STATISTICAL ANALYSIS PLAN

Study: CR0012

Product: Certrolizumab pegol

An open-label, multi-center study to assess the safety of Certrolizumab 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

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LIST OF ABBREVIATIONS

AE	adverse event
ATC	Anatomical Therapeutic Chemical classification system
BMI	body mass index
CSR	Clinical Study Report
CZP	Certrolizumab pegol
CV	coefficient of variance
EudraCT	European Clinical Trials Database
MedDRA®	Medical Dictionary for Regulatory Activities®
PCDAI	Pediatric Crohn's Disease Activity Index
PK	Pharmacokinetic
PT	Preferred Term
Q2W	every 2 weeks
Q4W	every 4 weeks
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
WHODRL	World Heath Organization Drug Reference List
WPAI	Work Productivity and Activity Impairment Questionnaire

1 INTRODUCTION

This SAP supports the final analysis for CR0012 CSR.

2 PROTOCOL SUMMARY

2.1 Study objective(s)

2.1.1 Primary objective(s)

The primary objective of the study is to assess the long-term safety and tolerability of CZP in children and adolescents with moderately to severely active CD.

2.1.2 Secondary objective(s)

Secondary objectives include further assessment of the long-term efficacy, PK, and immunogenicity of CZP treatment in this population.

2.2 Study variable(s)

2.2.1 Safety variable(s)

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

2.2.2 Efficacy variable(s)

2.2.2.1 Primary efficacy variable(s)

The primary efficacy variable is the proportion of subjects in clinical remission where clinical remission is defined as a PCDAI score ≤10.

2.2.2.2 Secondary efficacy variable(s)

Secondary variables include:

- 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

2.2.2.3 Other efficacy variable(s)

Other efficacy variables include:

- 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
- 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
- Actual scores of WPAI:CD for caregivers
- Change from Baseline (Week 0 of C87035) in scores of WPAI:CD for caregivers

2.2.3 Pharmacokinetic/pharmacodynamic variable(s)

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

2.3 Study design and conduct

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.

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 ≥40kg or 200mg for subjects 20 to <40kg sc Q2W for a total of 3 doses
- Continue dosing with CZP administered sc Q4W as 400mg for subjects ≥40kg or 200mg for subjects 20 to <40kg, 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.

2.3.1 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.

2.3.2 Anticipated regions and countries

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

2.4 Determination of sample size

This is an open-label study for subjects who completed Week 62 of C87035 or who were terminated from C87035 when the study was stopped by UCB (and completed all assessments required for Week62/Visit 23 at the time of termination) and as such no formal sample size has been determined.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be performed using SAS Version 9.1 or higher. All tables and listings will use Courier New font size 9.

Descriptive statistics will be displayed to provide an overview of the study results. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for the purpose of analysis. Unless otherwise noted, all percentages will be displayed to 1 decimal place. No percentage will be displayed for zero counts, and no decimal will be presented when the percentage is 100%. For continuous parameters, descriptive statistics will include number of subjects with available measurements (n), mean, standard deviation (SD), median, minimum, and maximum. Pharmacokinetic variables may also present the geometric mean, coefficient of variance, and 95% CI for the geometric mean as appropriate.

Decimal places for descriptive statistics will always apply the following rules:
- "n" will be an integer.
- Mean, SD, and median will use 1 additional decimal place compared to the original data.
- Coefficient of variance (CV[%]) will be presented with 1 decimal place.
- Minimum and maximum will have the same number of decimal places as the original value.

3.2 General study level definitions

CZP dose groups will be identified as "Low Dose" and "High Dose", respectively on column headers. These are defined 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 ≥40kg (≥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 ≥40kg (≥88lbs): 1 injection of 1mL

Table 1-1. Doses of CZP in CR0012

	CZP dose (mg) injections	
Treatment group	**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
≥40kg (≥88lbs)	2x1mL PFS/400mg	1x1mL PFS/200mg

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

For all by-visit AE and medication summaries, if a subject in the Low Dose group is re-induced, the subject will be summarized under the High Dose column from the time of re-induction onwards.

The population N's in the column headers will indicate the number of subjects who entered CR0012 on their respective High/Low dose groups despite whether a subject changed doses within the study. By-visit tables will show the number of subjects at each visit.

Reinduction visits will be included in table summaries only if they occur during a scheduled study week. A '(R)' will be used to indicate a visit summary that includes any reinduction visits (eg, Week 14 (R)).

3.3 Definition of Baseline values

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

3.4 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 to decide how to handle problems in the subject's data (eg, missing values, withdrawals, dropouts, protocol deviations). In addition, the review will be used to identify the use of rescue therapy. The pre-analysis reviewers should ensure that the results of this review are communicated to the study team before locking the database.

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

3.5 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.

3.6 Center pooling strategy

No pooling of centers is planned for this study.

3.7 Coding dictionaries

All AEs and medical history will be coded and classified by primary System Organ Class (SOC) and Preferred Term (PT) according to Version 20.1 of the Medical Dictionary for Regulatory Activities (MedDRA®).

All medications will be coded using World Health Organization Drug Reference List (WHO-DRL). Medical procedures will not be coded.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

No inferential statistics will be performed for the efficacy analysis. However, descriptive statistics for clinical response and clinical remission will be presented by subgroup variables of interest as defined in Section 4.4.

4.2 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.

4.3 Interim analyses and data monitoring

A DSMB reviews CR0012 safety data on an annual basis and can recommend modifying or stopping the study.

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

4.4 Examination of subgroups

No subgroup analysis for efficacy is planned since the total number of subjects participating in this study is small (n=16).

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The number of subjects who received any study medication, completed, prematurely discontinued the study along with reasons for discontinuation, and the number of subjects re-induced in C87035 and in CR0012 will be summarized by dose group and overall for the Safety Population. In addition,

discontinuations due to AEs will be presented in a separate table. Disposition information will also be listed.

5.2 Protocol deviations

The number and percentage of subjects with at least one protocol deviation and the number and percentage of subjects by type of deviation (inclusion criteria, exclusion criteria, withdrawal criteria, prohibited medication use, incorrect dose received, treatment non-compliance, and procedural non-compliance) will be presented by dose group and overall. All protocol deviations will be listed.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

Demographics will be summarized for the Safety Population by dose group and overall and will include age, age category (<12, ≥12 years), gender, race, ethnicity, height, weight, and body mass index (BMI). Note that for European Clinical Trials Database (EudraCT) regulatory requirements, age will also be presented categorically as (12 to <18, and 18 to 65 years). Demographic information will also be listed.

6.2 Medical history and concomitant diseases

Medical history and concomitant diseases will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 20.1) and summarized for the Safety Population. The number and percentage of subjects by system organ class and preferred term will be presented. Medical history and concomitant diseases will also be listed.

Procedure history and concomitant medical procedures will not be coded and summarized in tabular form, but will be listed for the Safety Population.

6.3 Prior and concomitant medications

Prior and concomitant medication will be coded according to the WHO Drug Reference List (SEP/2017).

Medications will be separated into prior and concomitant medications. If the imputed start and stop dates of medication are before the date of first administration of study medication, the medication will be classified as a prior medication. Medications that were taken after start of CZP treatment or medications which started prior to the first administration of CZP treatment but are still ongoing at the time of first administration of CZP will be defined as concomitant medications.

Start dates will be imputed as follows:

- Missing day will be imputed as the first day of the month. Missing month will be imputed as January

Stop dates will be imputed as follows:

- Missing day will be imputed as the last day of the month. Missing month will be imputed as December

Concomitant medications will be summarized for the Safety Population. Tables will present the Anatomical Therapeutic Chemical classification system (ATC) anatomical main group (Level 2) and therapeutic/pharmacological subgroup (Level 4) by dose group and overall.

Prior and concomitant medications will be listed.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

The number of weeks completed, number of expected doses, and number of doses received will be listed for the Safety Population. Definitions are provided below:

- Total weeks completed = [(last dose date – first dose date + 1) / 7]
  - If total weeks completed is <2, then total expected doses = 0 since first study dose administration begins at the Week 2
- If the subject did not re-induce, then
  - total expected doses = (total #weeks completed/4) + 1 rounded down to the nearest integer
- If the subject did re-induce, then
  - total expected doses = (total #weeks/4) + 2 rounded down to the nearest integer

8 SAFETY ANALYSES

All safety summaries will be based on the Safety Population and presented by dose group (separate columns for High Dose and Low Dose), and presented by weight category, and by age category, as appropriate.

For all by-visit AE and medication summaries, if a subject in the Low Dose group is re-induced, the subject will be summarized under the High Dose column from the time of re-induction onwards.

8.1 Extent of exposure

Descriptive statistics for the duration of CZP exposure (in years), and for CZP exposure (in mg) during the study will be presented by dose group and Total.

8.2 Adverse events

Treatment-emergent adverse events (TEAEs) will be summarized descriptively by primary SOC and PT. Table columns will include dose groups of CZP Low Dose, CZP High Dose, CZP Re-induction 400mg, and All CZP Doses, and report incidence, percent, and number of TEAEs. AEs will be defined as related to treatment if the relationship is recorded as possible, probable, highly probable, or missing. AEs will be defined as not related if the relationship is recorded as unlikely or none.

An overall summary of TEAEs, including the number of events, the number and percentage of subjects with any TEAE, with each severity, with each relationship to treatment, treatment related (defined as possible, probable, highly probable, or missing), SAEs, any TEAEs leading to withdrawal from the study, any TEAEs requiring dose change, and any TEAEs leading to death will be presented by dose group.

Other treatment-emergent adverse event tables will include:

- All TEAEs by primary SOC and PT
- All TEAEs by primary SOC, PT, and severity
- All TEAEs by primary SOC, PT, and relationship to study drug

- All TEAEs sorted by incidence in the All CZP Doses group by PT
- SAEs by primary SOC and PT
- Non-serious TEAEs with an incidence of >5% in the All CZP Doses group by primary SOC and PT
- TEAEs leading to withdrawal from the study by primary SOC and PT
- TEAEs occurring within 30 minutes of receiving an injection by primary SOC and PT
- Injection site reactions by primary SOC and PT
- Systemic injection reactions by primary SOC and PT
- SAEs by primary SOC, PT, and relationship
- Non-serious TEAEs by primary SOC, PT, and relationship
- TEAEs leading to death by primary SOC, PT, and relationship
- Non-serious TEAEs with an incidence of >5% in the All CZP Doses group by primary SOC, PT, and relationship
- Adverse Events of interest

Adverse events (AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.1. AEs of interest and the approach to summarize them will be briefly described below. Further information is provided in the guidance document (AE's of Interest – Cimzia Program 5January2018).

1. Serious infections, including opportunistic infections will be manually identified by a study physician using the Serious TEAE table. A separate table does not need to be produced. Opportunistic infections (including tuberculosis) will be summarized in a stand-alone table using UCB-defined search criteria.
2. Malignancies, including lymphoma will be presented in 2 tables using the Standardized MedDRA Query (SMQ) criteria "Malignant or unspecified tumours" and "Malignant tumours" respectively.
3. Serious cardiovascular events will be presented in a table using the following search criteria
    a. Serious cardiovascular events will be presented in a table using the following search criteria
        i. Serious cardiovascular events will be presented in a table using the following search criteria:
            1. Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ)
            2. Haemorrhagic central nervous system vascular conditions (SMQ)
            3. Ischaemic central nervous system vascular conditions (SMQ)
    b. All serious TEAEs which code to a PT included in the HLT "Ischaemic coronary artery disorders" except events coding to PT "Chest Pain" or "Chest discomfort"
    c. All serious TEAEs which code to a PT included in any of the following HLTs: "Heart Failures NEC", "Left Ventricular Failures", or "Right Ventricular

Failures" and which also code to the SOC of "Cardiac Disorders" as Primary SOC

4. Congestive heart failure AEs (defined as all AEs which code to a PT of "Cardiac failure congestive") will be manually identified by the study physician using the "Any TEAE" table. A separate table does not need to be produced to summarize this event.
5. Demyelinating-like disorders will be presented in a stand-alone table which is based on the SMQ = "Demyelination". The SMQ search should include all TEAEs which code to a PT included in Scope=Narrow group within the SMQ. TEAEs which code to a PT included in the Scope=Broad group within the SMQ should be excluded from the search.
6. Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia and leucopenia will be presented in a stand alone tables based on the SMQ = "Haematopoietic cytopenias". The SMQ search should include all serious TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups within the SMQ.
7. Serious bleeding events will be presented in a stand-alone table that is based on the SMQ = "Haemorrhage terms (excl laboratory terms) (SMQ)". The SMQ search should include all serious TEAEs which code to a PT included in the SMQ.
8. Lupus and lupus-like illness will be manually identified by the study physician using the "Any TEAE" table. A separate table does not need to be produced to summarize these types of events.
9. Serious skin reactions (eg, Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme) will be manually identified by the study physician using the "Any SAE" table. A separate table does not need to be produced to summarize these types of events.

8.3 Clinical laboratory evaluations

Actual laboratory values will be summarized descriptively by week, by dose group and Total. Change from Baseline to last available visit with laboratory values will be summarized descriptively by dose group and Total. If multiple laboratory assessments are taken at the last visit with available data, the last assessment will be used.

Shift tables that cross-tabulate Baseline (low, normal, high relative to normal range, and missing) by end of trial status will be presented by dose group and Total for each laboratory parameter.

The incidence rate of treatment-emergent markedly abnormal laboratory values (based on Common Terminology Criteria for Adverse Events criteria) will be presented by dose group and Total for hematology and biochemistry laboratory parameters only. See Section 13.1 for markedly abnormal criteria.

All laboratory values will be listed with markedly abnormal laboratory values flagged.

8.4 Vital signs, physical findings, and other observations related to safety

8.4.1 Vital signs

Actual vital signs values (systolic blood pressure, diastolic blood pressure, and pulse rate) will be summarized descriptively by week, by dose group and Total. Change from Baseline to last available visit with vital signs values will be summarized descriptively by dose group and Total. If multiple vital sign values are taken at the last visit with available data, the last assessment will be used.

Vital sign values will also be listed.

8.4.2 Height and Weight

Actual height and weight values will be summarized descriptively by week, by dose group and Total. Change from baseline to last available visit with height and weight values will be summarized descriptively by dose group and Total. If multiple height and weight values are taken at the last visit with available data, the last assessment will be used.

Height and weight values will also be listed.

8.4.3 Electrocardiograms

Not applicable as electrocardiograms were not collected in this study.

8.4.4 Other safety variable(s)

The number and percent of autoantibody levels (ANA and anti-dsDNA antibody) will be presented as normal or antibodies present for ANA, and as negative or positive for anti-dsDNA antibodies. This table will be presented for the CZP Low Dose group, CZP High Dose group, and for the All CZP Doses group. A similar table will be presented by age group.

9 EFFICACY ANALYSES

As the primary objective of this study is to evaluate safety, no primary or secondary efficacy variables are defined. Rather, efficacy variables will be measured to evaluate efficacy of long-term open label treatment with CZP.

All efficacy summaries, where applicable, will be presented by visit, dose group, weight, (20 to <40kg [44 to <88lbs] and ≥40kg [≥88lbs]) and age category (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 by 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. Higher scores indicate greater impairment and less productivity. The summaries will be presented separately for the WPAI:CD for children, WPAI:CD for working individuals with CD, and WPAI:CD for caregivers. Each of these 3 questionnaires have 6 questions with the WPAI for working individuals and for caregivers having similar questions, and the WPAI for children having questions which assess time missed and productivity at school rather than at work. In general, the 6 questions are (note that for children, the questions will be similar but related to school):

Questions:

[redacted]

The 4 domains are labeled and calculated as (note: domain labels for children will reflect time at school, but domain scores are calculated similarly):

- [redacted]: Q2/(Q2+Q4)
- [redacted]: Q5/10
- [redacted] Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4))x(Q5/10)]
- [redacted]: Q6/10

If appropriate for WPAI, indirect costs parameters will be summarized using descriptive statistics by period of onset.

10 PHARMACOKINETICS AND PHARMACODYNAMICS

10.1 Pharmacokinetics

Plasma concentrations of CZP at each visit will be summarized by anti-CZP antibody status (all subjects, antibody-positive, and antibody negative) for each age category, the overall population, and for each dose group. In addition, plasma concentrations will be summarized by weight category (<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 category and by dose 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. If there are more than 1 concentration available for the same timepoint, data will be listed as per the guidance found in the global convention document.

10.2 Pharmacodynamics

Not applicable.

11 OTHER ANALYSES

Not applicable

12 REFERENCES

Not Applicable

13 APPENDICES

13.1 Markedly abnormality criteria for laboratory data

Markedly abnormal laboratory values will be defined as those categorized as Grade 3 or 4 based on the Common Terminology Criteria for Adverse Events v3.0. Definitions of markedly abnormal values using the Grade 3 and Grade 4 cut points are given for hematology in Table 1 and Table 2, respectively. Definitions of markedly abnormal values using the Grade 3 and Grade 4 cut points are given for biochemistry in Table 3 and Table 4, respectively.

Table 1 Definitions of Grade 3 markedly abnormal hematology values

	Markedly Abnormal Definition	
Parameter (units)	Low	High
Hemoglobin (g/L)	<80 - 65	N/A
Platelets (X10E9/L)	<50.0 – 25.0	N/A
White blood cells (X10E9/L)	<2.0 – 1.0	N/A
Neutrophils (X10E9/L)	<1.0 - 0.5	N/A
Lymphocytes (X10E9/L)	<0.5 – 0.2	N/A

N/A=Not Applicable

Table 2 Definitions of Grade 4 markedly abnormal hematology values

	Markedly Abnormal Definition	
Parameter (units)	Low	High
Hemoglobin (g/L)	<65	N/A
Platelets (X10E9/L)	<25.0	N/A
White blood cells (X10E9/L)	<1.0	N/A
Neutrophils (X10E9/L)	<0.5	N/A
Lymphocytes (X10E9/L)	<0.2	N/A

N/A=Not Applicable

Table 3 Definitions of Grade 3 markedly abnormal biochemistry values

	Markedly Abnormal Definition	
Parameter (units)	Low	High
Sodium (mmol/L)	<130 - 120	>155 - 160
Potassium (mmol/L)	<3.0 – 2.5	>6.0 – 7.0
Calcium (mmol/L)	<1.75 – 1.5	>3.1 – 3.4
Glucose (mmol/L)	<2.2 – 1.7	>13.9 – 27.8
Creatinine	N/A	>3.0 – 6.0 x ULN
Albumin (g/L)	<20	N/A

Alkaline phosphatase	N/A	>5.0 – 20.0 x ULN
Gamma glutamyl transferase	N/A	>5.0 – 20.0 x ULN
Aspartate aminotransferase	N/A	>5.0 – 20.0 x ULN
Alanine aminotransferase	N/A	>5.0 – 20.0 x ULN
Bilirubin	N/A	>3.0 – 10.0 x ULN

N/A=Not Applicable

Table 4 Definitions of Grade 4 markedly abnormal biochemistry values

	Markedly Abnormal Definition	
Parameter (units)	Low	High
Sodium (mmol/L)	<120	>160
Potassium (mmol/L)	<2.5	>7.0
Calcium (mmol/L)	<1.5	>3.4
Glucose (mmol/L)	<1.7	>27.8
Creatinine	N/A	>6.0 x ULN
Albumin (g/L)	N/A	N/A
Alkaline phosphatase	N/A	>20.0 x ULN
Gamma glutamyl transferase	N/A	>20.0 x ULN
Aspartate aminotransferase	N/A	>20.0 x ULN
Alanine aminotransferase	N/A	>20.0 x ULN
Bilirubin	N/A	>10.0 x ULN

N/A=Not Applicable.

13.2 Impact III Questionnaire Scoring

The Impact III questionnaire is a 35-item measure of health-related quality of life in children with inflammatory bowel disease with a total score ranging from 35 (poor) to 175 (best). Total score is calculated as the sum of all 35 questions. Scores for the 6 domain scores of IBD Symptoms, Systemic Symptoms, Emotional Functioning, Social Functioning, Body Image, and Treatment/Interventions are calculated by summing the responses for questions within a domain (see table below).

Domain	Question (actual question number in parentheses)
IBD Symptoms	• [redacted] (1) • [redacted] (3) • [redacted] (10) • [redacted] (19) • [redacted] (21) • [redacted] (25) • [redacted] (31)
Systemic Symptoms	• [redacted] (6) • [redacted] (28) • [redacted] (32)
Emotional Functioning	• [redacted] up (4) • [redacted] (5) • [redacted] (11) • [redacted] (12) • [redacted] (13) • [redacted] (16) • [redacted] (29)
Social Functioning	• [redacted] (8) • [redacted] (9) • [redacted] (14) • [redacted] (17)

	• [redacted]riends (18) • [redacted] (20) • [redacted] (23) • [redacted] (27) • [redacted] (26) • [redacted]ies (30) • [redacted] (34) • [redacted] (35)
Body Image	• [redacted] (33) • [redacted] (7) • [redacted] (15)
Treatment/Interventions	• [redacted] (2) • [redacted] (22) • [redacted] (24)

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	13-Feb-2018 15:46 GMT+01
[redacted]	Clinical Approval	13-Feb-2018 16:09 GMT+01