Clinical Review

Administrative Application Information

Category	Application Information
Application type	Efficacy Supplement
Application number(s)	BLA 125160/S305 (SDN 2321)
Priority or standard	Standard
Submit date(s)	4/14/2022
Received date(s)	4/14/2022
PDUFA goal date	2/14/2023
Division/office	Division of Gastroenterology (DG)
Clinical Reviewer	Anil Nayyar, MBBS, MD, DM
Signatory	Tara Altepeter, MD Associate Director for Therapeutic Review
Review completion date	12/22/2022
Established/proper name	Certolizumab pegol
Proprietary name	Cimzia
Pharmacologic class	Tumor necrosis factor-alpha blocker
Applicant	UCB Inc.
Dosage form(s)/formulation(s)	Subcutaneous injection
Applicant proposed dosing regimen	Not applicable
Applicant proposed indication(s)/ population(s)	Not applicable
Regulatory action	Approval - change in labeling pediatric section 8.4
Approved dosage (if applicable)	Not applicable
Approved indication(s)/ population(s) (if applicable)	Not applicable
Approved SNOMED term for indication (if applicable)	Not Applicable

Table of Contents

1. Introduction and Background

Cimzia (CZP; certolizumab pegol), a tumor necrosis factor-α (TNF-α) blocker, was approved in 2008 for the treatment of adults with moderately to severely active Crohn's Disease (CD); the approved induction dose is CZP 400 mg, administered by subcutaneous (SC) injection, at Weeks 0, 2, and 4, followed by 400 mg Q4W for patients who responded to induction treatment at Week 6. CZP is also approved for the treatment of moderately to severely active rheumatoid arthritis (RA), active psoriatic arthritis, active ankylosing spondylitis, active non-radiographic axial spondyloarthritis, and subjects with moderately to severe plaque psoriasis who are candidates for the systemic therapy or phototherapy.

At the time of approval of CZP for CD, the Applicant was asked to conduct a study to assess the safety and efficacy of CZP in pediatric patients under the following postmarketing requirement.

> **PMR 2653-1**: A Phase II Open-Label Multi-Center Study to Assess the Safety and Efficacy of Certolizumab pegol in Children and Adolescents with Active Crohn's Disease.

The objectives of the PMR study were to evaluate the pharmacokinetics, safety, and clinical response, in pediatric patients, 6-17 years of age[1] with moderately to severely active CD, treated with CZP. The timelines were as follows:

> *Protocol Submission:* September 2008
> *Study Start Date:* June 2009
> *Final Report Submission:* October 2013[2]

The Applicant submitted this pediatric efficacy supplement (S-305) to fulfil the PMR 2653-1. The objective is to update the pediatric use section of the labeling with the findings of the PMR Study (CDP870-035). The Applicant does not intend to pursue a pediatric indication for CZP (for details see Section 2, Regulatory History).

2. Regulatory History

The pediatric PMR study (CDP870-035) was initiated in April 2009 and enrolled 99 subjects. Due to a higher-than-expected number of premature withdrawals (primarily due to lack of efficacy), the Applicant was asked to stop enrollment by the Data Safety Monitoring Board in June 2011. The Applicant notified the FDA of the enrollment suspension on June 14, 2011. The Division met with the Applicant on April 17, 2012, to discuss the preliminary findings from the suspended trial and a path forward; the study enrollment was terminated following data review and discussions in May 2012.

A total of 16 subjects, who either had completed the Study CDP870-035 or were still enrolled in that study at the time the study was terminated, were enrolled in another study (CR0012) to assess primarily the long-term safety. Subjects in the long-term safety study (CR0012) were continued on the doses they were receiving during the study CDP870-035. The Applicant proposed to conduct a new pediatric study (CD0003) and had several meetings with the Division to discuss various aspects of the proposed new study. In 2017, an agreement was reached on the proposed phase 2b, adaptive design, dose ranging study protocol (C87035). However, after the feasibility assessment, it was estimated that the study might take up to 15 years to enroll ~250 patients. Subsequently the Applicant submitted a revised study protocol and proposed (b) (4)

[1] Pediatric studies in children aged 0 to 5 years were waived as studies in this age group would be impossible or highly impractical due to the small number of pediatric CD patients <6 years of age.
[2] FDA later extended the submission date of the study report to January 2024.

(b) (4)

Issues related to the delay in conducting the PMR 2653-1 study were discussed with the Pediatric Research Committee (PeRC) in September 2020. Some of the key issues discussed included the long time taken by the Applicant to identify a more optimal pediatric dosing regimen, as well as that the proposed trial may take approximately 7-8 years for completion. The Committee members were concerned as to whether further assessment of the drug will provide a public health benefit, especially in view of the other marketed drugs available for the treatment of adult patients with IBD and other classes of drugs and biologics in development for this indication in pediatric patients.

The PeRC recommended releasing the Applicant from this PREA PMR on the basis that the product does not provide a meaningful benefit over existing therapies, the doses already studied failed to show a treatment effect, and it is unlikely to be used by a substantial number of patients due to the availability of other drugs.

Prior to this discussion with PeRC, the Division had asked the Applicant to submit the study feasibility assessment report. The Applicant appeared to be taking appropriate steps to design a program to assess efficacy and safety of CZP in pediatric patients with CD. The Division continued to work with the Applicant to explore if an efficacious dose could be identified by studying higher exposures in pediatric patients, which might provide a subcutaneous treatment option that is administered less frequently than the approved SC alternative within the same drug class, adalimumab. Therefore, releasing this PREA requirement was postponed until the final feasibility assessment report was submitted.

The Division received updated information on the feasibility assessment of the proposed Study CD0003 in May 2021 that included evaluation of several aspects e.g., pre-qualification assessments to identify suitable sites, understanding the willingness of the investigators to participate in the study, an estimation of the likely duration of study enrollment, and timeline for completion of the study. The Applicant contacted approximately 300 investigators, and only 10 sites expressed interest in participating in Study CD0003. As per projections based on the available investigators and sites, the last study participant was expected to be enrolled by January 2032; the Applicant would have provided the clinical study report with Week 52 data no sooner than April 2033.

After the submission of feasibility assessment report, the Applicant had a meeting with the Division in June 2021 regarding the impracticality of conducting the pediatric study in an acceptable time frame. The Applicant proposed to utilize data from pediatric studies CDP870-035 and CR0012 to fulfill the requirement for PMR 2653-1 and intended to provide a pediatric assessment from these studies to update labeling but not to pursue a pediatric indication.

The feasibility assessment conducted by the Applicant was considered reasonable and the Division agreed that it was impractical to perform the proposed Study CD0003. The Applicant was asked to submit a supplemental BLA with the study reports for both Studies CDP870-035 and CR0012 as well as update the pediatric use section of the labeling with the findings of the two studies.

3. Summary of Clinical Studies

The study design, efficacy and/or safety based on the two studies (CDP870-035 and CR0012) are summarized.

3.1. Study CDP870-035

3.1.1. Study design

Study CDP870-035 was an open-label Phase 3, randomized, multiple-dose, multicenter, parallel-group, 2-arm study to evaluate the pharmacokinetics, safety, and clinical response of pediatric patients, 6-17 years of age (weighing ≥20kg i.e., 44lb), with moderately to severely active CD treated with CZP.

A total of 160 subjects with a definitive diagnosis of active CD (subject having PCDAI >30) at screening, that was confirmed at least 2 months prior to screening by radiological, endoscopic, or histological evidence were planned to be enrolled in the induction period and 100 subjects were planned to be randomized, in a 1:1 ratio (50 subjects to the CZP high-dose group and 50 subjects to the CZP low-dose group) in the maintenance period. The Safety Population included all subjects enrolled in the study who received at least 1 injection of study treatment and efficacy evaluation was performed in the Full Analysis Set (FAS) which included subjects, irrespective of any protocol deviations, who received at least 1 injection of study treatment and had at least 1 efficacy measurement after the first injection. For details of the inclusion and exclusion criteria see Appendix A.

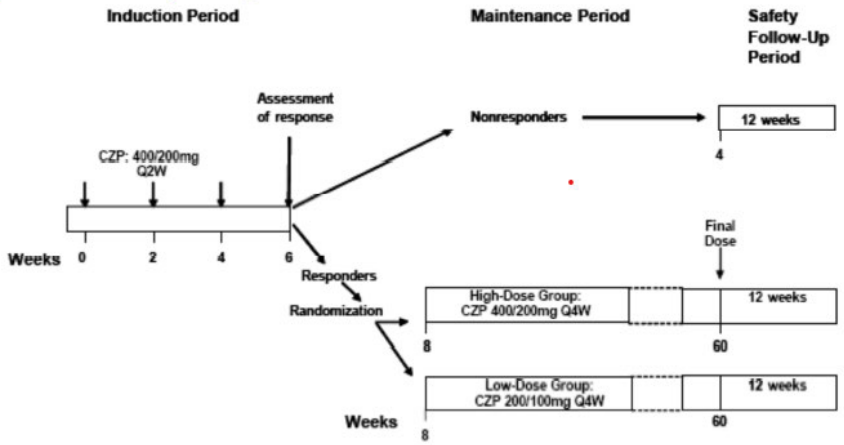
During the induction period (Weeks 0 to 6) of the study, subjects were administered weight based CZP (400 mg for subjects ≥40kg, and 200 mg for subjects weighing between 20 to <40kg), subcutaneously every 2 weeks (Q2W) for total of three times.

Subjects who showed a clinical response at Week 6 (defined as a decrease in the Pediatric CD Activity Index [PCDAI] score of ≥15 points from Week 0 and a total PCDAI score ≤30 points) were randomized in a 1:1 ratio to either high dose group or low dose group and received the following weight-based SC doses of CZP during the maintenance period, once every 4 weeks (Q4W) from Weeks 8 to 60.

- High-Dose group: CZP 400 mg for subjects ≥40 kg or 200 mg for subjects 20 to <40kg.
- Low-Dose group: CZP 200 mg for subjects ≥40 kg or 100 mg for subjects 20 to <40kg.

Subjects were stratified by age group (6 to 11 years and 12 to 17 years) and prior use of anti-TNF-α therapy; stratification by prior anti-TNF-α therapy was not enforced. Subjects who did not respond at Week 6 were withdrawn from the study (**Error! Reference source not found.**)

Figure 1: Schematic of the study design (Study CDP870-035)



Abbreviations: CZP, certolizumab pegol; Q2W, every 2 weeks; Q4W, every 4 weeks
Source: Figure 3-1 of the clinical study report (Study CDP870-035*)*

Subjects who showed loss of response during the maintenance period from Week 8 onwards received reinduction and maintenance treatments as described below. Loss of response was defined as an

increase in PCDAI score of ≥15 points compared to Week 6 at 2 consecutive visits at least 1 week apart, or an overall PCDAI score >30 points at any time during the maintenance period.

- Reinduction treatment: Subjects ≥40 kg received reinduction with CZP 400 mg, and subjects 20 to <40 kg received CZP 200 mg SC, Q2W for a total of 3 administrations.
- Maintenance treatment: Subjects ≥40 kg received CZP 400 mg SC Q4W, and subjects 20 to <40 kg received CZP 200 mg Q4 W, regardless of the subject's initial randomized dose group.

Briefly, subjects randomized to the high-dose maintenance group resumed the same maintenance dose following reinduction, while subjects initially randomized to the low-dose group received a higher maintenance dose of CZP for the remainder of the maintenance period. Only 1 reinduction was permitted during the maintenance period. If response was lost a second time, the subject was discontinued from the study (for details see Table 1). Tapering of corticosteroids, in subjects taking corticosteroids at baseline, was started at Week 2. However, subjects who could not tolerate the corticosteroid tapering were permitted to continue at a dose not higher than the Week 0 dose. Additionally, in the event of a flare in CD, corticosteroids could be reintroduced at the same dose as at Week 0 and corticosteroid tapering was attempted again to control symptoms. If a higher corticosteroid dose was needed, compared to Week 0, the subject was considered a treatment failure and withdrawn from the study.

Table 1: Study CDP870-035 - CZP dosing during induction and reinduction

Weight	Induction Q2W			Randomization	Maintenance Q4W	Reinduction Q2W			Post-reinduction Maintenance Q4W
	W0	W2	W4	W6	W 8 and thereafter	W0	W2	W4	W8 and thereafter
<40kg	200	200	200	Low-Dose	100	200	200	200	200
				High-Dose	200				
≥40kg	400	400	400	Low-Dose	200	400	400	400	400
				High-Dose	400				

Abbreviations: CZP, certolizumab pegol; Q2W, every 2 weeks; Q4W, every 4 weeks; W, Week.
Source: Adapted from Table 3-1 of the clinical study report.

Study assessments

During the induction period the study visits were at Weeks 1, 2, 4 and 6 and subjects were evaluated for efficacy and safety. The key assessments included, but were not limited to, the physical exam, weight, vital signs, and laboratory tests such as hematology, chemistry, C-reactive protein (CRP), antinuclear antibodies (ANA) and double stranded DNA (dsDNA), inflammatory bowel disease (IBD) serology, and plasma levels for CZP and anti-CZP. During the maintenance period, subjects had study visits every 4 weeks. Additional assessments included bone markers (osteocalcin, bone specific alkaline phosphatase, and n-telopeptides), wrist x-ray, and tanner stage (for details of the study assessments during the trial see Appendix B).

The original protocol included several efficacy variables. However, due to the premature termination of the study the Applicant analyzed only limited efficacy variables, as described below (for details of the originally planned efficacy variables see Appendix C). Note that the interpretation of efficacy results was difficult because of the mix of low and high CZP maintenance doses in the low dose group due to reinduction followed by a higher maintenance dose; additionally, there were a small number of subjects who completed the maintenance period. Furthermore, missing data were a major limitation based on the high number of premature discontinuations (see disposition Table 2).

Following efficacy variables were analyzed to support efficacy endpoints:

1. **Pediatric Crohn's Disease Activity Index (PCDAI)**
   PCDAI is a modification of the Crohn's disease activity index (CDAI), which is the accepted instrument to measure CD disease activity in clinical studies with adults. The PCDAI consists of 4 domains (laboratory, height/weight, examination, and history) with several assessments that are converted into a PCDAI score which can range from 0 to 100 points, with a higher score indicating more severe disease activity. In comparison with the CDAI, the PCDAI decreases the weighting given to subjective historical terms and adds height velocity and erythrocyte sedimentation rate (ESR) to the laboratory measures.[3, 4] The Investigator calculated subjects' PCDAI scores at Weeks 0, 2, 4, 6, 8, 12, 24, 36, 48, 60, and 62, or when a subject lost response during the study. PCDAI calculations were based upon a 1-week (7-day) recall of symptoms, as well as values for hematocrit, ESR, and albumin from the same clinic visit. The questionnaire is provided in Appendix D.

2. **C-reactive protein**
   Levels of CRP were assessed at screening (Week -6 to 0) and at Weeks 0, 2, 4, 6, 8, 12, 24, 36, 48, and 62. Note that CRP is a nonspecific marker of inflammation, but can be elevated by other conditions such as infection, injury, smoking, etc. Therefore, while a decrease in CRP, in patients with active CD, in response to therapy, may be considered supportive, it is not objective evidence that the drug has a beneficial effect on gut inflammation.[5]

3. **Erythrocyte sedimentation rate**
   The ESR, another nonspecific biomarker of inflammation, was assessed at screening (Week -6 to 0) and at Weeks 0, 2, 4, 6, 8, 12, 24, 28, 36, 48, 60, and 62.

4. **Tanner stages**
   Assessments of developmental stage on external genitalia and pubic hair (boys), and on breast and pubic hair (girls) were performed to determine Tanner stages at screening (Week -6 to 0) and at Weeks 36 and 62.

5. **IMPACT-III questionnaire**
   The IMPACT-III questionnaire was administered at Weeks 0, 6, 36, and 62; this is a disease-specific health-related quality of life (HRQOL) questionnaire, which was originally developed by Griffiths *et al*[6] and Otley *et al*.[7] for use in children with IBD. The IMPACT-III is a modified version of the original questionnaire, which contains 35 questions assessing the following 6 domains: bowel symptoms, systemic symptoms, emotional functioning, social functioning, body image, and treatment/interventions. For each question, there are 5 Likert response options. Total IMPACT scores range from 35 to 185 with higher scores indicating better HRQOL. Note that

[3] Hyams et al., Development and validation of a pediatric Crohn's disease activity index. J Pediatr Gastroenterol Nutr. 1991; 12:439-447.
[4] Otley et al. Assessing activity of pediatric Crohn's disease: which index to use? Gastroenterology. 1999; 116:527-531).
[5] Vermeire S et al. Laboratory markers in IBD: useful, magic, or unnecessary toys? Gut. 2006; 55:426-31.
[6] Griffiths AM et al. Development of a quality-of-life index for pediatric inflammatory bowel disease: dealing with differences related to age and IBD type. J Pediatr Gastroenterol Nutr. 1999;28: S46-S52.
[7] Otley A et al. The IMPACT questionnaire: a valid measure of health-related quality of life in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2002; 35:557-563.

IMPACT III is generally used for children aged ≥10 years in North America. The questionnaire is provided in Appendix E.

3.1.2. Disposition

Subject disposition for the overall study and maintenance period is provided in Table 2 and Figure 2.

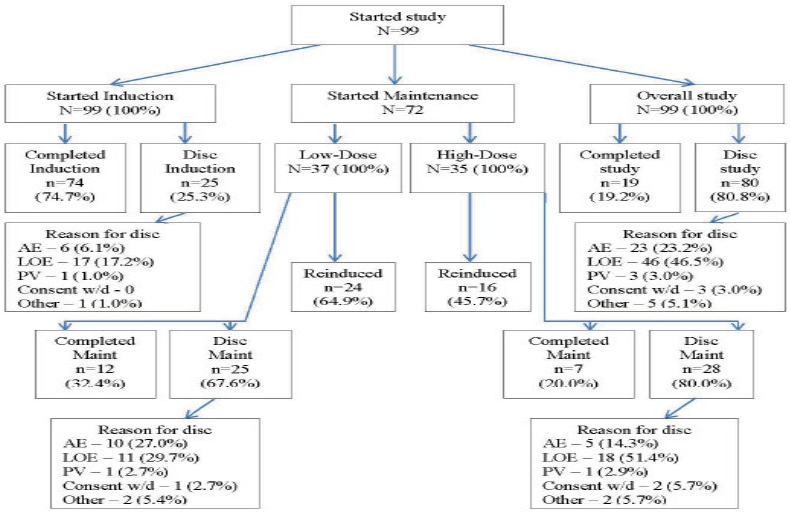
Table 2: Disposition for overall study and maintenance period (Safety population)

Study period	Induction Period	Maintenance Period		All subjects
		CZP Low-Dose	CZP High-Dose	
	N=99 n (%)	N=37 n (%)	N=35 n (%)	N=99 n (%)
Induction and Maintenance Periods				
Started period/study	99 (100)	37 (100)	35 (100)	99 (100)
Completed period/study	74 (75)	12 (32)	7 (20)	19 (19)
Discontinued	25 (25)	25 (68)	28 (80)	78 (78)
Adverse event	6 (6)	10 (27)	5 (14)	21 (21)
Lack of efficacy	17 (17)	11 (30)	18 (51)	46 (46)
Protocol violation	1 (1)	1 (3)	1 (3)	3 (3)
Consent withdrawn	0	1 (3)	2 (6)	3 (3)
Other	1 (1)	2 (5)	2 (6)	5 (5)
Maintenance Period				
		CZP Low-Dose	CZP High-Dose	All Subjects that Entered Maintenance
		N=37 n (%)	N=35 n (%)	N=72 n (%)
Started Maintenance	NA	37 (100)	35 (100)	72 (100)
Completed Maintenance	NA	12 (32)	7 (20)	19 (26)
Reinduced during Maintenance	NA	24 (65)	16 (46)	40 (56)
Discontinued Maintenance	NA	25 (68)	28 (80)	53 (74)
Adverse event	NA	10 (27)	5 (14)	15 (21)
Lack of efficacy	NA	11 (30)	18 (51)	29 (40)
Protocol violation	NA	1 (3)	1 (6)	2 (3)
Consent withdrawn	NA	1 (3)	2 (6)	3 (4)
Other	NA	2 (5)	2 (6)	4 (6)

Abbreviations: NA, not applicable

Source: Table 7-2 of the CSR (Study CDP870-035)

Figure 2: Overall disposition in the induction and maintenance periods (Safety population)



Source: Figure 7-1 of the CSR (Study CDP870035)

The study was prematurely discontinued by the DSMB, due to very high withdrawal rate and lack of efficacy. A total of 99 subjects participated in the induction period and 72 subjects entered the maintenance period (37 subjects randomized to the low-dose group and 35 subjects to the high-dose group). Overall, 19% subjects completed the entire study; 78% discontinued the study, primarily due to lack of efficacy (46%) and AE (21%).

- During the induction period 74/99 subjects (75%) completed the induction regimen and 25/99 subjects (25%) discontinued the study drug. The most common reasons for discontinuation were lack of efficacy (17%) and AE (6%).
- During the maintenance period, a large number of subjects discontinued the trial; only 12/37 (32%) of the low-dose group and 7/35 (20%) of the high-dose group subjects completed the study.

- Table ***3*** shows the extent of drug exposure during the maintenance period. The most common reasons for discontinuation were lack of efficacy (30% in the low dose and 51% in the high dose groups) and AEs (27% in the low dose and 14% in the high dose group).

Table 3: Extent of the exposure during the maintenance period

Duration of Exposure (Weeks)	Maintenance Low Dose (n/%)	Maintenance High Dose (n/%)
≥0	37 (100)	35 (100)
≥12	32 (86)	28 (80)
≥24	22 (59)	18 (51)
≥48	14 (38)	8 (23)
Completion of study	12 (32)	7 (20)

Source: Table 5.1 of the CSR (Study Medication Duration- Analysis Set: Safety Population)

Overall, AEs related to lack of efficacy included exacerbation of CD, pyrexia, arthralgia, diarrhea, abdominal pain. The common AEs related to be drug included diarrhea, abdominal pain, arthralgia, and pyrexia. Note that AEs related to drug that led to discontinuation(s), as described, are signs and symptoms associated with active Crohn's disease and suggest lack of efficacy, rather than drug associated toxicity. For details see section 3.1.6 Safety.

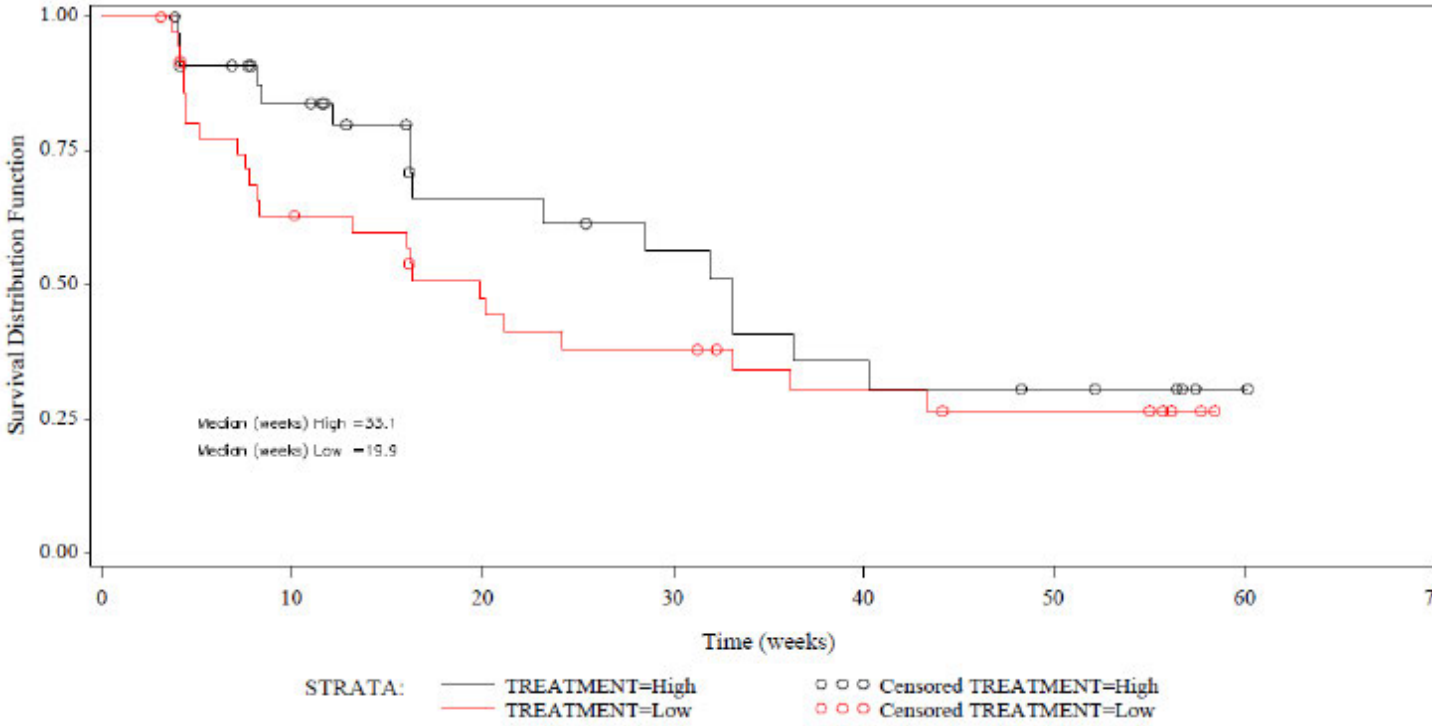
3.1.3. Reinduction treatment

A total of 40 subjects received reinduction treatment during the maintenance period; 28 of these subjects completed the entire 3-dose reinduction regimen, 7 subjects received 2 doses, and 5 subjects received only 1 dose. A numerically higher proportion (65%) of subjects in the low-dose group received reinduction treatment compared to the subjects in the high dose group (46%). Note that the observed lower rates of discontinuation and higher AE rate in the low-dose group compared to the high-dose group should be interpreted with caution; these differences as a higher proportion of subjects in the low-dose group received reinduction and were also shifted to the higher maintenance dose.

3.1.4. Time to reinduction

A total of 40 subjects received reinduction treatment during the maintenance period; there were a higher proportion [24/37 (65%)] of subjects in the low dose group compared to the high dose group [16/35 (46%)]. Figure 3 shows the time to reinduction by CZP treatment group.

Figure 3: Time to reinduction by treatment group



Source: Figure 8-1 of the CSR

In summary, a higher proportion of subjects in the low dose maintenance group received reinduction treatment compared to the high dose group (65% vs 46% respectively); additionally, the median time to reinduction treatment was shorter in the low dose group compared to subjects in the higher dose maintenance group (20 weeks vs 33 weeks, respectively).

3.1.5. Efficacy

The original protocol included several efficacy variables. However, due to the premature termination of the study, the Applicant analyzed only limited efficacy variables, as described below; no formal statistical testing was performed. For details of the originally planned efficacy variables see Appendix C.

3.1.5.1. Primary efficacy - Clinical remission

No subject achieved clinical remission (defined as subjects with PCDAI score ≤10 points) at Week 6, the end of induction period. For the maintenance period, the clinical remission rate, with 95% CI at Weeks 24 and 62 are shown in Table 4.

Table 4: Remission rates at 24 and 62 (Full analysis set)

Week	Statistics	Maintenance Period	
		CZP Low-Dose	CZP High-Dose
		N=37	N=35
24	n (%)	8 (22)	6 (17)
	CI	8.4, 34.9	4.7, 29.6
62	n (%)	9 (24)	6 (17)
	CI	10.5, 38.1	4.7, 29.6

Abbreviations: CI, confidence interval
Source: Adapted from Table 8-1 of the CSR (Study CDP870-035)

A higher proportion of subjects in the low-dose group achieved clinical remission at Weeks 24 [8/37 (22%)] and 62 [9/37 (24%)] compared to subjects in the high dose group [6/35 (17%)] at both Weeks 24 and 62. The numerically higher remission rates in the low dose group should be interpreted with caution, as they may be due to a higher proportion of subjects in this arm receiving reinduction doses, who were then continued on higher maintenance doses after the reinduction treatment. Therefore, the "low dose" group does not reflect true administration of the lower dose for the full maintenance period.

Subgroup analyses for clinical remission based on weight, age, sex, anti-drug antibody status, corticosteroid use at baseline, and prior anti-TNF-α use were not performed because of very high withdrawal rate due to lack of efficacy resulting in small number of evaluable subjects in each subgroup as well as due to subjects receiving mix of low and high maintenance doses.

3.1.5.2. Secondary efficacy

3.1.5.2.1. Clinical response

Seventy two subjects achieved clinical response (defined as a decrease from baseline in PCDAI score of ≥15 points and a total PCDAI score ≤30 points) at Week 6, the end of induction period. For the maintenance period, the clinical response rates with 95% CI at Weeks 24, and 62 are shown in Table 5.

Table 5: Response at Weeks 6, 24, and 62 (Full analyses set)

Week	Statistic	Maintenance Period	
		CZP Low-Dose	CZP High-Dose
		N=37	N=35
24	n (%)	14 (37.8)	11 (31.4)
	95% CI	22.2, 53.5	16.0, 46.8
62	n (%)	11 (29.7)	7 (20.0)
	95% CI	15.0, 44.5	6.7, 33.3

Abbreviations: CI, confidence interval
Source: Adapted from Table 8-5 of the CSR (study CDP870-035)

Similar to the results for clinical remission, a higher proportion of subjects achieved clinical response in the low-dose group [14/37 (38%) and 11/37 (30%) at Weeks 24 and 62, respectively] compared to

subjects in high dose group [11/35 (31%) and 7/35 (20%) at Weeks 24 and 62, respectively]. Numerically higher clinical response rate in the low dose group is likely due to a higher proportion of subjects receiving reinduction doses and continued on higher maintenance doses after the reinduction treatment.

No subgroup analyses for clinical response based on weight, age, sex, anti-CZP antibody status, corticosteroid use at baseline, and prior anti-TNF-α use were performed due to small number of subjects in subgroups.

3.1.5.2.2. Change in CRP

Overall, no meaningful change from baseline was observed in geometric mean CRP levels or geometric mean ratio at Weeks 6, 24, and 62. No meaningful differences were noted between the CZP dose groups; note that this is based on the number of subjects remaining in the study at each timepoint.

3.1.5.2.3. Change in erythrocyte sedimentation rate

Overall, no meaningful change was noted in geometric mean ESR or geometric mean ratio at Weeks 6, 24, and 62 compared to baseline. No meaningful differences were noted between the CZP dose groups; note that this is based on the number of subjects remaining in the study at each timepoint.

3.1.5.2.4. Tanner stage

Data for change in Tanner Stage were available for only 33/97 subjects at Week 36 and 17/97 subjects at Week 62. Due to the substantial missing data, no meaningful assessment can be made.

3.1.5.2.5. Corticosteroid tapering

Overall, 55/97 (57%) subjects were on corticosteroids at the time of study enrollment. During the maintenance period, similar proportion of subjects in the low dose and high dose groups [21/37 (57%) and 20/35 (57%), respectively], were on corticosteroids at baseline. Fifteen of the 21 (71%) and 13/35 (65%) subjects were able to taper the corticosteroids during the study; 5/21 (24%) and 3/20 (15%) subjects were considered in steroid free remission in the low and high dose group respectively at the time of the last available PCDAI score. These results should be interpreted with caution because only approximately 25% subjects completed the study. Additionally, there is a limitation of using PCDAI data from the last visit, before the study completion, for calculation of steroid free remission.[8]

3.1.5.2.6. Subject-reported outcomes (HRQOL)

Table 6 shows change from baseline in IMPACT-III scores during the maintenance period at Weeks 24, and 62. Note that the data were available for only 31 of the 72 (43%) subjects and 18/72 (25%) subjects at Weeks 36 and 62 respectively.

[8] No longer requiring corticosteroids at the end of the study was defined as 84 days past the last dose of study medication. Remission was assessed at the last visit where PCDAI data is available (which in many cases was not Week 62, given the premature termination of the study).

Table 6: Change from baseline in IMPACT-III scores at Weeks 24, and 62

Week	Statistic	Maintenance Period	
		CZP Low-Dose	CZP High-Dose
		N=37	N=35
36	n	19	12
	Baseline mean (SD)*	108.7 (19.56)	113.7 (27.06)
	Mean change (SD)	21.3 (14.99)	10.8 (26.68)
	95% CI for mean	14.1, 28.5	-6.2, 27.7
62	n	13	5
	Baseline mean (SD)*	111.8 (18.24)	106.2 (29.72)
	Mean change (SD)	29.8 (22.24)	3.6 (22.68)
	95% CI for mean	16.4, 43.3	-24.6, 31.8

* Baseline mean of IMPACT-III scores as presented are based on data from subjects that had values at the respective timepoint (Week 36 or 62).
Abbreviations: SD, standard deviation
Source: Adapted from Table 8-14 of the CSR (study CDP870-035)

Mean change in IMPACT-III scores at Weeks 36 and 62 were lower in the high dose group compared to the low dose group. The results in the low dose group showed a mean change of 21 and 30 at Weeks 36 and 62 and appear to be suggestive of clinical improvement as reported by Otley *et al* [9] [an increase of 10.8 points in IMAPCT-III score correlated with a 15-point decrease in PCDAI (i.e., clinical response)]. However, the data based on a small number of subjects completing the study (18/72; 25%), cannot be considered adequate to support demonstration of a meaningful clinical improvement. Patients who discontinued due to lack of efficacy and therefore did not have data at the timepoint of interest are not included in this analysis, which biases the results towards showing improvement.

Overall, the clinical, laboratory parameters, and patient reported outcomes do not support efficacy of the drug in pediatric population, 6 years to 17 years of age, at the doses evaluated. A high proportion of subjects required reinduction treatment due to loss of response early during the maintenance period. Despite receiving reinduction treatments a large proportion of subjects (~80%) discontinued the study due to lack of efficacy resulting in limited data generated to assess efficacy. Furthermore, due to higher proportion of subjects in the low dose group receiving reinduction treatment with subsequent high maintenance dose made the data uninterpretable for comparison of efficacy for the low and high dose groups.

3.1.6. Safety

The key safety assessments, in 99 subjects enrolled, included physical examination, vital signs, height, weight, and laboratory tests such as hematology, chemistry, CRP, ANA and dsDNA, IBD serology, and plasma levels for CZP and anti-CZP and adverse event recording.

Overall, 91/99 (92%) subjects reported at least 1 TEAE during the study; drug related TEAEs and serious TEAEs were reported by 66 /99 (67%) and 34/99 (34%) subjects, respectively. Discontinuations due to TEAEs occurred in 27/99 (27%) subjects. Injection reactions were reported by 27/99 (27%) subjects.

During the maintenance period, a higher proportion of subjects in the low dose group discontinued the study drug [10/37 (27%)] and had severe TEAEs [9/27 (24%)] compared to the high dose group [6/35 (17%) subjects discontinued and 4/35 (11%) had severe TEAEs] (Table 7). No trends were observed in the safety findings in the subgroup analyses by weight (<40kg vs ≥40kg) or age (6 to 11 years vs 12 to 17 years).

[9] Otley AR et al. IMPACT-III Is a valid, reliable, and responsive measure of health-related quality of life in pediatric Crohn's disease. J Pediatr Gastroenterol Nutr. 2006;43: S49.

Table 7: Overview of the treatment emergent adverse events

Adverse Events	Induction Period	Maintenance Period		All subjects (Induction and Maintenance Periods)
		CZP Low-Dose	CZP High-Dose	
	N=99 n (%)	N=37 n (%)	N=35 n (%)	N=99 n (%)
At least 1 TEAE	77 (78)	31 (84)	32 (91)	91 (92)
Serious TEAEs	19 (19)	7 (19)	8 (23)	34 (34)
TEAEs leading to discontinuation	11 (11)	10 (27)	6 (17)	27 (27)
Drug-related TEAEs	51 (51)	19 (51)	21 (60)	66 (67)
Maximum intensity				
Mild	24 (24)	2 (5)	10 (29)	9 (9)
Moderate	38 (38)	20 (54)	18 (51)	55 (56)
Severe	15 (15)	9 (24)	4 (11)	27 (27)
TEAEs leading to death	0	0	0	0
Injection reactions	26 (26.3)	3 (8)	8 (23)	27 (27)

Source: Table 3-1 of the summary of safety (CDP870-035)

The most common SAEs reported were exacerbation of CD (19/99; 19%) and infections/infestations (12/99; 12%). For additional information see Appendix F.

Overall, the TEAEs reported by ≥10% of subjects included exacerbation of CD, 35/99 (35%); pyrexia, 26/99 (26%); injection site pain, 22/99 (22%); vomiting, 16/99 (16%); headache, 15/99 (15%); arthralgia, 13/99 (13%); diarrhea, 12/99 (12%); abdominal pain, 12/99 (12%); as well as nausea and upper respiratory tract infection, 11/99 (11%). Note that the predominant AEs included several preferred terms (PT) that are consistent with uncontrolled CD, including intestinal and extra-intestinal symptoms such as diarrhea, abdominal pain, arthralgia, and pyrexia; these TEAEs are suggestive of lack of efficacy rather than TEAE related to study drug. There were no new safety signals. See appendix G for details on the AEs reported by ≥5% of subjects during the trial.

AEs of special interest of serious infections were reported in 3 subjects during induction period and 9 subjects during the maintenance period; these included anal abscess, clostridial infection, primary atypical pneumonia, viral infection, gastroenteritis, viral gastroenteritis, *Clostridium diff*icile colitis, perineal abscess, viral gastroenteritis, candidiasis, salmonellosis, and oral herpes. Other AEs of special interest of elevated transaminases were reported in 3 subjects, and pancytopenia and bleeding event in 1 subject each.

Overall, 26 of the 99 (26%) subjects reported at least 1 injection site reaction. The incidences were higher during the induction period and in the CZP high-dose maintenance group compared to the low dose group. The most common event was injection site pain reported in 21/99 (21%) subjects in the induction period. During the maintenance period, a higher proportion of subjects [6/35 (17%)] in the CZP high-dose group had injection site reaction compared to the CZP low-dose group [2/37 (5.4%)]. Two subjects reported systemic reactions. One subject, age 10 years with medical history of asthma, allergic rhinitis, and impetigo reported acute events of hypersensitivity, dyspnea, and urticaria following first injection of CZP; the event resolved after administration of diphenhydramine, steroids, and salbutamol. The second subject reported delayed event of vomiting in the high dose group. Both subjects were discontinued from the study. Note that a higher incidence of injection site reactions was observed in this pediatric population compared to the incidence reported in adults (~3%; Table 3 of the Cimzia labeling). However, the results should be interpreted with caution due to different patient population as well

limitations of cross study comparison. The serious AE of hypersensitivity was reported only in one subject who had predisposing illnesses such as asthma, allergic rhinitis, and impetigo.

3.2. Study CR0012

As stated above in Section 2 above, 16 subjects (4 in low dose and 12 in high dose group) participated in Study CR0012 to assess primarily the long-term safety up to 52 weeks. Subjects in this study were continued on the doses they received during Study CDP870-035; this study also had high discontinuation rate (62% subjects discontinued the study primarily due to lack of efficacy); only 6 subjects (37%) completed the study [3 subjects (75%) in low dose and 3 subjects (25%) in the high dose groups].

In study CR0012, 10 of the 16 subjects reported at least 1 TEAE. The SAEs reported in 5 subjects included exacerbation of CD, small intestinal obstruction, anal abscess, viral gastritis, viral pancreatitis, and suicide attempt. The majority of the TEAEs were reported in system organ class (SOCs) of gastrointestinal (8 subjects), infections and infestations (5 subjects), and investigations (3 subjects). The most common TEAEs (reported by ≥2 subjects), based on PT, were abdominal pain upper (4 subjects) and exacerbation of CD, nausea, stomatitis, nasopharyngitis, pain in extremity, dizziness, and cough (2 subjects each). The majority of the SAEs and common TEAEs were reported in the high dose maintenance treatment group.

No adverse events of special interest as well as TEAEs of hypersensitivity, injection site reactions, systemic injection reactions, or anaphylaxis were reported during the study. Given the very small sample size, and other limitations (such as selection bias for those who chose to enter the extension study) no meaningful conclusions can be drawn from this limited data.

4. Overall Summary of Efficacy and Safety

Efficacy:

In studies CDP870-035 and CR0012, efficacy was not demonstrated, at the doses evaluated, for the treatment of pediatric patients ages 6-17 years of age with active moderate to severe CD. A high proportion of subjects required reinduction treatment due to loss of response early during the maintenance period. Despite receiving reinduction treatments, a large proportion of subjects (~80%) discontinued the study due to lack of efficacy. Furthermore, a higher proportion of subjects in the low dose group receiving reinduction treatment with subsequent high maintenance dose, which made the data uninterpretable for comparison of the low and high dose groups for the maintenance treatment. It is difficult to ascertain the reasons for lack of efficacy in pediatric population. One of the possibilities could be the lack of selection of optimal doses. The pediatric doses were selected based on doses approved for the adult subjects. Note that the no exposure response was observed in adult studies for the US population, which may explain lack of efficacy at the doses evaluated during the pediatric trial.

Safety:

Based on the limited safety data available for the pediatric clinical study CDP870-035 and the long-term safety for Study CR0012, there appears to be no new safety signal; however, the safety profile of the evaluated doses cannot be fully characterized. The majority of the discontinuations due to AEs reported in Study CDP870-035 were related to lack of efficacy of the drug. Furthermore, due to high discontinuations and limited number of subjects available for analyses during the follow-up period as well as mixing of low and high doses during the maintenance period in the low dose group it is not possible to make meaningful comparison between the safety risk of low and high dose maintenance doses. Within the available (though limited) data, no clinically meaningful changes were observed in clinical hematology, biochemistry, vital signs, and EKG.

5. Labeling

5.1. The Applicant's proposal

The Applicant proposed to add the following text (underlined) in Section 8.4 Pediatric use:

Safety and effectiveness in pediatric patients have not been established. Due to its inhibition of TNFα, CIMZIA administered during pregnancy could affect immune responses in the *in utero*-exposed newborn and infant *[see Use in Specific Populations (8.1)].*

5.2. FDA's version of the labeling

(modified text in italics)

Safety and effectiveness in pediatric patients have not been established.

Cimzia was evaluated for the treatment of pediatric patients with moderately to severely active Crohn's disease. Efficacy was not demonstrated in an open-label, randomized, parallel-group, multiple dose study for a period of up to 62 weeks in 99 subjects aged 6-17 years. The study was ended prematurely because of a high number of patient discontinuations.

Due to its inhibition of TNFα, CIMZIA administered during pregnancy could affect immune responses in the *in utero*-exposed newborn and infant *[see Use in Specific Populations (8.1)].*

6. Conclusions / Recommended Regulatory Action

Efficacy was not demonstrated to support a new pediatric indication. As discussed above in Section 3.1, the majority of subjects discontinued CZP treatment. Based on the limited information available, no information can be included in Sections 1.2 (Indication), 6 (Adverse Events), and 14 (Clinical Studies) of the labeling.

The Applicant's proposal to include findings from Studies CDP870-035 and CR0012 in Section 8.4 appears generally reasonable. Edits were recommended for accurate representation of the data as summarized in Section 5.2 above. Agreement was reached with the applicant on the revised language for labeling on November 18, 2022.

The PeRC concurred with the Division's assessment and conclusions and recommended that the PREA PMR should be considered fulfilled for the ages studied in Study CDP870-035.

With the approval of this supplement, applicant will be notified that the PMR is considered fulfilled.

7. Signatory Comments

I concur with the assessments outlined in this clinical review. The Applicant made reasonable attempts to conduct the postmareketing study CDP870-035 to evaluate the use of CZP in pediatric patients. The trial was terminated prematurely on the recommendation of DSMB due to unexpectedly high rates of discontinuations that were primarily related to lack of efficacy. The available data are challenging to interpret given the high rate of premature discontinuations, overall early termination of the trial, as well

as large proportion of subjects that required re-induction and were subsequently treated with a dosage that differed from the as-randomzied treatment in the maintenance period.

The safety data, although subject to the limitations noted above, appears generally consistent with the safety profile of CZP in adults with CD. No new or unique safety signals were identified within the pediatric study.

The labeling will be updated (Section 8.4) to indicate at high level that efficacy was not demonstrated in the pediatric CD population.

I agree with the team's assessment to consider the PREA PMR fullfilled, and that requiring further evaluation of this product in pediatric CD patients is infeasible, and is unlikely to serve a public health need, given the variety of other treatment options available and in development.

Appendix A: Inclusion and Exclusion criteria

Inclusion criteria:

A subject was eligible for this study if he/she met the following criteria:

1. Subject and parent(s)/legally acceptable representative(s) were informed of the nature and aims of the study, were able to understand and follow instructions in the local language and gave written informed consent and assent for the subject to participate in this study.
2. Subject had a definitive diagnosis of active CD at Screening (Visit 1) confirmed at least 2 months prior to Screening by radiological, endoscopic, or histological evidence.
3. Subject had a PCDAI >30 (i.e., subject had active disease despite current treatment) at Week 0 (using the laboratory results at Screening [Visit 1] to determine the calculation).
4. Subjects weighed ≥20 kg (44 lb.).
5. Male and female subjects aged 6 to 17 years (inclusive) at the time of Week 0.
6. Subject had an electrocardiogram (ECG) at Screening [Visit 1] "within normal ranges" or "without any medically relevant abnormalities" as confirmed/documented by the Investigator.
7. The following tuberculosis (TB) screening criteria were met:
   a) Subject had no history of active TB prior to Screening (Visit 1).
   b) Subject had no signs or symptoms suggestive of active TB.
   c) Subject had a negative PPD (tuberculin skin test [TST]) skin test as defined by induration <5mm or negative enzyme-linked immunosorbent-based assay (ELISA) (e.g., QFT-GOLD)
   d) Subjects who had a positive PPD test defined as induration ≥5mm or a positive ELISA based assay (e.g., QFT-GOLD) were required to commit to prophylactic treatment (for example with isonicotinic acid hydrazide [INH] combined with vitamin B6 to prevent neuropathy), even if the subject had previously been vaccinated with Bacillus Calmette-Guérin (BCG). Additional prophylactic treatment and follow-up of subjects was at the discretion of the Investigator. Subjects who did not initiate prophylactic treatment for latent TB per Applicant requirement were not eligible to enter the study. Subjects were eligible to rescreen following a 30-day period on TB prophylaxis providing prophylaxis continued.
   e) All subjects should have taken a TB survey at Screening. Subjects deemed to have a high risk of latent TB were required to have TB prophylaxis initiated irrespective of PPD or ELISA based assay (e.g., QFT-GOLD) test results.
   f) Subjects had a chest x-ray taken within 3 months prior to first administration of study drug that was read by a qualified radiologist or pulmonary physician, with no evidence of current active TB or old inactive TB.
8. Subject's current or recent regimen of concomitant medication(s) fell within the definitions provided in Table A-1.

Table A-1. Inclusion criteria for concomitant medications and dosing regimens

Drug Class	Drug	Dose	Stable Treatment Period Prior to Screening (Visit 1)	Additional Comments
Corticosteroids	Prednisone or prednisolone	≤40 mg/day	≥1 week	While the current dose must have been stable for at least 1 week, the total duration of treatment must have been ≥2 weeks. Parenteral treatment with steroids within 2 weeks of Screening (Visit 1) was not permitted. Use of corticosteroids for an indication other than CD was not permitted with the following exception: sparing use of topical hydrocortisone for skin disease or not more than 800µg per day inhaled beclomethasone, or equivalent, for asthma was permitted.
	Budesonide	≤12 mg/day	≥1 week	
	Methylprednisolone	≤32 mg/day	≥1 week	
Immunosuppressants	Azathioprine, 6-mercaptopurine, methotrexate	N/A	N/A	Discontinuation of azathioprine, 6-mercaptopurine, or methotrexate at Screening (Visit 1) was mandatory. A subject could be considered for inclusion in the study following a 2-week Wash-Out Period.
Antibiotics for treatment of CD	e.g., ciprofloxacin, metronidazole	Stable dose	≥1 week	A course of antibiotic, antifungal, or antiviral therapy for an indication other than CD within 4 weeks prior to Screening (Visit 1) was not permitted.
Nonnarcotic analgesics	Nonsteroidal anti-inflammatory drugs (NSAIDs)/ cyclooxygenase-2 (Cox-2) inhibitors	Stable dose	≥1 week	

Abbreviations: CD, Crohn's disease; Cox-2, cyclooxygenase-2; NSAID, nonsteroidal anti-inflammatory drug.
Source: Table 3.2 of the CSR (Study (CDP870-035)

Exclusion criteria:

Subjects were excluded if they met any of the following criteria:

1. Subjects who scored >5 on the perirectal disease item of the PCDAI at Week 0.
2. Subjects with nonenterocutaneous fistulae were excluded.
3. Subject with signs or symptoms of bowel obstruction whose small bowel imaging supported obstruction.
4. Subject had short bowel syndrome as determined by the Investigator.
5. Subject had a functional colostomy or ileostomy. EXCEPTION: Subjects who had a temporary stoma in the past, which had been reversed, could be enrolled.
6. Subject had a surgical bowel resection within the past 6 months prior to Screening or was planning any resection at a time whilst enrolled in the study.
7. Subjects with clinical suspicion of intra-abdominal abscesses.
8. Subject had a positive stool laboratory result for enteric pathogens and/or parasites.
9. Exclusion criteria for subjects who had received prior investigational biological or anti-human TNF-α therapies:
   a) Subject had received any investigational biological therapies (within or outside a clinical trial) within 12 weeks prior to Screening (Visit 1) or had been dosed in any clinical trial using nonbiological therapies within 4 weeks prior to Screening (Visit 1).
   b) Subject had undergone previous treatment with another TNF-α agent (e.g., infliximab or adalimumab) where there was no clinical response (primary nonresponders).
   c) Subjects who were treated and had responded to another anti-TNF-α agent (estimated by the Investigator and documented by the subject's medical file) but had a loss of response as defined below were eligible provided the last dose was greater than 4 weeks prior to the Screening Visit.
      - Loss of response was defined as a lack of improvement or worsening of the clinical symptoms (liquid stools, abdominal pain, fever, drainage of existing fistulae, development of new fistulae, rectal bleeding, changing or introduction of new antidiarrheic medication) after 2 consecutive doses of any anti-TNF-α agent.
      - For subjects treated episodically with another anti-TNF-α agent, the initial response must have been clearly documented. Their loss of response after anti-TNF-α therapy, defined as no response, lack of improvement, or worsening of the clinical symptoms (liquid stools, abdominal pain, fever, drainage of existing fistulae, development of new fistulae, rectal bleeding, changing or introduction of new antidiarrheic medication) should have been evaluated between 2 to 6 weeks after the final dose.
      - Additionally, the decision regarding the entry of all subjects with loss of response after an episodic treatment with another anti-TNF-α agent should have been discussed and agreed upon with the Medical Monitor prior to enrollment in the study.
      - Subjects who had received natalizumab at any time.
10. Subjects who had received mycophenolate or thalidomide within 4 weeks prior to Screening (Visit 1).
11. Subjects who had received cyclosporin or tacrolimus within 6 months prior to Screening (Visit 1).
12. Subjects who had received parenteral corticosteroids within 2 weeks prior to Screening (Visit 1).
13. Subjects who had received corticosteroids or corticotrophins for indications other than CD within 2 weeks of Screening (Visit 1). EXCEPTION: sparing use of topical hydrocortisone for skin disease or not more than 800 µg per day inhaled beclomethasone, or equivalent, for asthma were permitted.
14. Subject had a current or recent history (within 6 months prior to Screening [Visit 1]) of significant and severe renal, hepatic, hematological, gastrointestinal other than CD, endocrine, pulmonary, cardiac, neurological, or cerebral disease including blood dyscrasia (e.g.,

pancytopenia, aplastic anemia), demyelinating disease (e.g., multiple sclerosis, myelitis, optic neuritis), or ischemic heart disease.

15. Subject had a current sign or symptom which may have indicated infection (e.g., fever, cough), a history of chronic infections (including herpes zoster), or recent (within 6 months prior to Screening [Visit 1]) serious or life-threatening infection.
16. Subject had a negative test for IgG against Varicella zoster (chicken pox).
17. Subjects who had not completed their primary vaccination series (i.e., must have had hepatitis B, Haemophiles influenzae Type B, MMR [measles, mumps, rubella], DTP [diphtheria, tetanus, and pertussis], and polio), or who were planning to have a live vaccination during the study period or 3 months after final dose of CZP.
18. Subject had a history of TB or a positive chest x-ray suggestive of TB.
19. Subjects with known concurrent viral hepatitis or subjects with acquired immune deficiency syndrome (AIDS) or known human immunodeficiency virus (HIV) infection.
20. Subject had a concurrent malignancy or a history of any malignancy at any time, excluding successfully treated squamous cell carcinoma of the skin.
21. Subject had concurrent bowel dysplasia or a history of bowel dysplasia in the 5 years prior to Screening (Visit 1).
22. Subject had a history of a lymphoproliferative disorder, including lymphoma, or signs and symptoms suggestive of lymphoproliferative disease at any time.
23. Subject had a known history or current drug (including cannabis) or alcohol abuse.
24. Subject was a pregnant or lactating female.
25. Female subjects of childbearing potential must have a negative pregnancy test result at Screening and Week 0 (Visits 1 and 2) to be eligible for study entry.
26. Subject was a female of childbearing potential or post puberty male and was not practicing or would not agree to practice an effective means of birth control. For subjects not currently sexually active, the subject and parent(s)/legally acceptable representative(s) should have agreed that the subject would employ an effective means of birth control should the subject become sexually active. Acceptable methods of birth control were hormonal contraceptives (including oral, injectable, or transdermal forms; stable at least 2 months prior to Screening [Visit 1] for subject taking them prior to study entry), implants, intrauterine device, barrier methods with spermicide, or surgical sterility. If a subject became sexually active during the study, acceptable methods of birth control (e.g., oral contraceptives) should have been employed. Use of contraceptives should have been continued for at least 10 weeks after the last dose of study medication.
27. Subject was not cooperative with or was unable to comply with the study procedures.
28. Subject had a known hypersensitivity or intolerance to CZP or PEG.

Appendix B: Study schedule of assessments

Assessments	Screen. Period	Induction Period				Status eval.[a]	Maintenance Period																Status eval.	SFU/ET
Study Week	-6 to 0	0	1	2	4	6[b]	8	12	13[g]	16	20	24	28	32	36	37	40	44	48	52	56	60	62	+12[m]
Visit Window (days)			±3	±3	±3	±3	±3	±7		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	SFU
Written informed consent	X																							
Assessment of inclusion and exclusion criteria	X	X																						
Demography	X																							
Life style	X																							
Crohn's disease history	X																							
Medical and surgical history	X																							
Assessment of childbearing potential	X	X				X		X				X			X				X				X	
Pregnancy test[c]	X	X		X	X	X	X	X				X			X				X			X	X	X
Physical examination	X					X						X											X	X
ECG	X																							
Chest x-ray[d]	X																							
TB test[e]	X																							
TB questionnaire	X	X						X				X			X				X			X		X
Test for *Varicella zoster* IgG [f]	X																							
Wrist x-ray [g]		X																				X		
Tanner stage	X														X								X	
Height	X														X								X	
Weight	X	X		X	X		X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	
Vital signs[h]	X	X		X	X		X			X		X		X	X		X		X		X		X	X
Adverse events	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/ concurrent medical procedures	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PCDAI		X		X	X	X	X	X				X			X				X			X	X	
ESR/hematocrit/ albumin for PCDAI	X	X		X	X	X	X	X				X			X				X			X	X	
CRP	X	X		X	X	X	X	X				X			X				X				X	
Hematology/ chemistry/ urinalysis	X	X		X	X	X	X	X				X			X				X			X	X	X
Stool microbiology	X																							
Certolizumab pegol plasma concentrations[k]		X	X		X	X		X				X			X	X			X				X	X

Appendix B: Continued on next page

Appendix B: Study schedule of assessments (Continued)

Assessments	Screen. Period	Induction Period				Status eval.[a]	Maintenance Period															Status eval.	SFU/ET
Anti-certolizumab pegol antibody plasma concentration[f]		X	X		X	X		X				X			X	X			X				X	X
Autoantibodies (ANA and dsDNA)		X	X		X	X		X				X			X	X			X				X	X
HACA to infliximab (anti-TNF experienced subjects only)		X																						
IBD serologies (PANCA, ASCA, OMPC, CBIRI)		X				X									X								X	
Bone markers (osteocalcin, bone specific alkaline phosphatase, n-telopeptides)		X													X								X	
IMPACT III		X				X									X								X	
WPAI: CD[j]		X			X		X	X				X			X				X				X	
FPS-R[k]		X		X	X		X	X				X			X				X			X		
Study drug administration		X		X	X		X	X		X	X	X	X	X	X		X	X	X	X	X	X		
Reinduction[l]		The clinic visit at which reinduction began was considered Reinduction Week 0 (first reinduction dose); followed by Reinduction Week 2 (second dose, 2 weeks after first dose) and Reinduction Week 4 (third dose, 2 weeks after second dose). Reinduction Week 4 should have coincided with the next regularly scheduled clinic visit and the subject should have resumed the original schedule of clinic visits thereafter. If reinduction could not be initiated at a scheduled clinic visit, cthe Study Monitor should have been contacted to determine the most appropriate way to resume the original schedule of clinic visits after reinduction. Reinduction Week 0 assessments: PCDAI including ESR, hematocrit, and albumin; IMPACT-III; WPAI:CD Reinduction Week 2 assessments: PCDAI including ESR, hematocrit, and albumin Reinduction Week 4 assessments: PCDAI including ESR, hematocrit, and albumin; WPAI:CD																							

ANA=antinuclear antibody; ASCA=anti-Saccharomyces cerevisiae antibody; CD=Crohn's disease; CBIRI=anti-CBir1 antibody; CRP=C-reactive protein; dsDNA=double-stranded deoxyribonucleic acid; ECG=electrocardiogram; ESR=erythrocyte sedimentation rate; ET=early termination; eval.=evaluation; FPS-R=Faces Pain Scale-Revised; HACA=human anti-chimeric antibodies; IBD=inflammatory bowel disease; IgG=immunoglobulin G; OMPC=anti-outer membrane protein C antibody; PANCA=perinuclear antineutrophil antibody; PCDAI=Pediatric Crohn's Disease Activity Index; PK=pharmacokinetic; PPD=purified protein derivatives; Q4W=every 4 weeks; QFT-GOLD=QuantiFERON-TB GOLD; Screen.=Screening; SFU=Safety Follow-Up; TB=tuberculosis; TNF=human tumor necrosis factor alpha; TST=tuberculin skin test; WPAI:CD=Work Productivity and Activity Impairment Questionnaire for CD

Note: Visit windows were provided to accommodate occasional scheduling difficulties; subjects should not have exceeded a total of 60 weeks of study treatment.

(a) Subjects considered responders at Week 6 (defined as a decrease from Week 0 in PCDAI score of ≥15 points and a total PCDAI score ≤30points) could continue into the Maintenance Period of the study. Subjects who were nonresponders or subjects who responded, but chose not to receive maintenance treatment, were discontinued from treatment but underwent the Safety Follow-Up Visit to assess safety and pharmacokinetic data.

(b) At Week 6, responders who continued into the Maintenance Period were randomized to the High-Dose group (CZP administered Q4W as 400mg for subjects ≥40kg or 200mg for subjects 20 to <40kg) or Low-Dose group (CZP administered Q4W as 200mg for subjects ≥40kg or 100mg for subjects 20 to <40kg).

(c) For all females postmenses, a serum pregnancy test was conducted during Screening (Visit 1); additionally, for all females postmenses, a urine pregnancy test was conducted at Weeks 0, 2, 4, 6, 8, 12, 24, 36, 48, 60, and 62, and at the Safety Follow-Up/Early Termination Visit.

(d) If a suitable chest x-ray was available that was taken within 3 months prior to first administration of study drug, no new x-ray needed to be taken.

(e) At Screening, all subjects were tested for tuberculosis. All sites used either the PPD skin test or QFT-GOLD test. The Mantoux tuberculin skin test must have been performed within 1 month prior to first administration of study drug.

(f) Test only to be performed if a positive Varicella zoster test result was not documented in the subject's medical file.

(g) Vital signs were collected 15 minutes prior to dosing and 30 minutes after dosing (with a ±5 minute window) at Weeks 0, 2, and 4.

(h) For all subjects who entered the study, plasma samples were collected to determine the concentration of CZP at Weeks 0, 1, 4, and 6 (during the Induction Period), at Weeks 12, 24, 36, 37, 48, and 62 (during the Maintenance Period), and at the SFU/Early Termination Visit. Samples were collected before dosing (except for Weeks 1, 6, and 37, and the SFU/Early Termination Visit when there was no dosing).

(i) Anti-CZP antibody concentrations in plasma were determined at Weeks 0, 1, 4, 6, 12, 24, 36, 37, 48, and 62 and at the SFU/Early Termination Visit (anti-CZP antibody measurements were made using the samples taken for PK measurements at these time points, so additional blood draws were not required).

(j) Days missed from school were assessed using the WPAI:CD for children. The time missed from work was assessed using the WPAI:CD for working individuals. The effect of the child's CD on the caregiver's productivity was assessed using the WPAI:CD for caregivers of children with CD.

(k) Injection site pain was assessed within 20 to 40 minutes after injection of CZP using the FPS-R.

(l) Subjects who lost response during the Maintenance Period (from Week 8 onwards), defined as an increase in PCDAI score of ≥15 points compared to Week 6 at 2 consecutive visits at least 1 week apart or an overall PCDAI score >30 points at any time during the Maintenance Period, could undergo 1 reinduction.

(m) SFU was done 12 weeks after last dose.

(n) Performed within 60 days prior to Baseline or within 30 days after Baseline.

(o) The PK and immunologic assessments at Visit 9 (Week 13) were removed per Amendment 2 and, therefore, Visit 9 did not take place. However, subsequent visits were not renumbered due to practical considerations.

Source: Table 3-7 of the CSR (study CDP870-035)

Appendix C: Originally planned efficacy variables

A. The primary efficacy endpoint

Proportion of subjects in clinical remission (defined as a PCDAI score ≤10) at Week 62.

B. Secondary efficacy endpoints

The study included the following secondary endpoints:

1. Absolute PCDAI scores
2. Change from Week 0 in PCDAI scores
3. Proportion of subjects achieving clinical response defined as a decrease of ≥15 points and a total PCDAI score ≤30 points) from Week 0 in PCDAI.
4. Proportion of subjects in clinical remission
5. CRP levels
6. Change from Week 0 in CRP levels
7. Erythrocyte sedimentation rate (ESR)
8. Change from Week 0 in ESR
9. Change from Week 0 in growth scores (Tanner stage [assessing puberty])
10. Corticosteroid tapering
11. Proportion of subjects in corticosteroid-free remission

C. Other efficacy endpoints

The study included the following other endpoints:

1. Absolute IMPACT III scores over time
2. Change from Week 0 in IMPACT-III scores
3. Planned exploratory variables were:
4. Absolute Faces Pain Scale-Revised (FPS-R) scores
5. Change from Week 0 in FPS-R scores
6. Days missed from school/work
7. Absolute WPAI:CD scores.
8. Change from Week 0 in WPAI:CD scores

Appendix D: PCDAI

Instructions on scoring are provided in the PCDAI's user guide following the questionnaire. Scoring items are marked with an asterisk (*).

HISTORY (Recall; 1 week)*

Abdominal pain*:

None	(0)
Mild – Brief, does not interfere with activities	(5)
Mod / severe - daily, longer lasting, affects activities, nocturnal	(10)

Stools (per day)*:

Formed stools or up to 1 liquid stool, no blood	(0)
Up to 2 semi-formed with small blood, or 2 to 5 liquid with or without small blood	(5)
Any gross bleeding, or > 6 liquid, or nocturnal diarrhea	(10)

Patient Functioning – General Well-Being*:

No limitation of activities, well	(0)
Occasional difficulty in maintaining appropriate activities, below par	(5)
Frequent limitation of activity, very poor	(10)

LABORATORY – (for Week 0 only, laboratory results from Screening done within 2 weeks of Week 0 are used; for all other calculations, use results from the same visit)

Hematocrit (%)	≤10 yrs:	≥33	(0)
		28-32	(2.5)
		<28	(5)
	Males 11-14yrs:	≥35	(0)
		30-34	(2-5)
		<30	(5)
	Males 15-19yrs:	≥37	(0)
		32-36	(2.5)
		<32	(5)
	Females 11-19yrs :	≥34	(0)
		29-33	(2.5)
		<29	(5)
ESR (mm/h)		<20	(0)
		20-50	(2.5)
		>50	(5)
ALBUMIN (g/dL)		≥3.5	(0)
		3.1-3.4	(5)
		≤3.0	(10)

EXAMINATION

Weight*:

Weight gain or voluntary weight stable/loss	(0)
Involuntary weight stable, weight loss 1-9%	(5)
Weight loss ≥10%	(10)

Height* - Score using (a) criteria when possible

a)	Height velocity ≥-1SD	(0)
	Height velocity < -1SD, >-2SD	(5)
	Height velocity ≤ -2SD	(10)
	OR	
b)	< 1 channel decrease	(0)
	≥1 to < 2 channel decrease	(5)
	≥ 2 channel decrease	(10)

Abdomen

No tenderness, no mass	(0)
Tenderness, or mass without tenderness	(5)
Tenderness, involuntary guarding, definite mass	(10)

Perirectal disease

None, asymptomatic tags	(0)
Inflamed tags or 1-2 indolent fistula(e) or fissure(s), scant drainage, no tenderness	(5)
Active fistula, drainage, tenderness, or abscess	(10)

Extra-intestinal Manifestations

Fever > 38.5°C for 3 days over past week, oral ulcers, definite arthritis, uveitis, erythema nodosum, P. gangrenosum

None	(0)
One	(5)
≥ Two	(10)

TOTAL SCORE _____

Source: Appendix 1 (PCDAI) of the clinical protocol amendment 2

Appendix E: IMPACT-III questionnaire

Question 1.	**How much has your stomach been hurting you in the past two weeks?**			
☐ Not at all	☐ Hardly hurting at all	☐ Hurting somewhat	☐ Hurting quite a bit	☐ Hurting very much

Question 2.	**Taking medicines or tablets bothers you**			
☐ Not at all	☐ Hardly bothers at all	☐ Bothers somewhat	☐ Bothers quite a bit	☐ Bothers very much

Question 3.	**How often has your inflammatory bowel disease prevented you from eating what you want in the past two weeks?**			
☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Very often

Question 4.	**How often have you been worrying about having a flare-up (increase of symptoms) in the last two weeks?**			
☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Very often

Question 5.	**How much does it bother you that you have an illness that does not just go away?**			
☐ Not at all	☐ Hardly bothers at all	☐ Bothers somewhat	☐ Bothers quite a bit	☐ Bothers very much

Question 6.	**How much energy did you have during the past two weeks?**			
☐ Very much energy	☐ Quite a bit of energy	☐ Some energy	☐ A little energy	☐ No energy at all

Question 7.	**How do you feel about your weight?**			
☐ I feel great about my weight	☐ I feel good about my weight	☐ I don't feel good or bad about my weight	☐ I feel bad about my weight	☐ I feel awful about my weight

Question 8.	**How has your inflammatory bowel disease affected your family?**			
☐ The effect has been great	☐ The effect has been good	☐ It has not affected our family	☐ The effect has been bad	☐ The effect has been awful

Question 9.	**How often did you have to miss out on certain things (hobbies, play, parties) because of your inflammatory bowel disease in the past two weeks?**			
☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Very often

Question 10.	**How often have you been bothered by diarrhea (loose or frequent bowel movements) in the past two weeks?**			
☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Very often

Appendix E continued next page

Appendix E: IMPACT-III questionnaire (continued)

Question 11.	**How often do you worry about health problems you might have in the future?**			
☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Very often

Question 12.	**How often do you think it is unfair that you have inflammatory bowel disease?**			
☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Very often

Question 13.	**During the past two weeks, were you ever angry that you have inflammatory bowel disease?**			
☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Very often

Question 14.	**Do you think too many rules or limits are placed on you because of your inflammatory bowel disease?**			
☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Very often

Question 15.	**How do you feel about the way you look?**			
☐ I think I look great	☐ I think I look good	☐ I don't think I look good or bad	☐ I think I look bad	☐ I think I look awful

Question 16.	**Are you embarrassed because of your bowel condition?**			
☐ Not at all	☐ **Hardly embarrassed at all**	☐ Embarrassed somewhat	☐ Embarrassed quite a bit	☐ Embarrassed very much

Question 17.	**Did you have fun during the past two weeks?**			
☐ Very often	☐ Often	☐ Sometimes	☐ Rarely	☐ Never

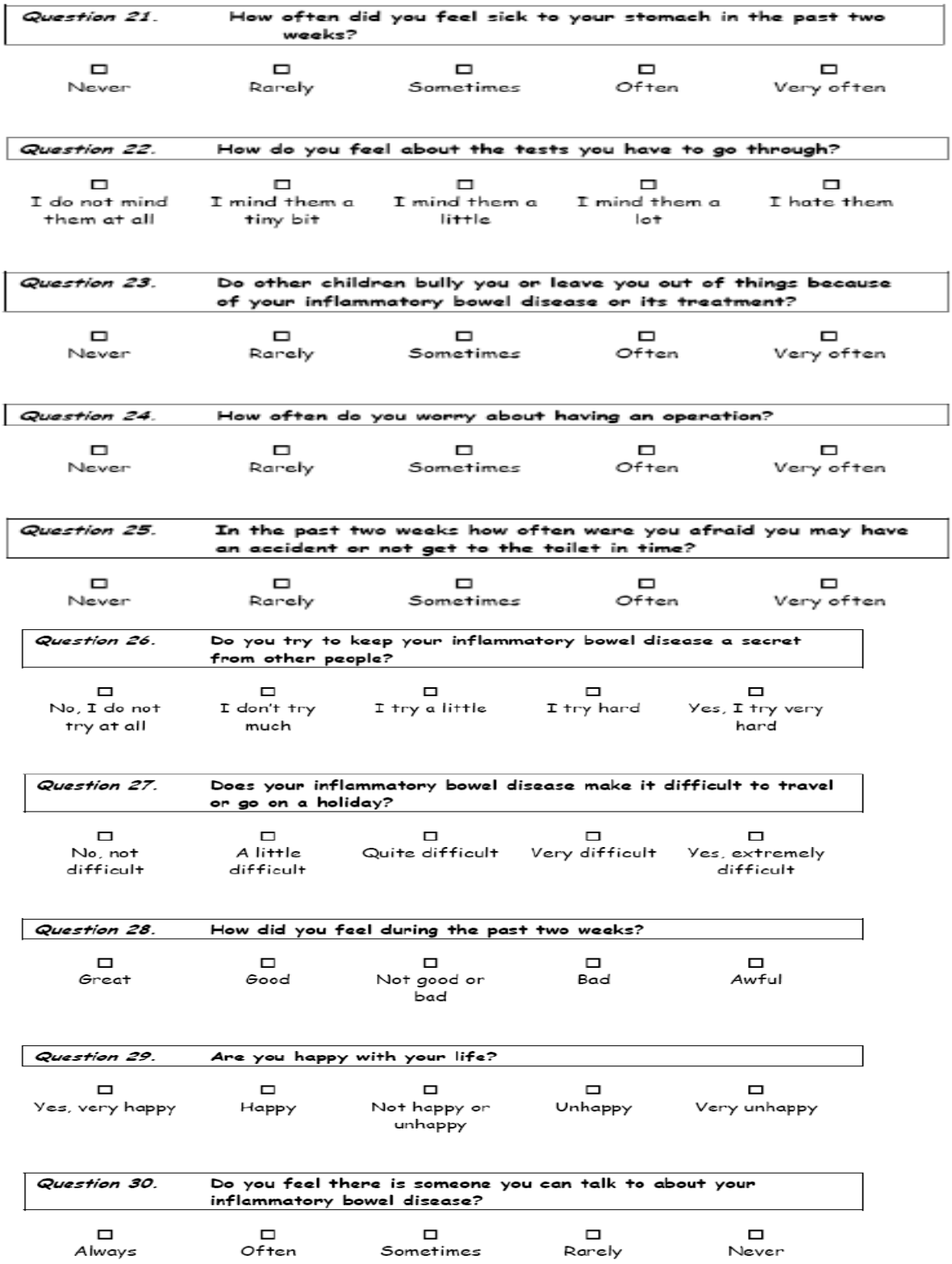
Question 18.	**Is it harder to make friends because of your inflammatory bowel disease?**			
☐ Not at all harder	☐ A little harder	☐ Quite a bit harder	☐ Much harder	☐ Very much harder

Question 19.	**How often do you worry about your stool (bowel movement) containing blood?**			
☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Very often

Question 20.	**Are you worried you cannot go out on a date or have a boyfriend or girlfriend because of your inflammatory bowel disease?**			
☐ Not at all worried	☐ Hardly worried at all	☐ Worried somewhat	☐ Worried quite a bit	☐ Worried very much

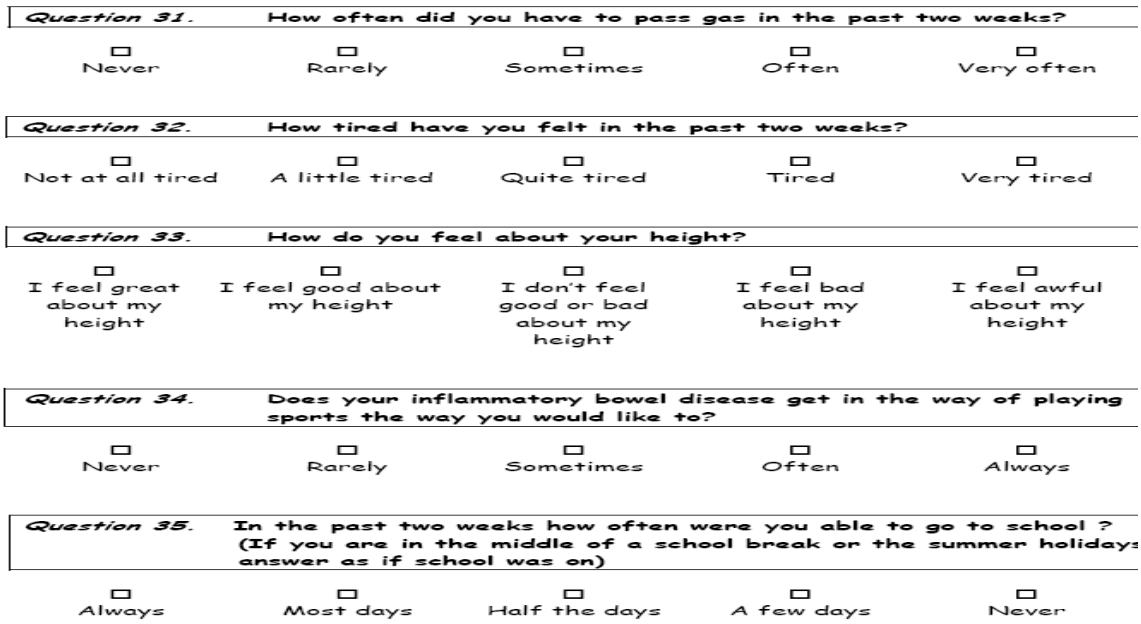
Appendix E continued next page

Appendix E: IMPACT-III questionnaire (continued)



Appendix E: Continued next page

Appendix E: IMPACT-III questionnaire (continued)



Question 31. How often did you have to pass gas in the past two weeks?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Very often

Question 32. How tired have you felt in the past two weeks?

☐ Not at all tired ☐ A little tired ☐ Quite tired ☐ Tired ☐ Very tired

Question 33. How do you feel about your height?

☐ I feel great about my height ☐ I feel good about my height ☐ I don't feel good or bad about my height ☐ I feel bad about my height ☐ I feel awful about my height

Question 34. Does your inflammatory bowel disease get in the way of playing sports the way you would like to?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

Question 35. In the past two weeks how often were you able to go to school ? (If you are in the middle of a school break or the summer holidays answer as if school was on)

☐ Always ☐ Most days ☐ Half the days ☐ A few days ☐ Never

The IMPACT questionnaire is a disease-specific health-related quality of life (HRQOL) questionnaire for use in children with IBD that was originally developed and validated by a Canadian team[10,11](Griffiths et al, 1999; Otley et al, 2002). The IMPACT III, a modified version of the original questionnaire, contains 35 questions assessing the following 6 domains: bowel symptoms, systemic symptoms, emotional functioning, social functioning, body image, and treatment/interventions. For each question, there are 5 Likert response options. Total IMPACT scores range from 35 to 185 with higher scores indicating better HRQOL. This questionnaire will be used to assess HRQOL of all subjects; however, it has only been validated for children aged ≥10 years in North America.

Source: Appendix 2 (IMPACT III) of the study protocol amendment 2

[10] Griffiths AM et al. Development of a quality-of-life index for pediatric inflammatory bowel disease: dealing with differences related to age and IBD type. J Pediatr Gastroenterol Nutr. 1999;28(4): S46-S52.

[11] Otley A et al. The IMPACT questionnaire: a valid measure of health-related quality of life in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2002;35(4):557-563.

Appendix F: Serious adverse events Study CDP870-035

APPEARS THIS WAY ON ORIG NAL

Error! Reference source not found. Shows serious adverse events reported by at least 2% subjects in study CDP870-035.

Table F-1: Serious treatment-emergent adverse events reported by at least 2% subjects

System Organ Class Preferred term	Induction Period	Maintenance Period		All Participants (Induction and Maintenance Periods)
		CZP Low-Dose	CZP High-Dose	
	N=99 n (%)	N=37 n (%)	N=35 n (%)	N=99 n (%)
At least 1 serious TEAE	19 (19.2)	7 (18.9)	8 (22.9)	34 (34.3)
Gastrointestinal disorders	13 (13.1)	7 (18.9)	4 (11.4)	24 (24.2)
Abdominal pain	0	1 (2.7)	1 (2.9)	2 (2.0)
Crohn's disease	12 (12.1)	5 (13.5)	2 (5.7)	19 (19.2)
Hematochezia	1 (1.0)	0	1 (2.9)	2 (2.0)
Infections and infestations	6 (6.1)	3 (8.1)	3 (8.6)	12 (12.1)
Gastroenteritis viral	2 (2.0)	0	0	2 (2.0)
Investigations	0	0	2 (5.7)	2 (2.0)
Weight decreased	0	0	2 (5.7)	2 (2.0)
Metabolism and nutrition disorders	3 (3.0)	0	2 (5.7)	5 (5.1)
Dehydration	3 (3.0)	0	0	3 (3.0)
Malnutrition	0	0	2 (5.7)	2 (2.0)

Source: Study CDP870-035 Table 3.8 summary clinical safety and CSR Addendum Table 16.18

Appendix G: Common adverse events Study CDP870-035

Table G-1 shows common treatment-emergent adverse events reported by at least 5% subjects in study CDP870-035.

Table G-1: Treatment-emergent adverse events reported by at least 5% subjects

System Organ Class Preferred term	Induction Period	Maintenance Period		All Participants
		CZP Low-Dose	CZP High-Dose	
	N=99 n (%)	N=37 n (%)	N=35 n (%)	N=99 n (%)
At least 1 TEAE	77 (77.8)	31 (83.8)	32 (91.4)	91 (91.9)
Gastrointestinal disorders	41 (41.4)	24 (64.9)	24 (68.6)	70 70.7)
Abdominal pain	4 (4.0)	4 (10.8)	5 (14.3)	12 (12.1)
Abdominal pain upper	4 (4.0)	5 (13.5)	2 (5.7)	9 (9.1)
Constipation	4 (4.0)	4 (10.8)	1 (2.9)	9 (9.1)
Crohn's disease	14 (14.1)	12 (32.4)	9 (25.7)	35 (35.4)
Diarrhea	7 (7.1)	4 (10.8)	3 (8.6)	12 (12.1)
Gastroesophageal reflux disease	2 (2.0)	2 (5.4)	2 (5.7)	5 (5.1)
Hematochezia	3 (3.0)	0	2 (5.7)	5 (5.1)
Mouth ulceration	2 (2.0)	3 (8.1)	3 (8.6)	8 (8.1)
Nausea	6 (6.1)	4 (10.8)	2 (5.7)	11 (11.1)
Stomatitis	2 (2.0)	2 (5.4)	2 (5.7)	6 (6.1)
Vomiting	8 (8.1)	4 (10.8)	6 (17.1)	16 (16.2)
General disorders and administration site conditions	37 (37.4)	17 (45.9)	15 (42.9)	51 (51.5)
Fatigue	3 (3.0)	4 (10.8)	0	7 (7.1)
Injection site pain	22 (22.2)	4 (10.8)	6 (17.1)	22 (22.2)
Pyrexia	14 (14.1)	8 (21.6)	9 (25.7)	26 (26.3)
Infections and infestations	27 (27.3)	24 (64.9)	15 (42.9)	54 (54.5)
Influenza	1 (1.0)	3 (8.1)	2 (5.7)	6 (6.1)
Nasopharyngitis	5 (5.1)	2 (5.4)	2 (5.7)	9 (9.1)
Sinusitis	2 (2.0)	4 (10.8)	1 (2.9)	6 (6.1)
Upper respiratory tract infection	0	8 (21.6)	3 (8.6)	11 (11.1)
Viral infection	2 (2.0)	4 (10.8)	3 (8.6)	9 (9.1)
Investigations	10 (10.1)	5 (13.5)	4 (11.4)	17 (17.2)
Weight decreased	4 (4.0)	2 (5.4)	2 (5.7)	7 (7.1)
Metabolism and nutrition disorders	10 (10.1)	5 (13.5)	4 (11.4)	17 (17.2)
Decreased appetite	4 (4.0)	4 (10.8)	1 (2.9)	9 (9.1)
Musculoskeletal and connective tissue disorders	14 (14.1)	10 (27.0)	5 (14.3)	24 (24.2)
Arthralgia	6 (6.1)	5 (13.5)	2 (5.7)	13 (13.1)
Nervous system disorders	13 (13.1)	7 (18.9)	7 (20.0)	22 (22.2)
Headache	9 (9.1)	6 (16.2)	4 (11.4)	15 (15.2)
Respiratory, thoracic and mediastinal disorders	17 (17.2)	6 (16.2)	6 (17.1)	26 (26.3)
Cough	7 (7.1)	4 (10.8)	2 (5.7)	11 (11.1)
Oropharyngeal pain	6 (6.1)	2 (5.4)	3 (8.6)	10 (10.1)
Skin and subcutaneous tissue disorders	13 (13.1)	8 (21.6)	6 (17.1)	23 (23.2)
Acne	3 (3.0)	1 (2.7)	1 (2.9)	5 (5.1)

System Organ Class Preferred term	Induction Period	Maintenance Period		All Participants
		CZP Low-Dose	CZP High-Dose	
	N=99 n (%)	N=37 n (%)	N=35 n (%)	N=99 n (%)
Rash	2 (2.0)	4 (10.8)	0	6 (6.1)

Source: Study CDP870-035 Table 3.3 of summary of clinical safety and CSR Addendum Post-hoc Table 16.2.2

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANIL K NAYYAR
12/22/2022 12:04:51 PM

TARA A ALTEPETER
12/22/2022 12:52:38 PM