

PROTOCOL CR0012

AN OPEN-LABEL, MULTICENTER STUDY TO ASSESS THE SAFETY OF CERTOLIZUMAB PEGOL IN CHILDREN AND ADOLESCENTS WITH ACTIVE CROHN'S DISEASE WHO COMPLETED C87035 OR WERE TERMINATED FROM C87035 WHEN THE STUDY WAS STOPPED BY UCB

PHASE 2B

IND Number: 11197

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Protocol/Amendment Number	Date	Type of amendment
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SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

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LIST OF ABBREVIATIONS

AE	adverse event
ANA	antinuclear antibody
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDP870	certolizumab pegol
CI	confidence interval
CDMS	clinical data management system
CRF	Case Report Form
CRO	contract research organization
CRP	C-reactive protein
CZP	certolizumab pegol
dsDNA	double-stranded deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ELISA	enzyme-linked immunosorbent assay
ESR	erythrocyte sedimentation rate
ET	Early Termination
EU	European Union
Fab'	antigen-binding fragment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
HIPAA	Health Insurance Portability and Accountability Act
HRQOL	health-related quality of life
IBD	inflammatory bowel disease
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INH	isonicotinic acid hydrazide (isoniazid)
IRB	Institutional Review Board

ITT	Intention-To-Treat
iv	intravenous
IVRS	Interactive Voice Response System
MedDRA [®]	Medical Dictionary for Regulatory Activities [®]
PCDAI	Pediatric Crohn's Disease Activity Index
PEG	polyethylene glycol
PFS	prefilled syringe
PK	pharmacokinetics
PPD	purified protein derivatives
PT	Preferred Term
Q2W	every 2 weeks
Q4W	every 4 weeks
QFT-GOLD	QuantiFERON [®] -TB GOLD
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous
SD	standard deviation
SFU	Safety Follow-Up
SOC	System Organ Class
SOP	Standard Operating Procedures
TB	tuberculosis
TNF	human tumor necrosis factor alpha
US	United States
WBC	white blood cell
WPAI:CD	Work Productivity and Activity Impairment Questionnaire for CD
WHODrg	World Health Organization Drug

1 SUMMARY

This is a Phase 2b, open-label, multicenter study to assess the safety of certolizumab pegol (CDP870, CZP) in children and adolescents with active Crohn's disease (CD) who completed C87035 or were terminated from C87035 when the study was stopped by UCB.

C87035 was a Phase 2, open-label, multicenter study to assess the safety, efficacy, pharmacokinetics (PK), and immunogenicity of CZP in children and adolescents ages 6 to 17 with moderately to severely active Crohn's disease. The study was performed as a postapproval commitment following the Food and Drug Administration (FDA) approval of CZP for the treatment of adults with moderately to severely active CD. [REDACTED]

[REDACTED] the decision was made to stop C87035 after determining it was inadequate to address the efficacy of CZP for labeling in pediatric subjects. Subjects ongoing in the study were given the opportunity to enter CR0012 without having completed C87035.

Certolizumab pegol, the investigational medicinal product (IMP) is a humanized antibody fragment antigen binding (Fab'), with specificity for human tumor necrosis factor alpha (TNF), conjugated to polyethylene glycol (PEG). The drug intended for use in this study is the liquid formulation of CZP in a prefilled syringe (PFS).

All subjects who complete Week 62 of C87035 or were terminated from C87035 when the study was stopped by UCB (and completed all assessments required for Week 62/Visit 23 at the time of termination) are eligible to enter this open-label extension study.

Following entry, subjects may continue on the CZP dose they were receiving at the end of C87035 (Low-Dose Group or High-Dose Group [weight adjusted in kg]) every 4 weeks (Q4W). The first clinic visit of this study should coincide with the last visit of C87035 (Week 62/Visit 23). Home administration of CZP by the subject/caregiver/appropriate designee as determined by the Investigator will be permitted following appropriate training at clinic visits. For subjects performing home administration, a phone call to the subject and/or the parents/caregiver will be performed by the Investigator (or designee) every 4 weeks between regular clinic visits. A Safety Follow-Up (SFU) Visit will be conducted 12 weeks after the last dose of study medication.

If a subject has not been previously reinduced in C87035, the subject is eligible for 1 reinduction due to loss of response in CR0012 (defined as an increase in Pediatric Crohn's Disease Activity Index [PCDAI] ≥ 15 points compared to Week 6 of C87035 at 2 consecutive visits at least 1 week apart or an overall PCDAI > 30 points at any time).

A Data and Safety Monitoring Board (DSMB) will periodically review all emerging safety data.

The primary objective of the study is to assess the longterm safety and tolerability of CZP in children and adolescents with moderately to severely active CD. As secondary objectives, this study further assesses the longterm efficacy, PK, and immunogenicity of CZP treatment in this population.

Safety variables to be evaluated are adverse events (AEs), laboratory parameters (hematology, biochemistry, urinalysis), vital signs, and autoantibodies (anti-nuclear antibody [ANA] and anti-double-stranded deoxyribonucleic acid [dsDNA] antibody).

The main efficacy variable is the proportion of subjects in clinical remission.

Other efficacy variables include: absolute score and change in PCDAI scores, proportion of subjects maintaining clinical response, absolute and change in both C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and change in growth scores (Tanner stage), absolute and change in bone marker values, absolute and change in IMPACT-III scores, days missed from school/work, absolute and change in Work Productivity and Activity Impairment Questionnaire for CD (WPAI:CD) scores, and concurrent medical procedures required during the study.

Pharmacokinetic and immunological variables include measurement of plasma concentrations of CZP and detection of anti-CZP antibodies.

2 INTRODUCTION

Tumor necrosis factor alpha is a key proinflammatory cytokine with a central role in the immune response. In CD, TNF activates similar processes, with gut epithelial tissue injury resulting from induction of proteases, prostaglandins, leukotrienes, eicosanoids, and other products, some of which (eg, prostaglandin E2) may also directly cause diarrhea by promoting mucosal secretion of chloride and potassium. In addition, both intestinal and peripheral phagocytes from subjects with active CD have the capacity to secrete increased amounts of TNF.

Several large double-blind, randomized clinical studies of biological products targeted at neutralizing TNF have demonstrated marked clinical benefit in subjects with active CD (Targan et al, 1997; Rutgeerts et al, 1999; Sandborn et al, 2001). Furthermore, it has been shown that sustained clinical benefit over a year can be achieved in subjects who respond to a first dose of anti-TNF therapy (Hanauer et al, 2002).

Several TNF-antagonists (including CZP [Cimzia[®]], adalimumab [Humira[®]], and infliximab [Remicade[®]]) have been approved for the treatment of CD.

Use of anti-TNF agents has been studied in pediatric patients suffering from CD. Infliximab has been approved in the United States (US) and the European Union (EU) for pediatric use (Hyams J et al, 2007) and adalimumab is currently under investigation in this population.

It is widely recognized that there exists an unmet need for new therapies for children and adolescents with active CD. The primary goal of treatment is to provide longterm reduction or remission in the signs and symptoms of their disease.

Certolizumab pegol is an engineered, humanized antigen-binding fragment (Fab' fragment) conjugated to PEG with specificity for human TNF. Certolizumab pegol (CIMZIA) has been approved in the US, Switzerland, Russia, Brazil, and Chile for reducing the signs and symptoms of CD and maintaining the clinical response in adult subjects with moderately to severely active disease who have had an inadequate response to conventional therapy.

Single intravenous (iv) and subcutaneous (sc) doses of CZP in healthy volunteers have been shown to have a predictable dose-related response with an approximately linear relationship between the dose administered and the maximum serum concentration (C_{max}) and the area under the CZP plasma concentration versus time curve (AUC). The terminal elimination phase half-life ($t_{1/2}$) was approximately 14 days for all dosage levels tested and the bioavailability of CZP when administered subcutaneously was approximately 80%. A similar PK profile was found in healthy Japanese and Caucasian subjects. The metabolism and route of excretion of CZP have not yet been fully elucidated.

The safety of CZP has been assessed in 2518 adult subjects with CD representing over 2837 patient years of exposure. Certolizumab pegol is well tolerated. The incidence of injection site reactions and hypersensitivity-type reactions was low. There were no reports of anaphylaxis or anaphylactoid-type reactions with CZP. All available data in CD show the safety of CZP is consistent with the known risks of anti-TNF therapies.

The risks of the present study are essentially those of experiencing an adverse effect following administration of CZP and for loss of response. As a therapeutic class, currently available TNF-antagonists are known to be associated with serious infections, particularly reactivation of tuberculosis (TB) and opportunistic fungal infections. An association has also been reported with TNF-antagonist therapy and the development of lymphoma and leukemia especially in children and adolescents, although it is not clear whether there is a causal relationship as confounding factors exist (eg, the increased risk of lymphoma and leukemia associated with autoimmune diseases and immunosuppression) themselves. Other cancer types also have been reported in association with TNF-antagonist use, but the causal relationship for these is unclear as well. Other serious AEs that have been infrequently reported in subjects treated with currently available TNF-antagonists (including CZP) include congestive heart failure, drug-induced lupus, new-onset psoriasis, seizures, demyelinating disorders, and pancytopenia.

For more information, please refer to the Investigator's Brochure.

3 STUDY OBJECTIVES

The primary objective of this open-label, multicenter study is to assess the longterm safety and tolerability of CZP in children and adolescents with moderately to severely active CD who completed C87035 or were terminated from C87035 when the study was stopped by UCB. The secondary objectives of this study are to assess the longterm efficacy, PK, and immunogenicity of CZP treatment on this population.

4 STUDY VARIABLES

4.1 Safety variables

- AEs
- Laboratory parameters (hematology, biochemistry, urinalysis)
- Vital signs
- Autoantibodies (ANA and anti-dsDNA antibody)

4.2 Efficacy variables

Main efficacy variable:

- Proportion of subjects in clinical remission (clinical remission is defined as a PCDAI score ≤ 10)

Other efficacy variables:

- Disease activity variables:
 - Absolute PCDAI scores
 - Change from Baseline (Week 0 of C87035) in PCDAI scores
 - Proportion of subjects maintaining clinical response (clinical response is defined as a decrease from Baseline (Week 0 of C87035) in PCDAI score of ≥ 15 points and a total PCDAI score ≤ 30 points)
 - CRP levels
 - Change from Baseline (Week 0 of C87035) in CRP levels
 - ESR values
 - Change from Baseline (Week 0 of C87035) in ESR values
 - Change from Baseline (Week 0 of C87035) in growth scores (Tanner stage [assessing puberty])
 - Bone marker values
 - Changes from Baseline (Week 0 of C87035) in bone marker values
- Subject-reported outcome variables:
 - Absolute IMPACT-III scores
 - Change from Baseline (Week 0 of C87035) in IMPACT-III score
 - Actual scores of WPAI:CD for children and for working individuals with CD
 - Change from Baseline (Week 0 of C87035) in scores of WPAI:CD for children and for working individuals with CD)
 - Concurrent medical procedures
- Caregiver-reported outcome variables:
 - Actual scores of WPAI:CD for caregivers
 - Change from Baseline (Week 0 of C87035) in scores of WPAI:CD for caregivers

4.3 Pharmacokinetic and immunological variables

- Plasma concentrations of CZP
- Detection of anti-CZP antibodies

5 STUDY DESIGN

5.1 Study description

This is a Phase 2, open-label, multicenter study in children and adolescents with moderately to severely active CD who completed C87035, or were terminated from C87035 when the study was stopped by UCB, to assess the longterm safety and tolerability of CZP.

All subjects who complete Week 62 of C87035 or were terminated from C87035 when the study was stopped by UCB (and completed all assessments required for Week 62/Visit 23 at the time of termination) are eligible for entry.

Subjects may continue on CZP at the dose they were receiving at the end of C87035 (Low-Dose Group or High-Dose Group [weight adjusted in kg; see [Section 7.2](#) and [Table 7-1](#)]) every 4 weeks until the subject reaches the age of 18 years or CZP is approved for use in the US by pediatric subjects with CD. The first clinic visit should coincide with the last visit of C87035 (Week 62/Visit 23). First study drug administration occurs 2 weeks later (Week 2) and subsequent clinic visits for safety and efficacy assessments are scheduled at 12-week intervals. After Week 2, subjects or parents/caregivers/appropriate designee as determined by the Investigator have the option of home administration of CZP upon appropriate training during a previous clinic visit(s) or continuing to have CZP administered every 4 weeks at the clinic. For subjects performing home administration, a phone call to the subject and/or the parents/caregiver will be performed by the Investigator (or designee) every 4 weeks between regular clinic visits in order to capture potential AEs and changes in concomitant medications, and to check compliance with home dosing. An SFU Visit will be conducted 12 weeks after the last dose of study medication for subjects.

Please refer to Study Schedule of Assessments in [Section 5.2](#) for visit-specific procedures and to [Section 5.3](#) for a schematic representation of the study.

A DSMB will periodically review all emerging safety data (see [Section 13.8](#)). Based on the safety data, the DSMB can recommend modifying or stopping the study.

Loss of response/reinduction

- *Subjects who were reinduced in C87035 are not eligible for reinduction in CR0012. Should loss of response occur in CR0012, the subject must be withdrawn.*
- *If there was no reinduction in C87035, 1 reinduction only is permitted in CR0012. If response is lost a second time in CR0012, the subject must be withdrawn.*

Loss of response, defined as an increase in PCDAI ≥ 15 points compared to Week 6 of C87035 at 2 consecutive visits at least 1 week apart, or an overall PCDAI > 30 points at any time, will result in reinduction and dosing as follows:

- The reinduction dose will be adjusted to the subject's weight: 400mg for subjects ≥ 40 kg or 200mg for subjects 20 to < 40 kg sc Q2W for a total of 3 doses
- Continue dosing with CZP administered sc Q4W as 400mg for subjects ≥ 40 kg or 200mg for subjects 20 to < 40 kg, regardless of the subject's previous randomized dose group

Summary of visits related to loss of response

1. Loss of response must be confirmed at a clinic visit where assessments and labs are performed to determine PCDAI score. Scores cannot be confirmed until lab results are received by central lab a few days after the clinic visit. Once loss of response is confirmed, sites must contact the subject to return for the first Reinduction Visit.
2. Reinduction Week 0 - subjects will receive the first dose for reinduction at the clinic.
3. Reinduction Week 2 occurs 2 weeks later for second dose at the clinic.
4. Reinduction Week 4 occurs 2 weeks later for third dose at the clinic.
5. Subject resumes the original schedule of clinic visits after reinduction. The clinic should contact the Study Monitor to determine the most appropriate way to resume the original schedule of clinic visits.

5.1.1 Study duration per subject

The maximum study duration of CZP treatment may be until the subject reaches the age of 18 years or CZP is approved for use in the US by pediatric subjects with CD. An SFU visit will be conducted 12 weeks following the last dose of study drug.

The end of the study is defined as the date of the last SFU visit of the last subject in the study.

5.1.2 Planned number of subjects and sites

It is anticipated that the approximately 30 to 40 centers which participated in C87035 will participate in this study. Those subjects who completed Week 62 of C87035 or were terminated from C87035 when the study was stopped by UCB (and completed all assessments required for Week 62/Visit 23 at the time of termination) may be enrolled in this study.

- First subject first visit: Jul 2010
- Last subject first visit: Jun 2012
- Last subject last visit: to be determined (including the SFU Visit)

5.1.3 Anticipated regions and countries

This study will be conducted in the US, Canada, Australia, and New Zealand.

5.2 Schedule of study assessments

Table 5-1. Schedule of study assessments

Visit or phone call (+/-7 days)	Treatment Period							SFU ^d
	Entry ^a	Visit	Phone call (home administration) or visit (clinic administration) ^b	Regular Clinic Visits ^b	Completion/ Early Termination	Unscheduled Visit ^e		
Week	0	2	Every 4 weeks beginning at Week 6 and in between regular clinic visits	Every 12 weeks beginning at Week 14				+12 weeks after last dose of study drug
Written informed consent	X							
Assessment of inclusion/exclusion criteria	X							
Demography	X							
Life style	C87035							
Crohn's disease history	C87035							
Medical and surgical history	C87035							
Assessment of childbearing potential	C87035				X		X	
Pregnancy test ^e	C87035				X		X	
Physical examination	C87035				X		X	
TB test	X							
TB questionnaire	X				X		X	
Tanner stage	C87035				X		X	
Height	C87035				X		X	
Weight	C87035				X		X	
Vital signs ^f	C87035	X			X		X	X

Table 5-1. Schedule of study assessments

Visit or phone call (+/-7 days)	Entry ^a	Visit	Treatment Period					SFU ^d
			Phone call (home administration) or visit (clinic administration) ^b	Regular Clinic Visits ^b	Completion/Early Termination	Unscheduled Visit ^c		
Week	0	2	Every 4 weeks beginning at Week 6 and in between regular clinic visits	Every 12 weeks beginning at Week 14			+12 weeks after last dose of study drug	
Adverse events ^a	C87035	X	X	X	X	X	X	
Concomitant medications ^a	C87035	X	X	X	X	X	X	
Concurrent medical procedures	C87035	X	X	X	X	X	X	
PCDAI	C87035			X	X	X		
ESR/hematocrit/albumin for PCDAI	C87035			X	X	X		
CRP	C87035			X	X	X		
Hematology/chemistry/urinalysis	C87035			X	X	X	X	
IMPACT III	C87035			X ⁱ	X	X		
WPAI:CD ^e	C87035			X ⁱ	X	X		
Certolizumab pegol plasma concentration ^h	C87035			X	X	X	X	
Anti-CZP antibody plasma concentration ⁱ	C87035			X	X	X	X	
Autoantibodies (ANA and anti-dsDNA)	C87035			X	X	X	X	
Bone markers (osteocalcin, bone specific alkaline phosphatase, n-telopeptides)	C87035			X ⁱ	X	X		

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Table 5-1. Schedule of study assessments

Visit or phone call (+/-7 days)	Entry ^a	Visit	Treatment Period				SFU ^d
			Phone call (home administration) or visit (clinic administration) ^b	Regular Clinic Visits ^b	Completion/Early Termination	Unscheduled Visit ^c	
Week	0	2	Every 4 weeks beginning at Week 6 and in between regular clinic visits	Every 12 weeks beginning at Week 14			+12 weeks after last dose of study drug
Study drug administration ^l		X	X	X			
Reinduction ^k	Loss of response must be confirmed at a clinic visit where assessments and labs are performed to determine PCDAI score. Scores cannot be confirmed until lab results are received by central lab a few days after the clinic visit. Once loss of response is confirmed, sites must contact the subject to return for the first Reinduction Visit. Reinduction Week 0 (first reinduction dose) is followed by Reinduction Week 2 (second dose, 2 weeks after first dose), and Reinduction Week 4 (third dose, 2 weeks after second dose). Subjects should return to the clinic for each Reinduction. Subject resumes the original schedule of clinic visits after reinduction. The clinic should contact the Study Monitor to determine the most appropriate way to resume the original schedule of clinic visits. Reinduction Week 0 assessments: PCDAI; ESR, hematocrit, and albumin; IMPACT-III; WPAI:CD Reinduction Week 2 assessments: PCDAI; ESR, hematocrit, and albumin Reinduction Week 4 assessments: PCDAI; ESR, hematocrit, and albumin; WPAI:CD						

ANA=antinuclear antibody; CRP=C-reactive protein; CZP=certolizumab pegol; dsDNA=double-stranded deoxyribonucleic acid (antibody); ESR=erythrocyte sedimentation rate; ET=Early Termination; PCDAI=Pediatric Crohn's Disease Activity Index; SFU=Safety Follow-Up; TB=tuberculosis; WPAI:CD=Work Productivity and Activity Impairment Questionnaire for CD

^aWeek 0 of CR0012 is equivalent to the last visit (Week 62; status evaluation) of C87035 with the following exceptions: written informed consent, assessment of inclusion/exclusion criteria, demography, TB testing, and TB questionnaire. Ongoing AEs and concomitant medications from C87035 will continue to be followed in CR0012. Other assessments will be taken from the C87035 database by UCB. Subjects who were terminated from C87035 when the study was stopped by UCB completed all assessments required for Week 62/Visit 23 at the time of termination.

^bAfter Week 2, subjects or parents/caregivers have the option of home administration of CZP upon appropriate training during a previous clinic visit(s) or can continue to have CZP administered every 4 weeks at the clinic. For subjects performing home administration, a phone call to the subject and/or the parents/caregiver will be performed by the Investigator (or designee) every 4 weeks between regular clinic visits in order to capture potential AEs and changes in concomitant medications, and to check compliance with home dosing. Subjects will have the option to either switch to home dosing or switch

Table 5-1. Schedule of study assessments

Visit or phone call (+/-7 days)	Treatment Period						
	Entry ^a	Visit	Phone call (home administration) or visit (clinic administration) ^b	Regular Clinic Visits ^b	Completion/Early Termination	Unscheduled Visit ^c	SFU ^d
Week	0	2	Every 4 weeks beginning at Week 6 and in between regular clinic visits	Every 12 weeks beginning at Week 14			+12 weeks after last dose of study drug

back to site administration at anytime during the study.

^cVital signs, concomitant medication, and AEs must be assessed at every Unscheduled Visit. Other safety and PK assessments (eg, CZP plasma sample) may be performed at the discretion of the Investigator as related to the nature of the visit.

^dThe SFU Visit should be performed 12 weeks after the final dose of study medication. For subjects continuing directly onto commercial CZP, a SFU Visit should be completed prior to the first dose of commercial drug administration.

^eFor all females post menses, a urine pregnancy test will be conducted at all regularly scheduled clinic visits except Week 2.

^fVital signs will be collected 15 minutes prior to dosing with a ± 5 minute window.

^gDays missed from school will be assessed using the WPAI:CD for children. The time missed from work will be assessed using the WPAI:CD for working individuals with CD. The effect of the child's CD on the caregiver's productivity will be assessed using the WPAI:CD for caregivers of children with CD.

^hPlasma samples will be collected to determine the concentration of CZP every 12 weeks starting at Week 14, and at the Completion/Early Termination and SFU Visits. Samples will be collected before dosing (except for the Completion/ET and SFU Visits when there is no dosing).

ⁱAnti-CZP antibody concentrations in plasma will be collected every 12 weeks starting at Week 14, and at the Completion/ET and SFU Visits (anti-CZP antibody measurements will be made using the samples taken for PK measurements at these time points, so additional blood draws will not be required).

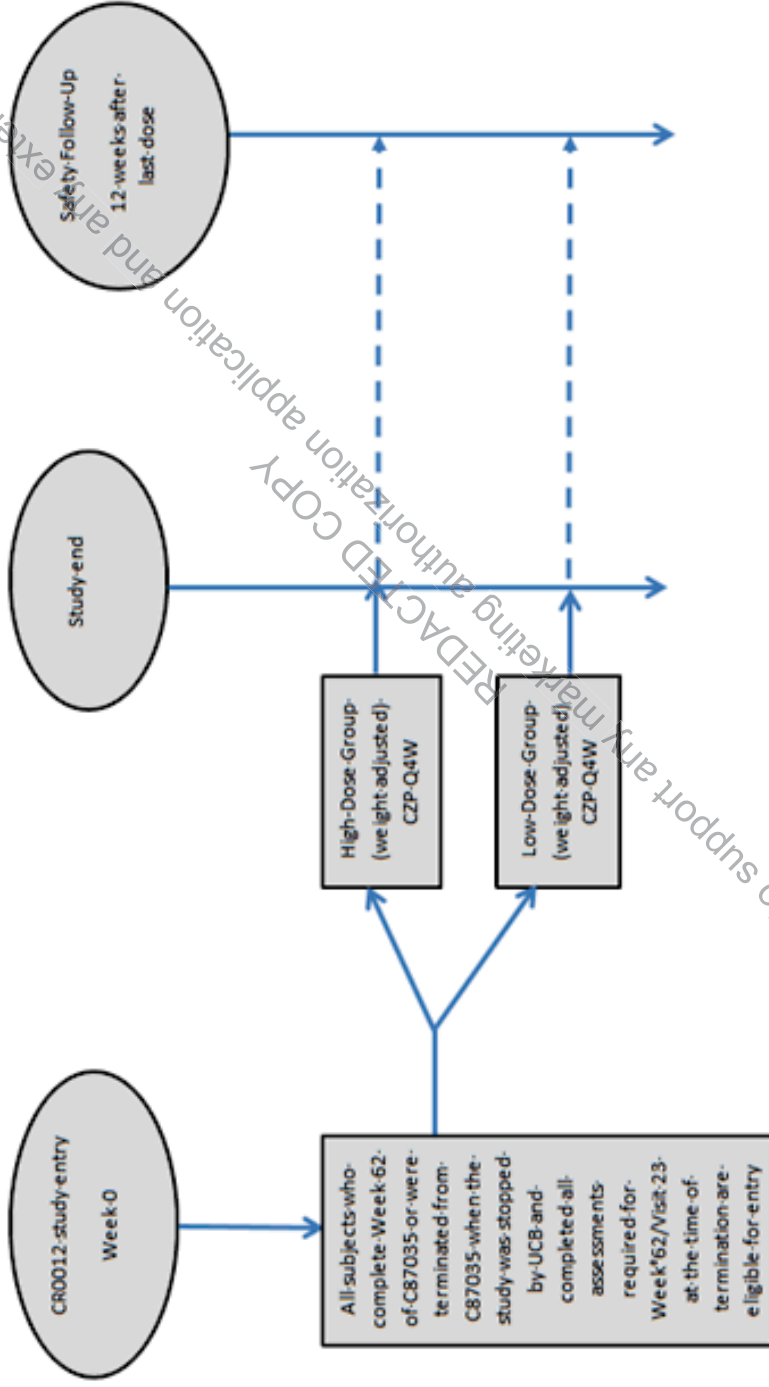
^jIf home administration is performed, sufficient study drug will be dispensed at the scheduled every 12-week clinic visit to last until the next scheduled clinic visit.

^kIf a subject has not been previously reintroduced in CR7035, the subject is eligible for 1 reintroduction due to loss of response in CR0012.

^lMeasured at Weeks 14, 26, 38, 50 and then every 12 months thereafter.

5.3 Schematic diagram

Figure 5-1: Schematic Diagram



CZP=certolizumab pegol; Q4W=every 4 weeks

5.4 Rationale for study design and selection of dose

Following the Food and Drug Administration (FDA) approval of CZP for the treatment of CD in adults, C87035 was a postapproval commitment to investigate the administration of CZP administration in children and adolescents with moderately to severely active CD. This study will provide continued treatment of CZP to subjects who completed C87035 or were terminated from C87035 when the study was stopped by UCB and who, in the Investigator's opinion, would benefit from continued administration of CZP.

The primary objective of this open-label study is to assess the longterm safety and tolerability of CZP in children and adolescents with moderately to severely active CD who completed C87035 or were terminated from C87035 when the study was stopped by UCB. The secondary objectives of this study are to assess the longterm efficacy, PK, and immunogenicity of CZP treatment on this population. Subjects may continue on CZP at the dose they were receiving at the end of C87035.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject or by the parent(s) or legally acceptable representative. The Consent form or a specific Assent form, where required, will be signed and dated by minors.
2. Subject/parent(s)/legally acceptable representative is considered reliable and capable of adhering to the protocol, visit schedule or medication intake according to the judgment of the Investigator.
3. Subject completed the C87035 study (Week 62 Visit) or was terminated from C87035 when the study was stopped by UCB and completed all assessments required for Week 62/Visit 23 at the time of termination.
4. Subject's current or recent regimen of concomitant medication(s) for CD should be stable through the study period (see [Section 7.8.1](#)).

6.2 Exclusion criteria

Subjects are not permitted to enroll in the study if the following criterion is met:

1. Subject did not complete the C87035 study (Week 62 Visit) or was terminated from C87035 when the study was stopped by UCB but did not complete all assessments required for Week 62/Visit 23 at the time of termination.

6.3 Withdrawal criteria

Subjects (or represented by their parent[s]/legally acceptable representative[s]) are free to withdraw from the study at any time, without prejudice to their continued care. Whenever possible, cases should be discussed with the UCB Study Physician or designee prior to withdrawing the subject. All subjects withdrawn due to an AE must be followed until resolution of the event or until subject is stable.

The Investigator may withdraw a subject from the study if in the opinion of the Investigator:

- The subject develops a clinically relevant medical condition that, in the opinion of the Investigator, jeopardizes or compromises the subject's ability to participate in this study.
- The subject develops an intolerable AE, as determined by the subject and/or Investigator, which cannot be controlled by appropriate therapy.
- The subject fails to comply with the protocol.
- Other safety issues arise during the course of the study.
- Subjects who require any of the following therapies must be withdrawn from study participation:
 - Anti-TNF therapy (other than CZP) or any biologic therapy for CD (eg, natalizumab)
 - Immunosuppressants (eg, azathioprine/6-mercaptopurin, or methotrexate)
 - Surgery related to exacerbation of CD (seton insertion per se is not to be considered surgery)
 - Inpatient hospitalization for exacerbation of CD
- The subject becomes pregnant (as evidenced by a positive pregnancy test) or plans to become pregnant during the study.
- The Investigator feels that it is in the subject's best interest to be withdrawn.
- Subjects must be withdrawn if requested by the Sponsor or a regulatory agency.
- Subjects who were reinduced once in C87035 cannot be reinduced in CR0012 and must be discontinued from CZP treatment at the time of loss of response.
- Subjects can undergo only 1 reinduction in this study; if response is lost a second time, the subject must be withdrawn from the study (see [Section 5.1](#)).

Any subject withdrawn from the study will be treated at the Investigator's discretion as per standard clinical practice.

Investigators should attempt to obtain information on subjects, in the case of withdrawal or discontinuation. For subjects considered as lost to follow-up the Investigator should make an effort (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents) to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The case report form (CRF) must document the primary reason for withdrawal or discontinuation.

Investigators should contact the Medical Monitor whenever possible to discuss the withdrawal of a subject in advance.

7 STUDY TREATMENTS

7.1 Description of investigational medicinal product(s)

The investigational product will be supplied under the responsibility of the Sponsor. The frequency at which the investigational product will be supplied to each individual site will be adapted to the availability of the investigational product, and expiry date of the investigational product. Study drug will be managed by the Interactive Voice Response System (IVRS) in order to ensure all sites have sufficient quantities of study drug available.

Drug supplies will consist of the following (allocated based on dosing [Table 7-1](#)):

- 1mL syringes with 25G needles of CZP, containing an injectable volume of 1mL (equivalent to a dose of 200mg)
- 0.5mL syringes with 25G needles of CZP, containing an injectable volume of 0.5mL (equivalent to a dose of 100mg)

Certolizumab pegol (acetate pH 4.7) is an anti-TNF, humanized antibody Fab' fragment conjugated with PEG.

7.2 Treatments to be administered

Details on drug dispensing and administration will be provided in the Pharmacy Manual.

Certolizumab pegol will be administered by the Investigator/designee during clinic visits. After Week 2, home administration of CZP by the subject or parent/caregiver/appropriate designee as determined by the Investigator will be permitted between scheduled clinic visits. Subjects/caregivers who do not choose home administration will continue to have CZP administered every 4 weeks at the clinic.

All Investigators and designees will be given instructions on the administration of study drug.

The PFS should be allowed to reach room temperature for a minimum of 30 minutes before injection. The acclimatization time must be followed very strictly. The maximum time for the product at room temperature is 2 hours.

Injections will be given *sc*; suitable areas include upper arm, lateral abdominal wall, and upper outer thigh. Each injection should be administered at a separate injection site and a rotation between the injection sites should be observed for each injection. Treatment of the injection site with an anesthetic cream (containing lidocaine and prilocaine; eg, EMLA[®]) prior to dosing is permissible. Dosing will be administered based on the subject's weight as specified in [Table 7-1](#).

Following study drug administration, the used PFS must be disposed appropriately (eg, using a sharps container).

Subjects will be observed for possible AEs for 30 minutes after each dose of study drug (1 or 2 injections) is administered, whether at clinic visits or at home, and subjects and/or parents/caregivers will be asked to contact the Investigator in case any reactions occur within the 2 hours following study drug injection.

The concentration of CZP is 200mg/mL. Depending on the dose, injections will be given sc as 1 or 2 injections of 1mL each resulting in doses of 200 and 400mg, respectively, or as 1 injection of 0.5mL resulting in a dose of 100mg. To achieve the appropriate doses, injections are administered as follows:

For subjects in the High-Dose Group (weight adjusted) CZP 400mg/200mg Q4W:

- Subjects weighing 20 to <40kg (44 to <88lbs): 1 injection of 1mL
- Subjects weighing \geq 40kg (\geq 88lbs): 2 injections of 1mL each

For subjects in the Low-Dose Group (weight adjusted) CZP 200mg/100mg CZP Q4W:

- Subjects weighing 20 to <40kg (44 to <88lbs): 1 injection of 0.5mL
- Subjects weighing \geq 40kg (\geq 88lbs): 1 injection of 1mL

Dosages and injections needed to achieve this dose are also presented in [Table 7-1](#).

A subject should only change dosing category during the course of the study if his/her weight increases by >2kg (4.4lbs) (measured at a clinic visit only) AND crosses the 40kg/88lb boundary (eg, a subject's weight increases from 39 to 41kg (from 85.8 to 90.2lbs). No dose adjustment is made for a weight decrease. In the event of a dose increase, the first injection of the higher dose must be administered at a clinic visit for all subjects, including those subjects performing home administration.

Table 7-1. Doses of CZP in CR0012

Treatment group	CZP dose (mg) injections ^a	
	High-Dose Group	Low-Dose Group
Dose frequency	Q4W	Q4W
Subject weight		
20 to <40kg (44 to <88lbs)	1x1mL PFS/200mg	1x0.5mL PFS/100mg
\geq 40kg (\geq 88lbs)	2x1mL PFS/400mg	1x1mL PFS/200mg

CZP=certolizumab pegol; PFS=prefilled syringe; Q4W=once every 4 weeks

Prior to CZP administration at home, subjects/caregivers/appropriate designee as determined by the Investigator will be trained by the site staff and provided written instructions on the schedule and fixed dose for injection, and the correct sc injection technique including 0.5ml and 1ml injections, as appropriate. Starting at Week 2, subjects/caregivers/appropriate designee as determined by the Investigator may administer the study medication under the supervision of the site staff to ensure that the study medication is being properly and safely injected. Once subjects/caregivers/appropriate designee as determined by the Investigator have been trained, the study medication may be administered at home. If administered at home, the subject/caregiver/appropriate designee as determined by the Investigator is requested to document the container number, date, and time point of administration of study

medication. All used PFSs will be disposed of by subjects/caregivers/appropriate designee as determined by the Investigator in an acceptable disposal (sharps) container directly after the administration. The subjects/caregivers return the documentation together with any used/unused containers at the next scheduled clinic visit. Subjects who are unable to self-administer the study treatment, those without a caregiver who can help, or those who choose not to self-inject, will continue to visit the clinic for study treatment administration between regular scheduled visits. In addition, subjects will have the option to either switch to home dosing or switch back to clinic administration at anytime during the study.

7.3 Packaging

Each site will receive uniquely numbered PFSs. The PFSs will be packaged in individual protective containers with a uniquely numbered carton.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

Each PFS will be inserted into a labeled individual container. Only the tear-off section (left section) of the label will be attached to the CRF at the time of administration (or dispensing to the subject/caregiver/appropriate designee as determined by the Investigator for home administration) to the subject, and the main section which will remain affixed to the individual container.

Prefilled syringes used for administration will be labeled with the same unique identifier (MED ID) as on the individual container.

Name, address and phone number of the Investigator will be included on the subject identification card (see [Section 14.2](#)).

7.5 Handling and storage requirements

The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access. All investigational products must be stored refrigerated at 2 to 8°C (35 to 46°F) and protected from light.

Appropriate storage conditions must be ensured either by controlled room temperature (2 to 8°C [35.6 to 46.4°F]), or by completing a temperature log in accordance with local requirements but at least once a day during the business week, with minimum and maximum temperatures reached over the time interval.

In case an out-of-range temperature is noted, it must be immediately communicated to the Sponsor before further use of the IMP.

The Clinical Project Manager (or designee) will transmit the out-of-range temperature (copy of the temperature log, duration of the out-of-range temperature, if available) to the Drug Supply Coordinator. Based on discussion with Quality Assurance, the Drug Supply

Coordinator will then provide the Clinical Project Manager (or designee) with instructions for the site regarding use of the IMP.

For IMP dispensed to the subject/caregiver/appropriate designee as determined by the Investigator for home dosing, the Investigator (or designee) will instruct the subject/caregiver/appropriate designee as determined by the Investigator to store the IMP following the instructions on the label. Cooler bags with freezer packs will be provided to transport home dosing supplies.

7.6 Drug accountability

A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost (due to breakage or wastage), not used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

Copies of completed dispensing records will be collected. Periodically and at the end of the study, all unused and expired investigational product (PFSs and container) will be collected and sent to the Sponsor (or designee) for destruction. All used PFSs will be disposed of by site staff in an acceptable disposal (sharps) container directly after the administration. All containers of the used PFSs must be kept until the accountability is checked by the monitor and can be destroyed afterwards.

The Investigator (or designee) is responsible for retaining all used and unused containers of IMP until returned or destroyed.

For home administration, any used/unused containers should be stored in provided containers and returned at the next clinic visit.

The Investigator may assign some of his/her duties for drug accountability at the study site to an appropriate pharmacist/designee.

Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol. The Investigator must ensure that the IMP is used only in accordance with the protocol.

7.7 Procedures for monitoring subject compliance

Subjects are expected to receive all doses of study drug as detailed in the schedule of assessments (Section 5.2). Any subject who deviates from the dosing schedule or misses any scheduled treatment should be reported to the Medical Monitor for determination of possible schedule adjustments and continued eligibility. These instances will be handled on a case-by-case basis.

At each visit after IMP is dispensed, subjects must return all unused IMP and empty IMP containers. Drug accountability must be done in the subject's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability form.

If a subject is found to be persistently noncompliant (missing 2 or more consecutive scheduled IMP doses or missing 3 or more doses), the Sponsor in conjunction with the Investigator will make a decision as to whether the subject should be withdrawn from the study.

7.8 Concomitant medication(s)/treatment(s)

The subject must not participate in any other clinical study or receive any unauthorized medication during the study period.

Should any treatment other than the investigational product be used, including over-the-counter products, an accurate record must be kept in the clinic chart (source documentation) and the CRF. This record should include the name of the drug, the dose, the date(s) of administration, and the indication for use.

7.8.1 Permitted concomitant treatments (medications and therapies)

Subjects should keep concomitant medications for CD (eg, aminosalicylates) stable through the study period.

Topical hydrocortisone for skin disorders or not more than 800µg per day inhaled beclomethasone, or equivalent, for asthma are permitted.

Subjects who use antidiarrheals on an as-needed basis should continue their use as required and at the usual dose.

Shortterm antibiotic use for the treatment of acute infections is permitted during the study.

Oral contraceptive use should continue at a stable medication and dose, if already used at C87035 entry. If a subject becomes sexually active during the study, acceptable methods of birth control (eg, oral contraceptives) should be employed.

If a subject experiences a concomitant illness requiring pain relief (eg, headache) during the course of the study, non-narcotic opiate analgesia (eg, ibuprofen) is recommended.

Subjects should not receive any live or attenuated vaccination during the study, or within 3 months after last dose of study drug. If a subject is scheduled for vaccination during the study, the Investigator must contact UCB or its representative to discuss the type of vaccination planned.

Treatment of the injection site with an anesthetic cream (containing lidocaine and prilocaine; eg, EMLA[®]) prior to dosing is permissible. Its use will be recorded as concomitant medication on the CRF.

Tuberculosis prophylactic treatment should be captured in the concomitant medication page of the CRF.

Other concomitant medications and doses for conditions other than CD may be adjusted as clinically appropriate during the study period. Any changes in concomitant medications must be recorded in the CRF.

7.8.2 Prohibited concomitant treatments (medications and therapies)

Use of corticosteroids or corticotrophins for indications other than CD is not permitted. However, topical hydrocortisone for skin disorders or not more than 800µg per day inhaled beclomethasone, or equivalent, for asthma is permitted.

Concomitant use of the following immunosuppressants is not permitted:

- Azathioprine, 6-mercaptopurine, or methotrexate
- Mycophenolate or thalidomide
- Cyclosporine or tacrolimus

Use of any experimental unregistered therapy or biological therapy (within or outside a clinical study) or participation in any clinical study using nonbiological therapies is not permitted.

7.8.3 Rescue therapy

Subjects who require the following defined rescue therapy to treat an exacerbation of CD at any time during the study will be treated as treatment failures from and including the time of receiving rescue therapy. For the purpose of this study, the defined rescue therapy which would classify the subject as treatment failure is as follows:

- Anti-TNF therapy (other than CZP) or any biologic therapy for CD (eg, natalizumab)
- Immunosuppressants (eg, azathioprine/6-mercaptopurin, or methotrexate)
- Surgery related to exacerbation of CD (seton insertion per se is not to be considered surgery)
- Inpatient hospitalization for exacerbation of CD
- Increase of corticosteroid dose above Week 0 of C87035 levels as defined below:
 - For subjects not taking corticosteroids at Week 0 of C87035
 - Any dose ≥ 10 mg/day prednisone (or equivalent) is considered rescue therapy
 - For subjects taking corticosteroids at Week 0 of C87035
 - Any increase $\geq 50\%$ of the Week 0 dose is considered rescue therapy
 - **OR**
 - Any dose >40 mg/day prednisone (or equivalent) is considered rescue therapy

7.9 Enrollment and numbering of subjects

To enroll a subject, the Investigator must contact the IVRS. Subjects will retain the unique subject number allocated in C87035. This unique subject number will be required in all communications between the Investigator (or designee) and the IVRS regarding a particular subject. The IVRS will allocate container numbers to the subjects based on the unique subject

number during the course of the study. Subject numbers and container numbers will be tracked via the IVRS and also will be required to be entered into the CRF.

The IVRS will allocate containers of study medication as appropriate to the visit schedule.

8 STUDY PROCEDURES BY VISIT

During the study, the acceptable window between the study visits is +/-7 days relative to entry (Week 0).

8.1 Entry Week 0

Week 0 of CR0012 is equivalent to Week 62 of C87035 with the exceptions noted below. Subjects who were terminated from C87035 when the study was stopped by UCB completed all assessments required for Week 62/Visit 23 at the time of termination.

Before any study-related procedures are performed, an IRB/IEC approved informed consent will be properly executed and documented. The written informed consent of the child's parent(s)/legally acceptable representative(s) must be obtained. In addition, where requested by local laws or by the IRB/IEC and according to the child's age/competence, the Assent form should be obtained from the child. The subjects and their parent(s)/legally acceptable representative(s) will be given adequate time to consider any information concerning the study given to them by the Investigator or designee. As part of the informed consent procedure, subjects and their parent(s)/legally acceptable representative(s) will be given the opportunity to ask the Investigator any questions regarding potential risks and benefits of participation in the study.

Assessments to be performed include:

- Written informed consent
- Inclusion/ exclusion criteria
- Demography
- TB test
- TB questionnaire

The following ongoing information must be continued to be followed from C87035 to CR0012:

- Adverse events
- Concomitant medications

8.2 Week 2 Visit

- Vital signs
- Adverse events
- Concomitant medications

- Concurrent medical procedures
- Study drug administration (including training and self-injection under supervision, as appropriate)
- Dispensing of drug to subject/caregiver/appropriate designee as determined by the Investigator, if appropriate for home dosing

8.3 Phone call (home administration) or visit (clinic administration) (every 4 weeks and in between regular clinic visits beginning at Week 6)

After Week 2, subjects and/or parents/caregivers have the option of home administration of CZP upon appropriate training during a previous clinic visit(s) or can continue to have CZP administered every 4 weeks at the clinic. For subjects performing home administration, a phone call to the subject and/or the parents/caregiver will be performed by the Investigator (or designee) every 4 weeks between regular clinic visits. Subjects will have the option to either switch to home dosing or switch back to site administration at anytime during the study.

Assessments performed during the phone call or at the clinic visit include:

- Adverse events
- Concomitant medications
- Concurrent medical procedures
- Study drug administration (check for compliance)

8.4 Regular clinic visits

8.4.1 Assessments every 12 weeks beginning at Week 14

- Assessment of childbearing potential (female subjects only)
- Urine pregnancy test (female subjects of childbearing potential only)
- Physical examination
- TB questionnaire
- Tanner stage
- Weight and height
- Vital signs
- Adverse events
- Concomitant medications
- Concurrent medical procedures
- PCDAI

- ESR/hematocrit/albumin for PCDAI
- CRP
- Hematology, clinical chemistry, and urinalysis
- Certolizumab pegol plasma concentration
- Anti-CZP antibody plasma concentration
- Autoantibody concentrations (ANA and anti-dsDNA)
- Study drug administration (including training and self-injection under supervision, as appropriate)
- Dispensing of drug to subject/caregiver/appropriate designee as determined by the Investigator, if appropriate for home dosing

8.4.2 Assessments at Weeks 14, 26, 38, 50 and then every 12 months thereafter:

- IMPACT III
- WPAI:CD (for children, for working individuals with CD, and for caregivers)
- Bone markers (osteocalcin, bone specific alkaline phosphatase, n-telopeptides)

8.5 Completion/Early Termination Visit

- Assessment of childbearing potential (female subjects only)
- Urine pregnancy test (female subjects of childbearing potential only)
- Physical examination
- TB questionnaire
- Tanner stage
- Weight and height
- Vital signs
- Adverse events
- Concomitant medications
- Concurrent medical procedures
- PCDAI
- ESR/hematocrit/albumin for PCDAI
- CRP
- Hematology, clinical chemistry, and urinalysis
- IMPACT III
- WPAI:CD (for children, for working individuals with CD, and for caregivers)

- Certolizumab pegol plasma concentration
- Anti-CZP antibody plasma concentration
- Autoantibody concentrations (ANA and anti-dsDNA)
- Bone markers (osteocalcin, bone specific alkaline phosphatase, n-telopeptides)

8.6 Reinduction visits

Loss of response must be confirmed at a clinic visit where assessments and labs are performed to determine PCDAI score. Scores cannot be confirmed until lab results are received by central lab a few days after the clinic visit. Once loss of response is confirmed, sites must contact the subject to return for the first Reinduction Visit.

Reinduction Week 0 assessments:

- PCDAI (using the ESR, hematocrit, and albumin results of the same visit)
- ESR, hematocrit, and albumin
- IMPACT-III
- WPAI:CD for children and/or WPAI:CD for working individuals
- WPAI:CD for caregivers of children with CD

Reinduction Week 2 assessments:

- PCDAI (using the ESR, hematocrit, and albumin results of the same visit)
- ESR, hematocrit, and albumin

Reinduction Week 4 assessments:

- PCDAI (using the ESR, hematocrit, and albumin results of the same visit)
- ESR, hematocrit, and albumin
- WPAI:CD for children and/or WPAI:CD for working individuals
- WPAI:CD for caregivers of children with CD
- Study drug administration will be performed at the clinic for all Reinduction injections (Weeks 0, 2, and 4). Subject resumes original schedule of clinic visits after reinduction. The clinic should contact the Study Monitor to determine the most appropriate way to resume the original schedule of clinic visits.

8.7 Unscheduled Visit

- Vital signs
- Adverse events

- Concomitant medications
- Concurrent medical procedures

Other safety and PK assessments (eg, CZP plasma sample) may be performed at the discretion of the Investigator as related to the nature of the visit.

8.8 Safety Follow-Up Visit

The SFU Visit is to be completed by all subjects 12 weeks after the final dose of study medication. For subjects who continue directly onto commercial CZP, a SFU Visit should be completed prior to the first dose of commercial drug administration.

- Urine pregnancy test (female subjects of childbearing potential only)
- Physical examination
- TB questionnaire
- Vital signs
- Adverse events
- Concomitant medications
- Concurrent medical procedures
- Hematology, clinical chemistry, and urinalysis
- Certolizumab pegol plasma concentration
- Anti-CZP antibody plasma concentration
- Autoantibody concentrations (ANA and anti-dsDNA)

9 SAFETY ASSESSMENTS

9.1 Adverse events

Adverse event information (duration, intensity, relationship to study drug, action taken, outcome, and seriousness will be recorded) will be obtained by observation and direct questioning of the subject and his/her parent(s)/legally acceptable representative(s), eg, “have you had any (other) medical problems since your last visit?” or “have you felt different in any way since your last visit?”

Ongoing AEs from C87035 will continue to be followed in CR0012. Adverse events will be assessed taken throughout the course of the study will be collected at every visit, phone contacts, and Unscheduled Visits.

9.1.1 Definition of adverse event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and

unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after signing the Informed Consent form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the CRF even if no investigational product was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs which recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the investigational product is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the subject's history or the Baseline Period (Week 0 of C87035).

9.1.2 Procedures for reporting and recording adverse events

Besides the Investigator's observations, the subject will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs, for example:

“Did you notice anything unusual about your health (since your last visit)?”

In addition, the Investigator should review any self-assessment procedures employed in the study.

9.1.3 Description of adverse events

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The CRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (eg, diary) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event CRF (including judgment of relationship to study medication) are described in the CRF completion guidelines.

9.1.4 Follow-up on adverse events

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow-up.

If an AE is still ongoing at the end of the study for a subject, follow-up should be provided until resolution/stable level of sequelae, the Investigator no longer deems that it is clinically significant, or until the subject is lost to follow-up. If no follow-up is provided, the Investigator must provide a justification. The follow-up will usually be continued for 12 weeks after the subject has discontinued their IMP.

9.1.5 Rule for repetition of an adverse event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of “worsening”,
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one.

9.1.6 Pregnancy

Should a subject become pregnant after the first intake of any IMP, UCB’s Global Clinical Safety and Pharmacovigilance (GCSP) department should be informed immediately. The subject should be withdrawn from the study as soon as pregnancy is known and the following should be completed:

- The subject should return for an early discontinuation visit.
- The subject should immediately stop the intake of the investigational medicinal product or be down-titrated as instructed at the early discontinuation visit.
- An SFU Visit should be scheduled 12 weeks after the subject has discontinued their IMP.

The Investigator must inform the subject of information currently known about potential risks and about available treatment alternatives.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, UCB will ask the Investigator or designee to contact the subject and his partner to request consent via the Partner Pregnancy Consent form. If the partner agrees to provide additional information, the Pregnancy Report and Outcome form will be forwarded to the subject’s partner for completion.

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the Investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed-up using the Pregnancy Report and Outcome form in which the Investigator has to report on the health of the mother and of the child. The health of the child must be followed for 30 days after birth for any significant medical issues.

In certain circumstances, UCB may request that follow-up is continued for a period longer than 30 days.

A pregnancy becomes a serious adverse event (SAE) in the following circumstances: miscarriage, abortion, or anomaly/birth defect of the child. Those SAEs must be additionally reported using the Investigator SAE Report form.

9.1.7 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the CRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other serious or nonserious AE. These events may be symptomatic, in that the excessive dosing results in clinical signs and symptoms, or the excessive intake may itself be a symptom.

9.1.8 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP so that Investigators, clinical study subjects, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the GCSP representative.

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at UCB may identify additional safety measures (examples: AEs, vital signs, laboratory or electrocardiogram [ECG] results) for which data will be periodically reviewed during the course of the study.

Refer to [Section 13.8](#) for details on the DSMB used in this study.

9.2 Serious adverse events

9.2.1 Definition of serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death
- Life-threatening
(Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious
- (Important medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, infections that require treatment with parenteral antibiotics, or the development of drug dependency or drug abuse.)
- Initial inpatient hospitalization or prolongation of hospitalization

(A patient admitted to a hospital, even if released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event]).

Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE since there is no AE upon which to assess the serious criterion. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.)

9.2.2 Procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact numbers for SAE reporting listed in the SAE Reporting section at the front of the protocol). The Investigator must forward to UCB (or its representative) a duly completed Investigator SAE Report form provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

An Investigator SAE Report form will be provided to the Investigator. The Investigator SAE Report form must be completed in English.

Additional information (eg, autopsy or laboratory reports) received by the Investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE Report form.

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the investigational product), up to 12 weeks from the end of the study for each subject, and to also inform participating subjects of the need to inform the Investigator of any SAE within this period. Serious adverse events that the Investigator thinks may be associated with the investigational product must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the Investigator's Brochure.

9.2.3 Follow-up of serious adverse events

An SAE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow-up.

Information on SAEs obtained after clinical database lock will be captured through the GCSP database without limitation of time.

9.3 Adverse events of interest

An AE of special interest is any AE which is listed in the European Risk Management Plan, or meets another commitment requiring nonstandard expedited reporting, even if the AE does

not fulfill the expedited reporting criteria of “serious”, “unexpected”, and “associated with the use of the drug.” Adverse events of special interest include:

- Serious infections including opportunistic infections
- Malignancies including lymphoma
- Congestive heart failure
- Demyelinating-like disorders
- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia
- Serious bleeding events
- Lupus and lupus-like illness
- Serious skin reactions (eg, Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme)

9.4 Immediate reporting of adverse events

The following AEs must be reported immediately:

- SAE: AE that the Investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AE of interest (see Section 9.3)

9.5 Laboratory measurements

Hematology assessments will include the following parameters: red blood cell (RBC) count, hemoglobin, hematocrit, platelets, white blood cell (WBC) count, neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

Clinical chemistry assessments will include the following parameters: Sodium, potassium, total calcium, glucose, creatinine, urea, total protein, albumin, alkaline phosphatase, gamma glutamyl aminotransferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin.

For urinalysis, urine protein and blood will be measured by the dipstick method. If positive, microscopic assessments will be done for WBC, RBC, and casts and microbiological culture will be undertaken.

Hematology, clinical chemistry, and urinalysis parameters will be assessed at entry Week 0, every 12 weeks starting at Week 14, and at the Completion/Early Termination (ET) and SFU Visits.

Instructions on blood sample collection, processing, storage, and shipping will be provided in the laboratory manual for this study.

For subjects undergoing reinduction, the parameters ESR, hematocrit, and albumin will be measured at Reinduction Weeks 0, 2, and 4.

9.6 Other safety measurements

9.6.1 Demographics

Demographics (date of birth, sex, and race) will be recorded at entry Week 0.

9.6.2 Assessment of childbearing potential

For female subjects, childbearing potential will be assessed every 12 weeks starting at Week 14, and at the Completion /Early Termination Visits.

9.6.3 Pregnancy test

For female subjects of childbearing potential, urine pregnancy tests will be performed every 12 weeks starting at Week 14, and at the Completion/ET and SFU Visits.

9.6.4 Physical examination

General appearance, ears, nose, throat, eyes, hair and skin, respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, neurological, and mental status will be assessed. Abnormalities will be recorded as an AE. Physical examination assessments will be performed every 12 weeks starting at Week 14, and at the Completion /ET and SFU Visits.

9.6.5 Tuberculin test

All sites may use either the purified protein derivatives (PPD) skin test or QuantiFERON[®]-TB GOLD test. Use of QFT-GOLD is acceptable provided the site has experience in organizing the QFT-GOLD testing; either the central laboratory or a local laboratory may be used. The test will be performed at entry Week 0.

Subjects who experience close contact with an individual with active TB during the conduct of the study must be referred to a physician specializing in TB to perform additional evaluations to exclude latent/active TB before subject may resume study treatment. Subjects who prematurely discontinue treatment for latent TB or who are noncompliant with prophylactic therapy must immediately discontinue further administration of study drug but need to complete the ET/SFU Visits.

9.6.5.1 Mantoux tuberculin skin test (PPD test)

A Mantoux tuberculin skin test (PPD test) will be performed following the instructions below. Multiple puncture tests like the Tine and Heaf tests are not acceptable methods of testing because the amount of tuberculin injected intradermally cannot be precisely controlled.

The intradermal injection of a measured amount of tuberculin is the standard method of detecting infection with *Mycobacterium tuberculosis*. One-tenth milliliter of PPD (5 TU PPD-S or 2TU of PPD-RT 23, as recommended by the World Health Organization) is injected into the inner surface of the forearm. Other areas may be used, but the forearm is preferred. The use of a skin area free of lesions and away from veins is recommended. The injection is made using a one-quarter- to one-half-inch (1cm), 27-gauge needle and a tuberculin syringe. The tuberculin should be injected by a qualified health care worker just

beneath the surface of the skin, with the needle bevel upward. A discrete, pale elevation of the skin (a wheal) 6 to 10mm in diameter should be produced when the injection is done correctly. If it is recognized that the first test was improperly administered, another test dose can be given at once, selecting a site several centimeters away from the original injection. A note in the record should indicate the site chosen for the second test. Study subject should be instructed not to scratch the site and to avoid covering the area with a bandage.

Tests should be read by a trained health care worker between 48 and 72 hours after injection. Reading should be performed in good light, with the forearm slightly flexed at the elbow. The basis of reading is the presence or absence of induration, which may be determined by inspection (from a side view against the light as well as by direct light) and by palpation. The diameter of induration should be measured transversely to the long axis of the forearm and recorded in millimeters even those classified as negative. Erythema should not be measured. Subjects should never be allowed to read their own tuberculin skin tests. If a subject fails to return within 72 hours to have the PPD skin test read, an ELISA-based assay, such as QFT-GOLD, must be performed.

An induration of ≥ 5 mm in response to the intradermal tuberculin skin test is considered to be a positive result and evidence for either latent or active TB.

In most countries, the most conservative definition of positivity for the tuberculin skin test is reserved for immunocompromised subjects, and this definition is to be applied here. The purpose of using this conservative definition of positivity is to maximize the likelihood of detecting latent TB.

9.6.6 Evaluation of signs and symptoms of TB

Signs and symptoms of TB will be evaluated for all subjects using the questionnaire "evaluation of signs and symptoms of tuberculosis" provided in [Section 17.1](#). This questionnaire should be used as a source document. The questionnaire will assist with the identification of subjects who may require prophylactic therapy for TB. A subject who answers "Yes" to the question

"[REDACTED]" is required to begin prophylactic treatment for latent TB. A "Yes" response to 1 or more of the other questions within the questionnaire should trigger further careful assessment of risk to determine if prophylactic or curative treatment for TB is required.

All subjects considered at high risk for TB infection will receive prophylactic TB treatment (eg, isonicotinic acid hydrazide [isoniazid; INH] therapy for 9 months [with vitamin B6]).

Subjects who do not initiate prophylactic treatment for latent TB per Sponsor requirement, prematurely discontinue prophylactic treatment for latent TB or are noncompliant with antituberculosis therapy, in the Investigator's opinion, must discontinue further use of study medication and be immediately withdrawn from study participation. Once withdrawn from study treatment, subjects should return for the ET Visit and complete all early withdrawal assessments, and complete a final SFU Visit 12 weeks after the last dose of study medication.

If active TB is suspected or confirmed, the subject must be withdrawn immediately from the study and discontinue study medication. The subject must return for the ET Visit and complete all early withdrawal assessments, and complete a final SFU Visit 12 weeks after the

last dose of study medication. Confirmed active TB is an SAE and must be captured on an SAE Report Form and provided to the Sponsor in accordance with SAE reporting requirements. As with all SAEs, periodic follow-up reports should be completed as per protocol requirement until such time as the TB infection resolves.

Follow-up information of the suspected or confirmed TB should be provided to UCB at least after 3, 9, and 12 months of start date of anti-TB treatment, including hematological and biochemical safety parameters, x-ray evolution, and TB diagnosis procedures used to follow up and confirm recovery of TB.

9.6.7 Vital signs

Systolic and diastolic blood pressure and pulse rate will be measured 15 minutes prior to dosing (with a ± 5 minutes window) in a sitting position at entry Week 0, Visit 2, every 12 weeks starting at Week 14, and at the Completion/ET, Unscheduled, and SFU Visits.

9.6.8 Concomitant medications

Details of all concomitant medications taken throughout the course of the study will be collected at every visit, phone contacts, and Unscheduled Visits. Ongoing concomitant medications from C87035 will continue to be followed in CR0012.

9.6.9 Medications for CD

Details of medication taken for the treatment of CD will be recorded throughout the study at scheduled site visits and via phone calls by the Investigator (designee) at every 4 week intervals between regular visits. In addition, information on medication taken as maintenance treatment for CD will be recorded throughout the study.

9.6.10 Autoantibodies

Autoantibody (ANA and anti-dsDNA) titers will be determined every 12 weeks starting at Week 14, and at the Completion/ET and SFU Visits.

Instructions on blood sample collection, processing, storage, and shipping will be provided in the laboratory manual for this study.

10 EFFICACY ASSESSMENTS

10.1 Disease activity/PCDAI

The subjects' disease activity will be assessed using the PCDAI. The PCDAI was developed by pediatric inflammatory bowel disease (IBD) experts and was validated at 12 North American institutions (Hyams et al, 1991). It is a modification of the Clinical 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 to the CDAI, the PCDAI decreases the weighting given to subjective historical terms, adds height velocity, and adds ESR to the laboratory measures included (Hyams et al, 1991; Otley et al, 1999). The PCDAI is provided in [Section 17.2](#).

The Investigator will calculate the subjects' PCDAI scores every 12 weeks starting at Week 14, and at the Completion/ET Visit. Calculation of PCDAI scores is also necessary to determine whether a subject loses response (Section 5.1). For subjects undergoing reinduction, PCDAI scores will be calculated at Reinduction Weeks 0, 2, and 4.

For the calculation of the PCDAI score at a particular visit (to assess efficacy of CZP treatment), values for hematocrit, ESR, and albumin are used from the same clinic visit. Thus, the PCDAI score calculation cannot be completed until the laboratory values have been received at the site.

Since portions of the PCDAI calculations are based upon a 1-week (7-day) history recall of symptoms, subjects and/or caregivers will be contacted prior to the visit with a reminder that this information needs to be provided at the visit.

10.2 Erythrocyte sedimentation rate

The ESR will be assessed every 12 weeks starting at Week 14, and at the Completion/ET Visit. Results of these measurements form part of the PCDAI assessments described in Section 10.1.

For subjects undergoing reinduction, ESR will be assessed at Reinduction Weeks 0, 2, and 4.

Instructions on blood sample collection, processing, storage, and shipping will be provided in the laboratory manual for this study.

10.3 C-reactive protein

Levels of CRP will be assessed every 12 weeks starting at Week 14, and at the Completion/ET Visit.

Instructions on blood sample collection, processing, storage, and shipping will be provided in the laboratory manual for this study.

10.4 Tanner stage

Assessments of subjects' developmental stages will be performed to determine the subjects' Tanner stages (Marshall and Tanner, 1969; Marshall and Tanner, 1970). These assessments will be performed every 12 weeks starting at Week 14, and at the Completion/ET Visit.

10.4.1 Bone markers

Markers of bone and collagen turnover, reflecting the childhood growth curve, will be measured at Weeks 14, 26, 38, 50 and then every 12 months thereafter, and at the Completion/ET Visit. These markers will include: osteocalcin, bone specific alkaline phosphatase, and n-telopeptides. Tests will be performed by a central laboratory facility.

Instructions on blood sample collection, processing, storage, and shipping will be provided in the laboratory manual for this study.

10.5 Height

Height will be recorded every 12 weeks starting at Week 14, and at the Completion/ET Visit. Height will be recorded after the shoes have been removed. Height should preferably be

measured with a wall-mounted stedometer. Results of these measurements form part of the PCDAI assessments described in [Section 10.1](#).

10.6 Weight

Weight will be recorded after removal of shoes and heavy clothing. Weight will be measured every 12 weeks starting at Week 14, and at the Completion/ET Visit.

Results of the weight measurement will be used to determine the subject's CZP dose as specified in [Table 7-1](#). In addition, results of these measurements form part of the PCDAI assessments described in [Section 10.1](#).

10.7 IMPACT-III

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 (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-III 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. The IMPACT-III questionnaire is provided in [Section 17.3](#). The IMPACT-III questionnaire will be administered at Weeks 14, 26, 38, 50 and then every 12 months thereafter, and at the Completion /ET Visit.

For subjects undergoing reinduction, the IMPACT-III questionnaire will be administered at Reinduction Week 0.

The IMPACT-III questionnaire is a copyright of the Pediatric Inflammatory Bowel Disease Working Group on Quality of Life (copyright 2002). The IMPACT-III has been provided under licences, by the Pediatric Inflammatory Bowel Disease Working Group and must not be copied, distributed, or used in any way without prior written permission by the Pediatric Inflammatory Bowel Disease Working Group.

10.8 Days missed from school/work (WPAI:CD for children and for working individuals with CD)

The Work Productivity and Activity Impairment Questionnaire for children with CD (WPAI:CD) is used to [REDACTED]

[REDACTED] If a subject has left school and is working, the WPAI:CD for working individuals is used instead of the WPAI:CD for children. If a subject is both attending school and working, both the WPAI:CD for children and the WPAI:CD for working individuals are used.

The WPAI:CD for children questionnaire contains 6 questions: [REDACTED]

[REDACTED], all 6 questions are completed, and [REDACTED]

[REDACTED], the subject completes only question number 6 to [REDACTED]. The 6 items are regrouped into 4 dimensions and the scores are expressed as percentages, with higher numbers indicating greater impairment and less productivity (Reilly et al, 2008).

The WPAI:CD for working individuals questionnaire contains 6 questions: [REDACTED]

The WPAI:CD for children questionnaire is administered to all subjects or the parent(s)/legally acceptable representative(s) and the WPAI:CD for working individuals questionnaire is only administered to subjects who work, under supervision of the Investigator or designee at Weeks 14, 26, 38, 50 and then every 12 months thereafter, and at the Completion /ET Visit.

For subjects undergoing reinduction, the WPAI:CD questionnaires will be administered at Reinduction Weeks 0 and 4.

The WPAI:CD questionnaire for children with CD (Section 17.4) and the WPAI:CD for working individuals are provided (Section 17.5).

10.9 Effect on the caregiver's work (WPAI:CD for caregivers)

The WPAI:CD questionnaire for caregivers of children with CD is used to [REDACTED]

[REDACTED] he questionnaire contains 6 questions:

[REDACTED] all 6 questions are completed, and if [REDACTED], the caregiver completes only question number 6 to reflect [REDACTED]. The 6 items are regrouped into 4 dimensions and the scores are expressed as percentages, with higher numbers indicating greater impairment and less productivity.

The questionnaire is administered under supervision of the Investigator or designee to the caregiver at Weeks 14, 26, 38, 50 and then every 12 months thereafter, and at the Completion/ET Visit.

For subjects undergoing reinduction, the WPAI:CD questionnaire will be administered at Reinduction Weeks 0 and 4.

The WPAI:CD questionnaire for caregivers of children with CD is provided in Section 17.6.

10.10 Concurrent medical procedures

Any concurrent medical procedures will be recorded throughout the course of the study at every visit, phone contacts, and Unscheduled Visits.

11 PHARMACOKINETICS AND IMMUNOLOGICAL ASSESSMENTS

Blood samples will be collected to determine plasma concentrations of CZP and anti-CZP antibodies every 12 weeks starting at Week 14, and at the Completion/ET and SFU Visits. All of these blood draws will be performed prior to study drug administration (except for the Completion/ET and SFU Visits when there is no dosing) and all of them coincide with the blood collection times for the assessment of hematology and clinical chemistry parameters, so that no additional blood sampling is required at these visits.

Time and date of each blood draw will be documented on the CRF.

Instructions on blood sample collection, processing, storage, and shipping will be provided in the laboratory manual for this study.

12 STUDY MANAGEMENT AND ADMINISTRATION

12.1 Adherence to protocol

The Investigator should not deviate from the protocol. In medical emergencies, the Investigator may use his/her medical judgment and may remove a study participant from immediate hazard before notifying UCB (or its representative) and the IRB/IEC in writing regarding the type of emergency and the course of action taken.

12.2 Monitoring

UCB (or designee) will monitor the study to meet the Sponsor's monitoring Standard Operating Procedures (SOPs), ICH-GCP guidelines, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a contract research organization (CRO) or a contract monitor.

The Investigator and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The Investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The Investigator will allow UCB (or designee) to periodically review all CRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of CRFs, ensure that all protocol requirements, applicable authorities regulations and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

12.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies of CRFs are not considered acceptable source documents. Source documents are original records in which raw data are first

recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or Quality of Life Questionnaires, for example. Source documents should be kept in a secure, limited access area.

The following data will be recorded directly in the CRF and will not appear in a source document as defined above: IMPACT-III and WPAI:CD.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the subject's source documents. The Investigator will authorize the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records such as holter monitor records or electroencephalogram records must be saved and stored as instructed by UCB (or designee).

12.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the CRF should be supported by source documents, unless otherwise specified in Section 13.2.1.

12.3 Data handling

12.3.1 Case report form completion

The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the CRFs and in all required reports.

Any change or correction to the CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. Use of correction fluid is not permitted.

Corrections made after the Investigator's review and signature of the completed CRF will be resigned and dated by the Investigator.

The Investigator should maintain a list of personnel authorized to enter data into the CRF.

Detailed instructions will be provided in the CRF completion guidelines.

12.3.2 Database entry and reconciliation

Case report forms/external electronic data will be entered/loaded in a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. Case report form data are entered into the clinical database using independent, double-data entry, with the exception of comment fields, which are verified by a second person.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data has been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

12.3.3 Subject Entry and Enrollment log/Subject Identification Code list

The subject's entry and enrollment will be recorded in the Subject Entry and Enrollment Log.

The Investigator will keep a Subject Identification Code list. This list remains with the Investigator and is used for unambiguous identification of each subject.

The subject's consent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

12.4 Termination of the study

Upon completion of the study, the monitor will conduct the following activities in conjunction with the Investigator, as appropriate:

- Return of all study data to UCB or its representatives while maintaining original source documents
- Data clarification and/or resolution
- Accountability, reconciliation, and arrangements for used and unused investigational products
- Review of site study records for completeness
- Discussion/reminder on archiving responsibilities
- Discussion of IRB/IEC requirements for study termination
- Arrangements for unused CRFs, lab supplies, and any other study related supplies

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the Investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused investigational products and other material in accordance with UCB procedures for the study.

12.5 Archiving and data retention

The Investigator will maintain adequate records for the study including CRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (ICH-GCP Guideline, Section 4.9.5). The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's study master file.

12.6 Audit and inspection

The Investigator will permit study-related audits mandated by UCB and inspections by domestic or foreign regulatory authorities, after reasonable notice.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH/GCP, and applicable regulatory requirements.

The Investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the Investigator will immediately inform UCB (or designee).

12.7 Good Clinical Practice

Noncompliance with the protocol, ICH/GCP, or local regulatory requirements by the Investigator, institution, institution staff, or designees of the Sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

13 STATISTICS

A description of statistical methods is presented below and will be described in more detail in the Statistical Analysis Plan (SAP).

13.1 Definition of analysis sets

The All Subject Population will include those subjects who are enrolled in the study. All available data entered into the database will be listed for this population.

The Safety Population will include all subjects enrolled who receive at least 1 injection of study treatment in this study. This population will be used to summarize the safety, PK, and immunological variables.

The Intention-to-Treat (ITT) Population will include all subjects irrespective of any protocol deviations who receive at least 1 injection of study treatment in this study and who have at least 1 efficacy measurement after the first injection of this study. This population will be used to summarize the efficacy variables.

13.2 General statistical considerations

Summary statistics will consist of sample size, frequencies, and corresponding percentages for categorical variables. For continuous variables, descriptive statistics (number of available observations, mean, median, standard deviation, minimum, and maximum) will be tabulated. Data summarized by visit will use nominal visits with the exception of data collected at withdrawal visits which will be summarized at the next scheduled nominal visit dependent on when the withdrawal visit occurs taking into account the allowable visit windows.

Summaries will be by treatment received at the end of C87035. Any other subgroups of interest such as subjects who have been reinduced in C87035 or reinduced during CR0012 will be detailed in the SAP.

For data such as Crohn's disease history which are only collected at the Screening Visit of C87035, these will be defined as the Baseline values. For data which are collected at Week 0 of C87035 and prior to receiving any study treatment, the last nonmissing value prior to receiving any treatment will be defined as the Baseline values.

All analyses will be performed using the SAS software package.

All AEs will be coded and classified by primary System Organ Class (SOC) and Preferred Term (PT) according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA[®]).

All medications will be coded using World Health Organization Drug (WHODrg).

13.3 Planned safety analyses

All safety summaries will be based on the Safety Population as a whole, by treatment group, weight, and age stratum.

Treatment emergent adverse events will be summarized descriptively by primary SOC, high level term, and PT. Additional tables will summarize AEs by severity and relationship to study drug, and separate tables will be generated for AEs leading to withdrawal from the study, SAEs, and deaths. Other AEs of special interest including, but not limited to, infections will also be summarized.

The specific set of AEs reported as injection reactions will also be summarized along with their classification as either injection site reactions or systemic hypersensitivity reactions (the latter being further classified as acute or delayed).

Actual laboratory values and changes from Baseline in laboratory values will be summarized. Shift tables to show the change from Baseline in the absolute values and details of treatment emergent markedly abnormal values (based on Common Terminology Criteria for Adverse Events criteria) will be presented by variable.

Actual vital signs values and change from Baseline in vital signs values will be summarized.

Autoantibody levels will be assessed via the presence or absence of ANA and anti-dsDNA, and data will be summarized.

Extent of exposure to treatment will be presented descriptively.

13.4 Planned efficacy analyses

As the primary objective of the study is to evaluate safety there are no primary or secondary efficacy variables. Rather, efficacy variables will be measured to evaluate efficacy of longterm open label treatment with CZP.

All efficacy summaries, where applicable, will be presented by visit, treatment group, weight (20 to <40kg [44 to <88lbs] and \geq 40kg [\geq 88lbs]) and age stratum (6 to 11 years and 12 to 17 years).

The proportion of subjects in clinical remission and the proportion of subjects in clinical response will be summarized using the number and percentage of subjects along with associated 95% confidence intervals (CI).

A subject who does not have all required data to derive a response status (response or remission) will be classified as a nonresponder/nonremitter at that particular time point. A subject who withdraws from the study or is reinduced, will be classified as a nonresponder/nonremitter from and including the time of withdrawal or reinduction.

If a subject receives rescue therapy, the subject will be considered as a treatment failure (nonresponder/nonremitter) from the timepoint of administration of first rescue therapy onwards.

Actual PCDAI scores and changes from Baseline in PCDAI scores will be summarized by presenting the mean, standard deviation (SD), 95% CI for the mean, median, minimum, and maximum values.

Levels of CRP and ESR and changes from Baseline in CRP levels and ESR (expressed as a ratio with the value measured at Baseline as denominator) will be summarized by presenting the geometric mean, coefficient of variation, 95% CI for the geometric mean, median, minimum, and maximum values.

IMPACT-III scores and changes from Baseline will be summarized by presenting the mean, SD, 95% CI for the mean, median, minimum, and maximum values.

The change from Baseline in growth score using the Tanner stage (assessing puberty), will be summarized using shift tables. Bone marker values and changes from Baseline in bone marker values will be summarized.

The proportion of days missed from school/work will be summarized by presenting the mean, SD, 95% CI for the mean, median, minimum, and maximum values.

Actual WPAI:CD scores and changes from Baseline in WPAI:CD scores will be summarized by presenting the mean, SD, 95% CI for the mean, median, minimum, and maximum values. The summaries will be presented separately for the WPAI:CD for children, WPAI:CD for working individuals with CD, and WPAI:CD for caregivers. Direct costs parameters will be summarized by period of onset using descriptive statistics.

13.5 Pharmacokinetics and immunological analyses

Plasma concentrations of CZP at each visit will be summarized and plotted by anti-CZP antibody status (all subjects, antibody-positive, and antibody negative) for each age stratum, the overall population, and for the treatment groups. In addition, plasma concentrations will be summarized and plotted by weight stratum (<40kg; ≥40kg) for the treatment groups.

Individual anti-CZP antibody concentrations will be listed and the incidence of anti-CZP antibody positive subjects will be summarized by study visit and overall incidence by age stratum and by treatment group. Anti-CZP antibody positive status is defined as a subject having a value >2.4units/mL anti-CZP antibody at any time during the study.

Additionally, the PK data collected in CR0012 may be used for population PK modeling to supplement or validate the pediatric model derived from the data obtained in C87035. If performed, the analysis and results of this modeling will be provided in a separate report.

13.6 Handling of protocol deviations

No Per Protocol population is defined in this study and thus no consideration with regards to deviations affecting such a population need to be considered. Nevertheless, for each interim analysis and final analysis, after all the data have been verified/coded/entered into the database, a review will be performed after last subject last visit. The purpose of this review will be to primarily check the quality of the data. The review will also help decide how to deal with problems in the subject's data (for example: missing values, withdrawals, drop outs, protocol deviations). In addition, the review will be used to identify the use of rescue therapy. The preanalysis reviewers should ensure that the results of this review are communicated to the study team before locking the database.

After the preanalysis review, resolution of all issues and documentation of all decisions, the database will be locked.

13.7 Handling of dropouts or missing data

For responder type variables, should a subject withdraw prior to completion of the study, then the subject will be classified as a nonresponder or nonremitter from and including the time of withdrawal.

A subject who does not have all the required data to derive a response status will be classified as a nonresponder or nonremitter at that particular time point.

If a subject receives rescue therapy or discontinues study treatment, then the subject will be classified as a treatment failure (nonresponder or nonremitter) from and including the time of the event, regardless of their score (PCDAI).

If a subject loses response and is reinduced, the subject will be classified as a nonresponder or nonremitter from and including the time of the reinduction.

In addition, for any other efficacy variables, no data will be used from and including the time of receiving rescue therapy in the summaries and analyses where relevant.

Unless part of an accepted imputation technique, any missing data during the study will remain missing.

If an AE has severity and/or relationship missing then the event will be assumed to be severe and/or highly probably related to the treatment.

For the WPAI:CD, handling of dropouts or missing data will be detailed in the SAP.

13.8 Planned interim analysis and data monitoring

A DSMB will review safety data. The DSMB members will be independent of the Sponsor and Investigators. The DSMB members will be informed by GCSP (or designee) of all SAEs at the time of expedited reporting and will review periodically all emerging safety data (SAEs, AEs, safety laboratory data). Based on the safety data, the DSMB can recommend modifying/stopping the study.

No interim analyses are planned. Should a regulatory authority request an interim analysis, this will be performed according to the request.

13.9 Determination of sample size

This is an open-label study for subjects who completed C87035 and as such no formal sample size has been determined.

14 ETHICS AND REGULATORY REQUIREMENTS

14.1 Informed consent

Subject's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject and his/her parent(s)/legally acceptable representative(s) in both oral and written form by the Investigator (or designee). Each subject and his/her parent(s)/legally acceptable representative(s) will have the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, the written Informed Consent form should be signed and personally dated by the subject, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator [or designee]). If applicable, a child Assent form may be used. The subject or his/her legal representative must receive a copy of the signed and dated Informed Consent/child Assent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the Informed Consent/child Assent form is amended during the study, the Investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended Informed Consent form by the IRB/IEC and use of the amended form.

All studies conducted at centers in the United States must include the use of a Health Insurance Portability and Accountability Act (ie, HIPAA) Authorization form.

The subject and his/her parent(s)/legally acceptable representative(s) may withdraw their consent to participate in the study at any time. A subject is considered as enrolled in the study

when his/her parent(s)/legally acceptable representative(s) has signed the Informed Consent form. A CRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained his/her written consent to participate in the study.

14.2 Subject identification cards

Upon signing the Informed Consent and Assent form (as applicable), the subject or legal representative will be provided with a subject identification card in the language of the subject. The Investigator will fill in the name of the study and medical emergency contact information. The Investigator will instruct the subject to keep the card with them at all times.

14.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, Informed Consent form, Investigator's Brochure, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The Investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The Investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on the Committee's requirements), at intervals appropriate to the degree of subject risk involved but no less than once per year. The Investigator should provide a final report to the IRB/IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active Investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, Investigators are to provide the Sponsor (or its representative) with evidence of such IRB/IEC notification.

14.4 Subject privacy

UCB staff (or designee) will affirm and uphold the subject's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the subject number assigned at Screening in C87035.

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports for deaths occurring during the study).

14.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

15 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the Investigator and/or CRO agreements as applicable.

16 REFERENCES

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Hanauer SH, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's Disease: the ACCENT I randomised trial. *Lancet.* 2002;359(9317):1541-49.

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Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child.* 1969;44(235):291-303.

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Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, et al. A short term study of chimeric monoclonal antibody cA2 to tumour necrosis factor alpha for Crohn's Disease. Crohn's Disease cA2 Study Group. *N Engl J Med*. 1997;37(15):1029-35.



17.2 Pediatric Crohn's Disease Activity Index

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

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 $\geq 10\%$	(10)

Height* - Score using (a) criteria when possible

a) Height velocity $\geq -1SD$	(0)
Height velocity $< -1SD, > -2SD$	(5)
Height velocity $\leq -2SD$	(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 $\geq 38.5^{\circ}\text{C}$ for 3 days over past week, oral ulcers, definite arthritis, uveitis, erythema nodosum, P. gangrenosum

None	(0)
One	(5)
\geq Two	(10)

TOTAL SCORE

PCDAI USER'S GUIDE

This guide is intended to help nurse coordinators and physicians complete the PCDAI in order to assess disease activity in children with CD participating in clinical trials.

HISTORY

All calculations are based upon a 1-week (7-day) history recall of symptoms. The history recall should be solicited from the patient and/or caregiver.

1. Abdominal pain

The descriptions in the PCDAI of “mild” and “moderate/severe” should be used to guide in scoring the pain. Note that duration, effect on activities, and nocturnal occurrence separate moderate/severe from mild. If pain varies in severity during the week, patient should be scored according to the most severe pain. However, mild pain should be present on at least two days to score 5 points rather than 0 points.

2. Stools

The intent is to score the stool pattern during the preceding week.

To facilitate scoring, first categorize the patient as having blood in the stool or not.

If there is no blood in the stool, score as follows:

- Formed stools or up to 1 loose stool daily = 0
- Two to five liquid or very loose stools on 1 or more days = 5
- Six or more liquid or very loose stools on 1 or more days or any nocturnal diarrhea = 10

If blood is present in the stool on any day during the past week, score as follows:

- Small amounts of blood in stool (on toilet paper or small spots in stool, etc.) = 5
- Any gross bleeding (large amounts on stool or colors the water in the toilet, etc.) = 10

3. Patient functioning, general well-being

If there is variation during the week, patient should be scored according to the most significant limitation of activity, even if only one day of the week, as long as likely due to Crohn's disease and not to an intercurrent illness.

PHYSICAL EXAMINATION

4. Weight

The intent is to assess the ability to normally maintain or gain weight.

Voluntary weight stable/loss means patient maintaining or losing weight on purpose.

Involuntary weight stable means patient wants to gain weight but cannot.

To calculate percentage weight loss use formula:

$$\frac{\text{Historic weight} - \text{Current weight}}{\text{Historic weight}} \times 100 = \% \text{ weight loss}$$

Take historic weight as maximal weight attained within preceding 4 to 6 months, excluding any value that reflects excess weight due to corticosteroid use.

5. Height

The intent is to assess the normalcy vs impairment of the patient's recent linear growth.

Note that post-pubertal patients will score 0 points. For patients still growing, there are 2 options for scoring. Method (a) is preferred. Method (b) to be used if data required for (a) are unavailable.

Method (a):

Height velocity (cm/year), the most sensitive parameter, should be used if reliable height measurements are available from the preceding 6 to 12 months.

Convert height increment during preceding 6 to 12 months into velocity (cm/year) as follows:

$$\frac{\text{Present height} - \text{Height 6-12 months previously}}{\text{Interval (months) between heights}} \times 12 = \text{Height velocity (cm/year)}$$

Using height velocity chart, determine centile for height velocity (see below for a copy).

Height velocity should ideally be plotted according to bone age rather than chronologic age. However, if maturity is appropriate for age (not delayed or advanced) it is reasonable to plot and score height velocity according to chronologic age.

In follow-up visits of short-term clinical trials less than 4 months duration, score height velocity the same as the initial score unless there has been an actual height gain.

Method (b):

If reliable height measurements from 6 to 12 months previously are lacking (often the case with newly diagnosed patients), use any earlier heights to assess previous height centile and compare with current height centile. Score according to degree of decrease in height centile.

Guidelines to calculate and incorporate the results of the Height velocity (cm/year) into the PCDAI

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Height Velocity Reference Values for Calculating the PCDAI (Males)

Age (years)	Height Velocity in cm per year (Males)		
	Minus 2SD	Minus 1SD	Mean
2.5	5.7	7	8.3
3	5.4	6.6	7.8
3.5	5.1	6.3	7.4
4	4.9	6	7.1
4.5	4.7	5.8	6.8
5	4.6	5.6	6.6
5.5	4.5	5.4	6.4
6	4.3	5.3	6.2
6.5	4.2	5.1	6
7	4.2	5	5.9
7.5	4.1	4.9	5.8
8	3.9	4.8	5.6
8.5	3.8	4.6	5.4
9	3.8	4.5	5.3
9.5	3.7	4.5	5.2
10	3.7	4.4	5.1
10.5	3.7	4.4	5.1
11	3.7	4.4	5.2
11.5	3.8	4.6	5.3
12	4	4.9	5.7
12.5	4.8	5.8	6.7
13	6.2	7.4	8.6
13.5	7.1	8.3	9.5
14	6.1	7.2	8.4
14.5	4.1	5.3	6.5
15	2.4	3.6	4.7
15.5	1.2	2.3	3.3
16	0.4	1.3	2.2
16.5	0.1	0.7	1.5
17	0.1	0.4	0.9
17.5	0.1	0.1	0.5

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Height Velocity Chart (males)

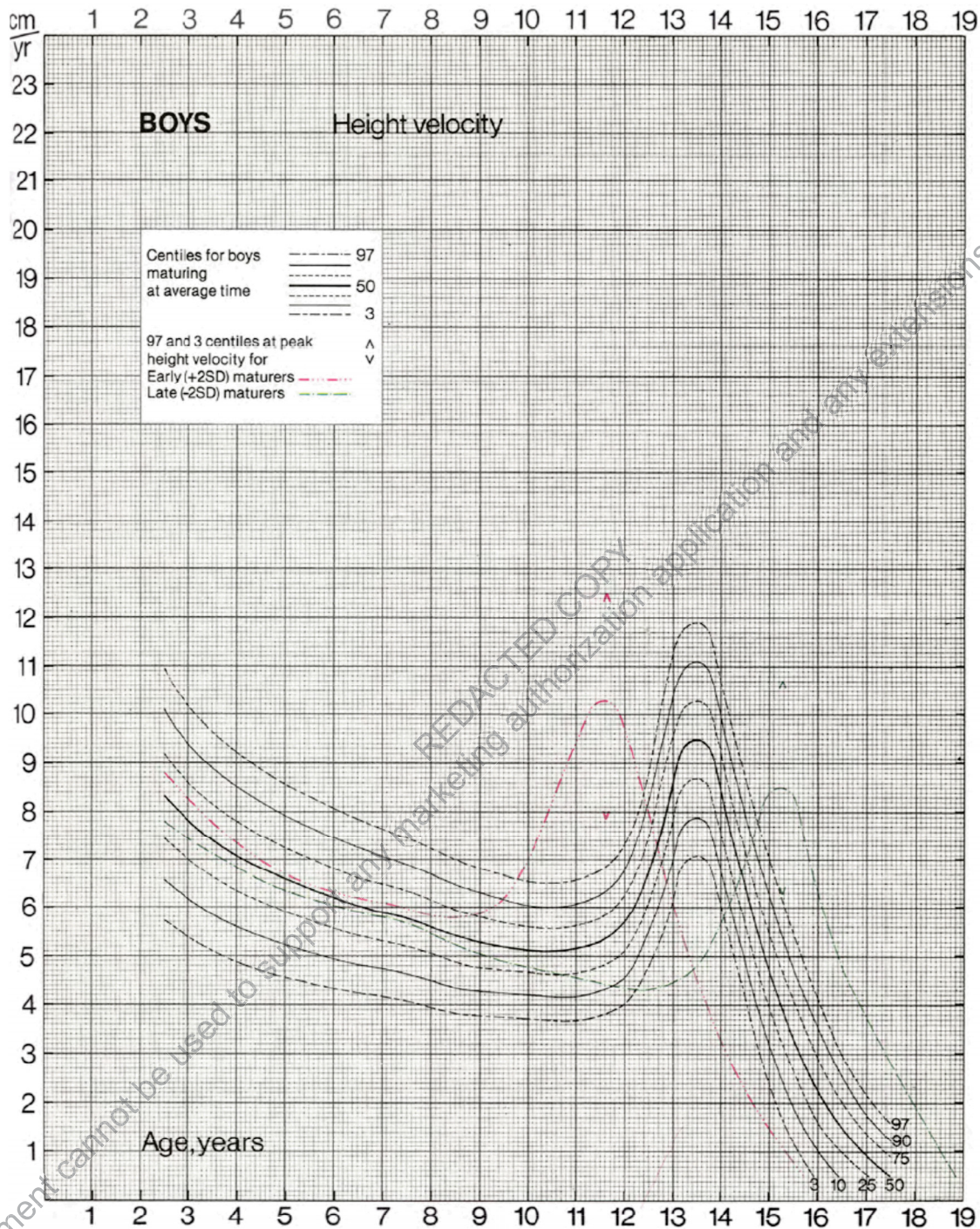


Fig. 4. Height velocity for American boys. Red line, 50th centile for boys 2 SD of tempo early; green line, 50th centile for boys 2 SD of tempo late. Λ and v, The 97th and 3rd centiles for peak velocities of early and late maturers, respectively.

Height Velocity Reference Values for Calculating the PCDAI
(Females)

Age (years)	Height Velocity in cm per year (Females)		
	Minus 2SD	Minus 1SD	Mean
2.5	5.9	7.3	8.6
3	5.5	6.9	8.1
3.5	5.2	6.4	7.6
4	4.9	6.1	7.2
4.5	4.7	5.8	6.8
5	4.6	5.6	6.6
5.5	4.5	5.5	6.4
6	4.4	5.3	6.2
6.5	4.3	5.2	6.1
7	4.3	5.2	6
7.5	4.3	5.1	5.9
8	4.2	5	5.8
8.5	4.2	4.9	5.7
9	4.2	5	5.8
9.5	4.3	5	5.8
10	4.4	5.3	6.2
10.5	4.7	5.7	6.8
11	5.7	6.6	7.7
11.5	6.1	7.2	8.3
12	5.2	6.3	7.3
12.5	3.6	4.8	5.9
13	2.4	3.3	4.3
13.5	1.3	2.2	2.9
14	0.4	1.1	1.8
14.5	0	0.5	1

This document cannot be used to support any marketing authorization application and any extensions or variations thereof

Height Velocity Chart (females)

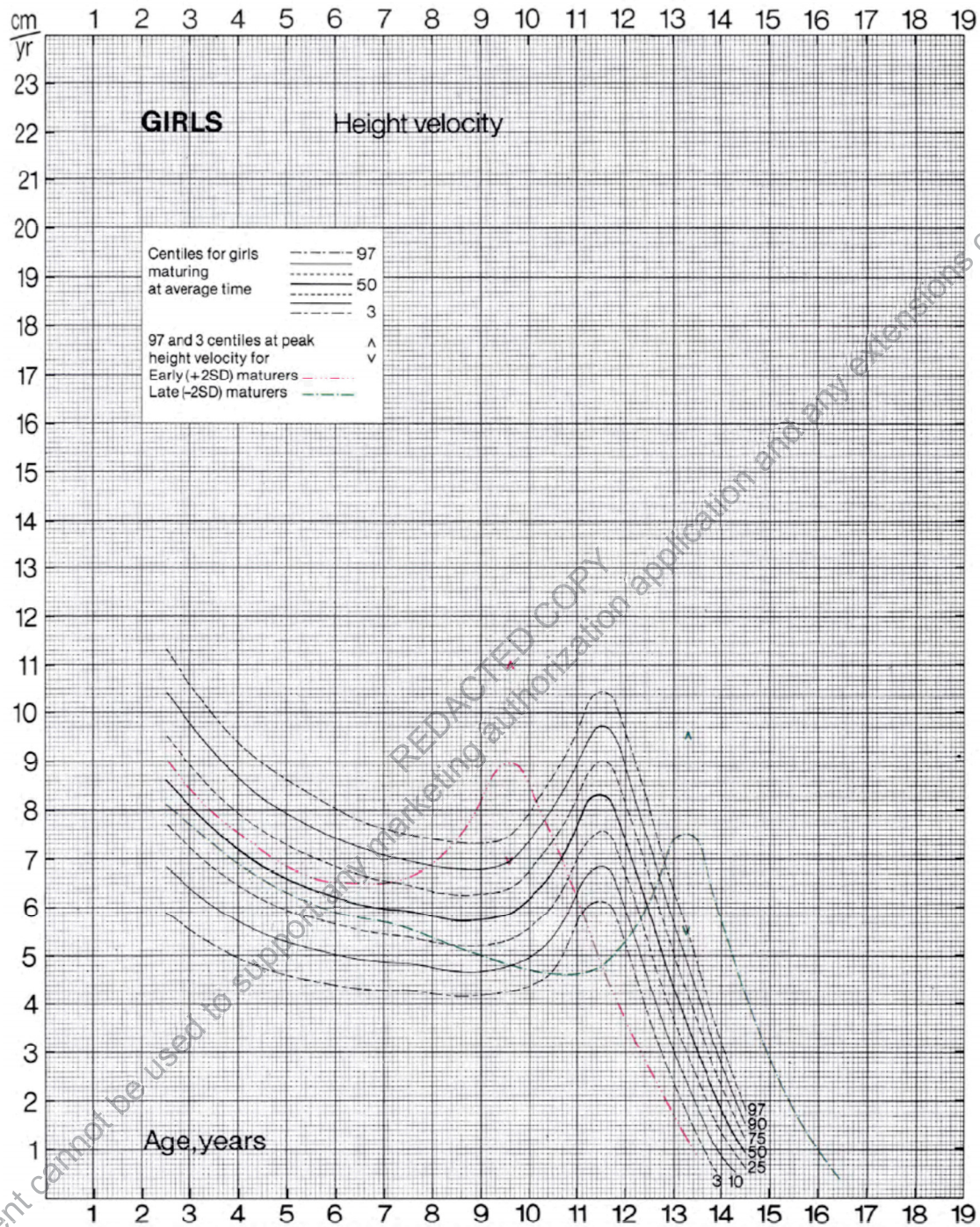


Fig. 6. Height velocity for American girls. Red line, 50th centile for girls 2 SD of tempo early; green line, 50th centile for girls 2 SD of tempo late. ^ and v, The 97th and 3rd centiles for peak velocities of early and late maturers, respectively.

Calculating height velocity:

1. Use the present height and height measurement during proceeding 6-12 months.
2. Calculate the height velocity as follows;

$$\frac{\text{Present height} - \text{Height (6 - 12 months previously)}}{\text{Interval (months) between heights}} \times 12 = \text{Height velocity (cm/year)}$$

Ideally, bone age rather than chronologic age should be used. However, if maturity is appropriate for age (not delayed or advanced) it is reasonable to use chronologic age.

Scoring for the PCDAI:

Velocity less than “Minus 2 SD” scores 10 points

Velocity between “Minus 2 SD” and “Minus 1 SD” scores 5 points

Velocity greater than “Minus 1 SD” scores zero points.

Example:

If the subject is a male who is 10 years old:

1. Use the present height and height measurement during proceeding 6-12 months.
2. Calculate the height velocity as per equation provided.
3. For example in this 10-years-old male the height velocity comes up to 4 cm/year.
4. Next step refer to the table for height velocity values reference for males (provided).
5. You will notice that the 4 cm height velocity falls between the range of minus2SD and minus1SD.
6. The score for the PCDAI will be (5 points) as per above scoring guideline.
7. Go to the PCDAI and enter the #5 and complete the scoring of the PCDAI.

References:

1. J.M. Tanner, Davies PSW. Clinical Longitudinal Standards for height and height velocity for North American children. J Pediatr 1985;107:317-29.
2. Jeffery Hyams, George D. Ferry, et al, development and validation of a pediatric Crohn's disease activity index. J of Pediatric Gastroenterology and Nutrition 1991;12:439-47.

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17.7 Protocol amendment #1

Rationale for the amendment

The telephone numbers for reporting SAEs during business hours or outside business hours have been indicated. The inclusion and exclusion criteria were simplified to include any subject who completed C87035. Pregnancy due to oral contraceptive failure is not considered an SAE; the change was made to comply with Sponsor SAE reporting procedures. An additional example of an important medical event relevant to subjects with CD (infections that require treatment with parenteral antibiotics) was provided. An inconsistency in Visit 2 vital signs compared to the Schedule of Study Assessments was corrected in Section 9.6.7.

Specific changes

Change # 1 – Serious adverse reporting telephone numbers (page 5)

Serious adverse event reporting (24h), safety related issues, and emergency unblinding	
Fax	Europe and Rest of the World (except Japan): +32 2 386 24 21 USA: +1 800 880 6949 Canada: +1 877 582 8842
Phone	Europe and Rest of the World (except Japan): +32 2 386 24 68 USA & Canada: +1 678 799 4007

Has been changed to:

Serious adverse event reporting (24h), safety related issues, and emergency unblinding		
Fax	Europe and Rest of the World (except Japan): +32 2 386 24 21 USA: +1 800 880 6949 Canada: +1 877 582 8842	
Phone	During business hours:	Outside business hours:
	Europe and Rest of the World (except Japan): +32 2 386 24 68 USA & Canada: +1 770 970 2709	Europe and Rest of the World (except Japan): +32 2 386 24 68 USA & Canada: +1 678 799 4007

Change #2 - Inclusion criterion (Section 6.1)

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject or by the parent(s) or legally acceptable representative. The Consent form or a specific Assent form, where required, will be signed and dated by minors.

2. Subject/parent(s)/legally acceptable representative is considered reliable and capable of adhering to the protocol, visit schedule or medication intake according to the judgment of the Investigator.
3. Subject satisfied the Inclusion criteria at time of entry into C87035 and completed the study (Week 62 Visit).
4. Subject's current or recent regimen of concomitant medication(s) for CD should be stable through the study period (see Section 7.8.1).

Has been changed to:

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject or by the parent(s) or legally acceptable representative. The Consent form or a specific Assent form, where required, will be signed and dated by minors.
2. Subject/parent(s)/legally acceptable representative is considered reliable and capable of adhering to the protocol, visit schedule or medication intake according to the judgment of the Investigator.
3. **Subject completed the C87035 study (Week 62 Visit).**
4. Subject's current or recent regimen of concomitant medication(s) for CD should be stable through the study period (see Section 7.8.1).

Change #3 - Exclusion criterion (Section 6.2)

Subjects are not permitted to enroll in the study if the following criterion is met:

1. Any exclusion criterion that would have prevented the subject from participation in C87035.

Has been changed to:

Subjects are not permitted to enroll in the study if the following criterion is met:

1. **Subject did not complete the C87035 study (Week 62 Visit).**

Change #4 – Pregnancy (Section 9.1.6; last paragraph)

A pregnancy becomes a serious adverse event (SAE) in the following circumstances: miscarriage, abortion, or anomaly/birth defect of the child. Pregnancy is considered as an SAE in case of contraceptive failure (eg, birth control pill taken each day without having been forgotten or use of permanent contraceptive devices). Those SAEs must be additionally reported using the Investigator SAE Report form.

Has been changed to:

A pregnancy becomes a serious adverse event (SAE) in the following circumstances: miscarriage, abortion, or anomaly/birth defect of the child. **Pregnancy is considered as an SAE in case of contraceptive failure (eg, birth control pill taken each day without**

~~having been forgotten or use of permanent contraceptive devices~~). Those SAEs must be additionally reported using the Investigator SAE Report form.

Change #5 – Definition of serious adverse event (Section 9.2.1; bullet 3)

- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious
- (Important medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

Has been changed to:

- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious
- (Important medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, **infections that require treatment with parenteral antibiotics**, or the development of drug dependency or drug abuse.)

Change #6 – Vital signs (Section 9.6.7)

Systolic and diastolic blood pressure and pulse rate will be measured 15 minutes prior to dosing (with a ± 5 minutes window) in a sitting position at entry Week 0, every 12 weeks starting at Week 14, and at the Completion/ET, Unscheduled, and SFU Visits.

Has been changed to:

Systolic and diastolic blood pressure and pulse rate will be measured 15 minutes prior to dosing (with a ± 5 minutes window) in a sitting position at entry Week 0, **Visit 2**, every 12 weeks starting at Week 14, and at the Completion/ET, Unscheduled, and SFU Visits.

17.8 Protocol Amendment 2

Rationale for the amendment

[REDACTED] the decision was made to stop C87035 after determining it was inadequate to address the efficacy of CZP for labeling in pediatric subjects. CR0012 was amended to allow subjects ongoing in C87035 to enter CR0012 without having completed C87035, and for treatment in CR0012 to be continued until a subject reached the age of 18 years or CZP is approved for use in the US by pediatric subjects with CD.

Additional updates were made to reflect the current UCB contacts, regulatory status of CZP, subject exposure, and to comply with the updated UCB definition of AEs of interest.

The format and style of the document was changed to comply with UCB's new document-authoring software; these changes are not specifically noted.

Specific changes:

1. Cover page

Old text:

PROTOCOL CR0012

AN OPEN-LABEL, MULTICENTER STUDY TO ASSESS THE SAFETY OF CERTOLIZUMAB PEGOL IN CHILDREN AND ADOLESCENTS WITH ACTIVE CROHN'S DISEASE WHO COMPLETED C87035

PHASE 2B

IND Number: 11197

Sponsor:

SCHWARZ BIOSCIENCES, INC.

A Member of the UCB Group of Companies

8010 Arco Corporate Drive

Raleigh, NC 27617

UNITED STATES

Protocol/Amendment Number	Date	Type of amendment
Final Protocol	07 May 2010	N/A
Amendment 1	29 Jun 2010	Substantial

New text:

PROTOCOL CR0012

AN OPEN-LABEL, MULTICENTER STUDY TO ASSESS THE SAFETY OF CERTOLIZUMAB PEGOL IN CHILDREN AND ADOLESCENTS WITH ACTIVE CROHN'S DISEASE WHO COMPLETED C87035 **OR WERE TERMINATED FROM C87035 WHEN THE STUDY WAS STOPPED BY UCB**

PHASE 2B

IND Number: 11197

Sponsor:

UCB BIOSCIENCES, INC.

~~A Member of the UCB Group of Companies~~

8010 Arco Corporate Drive

Raleigh, NC 27617

UNITED STATES

Protocol/Amendment Number	Date	Type of amendment
Final Protocol	07 May 2010	N/A
Amendment 1	29 Jun 2010	Substantial
Amendment 2	08 May 2012	Substantial

2. Page 2, Sponsor declaration

Old text:

Clinical Project Manager

[REDACTED] MS

[REDACTED]

Date/Signature

Clinical Study Biostatistician

[REDACTED] MS

[REDACTED]

Date/Signature

Study Physician

[REDACTED] MD

[REDACTED]

Date/Signature

Clinical Program Director

[REDACTED] PhD

[REDACTED]

Date/Signature

New text:

Clinical Project Manager

[REDACTED]

Date/Signature

Clinical Trial Biostatistician

[REDACTED] PhD

Date/Signature

Study Physician

[REDACTED], MD

Date/Signature

Clinical Program Director

[REDACTED], DVM

Date/Signature

3. Page 3, Study contact information

Old text:

Sponsor

SCHWARZ BIOSCIENCES, INC.

A Member of the UCB Group of Companies

8010 Arco Corporate Drive

Raleigh, NC 27617

UNITED STATES

Principal/Coordinating Investigator

Sponsor Study Physician

Name:	[REDACTED], MD
Address:	8010 Arco Corporate Drive Raleigh, NC 27617, USA
Phone:	[REDACTED]
Fax:	[REDACTED]

Clinical Project Manager

Name:	[REDACTED], MS
Address:	8010 Arco Corporate Drive Raleigh, NC 27617, USA
Phone:	[REDACTED]
Fax:	[REDACTED]

Clinical Study Biostatistician

Name:	[REDACTED], MS
Address:	208 Bath Road Slough, Berkshire, SL1 3WE, UK
Phone:	[REDACTED]
Fax:	[REDACTED]

Clinical Monitoring Contract Research Organization

Name:	Kendle International, Inc.
Address:	1200 Carew Tower 441 Vine Street Cincinnati, Ohio 45202
Phone:	+1 800 733 1572
Fax:	+1 513 381 7684

New text:

UCB BIOSCIENCES, INC.
8010 Arco Corporate Drive
Raleigh, NC 27617
UNITED STATES

Principal/Coordinating Investigator

Sponsor Study Physician

Name:	██████████, MD
Address:	8010 Arco Corporate Drive Raleigh, NC 27617, USA
Phone:	██████████
Fax:	██████████

Clinical Project Manager

Name:	██████████
Address:	8010 Arco Corporate Drive Raleigh, NC 27617, USA
Phone:	██████████
Fax:	██████████

Clinical Study Biostatistician

Name:	██████████, PhD
Address:	8010 Arco Corporate Drive Raleigh, NC 27617, USA
Phone:	██████████
Fax:	██████████

Medical Monitor

Name:	██████████, MD
Address:	5610 Point West Drive Oakwood, GA 30566
Phone:	██████████ ██████████
Fax:	██████████

Clinical Monitoring Contract Research Organization

Name:	PRA International
Address:	Glen Lake 6 4130 Parklake Avenue Raleigh, NC 27612
Phone:	919-786-8200
Fax:	919-786-8201

4. Section 1, Summary (paragraphs 1 through 6)

Old text:

This is a Phase 2b, open-label, multicenter study to assess the safety of certolizumab pegol (CDP870, CZP) in children and adolescents with active Crohn's disease (CD) who completed C87035.

C87035 was a Phase 2, open-label, multicenter study to assess the safety, efficacy, pharmacokinetics (PK), and immunogenicity of CZP in children and adolescents ages 6 to 17 with moderately to severely active Crohn's disease. The study was performed as a post approval commitment following the Food and Drug Administration (FDA) approval of CZP for the treatment of adults with moderately to severely active CD.

Certolizumab pegol, the investigational medicinal product (IMP) is a humanized antibody fragment antigen binding (Fab'), with specificity for human tumor necrosis factor alpha

(TNF), conjugated to polyethylene glycol (PEG). The drug intended for use in this study is the liquid formulation of CZP in a prefilled syringe (PFS).

All subjects who complete the Week 62 assessments in C87035 (up to 100 subjects anticipated) are eligible to enter this open-label extension study. Following entry, subjects may continue on the CZP dose they were receiving at the end of C87035 (Low-Dose Group or High-Dose Group [weight adjusted in kg]) every 4 weeks (Q4W) for a 52-week open-label Treatment Period. The first clinic visit of this study should coincide with the Week 62 Visit of C87035. Home administration of CZP by the subject/caregiver/appropriate designee as determined by the Investigator will be permitted following appropriate training at clinic visits. A Safety Follow-Up (SFU) Visit will be conducted 12 weeks after the last dose of study medication.

If a subject has not been previously reinduced in C87035, the subject is eligible for 1 reinduction due to loss of response in CR0012 (defined as an increase in Pediatric Crohn's Disease Activity Index [PCDAI] ≥ 15 points compared to Week 6 of C87035 at 2 consecutive visits at least 1 week apart or an overall PCDAI > 30 points at any time).

A Data and Safety Monitoring Board (DSMB) will periodically review all emerging safety data. Interim analyses will be performed on an annual basis starting from 1 year after the first subject's first visit in CR0012 has occurred.

New text:

This is a Phase 2b, open-label, multicenter study to assess the safety of certolizumab pegol (CDP870, CZP) in children and adolescents with active Crohn's disease (CD) who completed C87035 or were terminated from C87035 when the study was stopped by UCB.

C87035 was a Phase 2, open-label, multicenter study to assess the safety, efficacy, pharmacokinetics (PK), and immunogenicity of CZP in children and adolescents ages 6 to 17 with moderately to severely active Crohn's disease. The study was performed as a postapproval commitment following the Food and Drug Administration (FDA) approval of CZP for the treatment of adults with moderately to severely active CD. [REDACTED]

[REDACTED] the decision was made to stop C87035 after determining it was inadequate to address the efficacy of CZP for labeling in pediatric subjects. Subjects ongoing in the study were given the opportunity to enter CR0012 without having completed C87035.

Certolizumab pegol, the investigational medicinal product (IMP) is a humanized antibody fragment antigen binding (Fab'), with specificity for human tumor necrosis factor alpha (TNF), conjugated to polyethylene glycol (PEG). The drug intended for use in this study is the liquid formulation of CZP in a prefilled syringe (PFS).

All subjects who complete **Week 62 of C87035 or were terminated from C87035 when the study was stopped by UCB (and completed all assessments required for Week 62/Visit 23 at the time of termination)** are eligible to enter this open-label extension study.

Following entry, subjects may continue on the CZP dose they were receiving at the end of C87035 (Low-Dose Group or High-Dose Group [weight adjusted in kg]) every 4 weeks

(Q4W) ~~for a 52-week open-label Treatment Period~~. The first clinic visit of this study should coincide with the **last visit** of C87035 (**Week 62/Visit 23**). Home administration of CZP by the subject/caregiver/appropriate designee as determined by the Investigator will be permitted following appropriate training at clinic visits. **For subjects performing home administration, a phone call to the subject and/or the parents/caregiver will be performed by the Investigator (or designee) every 4 weeks between regular clinic visits.** A Safety Follow-Up (SFU) Visit will be conducted 12 weeks after the last dose of study medication.

If a subject has not been previously reinduced in C87035, the subject is eligible for 1 reinduction due to loss of response in CR0012 (defined as an increase in Pediatric Crohn's Disease Activity Index [PCDAI] ≥ 15 points compared to Week 6 of C87035 at 2 consecutive visits at least 1 week apart or an overall PCDAI > 30 points at any time).

A Data and Safety Monitoring Board (DSMB) will periodically review all emerging safety data. ~~Interim analyses will be performed on an annual basis starting from 1 year after the first subject's first visit in CR0012 has occurred.~~

5. Section 2, Introduction (paragraph 6 and paragraph 8)

Old text:

Paragraph 6 -

Certolizumab pegol is an engineered, humanized antigen-binding fragment (Fab' fragment) conjugated to PEG with specificity for human TNF. Certolizumab pegol (CIMZIA[®]) has been approved in the US and Switzerland for reducing the signs and symptoms of CD and maintaining the clinical response in adult subjects with moderately to severely active disease who have had an inadequate response to conventional therapy.

Paragraph 8 -

The safety of CZP has been assessed in 2192 adult subjects with CD representing over 2456 patient years of exposure. Certolizumab pegol is well tolerated. The incidence of injection site reactions and hypersensitivity-type reactions was low. There were no reports of anaphylaxis or anaphylactoid-type reactions with CZP. All available data in CD show the safety of CZP is consistent with the known risks of anti-TNF therapies.

New text:

Paragraph 6-

Certolizumab pegol is an engineered, humanized antigen-binding fragment (Fab' fragment) conjugated to PEG with specificity for human TNF. Certolizumab pegol (CIMZIA) has been approved in the US, Switzerland, **Russia, Brazil, and Chile** for reducing the signs and symptoms of CD and maintaining the clinical response in adult subjects with moderately to severely active disease who have had an inadequate response to conventional therapy.

Paragraph 8-

The safety of CZP has been assessed in **2518** adult subjects with CD representing over **2837** patient years of exposure. Certolizumab pegol is well tolerated. The incidence of

injection site reactions and hypersensitivity-type reactions was low. There were no reports of anaphylaxis or anaphylactoid-type reactions with CZP. All available data in CD show the safety of CZP is consistent with the known risks of anti-TNF therapies.

6. Section 3, Study objectives

Old text:

The primary objective of this open-label, multicenter study is to assess the longterm safety and tolerability of CZP in children and adolescents with moderately to severely active CD who completed C87035. The secondary objectives of this study are to assess the longterm efficacy, PK, and immunogenicity of CZP treatment on this population.

New text:

The primary objective of this open-label, multicenter study is to assess the longterm safety and tolerability of CZP in children and adolescents with moderately to severely active CD who completed C87035 **or were terminated from C87035 when the study was stopped by UCB**. The secondary objectives of this study are to assess the longterm efficacy, PK, and immunogenicity of CZP treatment on this population.

7. Section 5.1, Study description (paragraphs 1 through 6)

Old text:

This is a Phase 2, open-label, multicenter study in children and adolescents with moderately to severely active CD who completed C87035 to assess the longterm safety and tolerability of CZP.

All subjects who complete the Week 62 assessments in C87035 are eligible to enter this open-label study. Subjects may continue on CZP at the dose they were receiving at the end of C87035 (Low-Dose Group or High-Dose Group [weight adjusted in kg; see Section 7.2 and Table 7-1]) every 4 weeks for a 52-week open-label Treatment Period. The first clinic visit should coincide with the Week 62 visit of C87035. First study drug administration occurs 2 weeks later (Week 2) and subsequent clinic visits for safety and efficacy assessments are scheduled at 12-week intervals. After Week 2, subjects or parents/caregivers/appropriate designee as determined by the Investigator have the option of home administration of CZP upon appropriate training during a previous clinic visit(s) or continuing to have CZP administered every 4 weeks at the clinic. For subjects performing home administration, a phone call to the subject and/or the parents/caregiver will be performed by the Investigator (or designee) every 4 weeks between regular clinic visits in order to capture potential AEs and changes in concomitant medications, and to check compliance with home dosing. An SFU Visit will be conducted 12 weeks after the last dose of study medication for subjects.

Please refer to Study Schedule of Assessments in Section 5.2 for visit-specific procedures and to Section 5.3 for a schematic representation of the study.

A DSMB will periodically review all emerging safety data (see Section 13.8). Based on the safety data, the DSMB can recommend modifying or stopping the study.

Interim analyses will be performed on an annual basis starting from 1 year after the first subject's first visit in CR0012 has occurred.

Subjects who become ≥ 18 years during CR0012 may continue in the study at the Investigator's discretion.

New text:

This is a Phase 2, open-label, multicenter study in children and adolescents with moderately to severely active CD who completed C87035, **or were terminated from C87035 when the study was stopped by UCB**, to assess the longterm safety and tolerability of CZP.

All subjects who complete Week 62 of C87035 or were terminated from C87035 when the study was stopped by UCB (and completed all assessments required for Week 62/Visit 23 at the time of termination) are eligible for entry.

~~All subjects who complete the Week 62 assessments in C87035 are eligible to enter this open-label study.~~ Subjects may continue on CZP at the dose they were receiving at the end of C87035 (Low-Dose Group or High-Dose Group [weight adjusted in kg; see Section 7.2 and Table 7-1]) every 4 weeks **until the subject reaches the age of 18 years or CZP is approved for use in the US by pediatric subjects with CD.** The first clinic visit should coincide with the **last visit of C87035 (Week 62/Visit 23)**. First study drug administration occurs 2 weeks later (Week 2) and subsequent clinic visits for safety and efficacy assessments are scheduled at 12-week intervals. After Week 2, subjects or parents/caregivers/appropriate designee as determined by the Investigator have the option of home administration of CZP upon appropriate training during a previous clinic visit(s) or continuing to have CZP administered every 4 weeks at the clinic. For subjects performing home administration, a phone call to the subject and/or the parents/caregiver will be performed by the Investigator (or designee) every 4 weeks between regular clinic visits in order to capture potential AEs and changes in concomitant medications, and to check compliance with home dosing. An SFU Visit will be conducted 12 weeks after the last dose of study medication for subjects.

Please refer to Study Schedule of Assessments in Section 5.2 for visit-specific procedures and to Section 5.3 for a schematic representation of the study.

A DSMB will periodically review all emerging safety data (see Section 13.8). Based on the safety data, the DSMB can recommend modifying or stopping the study.

~~Interim analyses will be performed on an annual basis starting from 1 year after the first subject's first visit in CR0012 has occurred.~~

~~Subjects who become ≥ 18 years during CR0012 may continue in the study at the Investigator's discretion.~~

8. Section 5.1.1, Study duration per subject

Old text:

The maximum study duration of CZP treatment may be up to 52 weeks. An SFU visit will be conducted 12 weeks following the last dose of study drug.

The end of the study is defined as the date of the last SFU visit of the last subject in the study.

New text:

The maximum study duration of CZP treatment may be **until the subject reaches the age of 18 years or CZP is approved for use in the US by pediatric subjects with CD**. An SFU visit will be conducted 12 weeks following the last dose of study drug.

The end of the study is defined as the date of the last SFU visit of the last subject in the study.

9. Section 5.1.2, Planned number of subjects and sites

Old text:

It is anticipated that the approximately 30 to 40 centers which participated in C87035 will participate in this study. Those subjects who completed Week 62 of C87035 may be enrolled in this study (up to 100 subjects anticipated).

- First subject first visit: Jul 2010
- Last subject first visit: Jan 2013
- Last subject last visit: Mar 2014 (including the SFU Visit)

New text:

It is anticipated that the approximately 30 to 40 centers which participated in C87035 will participate in this study. Those subjects who **completed Week 62 of C87035 or were terminated from C87035 when the study was stopped by UCB (and completed all assessments required for Week 62/Visit 23 at the time of termination)** may be enrolled in this study.

- First subject first visit: Jul 2010
- Last subject first visit: **Jun 2012**
- Last subject last visit: **to be determined** (including the SFU Visit)

10. Section 5.2, Schedule of study assessments (Table 5-1)

Old text:

Table 5-1. Schedule of study assessments

	Entry ^a	Visit	Treatment Period						SFU ^d
			Phone call (home administration) or visit (clinic administration) ^b	Clinic Visits ^b	Completion/ Early Termination	Unscheduled Visit ^c			
Visit or phone call (+/-7 days)	0	2	6, 10, 18, 22, 30, 34, 42, 46	14, 26, 38, 50	52			62	
Written informed consent	X								
Assessment of inclusion/ exclusion criteria	X								
Demography	X								
Life style	C87035								
Crohn's disease history	C87035								
Medical and surgical history	C87035								
Assessment of childbearing potential	C87035			X	X			X	
Pregnancy test ^e	C87035			X	X			X	
Physical examination	C87035			X	X			X	
TB test	X								
TB questionnaire	X			X	X			X	
Tanner stage	C87035			X	X				

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Table 5-1. Schedule of study assessments

Visit or phone call (+/-7 days)	Entry ^a	Visit	Treatment Period						SFU ^d
			Phone call (home administration) or visit (clinic administration) ^b	Clinic Visits ^b	Completion/ Early Termination	Unscheduled Visit ^c			
Week	0	2	6, 10, 18, 22, 30, 34, 42, 46	14, 26, 38, 50	52			62	
Height	C87035					X			
Weight	C87035			X		X			
Vital signs ^f	C87035	X		X		X	X	X	
Adverse events ^a	C87035	X		X		X	X	X	
Concomitant medications ^a	C87035	X		X		X	X	X	
Concurrent medical procedures	C87035	X		X		X	X	X	
PCDAI	C87035			X		X			
ESR/hematocrit/albumin for PCDAI	C87035			X		X			
CRP	C87035			X		X			
Hematology/chemistry/urinalysis	C87035			X		X		X	
IMPACT III	C87035			X		X			
WPAI:CD ^g	C87035			X		X			
Certolizumab pegol plasma concentration ^h	C87035			X		X		X	
Anti-CZP antibody plasma concentration ⁱ	C87035			X		X		X	
Autoantibodies (ANA and anti-dsDNA)	C87035			X		X		X	
Bone markers (osteocalcin, bone specific	C87035			X		X			

Table 5-1. Schedule of study assessments

	Treatment Period							SFU ^d
	Entry ^a	Visit	Phone call (home administration) or visit (clinic administration) ^b	Clinic Visits ^b	Completion/Early Termination	Unscheduled Visit ^c		
Visit or phone call (+/-7 days)	0	2	6, 10, 18, 22, 30, 34, 42, 46	14, 26, 38, 50	52		62	
alkaline phosphatase, n-telopeptides)								
Study drug administration ^j		X	X	X				
Reinduction ^k	<p>Loss of response must be confirmed at a clinic visit where assessments and labs are performed to determine PCDAI score. Scores cannot be confirmed until lab results are received by central lab a few days after the clinic visit. Once loss of response is confirmed, sites must contact the subject to return for the first Reinduction Visit.</p> <p>Reinduction Week 0 (first reinduction dose) is followed by Reinduction Week 2 (second dose, 2 weeks after first dose), and Reinduction Week 4 (third dose, 2 weeks after second dose). Subjects should return to the clinic for each Reinduction. Subject resumes the original schedule of clinic visits after reinduction. The clinic should contact the Study Monitor to determine the most appropriate way to resume the original schedule of clinic visits.</p> <p>Reinduction Week 0 assessments: PCDAI: ESR, hematocrit, and albumin; IMPACT-III; WPAI:CD</p> <p>Reinduction Week 2 assessments: PCDAI: ESR, hematocrit, and albumin</p> <p>Reinduction Week 4 assessments: PCDAI: ESR, hematocrit, and albumin; WPAI:CD</p>							

ANA=antinuclear antibody; CRP=C-reactive protein; CZP=certolizumab pegol; dsDNA=double-stranded deoxyribonucleic acid (antibody); ESR=erythrocyte sedimentation rate; ET=Early Termination; PCDAI=Pediatric Crohn's Disease Activity Index; SFU=Safety Follow-Up; TB=tuberculosis; WPAI:CD=Work Productivity and Activity Impairment Questionnaire for CD

- a. Week 0 of CR0012 is equivalent to Week 62 (status evaluation) of C87035 with the following exceptions: written informed consent, assessment of inclusion/exclusion criteria, demography, TB testing, and TB questionnaire. Ongoing AEs and concomitant medications from C87035 will continue to be followed in CR0012. Other assessments will be taken from the C87035 database by UCB.
- b. After Week 2, subjects or parents/caregivers have the option of home administration of CZP upon appropriate training during a previous clinic visit(s)

Table 5-1. Schedule of study assessments

	Treatment Period						
	Entry ^a	Visit	Phone call (home administration) or visit (clinic administration) ^b	Clinic Visits ^b	Completion/Early Termination	Unscheduled Visit ^c	SFU ^d
Visit or phone call (+/-7 days)							
Week	0	2	6, 10, 18, 22, 30, 34, 42, 46	14, 26, 38, 50	52		62

or can continue to have CZP administered every 4 weeks at the clinic. For subjects performing home administration, a phone call to the subject and/or the parents/caregiver will be performed by the Investigator (or designee) every 4 weeks between regular clinic visits in order to capture potential AEs and changes in concomitant medications, and to check compliance with home dosing. Subjects will have the option to either switch to home dosing or switch back to site administration at anytime during the study.

- c. Vital signs, concomitant medication, and AEs must be assessed at every Unscheduled Visit. Other safety and PK assessments (eg, CZP plasma sample) may be performed at the discretion of the Investigator as related to the nature of the visit.
- d. The SFU Visit should be performed 12 weeks after the final dose of study medication. For subjects continuing directly onto commercial CZP, a SFU Visit should be completed prior to the first dose of commercial drug administration.
- e. For all females post menses, a urine pregnancy test will be conducted at all regularly scheduled clinic visits except Week 2.
- f. Vital signs will be collected 15 minutes prior to dosing with a ±5 minute window.
- g. Days missed from school will be assessed using the WPAI:CD for children. The time missed from work will be assessed using the WPAI:CD for working individuals with CD. The effect of the child's CD on the caregiver's productivity will be assessed using the WPAI:CD for caregivers of children with CD.
- h. Plasma samples will be collected to determine the concentration of CZP every 12 weeks starting at Week 14, and at the Completion/Early Termination and SFU Visits. Samples will be collected before dosing (except for the Completion/ET and SFU Visits when there is no dosing).
- i. Anti-CZP antibody concentrations in plasma will be collected every 12 weeks starting at Week 14, and at the Completion/ET and SFU Visits (anti-CZP antibody measurements will be made using the samples taken for PK measurements at these time points, so additional blood draws will not be required).
- j. If home administration is performed, sufficient study drug will be dispensed at the scheduled every 12-week clinic visit to last until the next scheduled

Table 5-1. Schedule of study assessments

	Treatment Period							SFU ^d
	Entry ^a	Visit	Phone call (home administration) or visit (clinic administration) ^b	Clinic Visits ^b	Completion/Early Termination	Unscheduled Visit ^c		
Visit or phone call (+/-7 days)								
Week	0	2	6, 10, 18, 22, 30, 34, 42, 46	14, 26, 38, 50	52		62	

clinic visit.

k. If a subject has not been previously reintroduced in C87035, the subject is eligible for 1 reintroduction due to loss of response in CR0012.

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New text:

Table 5-1. Schedule of study assessments

Visit or phone call (+/-7 days)	Treatment Period							SFU ^d
	Entry ^a	Visit	Phone call (home administration) or visit (clinic administration) ^b	Regular Clinic Visits ^b	Completion/ Early Termination	Unscheduled Visit ^e		
Week	0	2	Every 4 weeks beginning at Week 6 and in between regular clinic visits	Every 12 weeks beginning at Week 14			+12 weeks after last dose of study drug	
Written informed consent	X							
Assessment of inclusion/exclusion criteria	X							
Demography	X							
Life style	C87035							
Crohn's disease history	C87035							
Medical and surgical history	C87035							
Assessment of childbearing potential	C87035			X	X			
Pregnancy test ^e	C87035			X	X		X	
Physical examination	C87035			X	X		X	
TB test	X							
TB questionnaire	X			X	X		X	
Tanner stage	C87035			X	X			
Height	C87035			X	X			
Weight	C87035			X	X			
Vital signs ^f	C87035	X		X	X	X	X	

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Table 5-1. Schedule of study assessments

Visit or phone call (+/-7 days)	Treatment Period							SFU ^d
	Entry ^a	Visit	Phone call (home administration) or visit (clinic administration) ^b	Regular Clinic Visits ^b	Completion/Early Termination	Unscheduled Visit ^c		
Week	0	2	Every 4 weeks beginning at Week 6 and in between regular clinic visits	Every 12 weeks beginning at Week 14			+12 weeks after last dose of study drug	
Adverse events ^a	C87035	X	X	X	X	X	X	
Concomitant medications ^a	C87035	X	X	X	X	X	X	
Concurrent medical procedures	C87035	X	X	X	X	X	X	
PCDAI	C87035			X	X			
ESR/hematocrit/albumin for PCDAI	C87035			X	X	X		
CRP	C87035			X	X	X		
Hematology/chemistry/urinalysis	C87035			X	X	X	X	
IMPACT III	C87035			X ¹	X	X		
WPAI:CD ^g	C87035			X ¹	X	X		
Certolizumab pegol plasma concentration ^h	C87035			X	X	X	X	
Anti-CZP antibody plasma concentration ⁱ	C87035			X	X	X	X	
Autoantibodies (ANA and anti-dsDNA)	C87035			X	X	X	X	
Bone markers (osteocalcin, bone specific alkaline phosphatase, n-telopeptides)	C87035			X ¹	X	X		

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Table 5-1. Schedule of study assessments

Visit or phone call (+/-7 days)	Treatment Period						
	Entry ^a	Visit	Phone call (home administration) or visit (clinic administration) ^b	Regular Clinic Visits ^b	Completion/Early Termination	Unscheduled Visit ^c	SFU ^d
Week	0	2	Every 4 weeks beginning at Week 6 and in between regular clinic visits	Every 12 weeks beginning at Week 14			+12 weeks after last dose of study drug
Study drug administration ^l		X	X	X			
Reinduction ^k	Loss of response must be confirmed at a clinic visit where assessments and labs are performed to determine PCDAI score. Scores cannot be confirmed until lab results are received by central lab a few days after the clinic visit. Once loss of response is confirmed, sites must contact the subject to return for the first Reinduction Visit. Reinduction Week 0 (first reinduction dose) is followed by Reinduction Week 2 (second dose, 2 weeks after first dose), and Reinduction Week 4 (third dose, 2 weeks after second dose). Subjects should return to the clinic for each Reinduction. Subject resumes the original schedule of clinic-visits after reinduction. The clinic should contact the Study Monitor to determine the most appropriate way to resume the original schedule of clinic visits. Reinduction Week 0 assessments: PCDAI: ESR, hematocrit, and albumin; IMPACT-III; WPAI:CD Reinduction Week 2 assessments: PCDAI: ESR, hematocrit, and albumin Reinduction Week 4 assessments: PCDAI: ESR, hematocrit, and albumin; WPAI:CD						

ANA=antinuclear antibody; CRP=C-reactive protein; CZP=certolizumab pegol; dsDNA=double-stranded deoxyribonucleic acid (antibody); ESR=erythrocyte sedimentation rate; ET=Early Termination; PCDAI=Pediatric Crohn's Disease Activity Index; SFU=Safety Follow-Up; TB=tuberculosis; WPAI:CD=Work Productivity and Activity Impairment Questionnaire for CD

^aWeek 0 of CR0012 is equivalent to **the last visit** (Week 62; status evaluation) of C87035 with the following exceptions: written informed consent, assessment of inclusion/exclusion criteria, demography, TB testing, and TB questionnaire. Ongoing AEs and concomitant medications from C87035 will continue to be followed in CR0012. Other assessments will be taken from the C87035 database by UCB. **Subjects who were terminated from C87035 when the study was stopped by UCB completed all assessments required for Week 62/Visit 23 at the time of termination.**

^bAfter Week 2, subjects or parents/caregivers have the option of home administration of CZP upon appropriate training during a previous clinic visit(s) or can continue to have CZP administered every 4 weeks at the clinic. For subjects performing home administration, a phone call to the subject and/or the parents/caregiver will be performed by the Investigator (or designee) every 4 weeks between regular clinic visits in order to capture potential AEs and changes in concomitant medications, and to check compliance with home dosing. Subjects will have the option to either switch to home dosing or switch back to site administration at any time during the study.

^cVital signs, concomitant medication, and AEs must be assessed at every Unscheduled Visit. Other safety and PK assessments (eg, CZP plasma sample) may

Table 5-1. Schedule of study assessments

Visit or phone call (+/-7 days)	Treatment Period						
	Entry ^a	Visit	Phone call (home administration) or visit (clinic administration) ^b	Regular Clinic Visits ^b	Completion/Early Termination	Unscheduled Visit ^c	SFU ^d
Week	0	2	Every 4 weeks beginning at Week 6 and in between regular clinic visits	Every 12 weeks beginning at Week 14			+12 weeks after last dose of study drug

be performed at the discretion of the Investigator as related to the nature of the visit.

^dThe SFU Visit should be performed 12 weeks after the final dose of study medication. For subjects continuing directly onto commercial CZP, a SFU Visit should be completed prior to the first dose of commercial drug administration.

^eFor all females post menses, a urine pregnancy test will be conducted at all regularly scheduled clinic visits except Week 2.

^fVital signs will be collected 15 minutes prior to dosing with a ±5 minute window.

^gDays missed from school will be assessed using the WPAI:CD for children. The time missed from work will be assessed using the WPAI:CD for working individuals with CD. The effect of the child's CD on the caregiver's productivity will be assessed using the WPAI:CD for caregivers of children with CD.

^hPlasma samples will be collected to determine the concentration of CZP every 12 weeks starting at Week 14, and at the Completion/Early Termination and SFU Visits. Samples will be collected before dosing (except for the Completion/ET and SFU Visits when there is no dosing).

ⁱAnti-CZP antibody concentrations in plasma will be collected every 12 weeks starting at Week 14, and at the Completion/ET and SFU Visits (anti-CZP antibody measurements will be made using the samples taken for PK measurements at these time points, so additional blood draws will not be required).

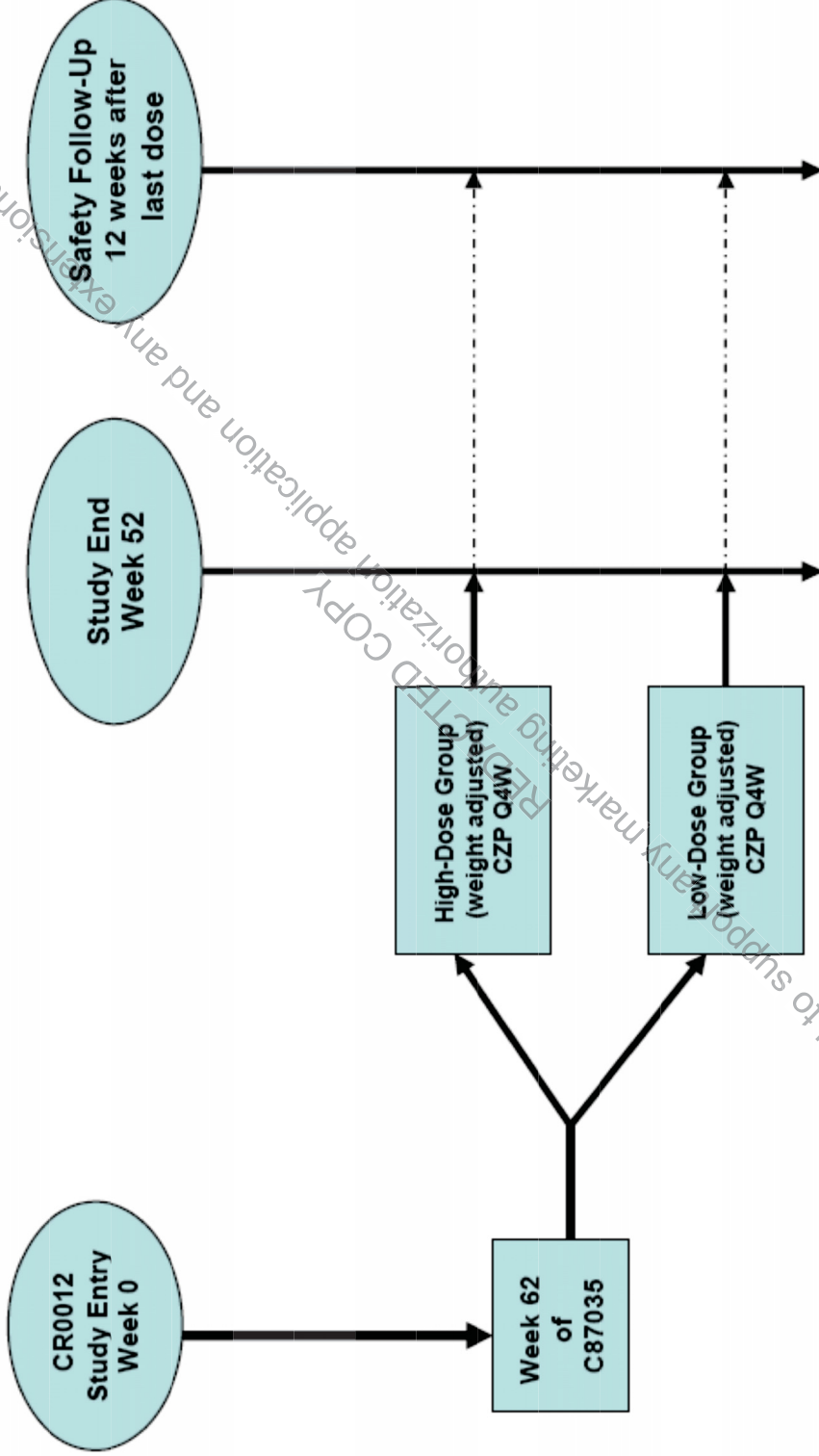
^jIf home administration is performed, sufficient study drug will be dispensed at the scheduled every 12-week clinic visit to last until the next scheduled clinic visit.

^kIf a subject has not been previously reintroduced in C87035, the subject is eligible for 1 reintroduction due to loss of response in CR0012.

^lMeasured at Weeks 14, 26, 38, 50 and then every 12 months thereafter.

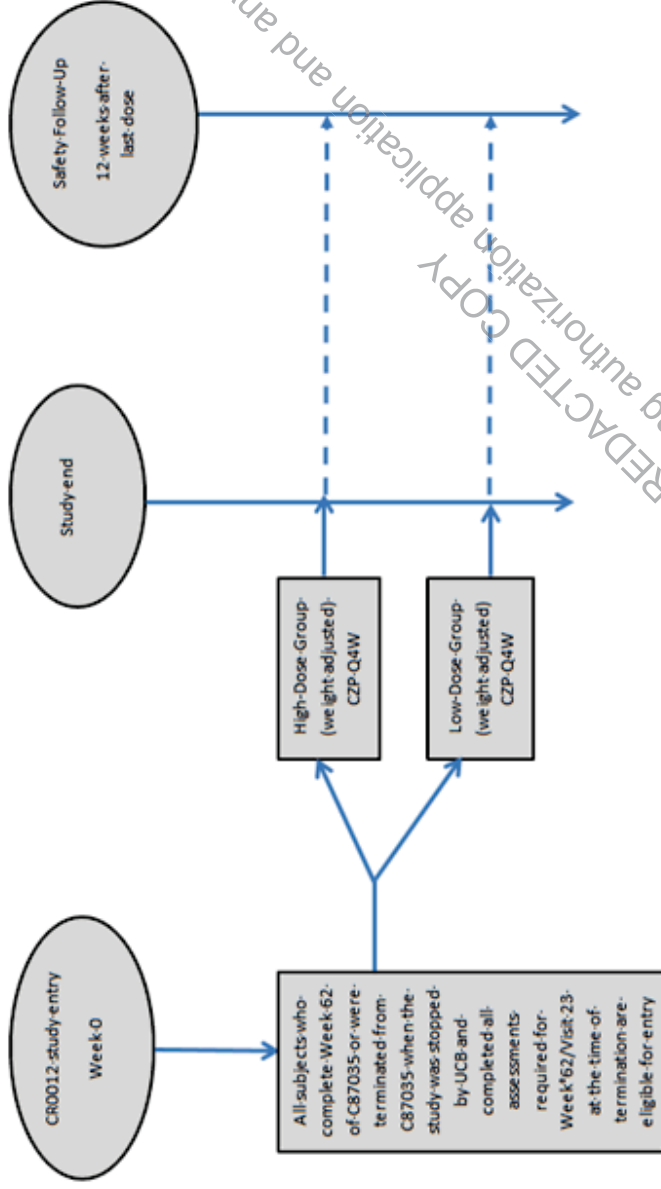
11. Section 5.3, Schematic diagram (figure)

Old text:



New text:

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CZP=certolizumab pegol; Q4W=every 4 weeks

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12. Section 5.4, Rational for study design and selection of dose

Old text:

Following the Food and Drug Administration (FDA) approval of CZP for the treatment of CD in adults, C87035 was a postapproval commitment to investigate the administration of CZP administration in children and adolescents with moderately to severely active CD. This study will provide continued treatment of CZP to subjects who completed C87035 and who, in the Investigator's opinion, would benefit from continued administration of CZP.

The primary objective of this open-label study is to assess the longterm safety and tolerability of CZP in children and adolescents with moderately to severely active CD who completed C87035. The secondary objectives of this study are to assess the longterm efficacy, PK, and immunogenicity of CZP treatment on this population. Subjects may continue on CZP at the dose they were receiving at the end of C87035.

New text:

Following the Food and Drug Administration (FDA) approval of CZP for the treatment of CD in adults, C87035 was a postapproval commitment to investigate the administration of CZP administration in children and adolescents with moderately to severely active CD. This study will provide continued treatment of CZP to subjects who completed **C87035 or were terminated from C87035 when the study was stopped by UCB** and who, in the Investigator's opinion, would benefit from continued administration of CZP.

The primary objective of this open-label study is to assess the longterm safety and tolerability of CZP in children and adolescents with moderately to severely active CD who completed **C87035 or were terminated from C87035 when the study was stopped by UCB**. The secondary objectives of this study are to assess the longterm efficacy, PK, and immunogenicity of CZP treatment on this population. Subjects may continue on CZP at the dose they were receiving at the end of C87035.

13. Section 6.1, Inclusion criteria (item #3)

Old text:

3. Subject completed the C87035 study (Week 62 Visit).

New text:

3. Subject completed the C87035 study (Week 62 Visit) **or was terminated from C87035 when the study was stopped by UCB and completed all assessments required for Week 62/Visit 23 at the time of termination.**

14. Section 6.2, Exclusion criteria (item #1)

Old text:

1. Subject did not complete the C87035 study (Week 62 Visit).

New text:

1. Subject did not complete the C87035 study (Week 62 Visit) **or was terminated from C87035 when the study was stopped by UCB but did not complete all assessments required for Week 62/Visit 23 at the time of termination.**

15. Section 7.7, Procedures for monitoring and subject compliance (final paragraph)

Old text:

If a subject is found to be persistently noncompliant (missing 2 or more consecutive scheduled IMP doses or missing 3 or more doses over the 52-week Treatment Period), the Sponsor in conjunction with the Investigator will make a decision as to whether the subject should be withdrawn from the study.

New text:

If a subject is found to be persistently noncompliant (missing 2 or more consecutive scheduled IMP doses or missing 3 or more doses **over the 52-week Treatment Period**), the Sponsor in conjunction with the Investigator will make a decision as to whether the subject should be withdrawn from the study.

16. Section 8.1, Entry Week 0

New text added at the beginning:

Week 0 of CR0012 is equivalent to Week 62 of C87035 with the exceptions noted below. Subjects who were terminated from C87035 when the study was stopped by UCB completed all assessments required for Week 62/Visit 23 at the time of termination.

17. Section 8.2, Week 2 Visit (final bullet)

Old text:

- Dispensing of drug to subject/caregiver/appropriate designee as determined by the Investigator, if appropriate for home dosing (for Weeks 6 and 10)

New text:

- Dispensing of drug to subject/caregiver/appropriate designee as determined by the Investigator, if appropriate for home dosing **(for Weeks 6 and 10)**

18. Section 8.3 (section heading text)

Old text:

Phone call (home administration) or visit (clinic administration) (Weeks 6, 10, 18, 22, 30, 34, 42, 46)

New text:

Phone call (home administration) or visit (clinic administration) (every 4 weeks and in between regular clinic visits beginning at Week 6)

19. Section 8.4 (section heading text and content)

Old text:

8.4 Weeks 14, 26, 38, 50 Visits

- Assessment of childbearing potential (female subjects only)
- Urine pregnancy test (female subjects of childbearing potential only)
- Physical examination
- TB questionnaire
- Tanner stage
- Weight and height
- Vital signs
- Adverse events
- Concomitant medications
- Concurrent medical procedures
- PCDAI
- ESR/hematocrit/albumin for PCDAI
- CRP
- Hematology, clinical chemistry, and urinalysis
- IMPACT III
- WPAI:CD (for children, for working individuals with CD and for caregivers)
- Certolizumab pegol plasma concentration
- Anti-CZP antibody plasma concentration
- Autoantibody concentrations (ANA and anti-dsDNA)
- Bone markers (osteocalcin, bone specific alkaline phosphatase, n-telopeptides)
- Study drug administration (including training and self-injection under supervision, as appropriate)

- Dispensing of drug to subject/caregiver/appropriate designee as determined by the Investigator, if appropriate for home dosing:
 - Week 14 (for Weeks 18 and 22)
 - Week 26 (for Weeks 30 and 34)
 - Week 38 (for Weeks 42 and 46)

New text:

8.4 Regular clinic visits

8.4.1 Assessments every 12 weeks beginning at Week 14

- Assessment of childbearing potential (female subjects only)
- Urine pregnancy test (female subjects of childbearing potential only)
- Physical examination
- TB questionnaire
- Tanner stage
- Weight and height
- Vital signs
- Adverse events
- Concomitant medications
- Concurrent medical procedures
- PCDAI
- ESR/hematocrit/albumin for PCDAI
- CRP
- Hematology, clinical chemistry, and urinalysis
- ~~IMPACT III~~
- ~~WPAI:CD (for children, for working individuals with CD and for caregivers)~~
- Certolizumab pegol plasma concentration
- Anti-CZP antibody plasma concentration
- Autoantibody concentrations (ANA and anti-dsDNA)
- ~~Bone markers (osteocalcin, bone specific alkaline phosphatase, n-telopeptides)~~
- Study drug administration (including training and self-injection under supervision, as appropriate)

- Dispensing of drug to subject/caregiver/appropriate designee as determined by the Investigator, if appropriate for home dosing
 - ~~Week 14 (for Weeks 18 and 22)~~
 - ~~Week 26 (for Weeks 30 and 34)~~
 - ~~Week 38 (for Weeks 42 and 46)~~
- **8.4.2 Assessments at Weeks 14, 26, 38, 50 and then every 12 months thereafter:**
 - **IMPACT III**
 - **WPAI:CD (for children, for working individuals with CD, and for caregivers)**
 - **Bone markers (osteocalcin, bone specific alkaline phosphatase, n-telopeptides)**

20. Section 8.5 (section heading text)

Old text:

Completion (Week 52)/Early Termination Visit

New text:

Completion/Early Termination Visit

21. Section 9.3 (section heading text and bullet list)

Old text:

Section heading-

Adverse events of special interest

Bullet list-

- Infections including serious opportunistic infections
- Malignancies including lymphoma and leukemia
- Congestive heart failure
- Demyelinating-like disorders
- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia
- Serious bleeding events
- Lupus and lupus-like syndrome
- Serious skin reactions (eg, Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme)

New text:

Section heading-

Adverse events of interest

Bullet list-

- **Serious** infections including opportunistic infections
- **Malignancies including lymphoma**
- Congestive heart failure
- Demyelinating-like disorders
- Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leucopenia
- Serious bleeding events
- Lupus and lupus-like **illness**
- Serious skin reactions (eg, Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme)

22. Section 9.4, Immediate reporting of adverse events (last bullet)

Old text:

- AE of special interest (see Section 9.3)

New Text:

- AE of **special** interest (see Section 9.3)

23. Section 10.4.1, Bone markers

Old text:

Markers of bone and collagen turnover, reflecting the childhood growth curve, will be measured every 12 weeks starting at Week 14, and at the Completion/ET Visit. These markers will include: osteocalcin, bone specific alkaline phosphatase, and n-telopeptides. Tests will be performed by a central laboratory facility.

Instructions on blood sample collection, processing, storage, and shipping will be provided in the laboratory manual for this study.

New text:

Markers of bone and collagen turnover, reflecting the childhood growth curve, will be measured at **Weeks 14, 26, 38, 50 and then every 12 months thereafter**, and at the Completion/ET Visit. These markers will include: osteocalcin, bone specific alkaline phosphatase, and n-telopeptides. Tests will be performed by a central laboratory facility.

Instructions on blood sample collection, processing, storage, and shipping will be provided in the laboratory manual for this study.

24. Section 10.7, IMPACT-III (first paragraph)

Old text:

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 (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-III 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. The IMPACT-III questionnaire is provided in Section 17.3. The IMPACT-III questionnaire will be administered every 12 weeks starting at Week 14, and at the Completion /ET Visit.

New text:

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 (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-III 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. The IMPACT-III questionnaire is provided in Section 17.3. The IMPACT-III questionnaire will be administered **at Weeks 14, 26, 38, 50 and then every 12 months thereafter** and at the Completion /ET Visit.

25. Section 10.8, Days missed from school/work (WPAI:CD for children and for working individuals with CD) (paragraph 4)

Old text:

The WPAI:CD for children questionnaire is administered to all subjects or the parent(s)/legally acceptable representative(s) and the WPAI:CD for working individuals questionnaire is only administered to subjects who work, under supervision of the Investigator or designee every 12 weeks starting at Week 14, and at the Completion /ET Visit.

New text:

The WPAI:CD for children questionnaire is administered to all subjects or the parent(s)/legally acceptable representative(s) and the WPAI:CD for working individuals questionnaire is only administered to subjects who work, under supervision of the Investigator or designee **at Weeks 14, 26, 38, 50 and then every 12 months thereafter**, and at the Completion /ET Visit.

26. Section 10.9, Effect on the caregiver's work (WPAI:CD for caregivers) (paragraph 2)

Old text:

The questionnaire is administered under supervision of the Investigator or designee to the caregiver every 12 weeks starting at Week 14, and at the Completion/ET Visit.

New text:

The questionnaire is administered under supervision of the Investigator or designee to the caregiver at **Weeks 14, 26, 38, 50 and then every 12 months thereafter**, and at the Completion/ET Visit.

27. Section 13.8, Planned interim analysis and data monitoring

Old text:

A DSMB will review safety data. The DSMB members will be independent of the Sponsor and Investigators. The DSMB members will be informed by GCSP (or designee) of all SAEs at the time of expedited reporting and will review periodically all emerging safety data (SAEs, AEs, safety laboratory data). Based on the safety data, the DSMB can recommend modifying/stopping the study.

In order to assess the continuing longterm safety and efficacy of CZP, interim analyses will be performed on an annual basis starting from 1 year after the first subject's first visit in CR0012 has occurred. The analyses will include all variables collected during the relevant period for all subjects included in the study at the time of the analysis. As no sample size calculation was performed, no formal statistical testing will be carried out and, thus, no adjustment to any significance level needs to be considered.

Should a regulatory authority request an additional interim analysis for a time other than as stated above, this will be performed according to the request.

New text:

A DSMB will review safety data. The DSMB members will be independent of the Sponsor and Investigators. The DSMB members will be informed by GCSP (or designee) of all SAEs at the time of expedited reporting and will review periodically all emerging safety data (SAEs, AEs, safety laboratory data). Based on the safety data, the DSMB can recommend modifying/stopping the study.

~~In order to assess the continuing longterm safety and efficacy of CZP, interim analyses will be performed on an annual basis starting from 1 year after the first subject's first visit in CR0012 has occurred. The analyses will include all variables collected during the relevant period for all subjects included in the study at the time of the analysis. As no sample size calculation was performed, no formal statistical testing will be carried out and, thus, no adjustment to any significance level needs to be considered.~~

No interim analyses are planned. Should a regulatory authority request an **additional** interim analysis ~~for a time other than as stated above~~, this will be performed according to the request.

18 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed Name

Date/Signature