## CLINICAL STUDY REPORT SYNOPSIS: PS0003 (CIMPACT)

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| **Name of company:** UCB Biopharma, SPRL | **Individual study table referring to part of the dossier:** Not applicable | *(For National Authority Use Only)* |
| **Name of finished product:** Cimzia® | **Volume**: Not applicable | |
| **Name of active ingredient:** certolizumab pegol | **Page:** Not applicable | |

**Title of study:** 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

**Investigator(s):** Seventy Investigators enrolled subjects in this study.

**Study site(s):** The study was conducted at 70 sites located in the USA, Western Europe, and Central/East Europe.

**Publication(s) (reference[s]):** None

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| **Study period:** Approximately 3 years, 10 months<br><br>**First subject enrolled:** 11 Feb 2015<br>**Last subject completed:** 17 Dec 2018 | **Phase of development:** Phase 3 |

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

The secondary objectives of the study were to:

- Compare the efficacy of CZP administered sc at the doses of CZP 400mg Q2W and CZP 200mg Q2W after a loading dose of CZP 400mg at Weeks 0, 2, and 4 to etanercept (ETN) administered sc bi-weekly at a cumulative weekly dose of 100mg in the treatment of moderate to severe chronic plaque PSO
- Assess the optimal initial treatment dose for the treatment of moderate to severe chronic plaque PSO
- Assess the optimal maintenance dose for the treatment of moderate to severe chronic plaque PSO
- Assess the safety and tolerability of CZP

The other objectives of the study were to demonstrate the effect of CZP on aspects of the disease:

- Improvement of skin related quality of life (Dermatology Life Quality Index [DLQI])
- Health status as measured by the European Quality of Life 5 dimensions, 3 levels (EQ-5D-3L)
- Productivity as measured by the Work Productivity and Activity Impairment Questionnaire-Specific Health Problem (WPAI-SHP)
- Fatigue as measured by the Fatigue Assessment Scale (FASca)
- Psoriatic nail disease (target nail) as measured by the modified Nail Psoriasis Severity Index

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(mNAPSI) in subjects with nail disease at Baseline

- Assess the safety and efficacy of long-term use of CZP

**Methodology:** This was a double-blind, parallel-group, randomized, placebo- and active-controlled, multicenter study with a double-blind, placebo-controlled maintenance period.

The study included 5 periods: the Screening Period, the Initial Treatment Period (double-blind, placebo- and active-controlled), the Maintenance Treatment Period (double-blind, placebo-controlled), the Open-label Extension (OLE) Treatment Period, and the 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 rerandomized, double-blind treatment from Weeks 16 to 48 was intended to collect information on dosing beyond initial treatment. Open-label treatment for an additional 96 weeks provided additional long-term safety data on the use of CZP for moderate to severe chronic plaque PSO.

During the 16-week Initial Treatment Period, subjects were randomized in a 3:3:3:1 ratio to receive either:

- 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

Subjects who achieved at least a 75% reduction from Baseline in Psoriasis Area and Severity Index (PASI) response (PASI75) at Week 16 continued therapy as follows:

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

Subjects who did not achieve a PASI75 response at Week 16 were removed from blinded study medication and received open-label CZP 400mg Q2W treatment via the escape arm of the study. Subjects in the escape arm were assessed from Weeks 32 through 48 and were withdrawn from the study if they did not achieve PASI50. All subjects who completed the Week 48 Visit in the escape arm continued to receive CZP 400mg Q2W or may have, at the discretion of the Investigator, had their dose decreased to CZP 200mg Q2W if they achieved a PASI75 response at Week 48.

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During the Maintenance Treatment Period, rerandomized subjects who no longer achieved PASI50 were removed from the Maintenance Treatment Period (any time from Week 20 to Week 48) and were considered to have relapsed. Upon relapse, subjects entered the Open-label Treatment Period at a dose of CZP 400mg Q2W.

All subjects who completed the Maintenance Treatment Period through Week 48 without relapse (with a PASI50 response at Week 48) received open-label CZP 200mg Q2W for up to an additional 96 weeks.

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

Subjects who received CZP 200mg Q2W and did not achieve a PASI50 response at OLE 12, OLE 24, OLE 36, OLE 48, OLE 60, OLE 72, or OLE 84 received CZP 400mg Q2W for at least 12 weeks. Subjects who received CZP 400mg Q2W for at least 12 weeks and did not achieve a PASI50 response were withdrawn from the study.

Subjects who received CZP 200mg Q2W and achieved 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 have had their CZP dose increased to 400mg Q2W, at the discretion of the Investigator.

Subjects who received CZP 400mg Q2W for at least 12 weeks and achieved a PASI75 response at OLE 12, OLE 24, OLE 36, OLE 48, OLE 60, OLE 72, or OLE 84 may have been switched to CZP 200mg Q2W, at the discretion of the Investigator.

**Number of subjects (planned and analyzed):** Approximately 540 subjects were planned; 162 subjects each for the CZP and ETN groups and 54 subjects for the placebo group. A total of 559 randomized subjects started the Initial Treatment Period; 165 subjects randomized to the CZP 200mg Q2W group, 167 subjects randomized to the CZP 400mg Q2W group, 170 subjects randomized to the ETN group, and 57 subjects randomized to the placebo group. For the Initial Treatment Period, a total of 559 subjects were included in the Randomized Set (RS) and 557 subjects were included in the Safety Set (SS). A total of 524 subjects were included in the Per Protocol Set (PPS).

For the Maintenance Treatment Period, a total of 559 subjects were included in the RS. For efficacy analyses, 533 subjects were included in the Maintenance Set (MS) and 310 subjects were included in the Week 16 Randomized Set (WK16RS). For safety analyses, a total of 534 subjects were included in the Maintenance Safety Set (MSS), and 520 subjects were included in the Treated with CZP Set (TCS).

For the Open-label Treatment Period, 472 subjects were included in the OLS. For efficacy analyses, the OLS included 34 subjects in the PBO/CZP 200mg Q2W group, 122 subjects in the CZP 200mg Q2W/CZP 200mg Q2W group, 41 subjects in the CZP 400mg Q4W/CZP 200mg Q2W group, 48 subjects in the CZP 400mg Q2W/CZP 200mg group, and 177 subjects in the Escape CZP 400mg Q2W/CZP 400mg Q2W group. Two additional treatment groups, consisting of subjects who relapsed, were summarized separately for the efficacy analyses: PBO/CZP 400mg Q2W (n=34) and Any CZP/400mg Q2W (n=16).

For the Combined Initial, Maintenance, and Open-label Treatment Period, 545 subjects were included in the TCS, including 373 subjects in the CZP 200mg Q2W group and 412 subjects in the CZP 400mg Q2W

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group.

**Diagnosis and main criteria for inclusion:** The study population included adults (≥18 years of age) with moderate to severe chronic plaque PSO for ≥6 months, defined as a Baseline PASI ≥12 and body surface area (BSA) ≥10% and Physician's Global Assessment (PGA) score ≥3, including both subjects who had received previous biologic treatment as well as those who were biologic treatment naïve. Subjects must not have been primary failures 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 with erythrodermic, guttate, or generalized pustular form of PSO were excluded.

**Test product, dose(s) and mode of administration, batch number(s):** Certolizumab pegol is an engineered humanized monoclonal antibody Fab' fragment with specificity for human tumor necrosis factor alpha (TNFα), manufactured in *Escherichia coli*. The antibody fragment is subsequently purified and conjugated with high molecular weight polyethylene glycol (40kDa).

Certolizumab pegol was supplied as a sterile, clear, colorless to slightly yellow liquid solution with a pH of approximately 4.7 in 1mL single-use, glass prefilled syringe (PFS) with a 25G ½-inch thin-wall needle for sc injection. Each syringe contained an injectable volume of 1mL at a concentration of 200mg/mL of CZP in 10mM sodium acetate buffer and 125mM sodium chloride as a tonicity agent.

Batch numbers: BX1012374, BX1012239, BX1012240, BX1012281, BX1012387, BX1012544, BX1012545, BX1012698, BX1012697, BX1012846, BX1012875, BX1012966, BX1013026, BX1013144, BX1013207, BX1013206, BX1013420, BX1013796, BX1013797, BX1013726, BX1013798, BX1013871, BX1013961, BX1013962, BX1013795, BX1014199, BX1014326, BX1014514, BX1014594, 227594, 234379, 234380

**Duration of treatment:** The duration of the study for each subject is up to 157 weeks, consisting of:

- Screening Period of up to 5 weeks
- Initial Treatment Period of 16 weeks (Week 0 to Week 16)
- Maintenance Treatment Period of 32 weeks (Week 16 to Week 48)
- Open-label Treatment Period of 96 weeks (Week 48 to Week 144)
- Safety Follow-up Period of 8 weeks (Week 144 to Week 152). Note: Ten weeks after final dose.

**Reference therapy, dose(s) and mode of administration, batch number(s):** Placebo (0.9% saline) was supplied as a sterile solution in a single-use glass PFS with a 25G ½ inch thin-wall needle for sc injection, containing an injectable volume of 1mL.

Batch numbers: BX1012240, BX1012281, BX1012387, BX1012544, BX1012697, BX1012846, BX1012966, BX1013026, BX1013144, BX1013206, BX1013795

Etanercept (Enbrel®) is commercially available and was supplied as a 50mg single-use PFS containing 0.98mL of a 50mg/mL solution of ETN, sucrose, sodium chloride, L-arginine hydrochloride, and sodium phosphate. Etanercept used in the USA was sourced in the USA, and ETN used in the EU was sourced in

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the EU.

**Criteria for evaluation:**

**Efficacy:** The primary efficacy variable was PASI75 at Week 12.

The secondary efficacy variables were:

- 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

The other efficacy variables are listed below and were evaluated at all scheduled visits (as applicable). This excluded the primary and secondary variables.

- PASI50, PASI75, PASI90, and PASI100
- Absolute and percent change from Baseline in PASI score
- Time to onset of action, defined as the time to PASI50
- Time to onset of action, defined as the time to PASI75
- Time to onset of action, defined as the time to PASI90
- 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)
- 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 visual analogue scale (VAS)
- Change from Baseline in FASca
- Change from Baseline in mNAPSI
- Direct medical resource use: all medical procedures, hospital stays, health care consultations not foreseen by protocol: number of concomitant medical procedures, number of health care provider consultations, number of hospitalizations, number of emergency room visits, length of hospital stay

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The following variables were considered key efficacy variables for the open-label extension analysis:

- PASI75, PASI90, and PASI100
- PGA Clear or Almost Clear (with at least 2-category improvement)
- Change from Baseline in DLQI and percent achieving DLQI remission

Key efficacy variables were summarized for the Combined Maintenance and Open-label Treatment Period for all subjects that did not relapse during the Maintenance Treatment Period. Key efficacy variables were also summarized for the Open-label Treatment Period for the subset of subjects who relapsed during the Maintenance Treatment Period. Efficacy variables that were not defined as key were summarized for the Open-label Treatment Period, where subjects who relapsed during the Maintenance Treatment Period were excluded.

**Pharmacokinetics:** All subjects provided samples for pharmacokinetic (PK) evaluation at Baseline; Weeks 1, 2, 4, 16, 24, 36, and 48; OLE Weeks 24, 48, 72, and 96 (End of Study [EOS]); the Early Withdrawal Visit; and the SFU Visit (10 weeks after final dose of CZP).

**Immunogenicity:** Plasma samples for the measurement of anti-CZP antibodies were collected at Baseline; Weeks 1, 2, 4, 16, 24, 36, and 48; OLE Weeks 24, 48, 72, and 96 (EOS); the Early Withdrawal Visit; and the SFU Visit (10 weeks after final dose of CZP).

**Safety:** Safety variables assessed were:

- Adverse events (AEs)
- Blood pressure
- Physical examination
- Clinical laboratory values (hematology, biochemistry, and urinalysis)
- Interferon-gamma release assay (IGRA) test for tuberculosis (TB)

**Statistical methods:** This final clinical study report presents the complete analysis of results through the end of the study. Descriptive statistics were displayed to provide an overview of the study results. For categorical variables, the number and percentage of subjects in each category was presented. The denominator for percentages was based on the number of subjects appropriate for the purpose of analysis for the respective treatment group, subset, and period.

A Baseline value for a subject was defined as the latest measurement for that subject up to and including the day of administration of first study medication, unless otherwise stated. If a Baseline value was missing or not collected, and a Screening value was available, the Screening value was utilized as the Baseline value. Baseline values for component scores were computed using components from the same visit when the relevant measurements were recorded prior to dosing. For example, if the Screening Visit had all of the components, but the Baseline Visit was missing one or more components, the Baseline value for the component score was calculated using the Screening Visit values.

Efficacy analyses during the Initial Treatment Period were performed using the RS. The PPS was used for

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a sensitivity analysis on the primary endpoint only. Efficacy analyses during the Maintenance Treatment Period were performed using the WK16RS or the MS. For the final analyses of key and other efficacy endpoints, the OLS was used. Safety summaries were performed using the SS, TCS, or MSS.

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 at a 2-sided alpha level of 0.05 or 0.025, depending on the scenario. Testing for both noninferiority and superiority of CZP over ETN were included as the final steps in the testing procedure. For superiority testing, each CZP dose was compared against ETN and was tested sequentially at an alpha of 0.025 or 0.05 depending on the scenario. For noninferiority testing, a 2-sided confidence interval (CI) of 95% or 97.5%, depending on the scenario, for the difference in the proportion of subjects who achieved PASI75 response was constructed. The statistical significance to evaluate superiority of CZP 400mg Q2W vs ETN and noninferiority of CZP 200mg Q2W vs ETN was evaluated simultaneously based on the Hochberg method.

*Analysis of the primary efficacy variable*. The primary analysis was 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. The Markov Chain Monte Carlo (MCMC) method for multiple imputations was used to account for missing values in the primary analysis of PASI75 at Week 12. This is a commonly used method for handling intermittent or monotonic missing data under the assumption of a missing at random (MAR) pattern of missingness. The multiple imputation procedure was based on the actual PASI score.

*Analysis of the secondary efficacy variables*. The PASI75 response at Week 12 was also compared between both CZP doses and ETN using the same model described for the primary analysis of the primary efficacy variable. The PASI90 and PGA responder rates at Week 12 as well as the PASI75, PASI90, and PGA responder rates at Week 16 were calculated and analyzed in the same manner described for the primary analysis of PASI75 response at Week 12. The analysis of the PASI75 responder rate at Week 48 was based on the WK16RS and was summarized only for the blinded rerandomized treatment groups. Missing data were handled based on nonresponder imputation (NRI).

**Summary and conclusions:**

**Subject disposition:**

A total of 559 randomized subjects started the Initial Treatment Period; 165 subjects randomized to the CZP 200mg Q2W group, 167 subjects randomized to the CZP 400mg Q2W group, 170 subjects randomized to the ETN group, and 57 subjects randomized to the placebo group. 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 200mg Q2W (96.4%), CZP 400mg Q2W (97.0%), and placebo (96.5%) groups, and slightly lower in the ETN group (93.5%); this difference is largely due to a higher percentage of subjects discontinuing due to an AE (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); overall, the most frequently reported primary reasons for discontinuation were consent

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withdrawn (7 subjects [1.3%]), AEs (6 subjects [1.1%]), and lost to follow up (6 subjects [1.1%]). Two of the 6 subjects who reported AE as the primary reason for discontinuation had serious, nonfatal events; 1 subject in the CZP 200mg Q2W group and 1 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.

A total of 533 subjects started the Maintenance Treatment Period, and 478 subjects (89.7%) completed Week 48. A total of 55 subjects (10.3%) discontinued during the Maintenance Treatment Period (prior to Week 48); overall, 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%]). Of the 11 subjects who discontinued due to an AE, 5 subjects discontinued due to nonserious, nonfatal AEs, and 6 subjects discontinued due to nonfatal serious AEs (SAEs). 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 compared with the combined blinded groups (15 of 310 subjects, 4.8%); this difference was largely due to meeting mandatory withdrawal criteria (failed to achieve at least 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 (8 of 223 subjects, 3.6%) compared with the combined blinded groups (3 of 310 subjects, 1.0%). All other reasons for discontinuation were low and similar between the combined blinded and combined escape groups.

A total of 472 subjects completed the Initial and Maintenance Treatment Periods and started the Open-label Treatment Period. The majority of subjects (396 subjects [83.9%]) who entered the Open-label Treatment Period completed OLE 96. A total of 76 subjects (16.1%) discontinued during the Open-label Treatment Period (prior to OLE 96); overall, the most frequently reported reason for discontinuation was adverse event (34 subjects [7.2%]) followed by consent withdrawn (17 subjects [3.6%]), other (12 subjects [2.5%]), and lost to follow up (10 subjects [2.1%]). Eleven of the 12 subjects who discontinued the study due to "other" did so for mandatory withdrawal due to PASI50 nonresponse; the remaining subject discontinued due to other: lack of efficacy on psoriatic arthritis (Subject [redacted] in the CZP 200mgQ2W/CZP 200mgQ2W/CZP 200mgQ2W group).

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**Efficacy results:**

**Efficacy during the Initial Treatment Period**

The statistical analysis of the primary efficacy variable (PASI75 responder rate at Week 12) and secondary efficacy variables at Week 12 (PGA and PASI90 responder rates) and at Week 16 (PASI75, PGA, and PASI90 responder rates) were evaluated using a fixed-sequence testing procedure. Based on this procedure, data from PS0003 demonstrated that treatment with CZP 200mg Q2W and CZP 400mg Q2W resulted in clinically meaningful and statistically significant improvements in PSO area and severity (as assessed by PASI75 and PASI90 responder rates) as well as global physician assessment of disease activity (via PGA responder rates).

The results of the primary analysis were supported and confirmed by similar findings from all sensitivity analyses and the analysis using the PPS.

Although the Initial Treatment Period was 16 weeks, the primary and secondary efficacy variables used Week 12 as the endpoint. This time point was chosen to allow for a fair comparison to the active comparator, ETN, for which dosing completed at 11.5 weeks. The Week 16 timepoint was also included as a secondary efficacy variable for comparisons to placebo to provide consistency with the other Phase 3 clinical studies of CZP treatment for PSO.

***Psoriasis area and severity***

- Statistically significant and clinically meaningful differences in PSO area and severity, as measured by the PASI75 and PASI90 responder rates, were observed for CZP-treated subjects compared with placebo-treated subjects. At Weeks 12 and 16, the PASI75 responder rates were significantly greater in both the CZP 200mg Q2W group (61.3% and 68.2%, respectively) and CZP 400mg Q2W group (66.7% and 74.7%, respectively) compared with the placebo group (5.0% and 3.8%, respectively; $p<0.0001$ for all comparisons). Similarly, PASI90 responder rates at Weeks 12 and 16 were significantly greater in both the CZP 200mg Q2W group (31.2% and 39.8%, respectively) and CZP 400mg Q2W group (34.0% and 49.1%, respectively) compared with the placebo group (0.2% and 0.3%, respectively; $p<0.0001$ for all comparisons).
- During the Initial Treatment Period, PASI75, PASI90, and PASI100 responder rates in both the CZP 200mg Q2W and CZP 400mg Q2W groups consistently increased over time through Week 16; PASI50 responder rates increased through Weeks 8 to 12 and were maintained through Week 16 in the CZP treatment groups.
- The improvements in PASI responder rates generally occurred rapidly following the initiation of treatment with CZP. Clinically meaningful differences versus placebo were observed for PASI50 and PASI75 responder rates starting at Week 4 for the CZP 200mg Q2W group and CZP 400mg Q2W group; for PASI90 responder rates at Week 8 for both CZP groups; and for PASI100 responder rates at Week 12 for both CZP groups.
- Clinically meaningful differences in time to achieving a PASI50, PASI75, and PASI90 response were observed for CZP-treated subjects compared with placebo-treated subjects during the Initial Treatment Period; time to achieving a PASI100 or a PGA response were not evaluated. The median

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times to achieving PASI50 responses were 56.0 days and 55.0 days for the CZP 200mg Q2W and CZP 400mg Q2W groups, respectively. The median times to achieving PASI75 responses were 84.0 days each for the CZP 200mg Q2W and CZP 400mg Q2W groups. The median times to achieving PASI90 responses were 115.0 days and 112.0 days for the CZP 200mg Q2W and CZP 400mg Q2W groups, respectively. The differences versus placebo for the CZP 200mg Q2W and 400mg Q2W groups resulted in nominal p-values <0.0001 for all comparisons.

- Numerically greater improvements in those endpoints assessing PSO area and severity were generally seen in the CZP 400mg Q2W group compared with the CZP 200mg Q2W group during the Initial Treatment Period. Comparing the CZP 400mg Q2W group to the CZP 200mg Q2W group, mean responder rates were numerically higher for PASI50 at Week 16 (difference in means of 5.9%), for PASI75 at Weeks 12 and 16 (difference in means of 5.4% and 6.5%, respectively), and for PASI90 at Week 16 (difference of 9.3%). Marginal differences were observed between the CZP dose groups for PASI100 responder rates at Week 16 (difference in means of 3.7%) and mean (percent) change from Baseline in PASI score at Week 16 (difference in means of 0.53 points and 4.12%, respectively).

***Subgroup analyses of the primary endpoint***

- All subgroups had a clinically meaningful difference from placebo in PASI75 responder rate at Week 12 for both CZP groups. In subgroups with sufficient sample sizes to make comparisons (n≥25), the PASI75 responder rates were generally higher in the CZP 400mg Q2W group compared with the CZP 200mg Q2W group, and in most cases, the PASI75 responder rates were higher in both CZP groups compared with the ETN group.
- Body weight and body mass index may influence the PASI75 responder rate. The PASI75 responder rate at Week 12 was lower in the higher quintiles compared with the lower quintiles in both CZP groups, whereas no trend was observed in the placebo group.
- No consistent differences were observed in PASI75 responder rates based on age (<40 years and ≥40 to <65 years); gender; race; ethnic origin; PSO disease duration; geographical region; prior biologic exposure; prior anti-TNF exposure; prior systemic therapy (nonbiologic); prior systemic chemophototherapy or phototherapy; any prior systemic treatment for PSO; previous exposure to at least 2 systemic treatments out of phototherapy, methotrexate, and cyclosporine (with no previous biologic exposure); Baseline PASI score; and Baseline PSO BSA.
  - It should be noted that the results of the subgroup analyses should be interpreted with caution given that the sample sizes of many of the subgroup categories were relatively small. In addition, potential interactions between subgroup categories may have influenced the results and cannot be adequately explored in this individual study due to the small group sizes. Of note, the responder rates in the CZP 200mg Q2W and 400mg Q2W groups were still clinically meaningfully greater than the responder rates observed in the corresponding placebo group. Across subgroups, a modest dose effect on responder rates was observed in some subgroups.

***Physician's global assessment of disease activity***

- At Weeks 12 and 16, PGA responder rates were significantly higher in both the CZP 200mg Q2W

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| **Name of company:** UCB Biopharma, SPRL | **Individual study table referring to part of the dossier:** Not applicable | *(For National Authority Use Only)* |
| **Name of finished product:** Cimzia® | **Volume**: Not applicable | |
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group (39.8% and 48.3%, respectively) and CZP 400mg Q2W group (50.3% and 58.4%, respectively) compared with the placebo group (1.9% and 3.4%, respectively; p≤0.0004 for all comparisons).

- PGA responder rates in both the CZP 200mg Q2W and CZP 400mg Q2W groups consistently increased through Week 16.
- The improvements in PGA responder rates occurred rapidly following the initiation of treatment with CZP; clinically meaningful differences versus placebo were observed for both CZP groups beginning at Week 4 and at all subsequent timepoints through Week 16.
- PGA responder rates at Weeks 8, 12, and 16 were numerically higher in the CZP 400mg Q2W group compared with the CZP 200mg Q2W group; differences in means were approximately 10% at Weeks 12 and 16.

***Health-related quality of life***

- Subjects in the CZP 200mg Q2W and CZP 400mg Q2W groups had clinically meaningful improvements in patients' Health Related Quality of Life (HRQoL; as assessed by the mean change from Baseline in the DLQI) compared with the placebo group.
  - At Week 16, the least squares (LS) mean (standard error) decrease (ie, improvement) from Baseline in DLQI using last observation carried forward imputation was -9.2 (0.50) points for the CZP 200mg Q2W group and -10.4 (0.50) points for the CZP 400mg Q2W group compared with -2.0 (0.81) points for the placebo group (p<0.0001 for both comparisons).
  - Consistently larger decreases from Baseline in the DLQI score were observed over time from Weeks 2 through 12 and subsequently maintained at Week 16 for the CZP 200mg Q2W group, whereas the DLQI score continued to improve through Week 16 for the CZP 400mg Q2W group.
- The percentages of subjects who were DLQI MCID responders (defined as a ≥4-point change in the DLQI score) in both the CZP 200mg Q2W and CZP 400mg Q2W groups were higher than placebo at each timepoint. At Week 16, 68.5% of subjects in the CZP 200mg Q2W group and 83.8% of subjects in the CZP 400mg Q2W group were DLQI MCID responders compared with 29.8% of subjects in the placebo group. The percentage of subjects who were DLQI MCID responders was numerically higher in the CZP 400mg Q2W group compared with the CZP 200mg Q2W group at Weeks 8, 12 and 16, with a difference between groups of approximately 15% at Week 16.
- Increasingly larger percentages of subjects in both the CZP 200mg Q2W and CZP 400mg Q2W groups achieved DLQI remission as compared with placebo at each timepoint. At Week 16, 38.2% of subjects in the CZP 200mg Q2W group and 46.1% of subjects in the CZP 400mg Q2W group had achieved DLQI remission compared with 10.5% of subjects in the placebo group. The percentage of subjects who had achieved DLQI remission was numerically higher in the CZP 400mg Q2W group compared with the CZP 200mg Q2W group at Weeks 12 and 16.
- Results of the DLQI were supported by clinically meaningful improvements versus placebo in overall health status (as assessed by EQ-5D-3L VAS and domains) following treatment with CZP 200mg Q2W and CZP 400mg Q2W during the Initial Treatment Period. Impairment while working and in

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daily activities due to PSO (as assessed by the WPAI-SHP) was reduced in the CZP treatment groups over placebo as early as Week 4 (first assessment) and was sustained through the Initial Treatment Period. Improvements observed in these patient-reported outcome (PRO) measures in the CZP 400mg Q2W group were comparable to and, in some cases, greater than those improvements seen in the CZP 200mg Q2W group.

**Efficacy during the Maintenance Treatment Period**

- During the Maintenance Treatment Period (based on the blinded maintenance groups), the improvements observed across the collection of efficacy endpoints assessed during the Initial Treatment Period (based on PSO severity and/or area; global physician-assessment of disease activity; PSO-specific HRQoL; and PRO measurements) were generally maintained through 32 weeks of maintenance treatment with CZP, regardless of dosing regimen. The response achieved at Week 48 following 32 weeks of maintenance treatment with CZP was clinically meaningful and well above the response observed with 32 weeks of maintenance treatment with placebo.

  Among subjects who were PASI75 responders at Week 16 who were initially treated with CZP then rerandomized to CZP or placebo, the following observations were made:

  – The majority of subjects (>79.5%) continued to be PASI75 responders at Week 48. This was most pronounced in the group that received CZP 400mg Q2W in both the Initial and Maintenance Treatment Periods where 98.0% continued to be PASI75 responders at Week 48.

  – The PASI90 responder rate was greater or similar at Week 48 in each group that received CZP treatment during the Maintenance Treatment Period compared with Week 16. The PASI90 responder rate improved from Weeks 16 to 48 (75.5% to 87.8%; difference of +12.3%) in the group that received CZP 400mg Q2W in both the Initial and Maintenance Treatment Periods, whereas the responder rate remained steady over the Maintenance Treatment Period for the group that switched from CZP 400mg Q2W to CZP 200mg Q2W (difference of -2.0% from Weeks 16 to 48). For subjects treated with CZP 200mg Q2W in the Initial Treatment Period who received either CZP 200mg Q2W or CZP 400mg Q4W (same cumulative monthly dose) during the Maintenance Treatment Period, overall improvements from Weeks 16 to 48 were observed in each group for PASI90 (11.4% and 9.1%, respectively). Similar trends were observed for the PASI100 responder rate in that there was a maintenance of response with continuing the same treatment (improvement from Week 16 to 48 of 18.4% for CZP 400mg Q2W/CZP 400mg Q2W and 15.9% for CZP 200mg Q2W/CZP 200mg Q2W).

  – The majority of subjects (≥61.4%) achieved a PGA response at Week 48 during the Maintenance Treatment Period. The PGA responder rate improved from Weeks 16 to 48 (81.6% to 87.8%; difference of +6.2%) in the group that received CZP 400mg Q2W in both the Initial and Maintenance Treatment Periods, whereas the other CZP maintenance groups (CZP 200mg Q2W/CZP 200mg Q2W, CZP 200mg Q2W/CZP 400mg Q4W, and CZP 400mg Q2W/CZP

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200mg Q2W) had an overall decrease in PGA responder rate.

  - Improvements in PASI score and DLQI score were generally maintained through Week 48 in all CZP maintenance groups. The percentage of subjects in DLQI remission was maintained or improved throughout the Maintenance Treatment Period. Improvement in DLQI remission was most pronounced in the group that received CZP 400mg Q2W in both the Initial and Maintenance Treatment Periods where 77.6% were in DLQI remission at Week 48, an increase from Week 16 of 18.4%, whereas improvements from Weeks 16 to 48 in the other CZP maintenance groups were ≤9.1%.
  - Time to relapse (not achieving a PASI50 response) was longer for subjects receiving CZP treatment in the Maintenance Treatment Period compared with subjects receiving placebo treatment ($p \leq 0.0027$ across all CZP maintenance groups vs placebo).

- The CZP maintenance treatments evaluated subjects initially treated with CZP 200mg Q2W who continued on the same CZP dosing regimen or received CZP 400mg Q4W (same cumulative monthly dose). Across the spectrum of efficacy endpoints, the 2 dosing regimens generally provided similar results.
- Switching to placebo for maintenance treatment resulted in a clinically meaningful worsening (relative to Week 16) over time of disease activity as assessed by PASI, PGA, DLQI, and PRO measurements.
- For those placebo subjects who did not achieve a PASI75 response by Week 16 (ie, the escape maintenance groups), treatment with open-label CZP 400mg Q2W in the Maintenance Treatment Period resulted in improvements across the spectrum of efficacy endpoints assessed that resembled a pattern of improvement similar to those subjects who were originally randomized to blinded CZP treatment in the Initial Treatment Period.
- No subjects experienced rebound, defined as a >125% increase from Baseline in PASI score within 14 weeks after the last dose of CZP treatment during the Initial Treatment Period in the subjects who were rerandomized to placebo during the Maintenance Treatment Period.

**Efficacy with CZP vs ETN**

- The CZP 400mg 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 200mg 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) and was determined to be statistically noninferior (difference of 8%; 95% CI: -2.9, 18.9) to ETN based on a prespecified 10% noninferiority margin.
- Across the totality of efficacy endpoints assessed during the Initial Treatment Period, the CZP 200mg Q2W group demonstrated greater numerical improvements over the ETN group in PASI responder rates; similar results to the ETN group were observed in PGA responder rates, DLQI response (ie,

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mean change from Baseline and percent of subjects in DLQI remission), and PRO measurements. The CZP 400mg Q2W group demonstrated consistently greater numerical improvements over the ETN group in PASI and PGA responder rates and percent of subjects in DLQI remission; similar results to the ETN group were observed in the mean change from Baseline in DLQI and PRO measurements.

- Subjects randomized to ETN who achieved a PASI75 response and were rerandomized to CZP 200mg Q2W achieved high levels of response out to Week 48.
- For those subjects randomized to ETN who did not achieve a PASI75 response by Week 16 (ie, the escape maintenance groups), treatment with open-label CZP 400mg Q2W in the Maintenance Treatment Period resulted in notable improvements across the spectrum of efficacy endpoints at Week 48.
- The effect of BMI and body weight on PASI75 responder rate at Week 12 was more profound in ETN than in CZP. The decrease in PASI75 responder rate from the fourth to fifth BMI quintile was approximately 35% for the ETN groups compared with approximately 15% to 20% for the CZP group. A similar trend was observed for weight.

**Efficacy during the Combined Maintenance and Open-label Treatment Period**

Efficacy was evaluated during the Combined Maintenance and Open-label Treatment Period in the subjects who were PASI75 responders at Week 16 and who maintained at least a PASI50 response throughout the Maintenance Treatment Period. Across the spectrum of key efficacy endpoints assessed, treatment with CZP 200mg Q2W during the Open-label Treatment Period demonstrated improvements that were generally maintained through OLE 96.

- For the CZP 200mg Q2W/CZP 200mg Q2W and CZP 400mg Q4W/CZP 200mg Q2W groups, PASI75, PASI90, PASI100, and PGA responder rates were generally maintained during the Maintenance Treatment Period with some fluctuations (Week 16 through OLE Entry). During the Open-label Treatment Period (OLE Entry through OLE 96), PASI75, PASI90, PASI100, and PGA responder rates were generally maintained or increased slightly through OLE 96.
- For the subjects on CZP 400mg Q2W during the Maintenance Treatment Period, PASI75, PASI90, PASI100, and PGA responder rates were generally maintained, with some fluctuations through OLE Entry. After these subjects dosed down to CZP 200mg Q2W during the Open-label Treatment Period, PASI75, PASI90, and PGA responder rates were generally maintained with a slight decline through OLE 96; PASI100 responder rates were maintained through OLE 96.
- Among subjects who were randomized to placebo during the Maintenance Treatment Period and did not relapse, PASI75, PASI90, PASI100, and PGA responder rates consistently declined over time through OLE Entry; after switching to CZP 200mg Q2W during the Open-label Treatment Period (PBO/CZP 200mg Q2W), PASI75, PASI90, PASI100, and PGA responder rates generally increased following OLE Entry and then were maintained through OLE 96. The majority (32 of 34 subjects) of these subjects had received active treatment during the Initial Treatment Period.

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- For subjects who remained on the same CZP dose throughout the Open-label Treatment Period (ie, nonadjusters), PASI75, PASI90, PASI100, and PGA responder rates were generally maintained through OLE 96.
- Improvements from Baseline in the DLQI and DLQI remission rates were observed in all CZP treatment groups which were generally maintained through OLE 96. The percentages of subjects who achieved DLQI remission in the CZP 200mg Q2W/CZP 200mg Q2W and CZP 400mg Q4W/CZP 200mg Q2W groups were generally maintained from Week 16 through OLE 96. The percentage of subjects who achieved DLQI remission in the CZP 400mg Q2W/CZP 200mg Q2W group increased from Week 16 to OLE Entry and then fluctuated before stabilizing back to values similar to OLE Entry. The percentage of subjects who achieved DLQI remission in the PBO/CZP 200mg Q2W group declined from Week 16 to OLE Entry and then was regained in the Open-label Treatment Period.

**Efficacy during the Combined Initial, Maintenance, and Open-label Treatment Period**

Maintenance of response during the Combined Initial, Maintenance, and Open-label Treatment Period was evaluated for the subset of subjects who were PASI75, PASI90, or PGA responders (Clear or Almost Clear) at Week 16; these subjects were all PASI75 responders at Week 16 and were further evaluated based on their PASI90 or PGA response at Week 16. In addition, this summary includes only subjects who did not relapse during the Maintenance Treatment Period. The treatment groups described represent subjects who received the same treatment through Week 48/OLE Entry and then either remained on CZP 200mg Q2W (CZP 200mg Q2W/CZP 200mg Q2W/CZP 200mg Q2W) or dosed down from CZP 400mg Q2W to CZP 200mg Q2W (CZP 400mg Q2W/CZP 400mg Q2W/CZP 200mg Q2W) during the Open-label Treatment Period.

- Subjects treated with CZP 200mg Q2W throughout the study who were PASI75, PASI90, or PGA responders at Week 16 demonstrated maintenance of PASI75, PASI90, and PGA responder rates through OLE 96.
- Subjects treated with CZP 400mg Q2W during the Initial and Maintenance Treatment Periods, but who dosed down to CZP 200mg Q2W during the Open-label Treatment Period who were PASI75, PASI90, or PGA responders at Week 16 demonstrated maintenance of PASI75, PASI90, and PGA responder rates through OLE Entry with a gradual decline in rates through OLE 96.

**Efficacy results for the Escape CZP 400mg Q2W/CZP 400mg Q2W group**

- Although the data in this section are for the results of open-label CZP treatment, this treatment group represents the longest exposure to CZP 400mg Q2W for up to 128 weeks (~2.5 years). Improvements across the spectrum of efficacy endpoints assessed were observed up to Week 32 (ie, up to 16 weeks of CZP treatment) and generally maintained through OLE 12 and OLE 96 (ie, up to 40 and 128 weeks of CZP treatment, respectively) (Table 1).

## Table 1: PGA, PASI75, PASI90, and PASI100 responder rates over time – Combined Maintenance and Open-label Treatment Period (OLS [MCMC])

| Parameter Statistic | Escape CZP 400mg Q2W/ CZP 400mg Q2W [a] N=177 | | |
|---|---|---|---|
| | Week 32 (ie, 16 weeks of open-label CZP treatment) | OLE 12 (ie, 44 weeks of open-label CZP treatment) | OLE 96 (ie, 128 weeks of open-label CZP treatment) |
| **PGA responder rates over time** | | | |
| Responder rate (%) | 62.1 | 70.8 | 65.2 |
| **PASI75 responder rates over time** | | | |
| Responder rate (%) | 80.4 | 89.4 | 86.7 |
| **PASI90 responder rates over time** | | | |
| Responder rate (%) | 39.0 | 61.0 | 55.1 |
| **PASI100 responder rates over time** | | | |
| Responder rate (%) | 15.1 | 25.4 | 19.7 |

CZP=certolizumab pegol; MCMC=Markov Chain Monte Carlo; PASI50=at least 50% reduction from Baseline in Psoriasis Area and Severity Index; PASI75/90/100=at least 75%/90%/100% reduction from Baseline in Psoriasis Area and Severity Index; PGA=Physician's Global Assessment; Q2W=every 2 weeks

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

Note: Dose adjustments after Week 48 were not considered in this table

Note: Estimates of the responder rate were based on using a logistic regression model with factors for treatment, region, and prior biologic exposure (yes/no) 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. Subjects who should have been withdrawn at Week 32 or later due to lack of PASI50 response or subjects on CZP 400mg Q2W (for at least 12 weeks) during the Open-label Treatment Period who did not achieve a PASI50 response during the Open-label Treatment Period and should have been mandatorily withdrawn were treated as nonresponders for subsequent time points. All other missing data were imputed using multiple imputations based on MCMC methodology. In cases where no data were missing at a visit, the logistic regression was performed on the observed data.

[a] In the Escape CZP 400mg Q2W/CZP 400mg Q2W group, subjects escaped from their randomized treatment (eg, CZP 200mg Q2W, CZP400mg Q2W, or placebo) at Week 16

**Efficacy results for subjects who relapsed during the Maintenance Treatment Period (PBO/CZP 400mg Q2W and Any CZP/CZP 400mg Q2W groups)**

Subjects in the double-blind Maintenance Treatment Period who did not achieve a PASI50 response during this treatment period were considered to have relapsed. Upon relapse, subjects entered the Open-label Treatment Period at a dose of CZP 400mg Q2W.

- Subjects who relapsed while on placebo during the Maintenance Treatment Period rapidly regained their PASI75, PASI90, PASI100, and PGA response upon switching to CZP 400mg Q2W following OLE Entry; during the Open-label Treatment Period, PASI100 responder rates generally increased through OLE 96 (32.4%) while some decline in PASI75, PASI90, and PGA responder rates were observed through OLE 96 (70.6%, 52.9%, and 55.9%, respectively).
- Subjects who relapsed while on any dose of CZP during the Maintenance Treatment Period, regained PASI75, PASI90, and PGA response following OLE Entry that was generally maintained through OLE 96 (43.8%, 25.0%, and 37.5, respectively); however, the response was to a lesser extent than those subjects who relapsed while on PBO. Among subjects who relapsed while on any dose of CZP, too few subjects achieved PASI100 at any point during the Open-label Treatment Period to draw conclusions.
- Improvements from Baseline in the DLQI and DLQI remission rates increased from Week 16 and were generally maintained from OLE Entry through OLE 96, with 50% of subjects in the PBO/CZP 400mg Q2W group and 31.1% of subjects in the Any CZP/CZP 400mg Q2W group achieving DLQI remission at OLE 96.

**Pharmacokinetics results:**

The observed plasma concentrations of CZP were consistent with the dosing regimens for the different treatment groups.

The lower plasma concentrations of CZP observed in subjects who were anti-CZP antibody (ADAb) positive were as expected.

**Immunogenicity results:**

During the Combined Initial and Maintenance Treatment Period, as expected, the percentage of subjects who were anti-CZP antibody positive was higher in subjects in the CZP 200mg Q2W group than in the CZP 400mg Q2W group. In the CZP 200mg Q2W group the percentages of subjects who were anti-CZP antibody positive at Weeks 16 and 48 were 19.2% and 21.2% (19 and 21 of 99 subjects), respectively, while the corresponding percentages of subjects in the CZP 400mg Q2W group who were anti-CZP antibody positive at Weeks 16 and 48 were 4.3% and 5.4% (4 and 5 of 92 subjects), respectively. Both groups included subjects who escaped from their initial treatment to CZP 400mg Q2W at Week 16.

There appears to be an association between anti-CZP antibody positivity and lower efficacy in some subjects, presumably when anti-CZP antibody positivity leads to a significant lowering of plasma concentration of CZP.

Of the 362 subjects in the PKS, only 7 subjects were anti-CZP antibody positive for the first time during the Open-label Treatment Period, 4 subjects while receiving CZP 200mg Q2W and 3 subjects while receiving CZP 400mg Q2W.

While persistent high anti-CZP antibody responses with resulting falls in CZP concentration were observed in some subjects, in other subjects the anti-CZP antibody responses were transient and often associated with only transient falls in the CZP concentration.

**Safety results:**

*Safety conclusions from the 16-week Initial Treatment Period*

Analyses of treatment-emergent AEs (TEAEs) for the Initial Treatment Period were summarized by Weeks 0 to 12 for the 4 randomized treatment groups (CZP 200mg Q2W, CZP 400mg Q2W, ETN, and placebo) and by Weeks 0 to 16 without the ETN group since these subjects completed ETN treatment by Week 12. The trends for the CZP and placebo groups were similar when summarized by the first 12 weeks or the first 16 weeks.

- The safety profile was comparable between CZP treatment and placebo during the Initial Treatment Period (Weeks 0 to 12) with the exception of higher incidence rates (IRs) with CZP treatment for Investigations (particularly in the CZP 400mg Q2W group) as well as Injury, poisoning, and procedural complications (neither was driven by a particular preferred term [PT] or treatment group). Of the most common PTs (incidence of >5% in any treatment group), none occurred at a higher incidence in the All CZP group compared with the placebo group.
- Overall, most TEAEs were mild or moderate in intensity and were not considered by the Investigator as related to study medication.
- While the incidence of SAEs overall was marginally higher in the CZP 400mg Q2W group compared with the CZP 200mg Q2W group during the Initial Treatment Period, both groups had a lower incidence than the placebo group. The incidences of TEAEs overall, the most common TEAEs by PT, and TEAEs leading to discontinuation were similar between the CZP 200mg Q2W and CZP 400mg Q2W groups.
- The safety profile of CZP treatment for 12 weeks, including the type and incidence of TEAEs, was comparable to ETN treatment. In particular, the incidence and IRs were similar between both CZP groups and ETN for hepatic events and markedly abnormal liver function test (LFT) elevations. The incidences of TEAEs leading to discontinuation and injection site reactions were marginally higher in the ETN group compared with the 2 CZP groups.

*Safety conclusions from the 32-week Maintenance Treatment Period (Weeks 16 to 48)*

- During the 32-week Maintenance Treatment Period, the overall incidences of TEAEs, severe TEAEs, related AEs, SAEs, and TEAEs leading to discontinuation were generally similar across CZP treatment groups, although some variability was noted with the CZP 400 Q4W group relative to the other CZP groups, which is likely due to the relatively low number of subjects in that group.
- Continuing CZP treatment at either dose (200mg Q2W or 400mg Q2W) for an additional 32 weeks beyond the Initial Treatment Period of 16 weeks was not associated with any increased risk based on exposure-adjusted IRs.

*Safety conclusions from the entire study (Week 0 to OLE 96 [Initial, Maintenance and Open-label Treatment Periods])*

- Overall, the safety profile for up to 144 weeks of CZP treatment was consistent with that expected in subjects with moderate to severe chronic plaque psoriasis receiving an anti-TNFα agent and with the known profile of CZP. No new safety signals were identified for any dose tested following a review of TEAEs, biochemistry values, hematology values, or vital signs that have not been previously observed in other studies with CZP in subjects with psoriasis or other indications.
- Most TEAEs were mild or moderate in intensity, were not considered by the Investigator as related to study medication, and did not lead to discontinuation of CZP.
- Overall, the safety profile was comparable between the 200mg Q2W dose and the 400mg Q2W dose with no apparent dose effect with long-term CZP exposure.
- The exposure-adjusted IR of any SAE, including serious infections and other TEAEs of interest, such

as malignancies, cardiovascular events, hematopoietic cytopenias, and bleeding events, during the entire study was low for both the CZP 200mg Q2W and CZP 400mg Q2W doses (Table 2).

- There was 1 diagnosis of primary progressive multiple sclerosis during the study with symptoms of gait disturbance identified predating entry into the clinical study (no AE occurred during the study).
- No lupus or lupus-like events and no serious skin reactions were reported during the study.
- Furthermore, the results suggest that there was no increase in the exposure-adjusted IR of any TEAEs or SAEs for the CZP 400mg Q2W group compared with the CZP 200mg Q2W group after long-term CZP exposure.
- Maintaining CZP treatment at either dose (200mg Q2W or 400mg Q2W) for up to an additional 128 weeks beyond the Initial Treatment Period of 16 weeks was not associated with an increased safety risk compared with the Initial Treatment Period in this study.

## Table 2: Comparison of incidence and exposure-adjusted IRs across treatment periods for select safety parameters

| Category / Period | CZP 200mg Q2W | | | CZP 400mg Q2W | | | All CZP | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n (%) | IR | N | n (%) | IR | N | n (%) | IR |
| **TEAEs** | | | | | | | | | |
| Initial (Weeks 0 to12) [a] | 165 | 78 (47.3) | 299.48 | 167 | 82 (49.1) | 309.21 | 332 | 160 (48.2) | 304.39 |
| Combined Initial and Maintenance (Weeks 0 to 48) [b] | 265 | 175 (66.0) | 214.03 | 354 | 230 (65.0) | 201.33 | 520 | 360 (69.2) | 195.60 |
| Open-label (Week 48 to OLE 96) [c] | 291 | 197 (67.7) | 83.32 | 256 | 155 (60.5) | 79.06 | 472 | 327 (69.3) | 78.61 |
| Combined Initial, Maintenance, and Open-label (Week 0 to OLE 96) [b] | 373 | 276 (74.0) | 129.46 | 412 | 299 (72.6) | 132.74 | 545 | 446 (81.8) | 119.85 |
| **SAEs** | | | | | | | | | |
| Initial (Weeks 0 to12) [a] | 165 | 1 (0.6) | 2.68 | 167 | 4 (2.4) | 10.56 | 332 | 5 (1.5) | 6.65 |
| Combined Initial and Maintenance (Weeks 0 to 48) [b] | 265 | 12 (4.5) | 7.69 | 354 | 23 (6.5) | 11.25 | 520 | 35 (6.7) | 9.80 |
| Open-label (Week 48 to OLE 96) [c] | 291 | 27 (9.3) | 6.00 | 256 | 28 (10.9) | 7.88 | 472 | 55 (11.7) | 6.83 |
| Combined Initial, Maintenance, and Open-label (Week 0 to OLE 96) [b] | 373 | 37 (9.9) | 6.28 | 412 | 51 (12.4) | 9.41 | 545 | 86 (15.8) | 7.67 |
| **Serious infections** | | | | | | | | | |
| Combined Initial, Maintenance, and Open-label (Week 0 to OLE 96) [b] | 373 | 8 (2.1) | 1.29 | 412 | 10 (2.4) | 1.71 | 545 | 18 (3.3) | 1.49 |
| **Serious opportunistic infections** | | | | | | | | | |
| Combined Initial, Maintenance, and Open-label (Week 0 to OLE 96) [b] | 373 | 1 (0.3) | 0.16 | 412 | 2 (0.5) | 0.34 | 545 | 3 (0.6) | 0.25 |

## Table 2: Comparison of incidence and exposure-adjusted IRs across treatment periods for select safety parameters

| Category / Period | CZP 200mg Q2W | | | CZP 400mg Q2W | | | All CZP | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n (%) | IR | N | n (%) | IR | N | n (%) | IR |
| **Malignancies** | | | | | | | | | |
| Combined Initial, Maintenance, and Open-label (Week 0 to OLE 96) [b] | 373 | 4 (1.1) | 0.63 | 412 | 4 (1.0) | 0.68 | 545 | 6 (1.1) | 0.49 |
| **Serious cardiovascular events** | | | | | | | | | |
| Combined Initial, Maintenance, and Open-label (Week 0 to OLE 96) [b] | 373 | 2 (0.5) | 0.32 | 412 | 3 (0.7) | 0.51 | 545 | 5 (0.9) | 0.41 |
| **Demyelinating-like disorders** | | | | | | | | | |
| Combined Initial, Maintenance, and Open-label (Week 0 to OLE 96) [b] | 373 | 0 | - | 412 | 1 (0.2) | 0.17 | 545 | 1 (0.2) | 0.08 |
| **Hematopoietic cytopenias** | | | | | | | | | |
| Combined Initial, Maintenance, and Open-label (Week 0 to OLE 96) [b] | 373 | 0 | - | 412 | 0 | - | 545 | 0 | - |
| **Serious bleeding events** | | | | | | | | | |
| Combined Initial, Maintenance, and Open-label (Week 0 to OLE 96) [b] | 373 | 1 (0.3) | 0.16 | 412 | 3 (0.7) | 0.51 | 545 | 4 (0.7) | 0.33 |

CZP=certolizumab pegol; IR=incidence rate; OLE=Open-label Extension; Q2W=every 2 weeks; SAE=serious adverse event; TEAE=treatment-emergent adverse event

[a] Analyzed for the Safety Set.
[b] Analyzed for the Treated with CZP Set.
[c] Analyzed for the Open-label Extension Set.

**Conclusions:**

Treatment with CZP 200mg Q2W and CZP 400mg Q2W resulted in clinically meaningful and statistically significant improvements over placebo in PSO area and severity (assessed by PASI75 and PASI90 responder rates), and global physician assessment of disease activity (assessed by PGA responder rate) through 16 weeks of treatment. Long-term efficacy with continuous CZP treatment was demonstrated in this study as these initial improvements were consistently maintained through the 32-week Double-blind Maintenance Treatment Period and continued to be maintained up to 96 weeks in the Open-label Treatment Period.

A consistent trend was observed across the spectrum of efficacy endpoints that treatment with CZP 400mg Q2W in the Initial and Maintenance Treatment Periods provided greater efficacy than reducing the dose to CZP 200mg Q2W after PASI75 was achieved or treatment with CZP 200mg Q2W in both the Initial and Maintenance Treatment Periods.

Those subjects who were initially treated with CZP and rerandomized to placebo for maintenance treatment had a considerable loss of efficacy response over time, but no subjects experienced a rebound effect defined as a >125% increase from Baseline in PASI score within 14 weeks after the last dose of CZP treatment during the Initial Treatment Period. The subjects who were treated with placebo during the Maintenance Treatment Period and did not relapse regained response in the Open-label Treatment Period after resuming treatment with CZP that was similar to the response observed in the other CZP treatment groups.

Among subjects who relapsed (ie, did not achieve a PASI50 response at any point during the Maintenance Treatment Period), efficacy response was generally regained and then maintained through the Open-label Treatment Period, but not to the same level of response of subjects who did not relapse. In addition, the response among subjects who relapsed while on any dose of CZP was to a lesser extent than those subjects who relapsed while on placebo.

The safety profile for CZP in subjects with moderate to severe chronic plaque PSO in PS0003 was similar to that observed in previous studies with CZP and was consistent with that expected in subjects receiving anti-TNFα therapy. No notable differences were observed in the safety profile between CZP 200mg Q2W and CZP 400mg Q2W with no increased risk observed with higher or longer exposure to CZP. No new safety signals have been identified following CZP treatment for up to 144 weeks. Overall, considering both efficacy and safety results, this study demonstrated a positive benefit-risk balance of CZP treatment with CZP 200mg Q2W and CZP 400mg Q2W in subjects with moderate to severe PSO.

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