 200mg Q2W group (1.7%) with the incidence of the placebo group in-between (3.7%), and drug related TEAEs seemed to be slightly more common in the patients receiving the highest dose with figures of 12.7%, 12.9% and 15.8% of the placebo, CZP 200 mg Q2W and CZP 400mg Q2W respectively of pool S1. There was no difference of drug related TEAEs between CZP groups and only marginally higher percentage of severe TEAEs for 400 mg Q2W when evaluating pool S4.

With respect to types of TEAEs, there seem to be no new or unexpected findings of the overall observed in the psoriasis studies. From the presentation of safety pool S1 the most frequently reported SOC was Infections and infestations with 30.9% in the 200 mg Q2W group and 36.3 % in the 400 mg Q2W group respectively. A small trend toward a dose response was observed in the SOCs of General disorders and administration site conditions and Respiratory, thoracic and mediastinal disorders. There is in addition a difference in the frequency of reports from SOC Nervous system 5.1% vs 9.4%. The driver for the difference in General disorders and administration site conditions was the injection site reactions high level term (HLT). The most frequently reported TEAEs (by PT) in the CZP 400mg Q2W and CZP 200mg Q2W groups were nasopharyngitis (12.6% and 12.0%, respectively) and upper respiratory tract infection (6.7% and 4.9%, respectively). It is agreed with the applicant that from the presentation of safety data in Pool S4, these differences have decreased and the exposure-adjusted IRs in the 2 CZP dose groups were generally comparable though the SOC General disorders and administration site conditions with injection site reactions remain higher in the 400 mg Q2W group. Still, the trend towards a slightly higher incidence of TEAES and SAEs in the 400 mg Q2W group compared to the 200 mg Q2W group in the analyses of the safety pools 1 and 2 is noted, and there is a possibility that a population exposed to a higher dose will be at higher risk of developing adverse drug reactions.

The incidence of any TEAE leading to discontinuation of study medication was low and similar between the CZP 400mg Q2W and CZP 200mg Q2W groups. TEAEs leading to discontinuation of study medication were most commonly reported in the SOC of Infections and infestations (pool S4).

Three deaths were reported; two due to motor vehicle accidents and one due to exacerbation of chronic obstructive pulmonary disease. All 3 fatal events were considered not related to study medication. The majority of SAEs reported during the maintenance treatment period (Weeks 16 to 48) in the Phase 3 studies pool S4 were within SOCs Infections and Infestations and Injury, poisoning and procedural complications.

A number of Adverse Events of Special Interest (AESI) were specifically addressed such as serious infections, including opportunistic infections, malignancies, congestive heart failure and MACE, demyelinating-like disorders, lupus and lupus-like illness, serious skin reactions, injection site reactions, hypersensitivity reactions, psoriasis and other subtypes of psoriasis, immunogenicity, hematopoietic cytopenia, serious bleeding events and hepatobiliary events.

Cimzia affects the immune system and it is well known that it causes an overall increased infection risk similar to other anti-TNFs. It is noted that no (0 %) serious infections were reported for the lower

dose 200 mg Q2W group during the first 16 week treatment period (pool S1) compared to two subjects (0.6%) with three individual occurrences of serious infections of the 400 mg Q2W group (IR=1.92 per 100 subject-yrs). During the maintenance period (pool S4) three subjects (0.9%) reported 3 occurrences of serious infections (IR=1.48 per 100 subject-yrs) in the 200 mg Q2W group compared to six subjects (1.1%) reporting 7 individual occurrences of serious infections (IR = 1.93 per 100 subject-yrs) in the 400 mg Q2W group.

With respect to AESI other than infections there are no significant findings except that incidence rates of hepatobiliary events of the exposure-adjusted IRs in Pool S3 were slightly higher for the phase 3 CZP 400mg Q2W group compared to the phase 3 CZP 200mg Q2W group and in line with the discussion above of ADRs in general and Infection related ADRs there is a possibility that a population exposed to a higher dose will be at higher risk of developing hepatobiliary reactions.

Immunological events, allergic reactions and TEAEs related to hypersensitivity including one reported anaphylactoid reaction do not support any amendments to the SmPC.

Studies with immunomodulatory agents have shown an increased risk for NMSC in patients with long standing psoriasis disease and a history of several previous therapies for the treatment of psoriasis and there is a possible association between NMSC risk and immunomodulatory therapy in psoriasis patients. There is a possibility that a population exposed to a higher dose of CZP will be at higher risk of developing NMSC.

Laboratory findings did not reveal emergent shift pattern of biochemistry or hematologic parameters.

Intrinsic (age, gender, and race) and extrinsic factors (region) did not appear to influence the safety of treatment with CZP. Seven pregnancies occurred in 6 subjects. A cumulative review of all pregnancy cases was made in the PSUR 7 Assessment Report. A cumulative review of pregnancies is requested to be provided also in the next PSUR.

Drug-drug interactions have not been specifically evaluated in the PSO clinical development program.

2.5.2. Conclusions on clinical safety

In the Cimzia clinical program for psoriasis, 1112 subjects have been exposed to at least 1 dose of certolizumab up to the cut-off date 06 Mar 2017. The initially proposed dosing schedule for Cimzia was higher than previously approved dosing schedules of RA and other arthritis conditions, this was further discussed during the application and the maintenance dose finally recommended as being 200 mg Q2W unless insufficient response is achieved (please refer to previous discussion in clinical efficacy).

The safety profile of certolizumab in psoriasis does not appear different from what that previously observed with certolizumab in other indications and is in line with other anti-TNFs. Serious AEs were reported in 3 % of all subjects receiving CZP during the initial placebo controlled trial period of 16 weeks and by 4.8 % of all subjects receiving CZP during the 16-48 weeks trial maintenance period. Three deaths were reported, none of these were considered related to the study drug by the investigators. The rate and severity of adverse reactions do not give any major cause of concern in comparison with the experience of other indications but drug related TEAEs and SAEs in general seemed to be slightly more common in the patients receiving the highest dose in some of the analyses of the safety pools. This trend could not be excluded for serious infections, non-melanoma skin cancer and for hepatobiliary events in some of the separate analyses as well. In conclusion, there is a possibility that a psoriasis population exposed to a higher dose may be at higher risk of developing adverse drug reactions. ADRs within the Infections SOC with nasopharyngitis and upper respiratory tract infections most commonly reported are followed by ADRs reported within the SOC Skin and subcutaneous tissues and SOC Musculoskeletal and connective tissue disorders and the SOC of General

disorders and administration site conditions and Respiratory, thoracic and mediastinal disorders, mainly due to injection site reactions. For the other AESI, no new or unexpected findings were overall observed in the psoriasis studies.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 13.2 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 13.2 with the following content:

Safety concerns

Summary of the safety concerns	
Important identified risks	• Infections including TB and serious opportunistic infections
	• Moderate to severe congestive heart failure (NYHA class III/IV)
	• Hypersensitivity reactions
	• Malignancies including lymphoma, leukemia, Merkel cell carcinoma, Hepatosplenic T-cell lymphoma, and melanoma
	• Demyelinating-like disorders
	• Aplastic anemia, neutropenia, thrombocytopenia, pancytopenia, and leukopenia
	• Lupus and lupus-like illness
	• Immunogenicity including sarcoidosis
	• New onset or worsening of psoriasis (including palmoplantar pustular psoriasis) and related conditions
	• Hepatobiliary events including hepatitis, hepatitis B virus reactivation, hepatic enzymes increased, and cholestasis
Important potential risks	• Cardiac ischemia and cerebrovascular ischemia

Summary of the safety concerns	
	• Serious bleeding events
Missing information	• Pregnancy
	• Children and adolescents
	• Live vaccines
	• Use in patients with hepatitis C/HIV+
	• Treatment withdrawal and re-introduction in patients with early axial spondyloarthritis
	• Long-term use in plaque psoriasis

Pharmacovigilance plan

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
ARTIS (RA0021) (Registry, category 3)	To provide short- and long-term safety data from the use of CZP in Sweden for RA patients. The aim is to provide data on major comorbidities by means of objective registry-based data on disease defined by being "serious" as understood by regulators.	In general, registries capture events related to important identified and potential risks.	Ongoing	Annual interim reports are submitted to EMA as a stand alone submission under reference MEA005 (postauthorization measure). Final report to be provided by 31 Jul 2018
RABBIT (RA0020) (Registry, category 3)	Description of long term efficacy of a treatment with biologics, of time spent under therapy, of reasons for a change in therapy as well as description of disease course under therapy and where applicable after end of therapy Examination of long-term outcomes of biologic therapy compared to conventional DMARD therapy Determination of direct	In general, registries capture events related to important identified and potential risks.	Ongoing	Annual interim reports are submitted to EMA as a stand alone submission under reference MEA005 (postauthorization measure). Final report to be provided by 31 Jul 2018

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	and indirect costs of biologic therapy compared to conventional DMARD therapy			
NDB (RA0005) (Registry, category 3)	The purpose of the study is to obtain safety and outcome data on RA patients receiving certolizumab pegol (Cimzia®) and other RA treatments. Please note that this purpose is broader than just the evaluation of certolizumab pegol	In general, registries capture events related to important identified and potential risks.	Ongoing	Annual interim reports are submitted to EMA as a stand alone submission under reference MEA005 (postauthorization measure). Final report to be provided by 31 Jul 2018
BSRBR (RA0022) (Registry, category 3)	The risk associated with certolizumab therapy for the following endpoints (events of special interest – ESI) will be evaluated: Aplastic anemia / pancytopenia /neutropenia Congestive heart failure Cerebrovascular accident Demyelination /optic neuritis Infusion/ immunologic reaction Lymphoproliferative malignancy Malignancy Myocardial infarction/Acute Coronary Syndrome Pregnancy Pulmonary embolism Serious infection Tuberculosis Death Hepatic dysfunction/failure	In general, registries capture events related to important identified and potential risks.	Ongoing	Annual interim reports are submitted to EMA as a stand alone submission under reference MEA005 (postauthorization measure). Final report to be provided by 31 May 2019

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	Lower Gastrointestinal Ulcer/bleed/perforation			
Pregnancy • Participation in a US-based pregnancy (OTIS [RA0023]) • Surveillance of registries (RABBIT [RA0020] and BSRBR [RA0022]) (Category 3)	To gather pregnancy data in a proactive and systematic way	Missing information Pregnancy	Ongoing	Data will be provided concomitantly with the PSURs
UP0038 Postapproval safety study for healthcare provider and patient surveys (Category 3)	To assess the effectiveness of the educational materials	A Prescriber Guide is distributed for the risks related to the following: infections, congestive heart failure, and hypersensitivity. A Patient Alert Card is distributed for the risks related to the following: infections, congestive heart failure, hypersensitivity, malignancies, hepatobiliary events, serious bleeding events, and live vaccines.	Ongoing	When available, full results will be presented in one of the planned RMP updates (see Part VII Annex 10)
AS005 Phase 3b Multicenter, open-label (Part a) followed by a randomized, double-blind, parallel-group, placebo-controlled study (Part b) to evaluate maintenance of remission in	Evaluate whether a subject in no or low disease activity will remain in no or low disease activity following withdrawal or dose reduction of CZP. The study will also collect information on efficacy and safety of re-treatment.	Missing information Treatment withdrawal and re-introduction in patients with early axial spondyloarthritis	Ongoing	Q3 2019

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
subjects with active axSpA receiving either CZP 200mg Q2W or 200mg Q4W as compared to placebo (Category 3)				
PS0002 Open label maintenance period (Category 3)	Assess the safety and efficacy of long-term use of CZP	Missing information Long-term use in plaque psoriasis	Ongoing	Q2 2019
PS0003 Open label maintenance period (Category 3)	Assess the safety and efficacy of long-term use of CZP	Missing information Long-term use in plaque psoriasis	Ongoing	Q3 2019
PS0005 Open label maintenance period (Category 3)	Assess the safety and efficacy of long-term use of CZP	Missing information Long-term use in plaque psoriasis	Ongoing	Q2 2019

Risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important identified risks		
Infections including TB and serious opportunistic infections	SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.3 (Contraindications) SmPC Section 4.6 (Fertility, Pregnancy and Lactation) SmPC Section 4.8 (Undesirable Effects)	Educational program (Prescriber Guide and Patient Alert Card)
Moderate to severe congestive heart failure (NYHA class III/IV)	SmPC Section 4.4 (Special warnings and precautions for use)	Educational program (Prescriber Guide and Patient Alert Card)

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	SmPC Section 4.3 (Contraindications) for CHF SmPC Section 4.8 (Undesirable effects)	
Hypersensitivity reactions	SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.3 (Contraindications)	Educational program (Prescriber Guide and Patient Alert Card)
Malignancies including lymphoma, leukemia, Merkel cell carcinoma, Hepatosplenic T-cell lymphoma, and melanoma	SmPC Section 4.8(Undesirable effects) SmPC Section 4.4 (Special warnings and precautions for use)	Educational program (Patient Alert Card)
Demyelinating-like disorders	SmPC Section 4.4 (Special warnings and precautions for use)	None
Aplastic anemia, neutropenia, thrombocytopenia, pancytopenia, and leukopenia	SmPC Section 4.8 (Undesirable effects) SmPC Section 4.4 (Special warnings and precautions for use)	None
Lupus and lupus-like illness	SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects)	None
Immunogenicity including sarcoidosis	SmPC Section 4.8 (Undesirable effects) SmPC Section 5.1 (Pharmacodynamic properties)	None
New onset or worsening of psoriasis (including palmoplantar pustular psoriasis) and related conditions	SmPC Section 4.8 (Undesirable effects)	None
Hepatobiliary events including hepatitis, hepatitis B virus reactivation, hepatic enzyme increased, and cholestasis	SmPC Section 4.2 (Posology) SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects)	Educational program (Patient Alert Card)
Important potential risks		
Cardiac ischemia and cerebrovascular ischemia	SmPC Section 4.8 (Undesirable effects)	None
Serious bleeding events	SmPC Section 4.4 (Special warnings and precautions for use)	Educational program (Patient Alert Card)

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Missing information		
Pregnancy	SmPC Section 4.6 (Fertility, pregnancy, and lactation) SmPC Section 4.8 (Undesirable effects)	None
Children and adolescents	SmPC Section 4.2 (Posology) SmPC Section 4.4 (Special warnings and precautions for use) regarding pediatric malignancy SmPC Section 4.6 (Fertility, pregnancy and lactation)	None
Live Vaccines	SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.6 (Fertility, pregnancy and lactation)	Educational program (Patient Alert Card)
Use in patients with hepatitis C/HIV+	SmPC Section 4.4 (Special warnings and precautions for use).	None
Treatment withdrawal and re-introduction in patients with early axial spondyloarthritis	SmPC Section 4.2: Posology and method of administration	None
Long-term use in plaque psoriasis	The safety profile of CZP in long-term use in plaque psoriasis is further evaluated in open label extension studies and through routine PhV processes.	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Psoriasis is a chronic, non-communicable, painful, immunologically-mediated, disfiguring and disabling inflammatory skin disease.

3.1.2. Available therapies and unmet medical need

Despite the availability of multiple therapeutic modalities, the treatment of chronic moderate to severe psoriasis remains challenging. Although various topical treatments (eg, steroids, tar, anthralin [dithranol], calcipotriene, and tazarotene) are commonly used to treat milder cases of psoriasis, they are generally not suitable for treating more severe forms of the disease. Moreover, topical steroids can be associated with adverse events (AEs) such as skin atrophy, striae formation, suppression of the hypothalamic pituitary adrenal axis, and tachyphylaxis. Phototherapy (narrowband or broadband ultraviolet B [UVB] or the combination of psoralen [a photosensitizing drug] plus ultraviolet A light [PUVA]) is often effective and generally well tolerated but inconvenient (2 to 3 treatments weekly) and sometimes unavailable due to the need for specialized equipment. Therefore, compliance and subsequently efficacy are rarely sustained over the long-term. Toxicities include sunburn, photo-aging, and increased risk of skin cancer, particularly with PUVA.

Conventional systemic therapies include MTX, acitretin, and cyclosporine. Although effective, each is associated with significant toxicities, particularly organ damage with long-term administration, and each agent has recommended limitations for long-term administration. Rotational therapy is employed to minimize these significant side effects, though no evidence exists that rotational strategies can lessen the risk of serious adverse events (SAE). The chronicity of psoriasis, the cumulative toxicities of these agents and the restrictions with their lifetime use often make these agents unsuitable as a long-term solution. Apremilast, an oral selective inhibitor of the enzyme phosphodiesterase 4, was recently approved for the treatment of psoriasis. Safety and tolerability concerns for apremilast include diarrhea, depression, weight decrease, and drug interactions.

A variety of biologic systemic therapies have been developed and approved for the treatment of psoriasis, including anti-tumor necrosis factor alpha (TNFα) agents (infliximab, adalimumab, etanercept), an IL-12/23 antagonist (ustekinumab), Il23 antagonist (guselkumab) and more recently, IL-17A inhibitors (secukinumab and ixekizumab).

3.1.3. Main clinical studies

Short-term efficacy
Three phase 3 studies (CIMPASI 1, CIMPASI 2 and CIMPACT) with adequate design and performed in a relevant psoriasis population were submitted to support an indication for Cimzia in moderate to severe plaque psoriasis. All three studies met their primary end-points; to demonstrate superiority vs. placebo with respect to PASI75 response and PGA Clear or almost clear (with at least 2-category improvement) response at Week 16 in the CIMPASI studies (co-primary end-points) and to demonstrate superiority vs. placebo for PASI75 response at Week 12 in study CIMPACT. Both CZP dose regimens studied (400 mg Q2W and 200 mg Q2W after three initial loading doses of 400 mg) were superior to placebo.

For the pooled CIMPASI studies, PASI75 response for the placebo, CZP 200 mg and CZP 400 mg groups at Week 16 were 10%, 77% and 82%, respectively. Corresponding PGA responder rates were 3%, 57% and 65%, respectively. In study CIMPASI-2 the response rates were higher than in CIMPASI-1 but there were virtually no dose differences in PASI75 and PGA response rates.

In study CIMPACT, PASI75 response at Week 12 was 61% for CZP 200 mg, 67% for CZP 400 mg and 5% for placebo. Corresponding PGA response rates at Week 12 (secondary end-point in this study), were 40% in the CZP 200 mg Q2W group, 50% in the CZP 400 mg Q2W group and 2% in the placebo group.

In study CIMPACT, the anti TNF alfa antibody etanercept (Enbrel®) was included as active comparator. Superiority vs. etanercept could be concluded for PASI75 at Week 12 for the higher 400 mg CZP dose (66.7% vs. 53.3%, p=0.0152) and non-inferiority for the 200 mg dose (61.3% vs. 53.3%; 8% difference, 95% CI: -2.9; 18.9). For PGA response at Week 12 in CIMPACT (secondary end-point), there was no difference in response for this variable for the 200 mg CZP dose vs. ETN (40% vs. 39%) while the 400 mg CZP dose showed a larger response (50%) than ETN.

For the secondary end-point PASI90 response at week 16, both CZP dose arms were statistically significantly superior to placebo in all three studies. For the pooled studies (pool E1), PASI90 was 45% for the 200 mg dose, 52% for the 400 mg dose and 1.6% for placebo.

The PASI100 responder rates at Week 16 in Pool E1 were 13% in the CZP 200 mg Q2W group and 15% in the CZP 400 mg Q2W group compared with 0.7% in the placebo group.

Change in DLQI (Dermatology Life Quality Index), a well-known and commonly used QoL scale in dermatology, was another secondary endpoint. Improvement in health related quality of life measured by the mean change from Baseline in DLQI was observed for CZP-treated subjects compared with placebo-treated subjects at Week 16 in all three studies.

Onset of effect started at about 4 weeks where a separation from placebo could be observed for both dose groups. It can be noted that due to the initial loading dose scheme for the 200 mg Q2W arm, both dose groups received the same treatment for the first weeks of the initial period.

Long-term efficacy (maintenance treatment)

In the CIMPASI studies, PASI75 and PGA response rates at Week 48 overall showed maintained or increased response rates compared with Week 16. The 400 mg Q2W dose tended to show higher response than 200 mg QW both at Week 16 and 48.

In study CIMPACT, in patients who were PASI75 responders at Week 16 for subjects initially randomized to CZP, >79% in each group that received CZP treatment during the Maintenance Treatment Period continued to be PASI75 responders at Week 48. In the group that received CZP 400 mg Q2W in both the Initial and Maintenance Treatment Periods, 98% continued to be PASI75 responders at Week 48. For subjects who stopped CZP and were re-randomized to placebo during the maintenance period, the PASI75 responder rate decreased from Week 16 to Week 48. For the groups initially treated with CZP 200 mg Q2W, the PASI75 responder rate was numerically greater at Week 48 in the treatment group receiving CZP 400mg Q4W compared with the treatment group continuing on CZP 200mg Q2W during the Maintenance Treatment Period (89% vs. 80%). A similar pattern was observed for the PGA Clear or almost clear response.

Rebound was assessed in studies CIMPACT and the Phase 2 study, C87040, with a definition in accordance with the CHMP Psoriasis Guideline. No patient in either study met the definition of having a rebound effect. Limited data from the phase 2 studies C87040/C87044 on response to retreatment after withdrawal of CZP among responders suggest that patients who responded to CZP may achieve similar PASI scores upon retreatment.

Nail involvement assessed via mNAPSI was an "other" endpoint for CIMPASI-1 and CIMPASI-2. Mean changes from Baseline at Week 48 in the mNAPSI score suggest that CZP treatment can improve psoriatic nail disease.

Sub-group analyses

Adequate sub-group analyses have been performed and the presented results did not show any major deviating results for any particular sub-group. Efficacy was observed both in subjects with or without a history of prior systemic treatment of psoriasis.

No formal dose ranging study with a wide range of dose levels was performed to support the posology of CZP in the indication plaque psoriasis however data are available in other indications. In the Phase 2 study C87040, two different dose levels were studied (CZP 200 mg Q2W and CZP 400 mg Q2W) and these two doses were also studied in phase 3, both for initial treatment and for maintenance treatment Concerning the choice of dose, the response rates were generally about 5-10% higher for the 400 mg Q2W vs. the 200 mg Q2W dose regimen for the primary end-points as well as for secondary end-points. In study CIMPASI-2 there were no or small differences between the two doses. In this study, the response rates were also generally higher compared with the CIMPASI-1 and CIMPACT studies, for unknown reasons. However, the difference was not large and CIMPASI-1 and CIMPACT on the other hand showed very similar results for Week 16 data. In conclusion, the CHMP decided to recommend the 200mg Q2W as maintenance treatment. The 400mg Q2W could be used in case of insufficient response.

Concerning immunogenicity, the lower CZP dose of 200 mg showed a higher incidence of ADAb positivity compared with the CZP 400 mg group. The mean responder rates were lower at Week 16 and Week 48 in ADAb positive subjects compared with ADAb negative subjects in both the CZP dose groups, although not all ADAb positive subjects had a reduction in their CZP response.

3.2. Favourable effects

3.3. Uncertainties and limitations about favourable effects

The information available on relapse and rebound is fairly limited. In CIMPACT, 47 patients were available for assessment of rebound and the data did not give cause for concern since no patient met the definition of rebound. In conclusion, no specific claims about efficacy upon retreatment in psoriasis are given in the SmPC.

At present, no efficacy data beyond 1 year is available, but long term open-label extension periods of the studies are ongoing.

In sub-group analyses, patients in the lower baseline body weight quintiles generally had somewhat higher PASI75 and PGA response rates compared with those in the higher weight quintiles. The differences were not dramatic, though. However, a body weight adjusted posology is not proposed for Cimzia in psoriasis and is not considered warranted.

Efficacy was observed both in subjects with or without a history of prior systemic treatment of psoriasis. The exclusion of patients who were primary failures to any prior biologic therapy leads to lack of information about the response to CZP in this group. Therefore, it was recommended to mention in section 5.1 of the SmPC that patients who were 'primary' non-responders on any prior biologic therapy (defined as no response within the first 12 weeks of treatment) were excluded since this may influence clinical decision-making, given that several alternative biologic treatment options are available.

3.4. Unfavourable effects

The safety profile of certolizumab pegol is overall as expected for a TNF inhibitor. The product has been on the market for almost a decade and is presently used for the treatment of rheumatoid

arthritis, psoriatic arthritis and axial spondyloarthritis. Special warnings and precautions are in line with the class with an increased risk of serious infections including tuberculosis and opportunistic infections and hepatitis B virus reactivation; a potential role in the development of malignancies and lymphoproliferative disorders, contraindication in moderate to severe congestive heart failure, associated with haematological reactions, demyelinating disease, seizures and autoimmunity and immunosuppression.

In the performed studies supporting this application of a new treatment indication of moderate to severe plaque psoriasis, the proposed posology in adult patients with plaque psoriasis of 400mg Q2W is higher compared with the approved in rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis.

Overall, 1112 subjects have been exposed to CZP in the PSO (psoriasis) clinical development program. Four safety pools were used; one for subjects who received study drug (CZP or placebo) of the initial 16 weeks placebo controlled phase 3 studies (S1) , one for exposed subjects (CZP or placebo) during the placebo-controlled initial treatment period in Phase 2 study C87040 and in the 3 placebo-controlled Phase 3 studies in subjects with chronic plaque PSO (S2); one for CZP exposed subjects during the initial, maintenance, or OLE treatment periods in the phase 2/3 studies (S3) and finally one safety pool consisting of subjects who received study drug (CZP or placebo) during the maintenance treatment period (Weeks 16 to 48) in the Phase 3 studies (S4). Safety was summarized primarily based on the Pool S1 and the Pool S4 analysis sets. In addition to this, a specially designed pool of 4 studies (placebo-controlled and OLE) in rheumatoid arthritis provides additional supporting safety data for the PSO dose regimens used in the Phase 3 program and, specifically, longer term safety data for the 400mg Q2W dose.

Serious AEs were reported in 3 % of all subjects receiving CZP during the initial placebo controlled trial period of 16 weeks and by 4.8 % of all subjects receiving CZP during the16-48 weeks trial maintenance period. Three deaths were reported, none of these were considered related to the study drug by the investigators. ADRs within the Infections SOC with nasopharyngitis and upper respiratory tract infections most commonly reported are followed by ADRs reported within the SOC Skin and subcutaneous tissues and SOC Musculoskeletal and connective tissue disorders and the SOC of General disorders and administration site conditions and Respiratory, thoracic and mediastinal disorders, mainly due to injection site reactions. For the other AESI, no new or unexpected findings were overall observed in the PSO studies. The incidence of any TEAE leading to discontinuation of study medication was low and similar between the CZP 400mg Q2W and CZP 200mg Q2W groups. TEAEs leading to discontinuation of study medication were most commonly reported in the SOC of Infections and infestations (pool S4).

The rate and severity of adverse reactions do not give any major cause of concern in comparison with the experience of other indications but drug related TEAEs and SAEs in general seemed to be slightly more common in the patients receiving the highest dose compared to patients receiving the lower dose, in some of the analyses of the safety pools. This trend could not be excluded for serious infections and for hepatobiliary events in some of the separate analyses as well. It is noted that no (0 %) serious infections were reported for the lower dose 200 mg Q2W group used in the studies during the first 16 week treatment period (pool S1) compared to two subjects (0.6%) with three individual occurrences of serious infections of the 400 mg Q2W group (IR=1.92 per 100 subject-yrs). During the maintenance period (pool S4) three subjects (0.9%) reported 3 occurrences of serious infections (IR=1.48 per 100 subject-yrs) in the 200 mg Q2W group compared to six subjects (1.1%) reporting 7 individual occurrences of serious infections (IR = 1.93 per 100 subject-yrs) in the 400 mg Q2W group. Incidence rates of hepatobiliary events of the exposure-adjusted IRs in one of the safety pools (Pool S3) were slightly higher for the phase 3 CZP 400mg Q2W group compared to the phase 3 CZP 200mg Q2W group.

3.5. Uncertainties and limitations about unfavourable effects

Cimzia is a biological medicinal product that has a high affinity for human TNFα. The product has been on the market for almost a decade and its safety profile is considered well characterised. Its action, similar to other anti TNFs, raises the potential risks of infection and immune dysfunction.

The rate and severity of adverse reactions in the submitted data of performed studies do not give any major cause of concern in comparison with the experience of other indications but drug related TEAEs and SAEs in general seemed to be slightly more common in the patients receiving the highest dose compared to patients receiving the lower dose, in some of the analyses of the safety pools. This trend could not be excluded for serious infections and for hepatobiliary events in some of the separate analyses as well. There is a possibility that a population exposed to a higher dose will be at higher risk of developing adverse drug reactions,

Published studies have shown an increased risk for NMSC in patients with long standing psoriasis disease and a history of several previous therapies for the treatment of psoriasis and a possible association between NMSC risk and immunomodulatory therapy in psoriasis patients. The proposed higher dosage of certolizumab during long term treatment (400 mg Q2W) was discussed in relation to this by the PRAC. However, the extensive safety data available for anti-TNF medicinal products, including certolizumab pegol in already approved indications, as well as extensive experience in psoriasis with other anti-TNF medicinal products, and that the product information for certolizumab pegol already has a lot of information in relation to e.g. skin malignancies, which could be a particular concern in this new population was considered to give sufficient assurance that the benefit risk balance is not affected.

3.6. Effects Table

Effects Table for Certolizumab Pegol (Cimzia) in moderate to severe plaque psoriasis

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
PASI75 at Week 16	Proportion of patients with at least 75% improvement from baseline PASI at 16 weeks	%	CZP 200mg Q2W: 74.5 CZP 400mg Q2W: 80.1	Placebo: 7.5	P-value vs. Placebo: <0.0001 for both doses (MCMC)	Pool E1 (CIMPASI 1+2, CIMPACT)
PGA Clear or almost clear at Week 16	Proportion of patients achieving a physician global score of clear/almost clear at 16 weeks	%	CZP 200mg Q2W: 54.6 CZP 400mg Q2W: 63.7	Placebo: 2.8	P-value vs. Placebo: <0.0001 for both doses (MCMC)	Pool E1 (CIMPASI 1+2, CIMPACT)
PASI75 at Week 12	Proportion of patients with at least 75% improvement from baseline PASI at 12 weeks	%	CZP 200mg Q2W: 61.3 CZP 400mg Q2W: 66.7	Placebo: 5.0 ETN: 53.3	Estimate (95% CI) for difference in proportion of responders vs ETN: 200 mg CZP: 8.0 (-2.9, 18.9) 400 mg CZP: 13.4 (2.7, 24.1)	CIMPACT
PASI 90	Proportion of	%	CZP 200mg	Placebo:	P-value vs. Placebo:	Pool E1

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
at Week 16	patients with at least 90% improvement from baseline PASI at 16 weeks		Q2W: 44.5 CZP 400mg Q2W: 52.2	1.6	<0.0001 for both doses (MCMC)	(CIMPASI 1+2, CIMPACT)
Unfavourable Effects						
Any TEAEs	CZP 200 mg Q2W n/% 197/56.3	CZP 400mg Q2W n/% 217/63.5	Placebo n/% 97/61.8		There is a possibility that a population exposed to a higher dose will be at higher risk of developing adverse drug reactions	Safety pool 1
Serious TEAEs	CZP 200 mg Q2W n/% 5/1.4	CZP 400mg Q2W n/% 16/4.7	Placebo n/% 7/4.5		Concern according to above	Safety pool 1
Drug-related TEAEs	CZP 200 mg Q2W n/% 45/12.9	CZP 400mg Q2W n/% 54/15.8	Placebo n/% 20/12.7		Concern according to above	Safety pool 1
Infections and Infestations	CZP 200 mg Q2W IR/100 subject-yrs 121.6	CZP 400mg Q2W IR/100 subject-yrs 146.6	Placebo IR/100 subject-yrs 136.2			Safety pool 1
Naso-pharyngitis	CZP 200 mg Q2W IR/100 subject-yrs 42.2	CZP 400mg Q2W IR/100 subject-yrs 44.1	Placebo IR/100 subject-yrs 43.1			Safety pool 1
Serious infections and infestations	CZP 200 mg Q2W IR/100 subject-yrs 0	CZP 400mg Q2W IR/100 subject-yrs 1.9	Placebo IR/100 subject-yrs 0		Infections are important adverse reactions of certolizumab and most commonly lead to discontinuation of study medication during the performed studies (SOC of Infections and infestations) and although reported serious infections are only marginally increased in the group receiving the highest dose there is a possibility that a population exposed to a higher dose will be at higher risk of developing serious infections.	Safety pool 1
Any TEAEs **Serious TEAEs**	CZP 200 mg Q2W IR/100 subject-yrs 198.3 IR/100 subject-yrs 9	CZP 400mg Q2W IR/100 subject-yrs 198.3 IR/100 subject-yrs 8.2			In the safety analyses of Pool S4, the exposure-adjusted IRs in the 2 CZP dose groups were generally comparable, suggesting that the risks after longer exposure under both CZP dose regimens may be similar. However, there is an uncertainty of long term safety with the higher dose in the psoriasis population	Safety pool 4

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

CZP has demonstrated clearly statistically significant and clinically relevant effects vs. placebo. All three phase 3 studies met their primary end-points to demonstrate superiority vs. placebo with respect to PASI75 response and PGA response at Week 16 and Week 12. Secondary end-points were also met, e.g. PASI90 response and change in DLQI vs. placebo. The onset of efficacy is fast. Patient reported outcomes support the results described above. The results are clearly clinically relevant. Thus, a short-term effect of CZP in moderate to severe plaque psoriasis has been established. Also for maintenance treatment, clinically relevant response rates were observed over time. The 400 mg Q2W showed slightly higher response rates vs. the lower dose regimens (200 mg Q2W and 400 mg Q4W) for maintenance treatment.

Even if a formal dose ranging study has not been performed with CZP in psoriasis, the dose levels chosen have shown clearly beneficial effects in psoriasis. About 5-10% higher response rates were observed for the 400 mg Q2W vs. the 200 mg Q2W dose regimen for the primary and secondary end-points (e.g. PASI90) and the response during maintenance was also higher for the 400 mg dose. In one of the three studies (CIMPASI-2), there was however virtually no difference between the two doses.

Efficacy was observed both in subjects with or without a history of prior systemic treatment of psoriasis. There are no data available in patients who were primary failures to any prior biologic therapy (defined as no response within the first 12 weeks of treatment).

The indication initially proposed for Cimzia was "treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy". This wording was questioned as a Major Objection since the data do not support the part related to phototherapy. It differed from recently approved monoclonal antibodies, e.g. secukinumab, ixekizumab and brodalumab targeting IL-17A, as well as for the anti TNF alfa antibody adalimumab (Humira), since these products do not include the part concerning phototherapy. Therefore the agreed indication was revised to "Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy".

Concerning safety, the product has been on the market for almost a decade and its safety profile is well characterised. Its action, similar to other anti TNFs, raises the potential risks of infection and immune dysfunction. An uncertainty regarding the proposed higher dosage of certolizumab and risks related to NMSC during long term treatment were discussed.

3.7.2. Balance of benefits and risks

Cimzia (CZP) has demonstrated a positive effect on the treatment of moderate to severe plaque psoriasis, which is deemed clinically relevant. Both dose levels studied have shown efficacy vs. placebo with somewhat more patients (usually 5-10%) responding to the proposed higher dose of 400 mg Q2W.

The safety profile in patients with moderate to severe plaque psoriasis is similar to that known from other indications in which Cimzia is approved. The exposure-adjusted incidence rates were slightly higher in the CZP 400mg Q2W group compared with the CZP 200mg Q2W group during the Initial Treatment Period. However, it is agreed that the overall TEAE rates for the CZP 400mg Q2W dose during the Initial Treatment Period were comparable to placebo. It can be concluded that that the incidence rate of the total number of TEAEs after an additional 32 weeks of exposure does not seem to increase. As for the risk of separate TEAEs such as infections, hepatic events and malignancies of the CZP 400mg Q2W dose compared to CZP 200mg Q2W dose it is difficult to draw firm conclusions given the low number of events overall.

The Applicant was asked to discuss an alternative posology, i.e. to start on the 200 mg Q2W dose with a possibility to increase the dose to 400 mg Q2W in case of inadequate response. Analyses based on study CIMPACT were performed to provide efficacy data for patients who were PASI non-responders at Week 16. The reason for a patient being a non-responder at Week 16 may not be solely related to dose but also to other, patient-related factors. Still, it can be expected that individual patients not responding adequately to 200 mg QW may benefit from an increased dose.

In conclusion, the CHMP considered that the recommended posology would be to initiate the treatment with a loading dose at 400 mg Q2W up to 4 weeks and then decrease the dose to 200mg Q2W for the maintenance period. A 400 mg dose could still be considered in case of insufficient response.

Concerning safety, no definite conclusion can be drawn that the safety profile of long term dosing with CZP 400mg Q2W significantly differs from CZP 200mg Q2W since some of the events are too sparse to evaluate.

3.8. Conclusions

The overall benefit risk for Cimzia in the treatment of moderate to severe plaque psoriasis in adult patients is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include plaque psoriasis in adult patients for Cimzia; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 13.2 has also been submitted.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication for the treatment of moderate to severe plaque psoriasis in adult patients who are candidate to systemic therapy.

Summary

Three phase 3 studies (CIMPASI 1, CIMPASI 2 and CIMPACT) were submitted to support an indication for Cimzia in moderate to severe plaque psoriasis. All three studies met their primary end-points; to demonstrate superiority vs. placebo with respect to PASI75 response and PGA Clear or almost clear (with at least 2-category improvement) response at Week 16 in the CIMPASI studies (co-primary end-points) and to demonstrate superiority vs. placebo for PASI75 response at Week 12 in study CIMPACT. Both CZP dose regimens studied (400 mg Q2W and 200 mg Q2W after three initial loading doses of 400 mg) were superior to placebo.

In study CIMPACT, the anti TNF alfa antibody etanercept (Enbrel®) was included as active comparator. Superiority vs. etanercept could be concluded for PASI75 at Week 12 for the higher CZP 400 mg dose (66.7% vs. 53.3%, p=0.0152) and non-inferiority for the 200 mg dose (61.3% vs. 53.3%; 8% difference, 95% CI: -2.9; 18.9). For PGA response at Week 12 in CIMPACT (secondary end-point), there was no difference in response for this variable for the 200 mg CZP dose vs. ETN (40% vs. 39%) while the 400 mg CZP dose showed a larger response (50%) than ETN.

The safety profile of Cimzia 400 mg every 2 weeks and Cimzia 200 mg every 2 weeks were generally similar.
In conclusion, the submitted clinical studies support an update of sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC. The Package leaflet is updated accordingly.

Attachments

1. SmPC and Package Leaflet (changes highlighted).

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 11 May 2018. The principles to be applied for the deletion of CCI are published on the EMA website at
   http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500124536.pdf.

2. The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.

4. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, or prior to the next regulatory activity, whichever is first. *(*For additional guidance see chapter 4.1 of the *Harmonised Technical Guidance for eCTD Submissions in the EU*.