NOVARTIS

Clinical Development

ACZ885

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An open-label, single-arm, active-treatment, efficacy and safety study of canakinumab (ACZ885) administered for at least 48 weeks in Japanese patients with Systemic Juvenile Idiopathic Arthritis (SJIA)

RAP Module 3 – Detailed Statistical Methodology

Author: [redacted], Trial Statistician

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Version	Date	Changes
Draft 1.0	26-Nov-2014	First draft
Draft 1.1	08-Jan-2015	Second draft after RAP review meeting 1
Draft 1.2	27-Jan-2015	Third draft after RAP review meeting 2
Draft 1.3	09-Feb-2015	Final draft. Confirmed that successful steroid tapering would be assessed as the change from baseline instead of the change from week 8 during the final RAP review on the draft 1.2.
Final 2.0	10-Feb-2015	Final version
Amendment 1	18-Jan-2017	Changed the definition of safety set. Added the list of study duration, disposition and AEs related to study treatment by center Changed the age group category to include a patient whose derived age is one year old. Added the subgroup analysis of weight groups for primary endpoints and adverse events. Added the categorical variable of prior use of Tocilizumab as baseline characteristics. Changed the summary table of flares. Changed the cut-off for exposure table. Added the summary of total exposure in patient years. Changed the exposure adjusted event will be provided per 100 patients years. Changed the cut-off for summary of Aes by onset period. Added box plots of some key laboratory data for a 28 week analysis. Added the abnormality criteria based on CTC grades for hemoglobin. Added the AE/SAE tables for the requirements of ClinicalTrials.gov for the final analysis.
Amendment 2	11-Apr-2017	[redacted] Added the list of normal range for hematology differential counts of leucocytes.

1 Statistical methods planned in the protocol and determination of sample size

Data will be analyzed by Novartis according to the data analysis section 9 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details will be provided, as applicable, in Appendix 16.1.9 of the CSR.

1.1 Statistical and analytical plans

The planned analysis is described in Section 9 (Data analysis) of the study protocol which is available in Appendix 16.1.1 of the CSR.

This document covers statistical and analytical plans for a 28 week analysis, a 48 week analysis and the final analysis, see also Section 1.10.

With a small number of patients in this study, the efficacy and safety results will be presented in a descriptive manner. Continuous variables will be summarized by mean, standard deviation, median, minimum, maximum, (Q1, Q3 if appropriate) and number of patients with non-missing data. Categorical variables will be summarized by absolute frequencies and percentages.

1.2 Subjects and treatments

The following populations will be defined for this trial:

Full analysis set (FAS): The FAS will consist of all patients who received at least one dose of study drug.

Safety set: The Safety set will consist of all patients who received at least one dose of study drug.

The PD "No written informed consent was obtained before any assessments were performed" (INCL01) will lead to exclusion of patients from any analysis sets. Patients who did not receive study drug will be identified by the PD "Patient was not exposed to study medication at any visit" (TRT02).

The following study epochs will be considered for analysis:

- **Screening** epoch: before the first study treatment
- **Open label treatment** epoch : the first study treatment to the end of study (EOS) visit

1.3 Assessment windows, baseline and post baseline definitions

1.3.1 Baseline and post baseline definition

Baseline is the last assessment (including unscheduled visits) obtained before the first dose of study treatment (Day 1) unless otherwise specified. The assessments during screening epoch can be baseline values (as shown in Table 1-1). All assessments obtained after the first dose of study treatment are considered as post-baseline unless otherwise specified.

1.3.2 Assessment windows

The visit numbers as reported in the eCRF will be used except for end of study (EOS) visit (visit=199), which will be mapped according to Table 1-1.

Table 1-1 Visit window

Protocol defined				Time point to be analyzed	Visit window (days) for mapping end of study visit
Epoch	Visit	Week	Day		
Screening	1	-4	-28 to -1	Baseline	-28 to -1
Open label treatment	101	1	1	Baseline	1
	102	1	3	Day 3	2-4
	103	2	15	Week 2	5-16
	104	4	29	Week 4	17-31
	105	8	57	Week 8	32-60
	106	12	85	Week 12	61-88
	107	16	113	Week 16	89-116
	108	20	141	Week 20	117-144
	109	24	169	Week 24	145-172
	110	28	197	Week 28	173-200
	111	32	225	Week 32	201-228
	112	36	253	Week 36	229-256
	113	40	281	Week 40	257-284
	114	44	309	Week 44	285-312
	115	48	337	Week 48	313-340
	116, 117, …	Every 4 weeks	X	Every 4 weeks	(X-24) – (X+3)

1.4 Patient disposition, demographics and other baseline characteristics

1.4.1 Subject disposition

The number of patients screened, completed screening phase, and discontinued screening phase with the reasons for screen failures will be provided.

The number and percentage of patients in the safety set who completed treatment phase and who discontinued treatment phase prematurely with the reasons for discontinuation will be presented. At a 28 week analysis or a 48 week analysis, the number and percentage of patients in the safety set who completed Week 28 or Week 48 visit will be presented as completing treatment phase for the cut-off analyses.

For each protocol deviation, the number and percentage of patients for whom the deviation applies will be tabulated for the Safety set.

The FPFV and LPLV dates, the number of patients who had IC, treated, discontinued and had AEs related to study drug treatment will be provided by center at a 28 week analysis.

1.4.2 Background and demographic characteristics

The following common demographic variables will be summarized and listed for the Safety set.

Continuous variables:

- Age at screening (years)
- Height (cm)
- Weight (kg)
- Body mass index (BMI)

Body Mass Index (*BMI*) will be calculated when both of height and weight are available, using the following formula:

$$BMI = (\text{body weight in kilograms}) / (\text{height in meters})^2$$

Categorical variables:

- Age categories (<4, ≥4-<6, ≥6-<12, ≥12-<20)
- Weight categories (≤25, >25 ≤50, >50 ≤75, >75)
- Sex
- Race
- Ethnicity

The following disease history and baseline characteristics will be summarized for the Safety set.

Continuous variables:

- Onset age (years), which will be derived from the first diagnosis date from medical history and the date of birth
- Body temperature (°C)
- Time from SJIA diagnosis to study entry (days)
- Level of C-reactive protein at baseline (standardized in mg/L)
- Oral prednisone equivalent dose at baseline (mg/kg/day)
- Physician's global assessment of disease activity (VAS) (mm)
- Parent's or patient's assessment of overall wellbeing (VAS) (mm)
- Number of active joints
- Number of joints with limitation of motion
- CHAQ Functional ability score

Categorical variables:

- Oral prednisone equivalent dose at baseline (>0 to <=0.4, >0.4 mg/kg/day)
- Rash (Yes, No)
- Morning stiffness (Yes, No)
- Fever past week (Yes, No)
- Fever for 2 days (Yes, No)
- Clinical assessment: Serositis (Normal, Clinically insignificant abnormality, Clinically significant abnormality)
- Clinical assessment: Splenomegaly (Normal, Clinically insignificant abnormality, Clinically significant abnormality)
- Clinical assessment: Hepatomegaly (Normal, Clinically insignificant abnormality, Clinically significant abnormality)
- Clinical assessment: Lymphadenopathy (Normal, Clinically insignificant abnormality, Clinically significant abnormality)
- Spleen ultrasound (Sonography) (Normal, Clinically insignificant abnormality, Clinically significant abnormality)
- Liver ultrasound (Sonography) (Normal, Clinically insignificant abnormality, Clinically significant abnormality)
- Number of active joints (≤ 26, >26)
- Prior use of Tocilizumab (Yes, No)

For the following assessments at screening: Hepatitis and HIV, chest x-lay, T-spot test, a patient listing will be provided.

1.4.3 Medical history

Any significant prior or active medical condition at the time of signing informed consent will be coded using the MedDRA dictionary. These medical conditions will be summarized by primary system organ class and preferred term for the Safety set.

1.5 Study medication

The exposure to study drug (number of injections), duration of exposure (days) and total exposure in patient years will be summarized and listed for the Safety set. The number and percentage of patients of certain durations (any exposure, ≥4 weeks (28 days), ≥12 weeks (84 days), ≥24 weeks (168 days), ≥36 weeks (252 days), ≥48 weeks (336 days), etc.) will be provided.

The duration of exposure (days) will be calculated as

Duration of exposure (days) = the day of the last study visit – the day of first dose of study treatment + 1.

The total exposure in patient years will be calculated as the total subject days divided by 365.25.

1.6 Concomitant medication

The number and percentage of patients taking prior medication, concomitant medication will be summarized in separate tables by preferred term and Anatomical Therapeutic Classification (ATC) class for the Safety set. Rescue medications (Corticosteroids) will be summarized separately from other medications.

Prior medications will be defined as treatments taken and stopped prior to first dose of study treatment. Any medications given at least once between the day of first dose of study treatment and the day of the last study visit will be concomitant medications, including those which were started pre-baseline and continued into the treatment period.

In addition, the number and percentage of patients using non-drug therapies and procedures will be summarized by primary system organ class and preferred term.

1.7 Efficacy evaluation

1.7.1 Analysis of the primary variable

1.7.1.1 Primary variable

The co-primary efficacy variables are the proportion of patients who achieve a minimum adapted ACR Pediatric 30 criteria at Week 8 and the proportion of patients who are able to taper corticosteroids successfully at Week 28. The analysis of the co-primary efficacy variables will be based on the FAS.

ACR Pediatric 30 at Week 8

The response variable derived by [redacted] will be used in the analysis.

Successful tapering of corticosteroids at Week 28

Prednisone equivalent dose (mg/kg/day) of oral steroids will be calculated to derive successful tapering of corticosteroids (see Section 2.1).

Successful oral steroid tapering will be defined as meeting one of the following:

1. Patients with prednisone equivalent dose > 0.8 mg/kg/day at baseline are able to reduce their dose to ≤ 0.5 mg/kg/day.
2. Patients with prednisone equivalent dose from ≥ 0.5 mg/kg/day and ≤ 0.8 mg/kg/day at baseline are able to reduce their dose by at least 0.3 mg/kg/day.
3. Patients with any initial prednisone equivalent dose at baseline are able to reduce their dose ≤ 0.2 mg/kg/day.
4. Patients with prednisone equivalent dose ≤ 0.2 mg/kg/day at baseline are able to reduce their dose with any reduction

AND maintaining a minimum adapted ACR 30 pediatric criterion.

The oral steroid dose at baseline and Week 28 will be the measurement on the date of baseline (Day 1) and one day before Week 28 on the concomitant medication page. To calculate the dose per weight, the last available weight on or before the measurement will be used.

When a patient continued the study, if there is no concomitant oral steroid data at the assessment day, it will be considered as steroid free (0mg).

If patients use more than 2 oral steroids, total dose per day will be used.

1.7.1.2 Statistical hypothesis, model, and method of analysis

For ACR response, a frequency table with the number and percentage of patients achieving a minimum adapted ACR pediatric 30 criteria at Week 8 will be provided.

For corticosteroid tapering, a frequency table with the number and percentage of patients able to taper oral steroids successfully at Week 28 will be provided.

With a small number of patients in this study, the efficacy results will be presented in a descriptive manner. Neither a statistical model nor a statistical hypothesis is defined.

1.7.1.3 Handling of missing values/discontinuations in efficacy analyses

For the analysis of adapted ACR pediatric 30/50/70/90/100 criteria at Week 8, missing response will be imputed with non-responder regardless of the reason for missing data (non-responder imputation). This imputation method will be also applied to the analyses of adapted ACR pediatric 30/50/70/90/100 criteria by visit up to Week 8. After Week 8, no imputation will be applied.

For the analysis of corticosteroid tapering at Week 28, missing Week 28 value will be imputed with the last available corticosteroid data from Week 8 visit to Week 28 visit, i.e. the last observation carried forward (LOCF) approach will be applied. If patients early discontinued the study before Week 8, they will be considered corticosteroid tapering failures. After Week 28, no imputation will be applied.

For the other efficacy analyses, missing values will not be imputed. The percentage will be calculated based on the number of patients with an assessment at the visit.

1.7.1.4 Supportive analyses

For corticosteroid tapering, the primary analysis will be repeated for patients completed Week 8 visit and patients with prednisone equivalent dose > 0.2 mg/kg/day at baseline.

Dose level at Week 28 based on the definition of successful tapering will be summarized by dose level at baseline.

1.7.2 Analysis of secondary variables

All efficacy endpoints will be summarized using the FAS. The variables derived by [redacted] will be used in the analysis.

Adapted ACR pediatric criteria

Patients will be classified into the following categories to characterize their magnitude of efficacy response: Non-Responder (< minimum adapted ACR Pediatric30), achieved minimum adapted ACR Pediatric 30, achieved minimum adapted ACR Pediatric 50, achieved minimum adapted ACR Pediatric 70, achieved minimum adapted ACR Pediatric 90, and achieved minimum adapted ACR Pediatric 100.

A frequency table with the number and percentage of patients in each category will be presented by visit.

Components of the adapted ACR pediatric criteria

For the following ACR individual components, summary statistics for the observed values and the change/percent change from baseline will be provided by visit.

- Physician's Global Assessment of disease activity on a 0-100 mm VAS from 0 mm = no disease activity to 100 mm = very severe disease activity.
- Parent's or patient's (if appropriate in age) Global Assessment of Patient's overall well-being on a 0-100 mm VAS from 0 mm= very well to 100 mm= very poor in the CHAQ©.
- Functional ability: Childhood Health Assessment Questionnaire (CHAQ©)
- Number of joints with active arthritis using the ACR definition
- Number of joints with limitation of motion
- Standardized CRP (mg/ L)

For absence of intermittent fever, a frequency table with the number and percentage of patients in each category (absent or present) will be presented by visit.

ACR pediatric criteria 50/70 and CRP criteria

For the following combination criteria of ACR and standardized CRP, a frequency table with the number and percentage of patients in each category (absent or present) will be presented by visit.

- ACR 50 and normal CRP (< 10 mg/L)
- ACR 70 and normal CRP (< 10 mg/L)
- ACR 50 and elevated CRP (≥ 10 mg/L)
- ACR 70 and elevated CRP (≥ 10 mg/L)

Flare

Flare will be defined by at least 1 of the following:

1. Reappearance of SJIA-related (e.g. not due to infection) fever (>38°C) lasting for at least 2 consecutive days AND/OR

2. Flare according to the JIA pediatric criteria for flare (all criteria must be met):
    - ≥ 30% worsening in at least 3 of the 6 response variables and
    - ≥ 30% improvement in at not more than 1 of the 6 response variables
        - if the Physician or Parent Global Assessment is one of the 3 response variables used to define flare, worsening of ≥ 20 mm must be present,
        - if the number of active joints or joints with limitation of motion is one of the 3 response variables used to define flare, worsening in ≥ 2 joints must be present
        - if CRP is used to define flare, CRP must be > 30 mg/L

A frequency table with the number and percentage of patients who had flare will be presented by the specified time intervals (≤ Day 3, >Day 3 ≤Week 2, >Week 2 ≤Week 4, etc.).

Inactive Disease

Inactive disease will be defined in two ways.

1. It is defined as meeting all of the following
    - No joints with active arthritis;
    - No fever (body temperature ≤ 38°C);
    - No rheumatoid rash, serositis, splenomegaly, hepatomegaly or generalized lymphadenopathy attributable to JIA;
    - Normal CRP;
    - Physician's Global Assessment of disease activity indicating no disease activity ≤ 10mm.
2. Duration of morning stiffness ≤15 minutes will be added to the first definition.

A frequency table with the number and percentage of patients achieving inactive disease (with and without duration of morning stiffness) will be presented by visit.

Parent's or patient's assessment of pain (0-100 mm VAS from CHAQ©)

Summary statistics for the observed values and the change/percent change from baseline will be provided by visit.

Oral steroid tapering over time from Week 8

By visit summarizes of the oral steroid tapering will be provided from Week 12 by 4 weeks up to Week 48 and by 12 weeks after Week 48 at the same assessment visits as ACR responses.

The number and percentage of patients who were able to taper corticosteroids successfully over time will be provided. The oral steroid dose at each assessment visit will be the measurement at one day before the assessment visit and the dose per weight will be calculated using the last available weight on or before the measurement. Successful oral steroid tapering will be derived using the same definition of the primary variable.

In addition to the primary efficacy variable, patients will be classified into three categories: steroid free, reached a steroid dose >0 - ≤ 0.2 mg/kg, or did not reach a steroid dose ≤ 0.2 mg/kg (>0.2 mg/kg). The number and percentage of patients in each category will be provided over time.

Summary statistics for oral steroid (prednisone equivalent dose) and the change/percent change from baseline over time will be provided.

Health-related Quality of Life

Changes in health-related quality of life will be measured using the CHAQ©.

Summary statistics for the absolute values and the changes from baseline of the CHAQ© total score (Functional ability score, which will be summarized as one component of ACR pediatric criteria) and 8 domain scores (Dressing and personal care, Getting up, Eating, Walking, Hygiene, Reach, Grip, Activities, 0-3 range for each) will be provided at Week 8, Week 28, Week 48 and EOS for the FAS.

Patients will be categorized as having an improvement in functional ability score (decrease ≥ 0.19) from baseline; or worsening (increase ≥0.13) from baseline; or neither an improvement nor a worsening. A frequency table with the number and percentage of patients in each category will be provided by visit for the FAS.

[redacted]

1.8 PK, PD [redacted]

All patients who have evaluable PK and PD measurements in the FAS will be included in the data analysis.

1.8.1 Pharmacokinetic variables

Canakinumab concentrations will be summarized by means of arithmetic and geometric mean, median, standard deviation, minimum and maximum, coefficient of variation for arithmetic and geometric mean, the number of non-missing data points and the number of data points greater than zero. All information collected will be listed.

1.8.2 Pharmacodynamics

Total Interleukin-1 beta (IL-1β) will be summarized by means of arithmetic and geometric mean, median, standard deviation, minimum and maximum, coefficient of variation for

arithmetic and geometric mean, the number of non-missing data points and the number of data points greater than zero. All information collected will be listed.

1.9 Safety evaluation

1.9.1 Adverse events

All Safety endpoints will be summarized using the Safety set.

Adverse events

Adverse events (AEs) will be coded using the MedDRA dictionary that provides the primary system organ class (SOC) and preferred term (PT) information.

Treatment emergent AEs (events started after the first dose of study treatment) will be summarized by presenting, the number and percentage of patients having any adverse event, having any adverse event in each primary SOC and having each individual adverse event based on the PT. The following summary tables will be provided.

- All treatment emergent AEs regardless of study drug relationship by SOC and PT
- All treatment emergent AEs regardless of study drug relationship by maximum severity, SOC and PT
- All treatment emergent AEs regardless of study drug relationship, leading to study drug discontinuation, by SOC and PT
- All treatment emergent AEs regardless of study drug relationship, requiring concomitant medication or non-drug therapy, by SOC and PT
- Death regardless of study drug relationship by SOC and PT
- Treatment emergent serious AEs regardless of study drug relationship by SOC and PT
- Treatment emergent AEs related to study drug treatment by SOC and PT
- Treatment emergent serious AEs related to study drug treatment by SOC and PT

Treatment emergent AEs will also be summarized by SMQ.

Exposure adjusted event rate (per 100 patient-years) of treatment emergent AEs will be summarized by SOC and PT. The event rate (ER) per 100 patient-years will be calculated as

ER = 100 × (total number of occurrence of events/ total patient-years),

where total patient-years is the sum of all patient's exposure times, i.e. duration of exposure from the day of the first dose of study treatment to the day of the last study visit, mentioned in Section 1.5.

To support the registration dossier, treatment emergent AEs will also be summarized by onset period. The following intervals will be used:

0-<4 weeks (1-<28 days)

≥4-<12 weeks (≥28-<84 days)

≥12-<24 weeks (≥84-<168 days)

≥24-<36 weeks (≥168-<252 days)

≥36-<48 weeks (≥252-<336 days)

≥48 weeks (≥336 days).

Treatment emergent AEs will be summarized by SOC and PT and by the following subgroups:

Baseline age: <4, ≥4-<6, ≥6-<12, ≥12-<20 years

Prior use of Tocilizumab: Yes, No

Sex: Male, Female

Weight group: ≤25, >25 ≤50, >50 ≤75, >75 kg

All other information collected on eCRF will be listed as appropriate. For AEs reported prior to the first dose of study treatment (in screening period), only the patient listings will be provided.

Potential and identified risk analysis

For potential and identified risks, the comprehensive search will be performed for all treatment emergent AEs, based on the latest Case Retrieval Strategy.

The number and percentage of patients having the events will be provided. Listings will be provided presenting which patients experienced which risk.

Requirements of ClinicalTrials.gov

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the Safety set.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

These tables will be provided at the final analysis.

1.9.2 Laboratory evaluations

Laboratory parameters will be summarized by presenting descriptive statistics for hematology and biochemistry. The absolute values and change from baseline will be summarized by visit presenting mean, standard deviation, median, minimum, maximum and number of patients with non-missing data. Change from baseline will be summarized for patients with both baseline and post baseline values.

Shift tables of baseline to the worst post baseline value and to the last post baseline value based on normal ranges will be provided for hematology and biochemistry.

Incidence rates of notable abnormalities newly occurred after baseline (see Section 2.3) will be presented.

To support the registration dossier, box plots will be provided for the following key laboratory test by visit. These figures will be presented only for a 28 week analysis.

Hematology: Absolute neutrophils, Platelet count, WBC, Hemoglobin

Biochemistry: ALT, AST, Creatinine clearance, Total bilirubin, ALP

All information collected will be listed by patient and abnormal values will be flagged.

1.9.3 Vital signs

Vital signs will be summarized by presenting descriptive statistics for the absolute values and changes from baseline. Change from baseline will be summarized for patients with both baseline and post baseline values.

Incidence rates of notable abnormalities newly occurred after baseline (see Section 2.3) will be presented.

All information collected will be listed by patient and abnormal values will be flagged.

1.9.4 ECG

ECG measurements will be summarized by presenting descriptive statistics for the absolute values and changes from baseline. Change from baseline will be summarized for patients with both baseline and post baseline values.

All information collected will be listed by patient.

1.9.5 Special assessments

For the special assessments like serositis, splenomegaly, hepatomegaly, lymphadenopathy, sonography of spleen and liver, the overall interpretation (normal, clinically insignificant abnormality, clinically significant abnormality) will be summarized descriptively by shift tables. Further specified clinically significant abnormalities will be listed.

1.9.6 Tolerability

Local injection site tolerability will be assessed by injection site reaction adverse events (separately from the adverse event page). Each patient will be classified into one of the following four categories (based on AE ATC grade):

1. No local injection site reaction AEs at any time in the trial.
2. A mild local injection site reaction (grade 1) AE reported on at least one occasion but no moderate or severe/potentially life threatening local injection site reaction AEs reported.
3. A moderate local injection site reaction (grade 2) AE reported on at least one occasion but no severe/potentially life threatening local injection site reaction AE reported.
4. A severe (grade 3) or potentially life threatening (grade 4) local injection site reaction AE observed on at least one occasion.

The number and percentage of patients in each category will be presented.

1.9.7 Immunogenicity

A listing will be presented for patients who develop immunogenicity for the safety set.

1.9.8 TB risk assessment

A listing will be presented for patients who have TB risk assessments for the safety set.

1.9.9 Pregnancy test

A listing will be presented for female patients who have assessments of urine pregnancy test. Serum HCG results will be listed in the regular laboratory listing.

1.9.10 Liver safety data

Summary tables of liver laboratory values or adverse events will be provided as a part of general laboratory tables or AE tables. A listing will be presented for patients who have liver events for the safety set.

1.9.11 Adjudication committee data

Three independent adjudication committees are planned: MAS, Infections, and Malignancies. The data reported by the adjudication committees will be listed.

1.10 Interim analyses

Two cut-off analyses will be performed on the efficacy and safety data during the study:

One will be at week 28, to support the registration dossier and the other will be at week 48 to supplement the dossier with long-term safety data.

At the cut-off analyses, all efficacy and safety data collected up to 28 week or 48 week visit will be reported. For patients who early discontinued, the EOS visit will be remapped using the pre-defined time window before the data cut-off. When the data up to the specific timepoints cannot be extracted (e.g. PDs related to unscheduled visits), all data available at data base lock will be reported.

1.11 Determination of sample size

No statistical sample size calculation was performed.

2 Clinical Study Report - Appendix 16.1.9 Documentation of statistical methods

2.1 Calculation of prednisone equivalent dose (mg/kg/day) of oral steroids

Prednisone equivalent dose (mg/kg/day) of oral steroids will be calculated using the following conversion factors.

Table 2-1 Conversion factors for steroid medications

Medication	Conversion factor
Betamethasone	0.12
Hydrocortisone	4
Cortisone	5
Deflazacort	1.2
Dexamethasone	0.15
Methylprednisolone	0.8
Prednisolone	1
Triamcinolone	0.8
Prednisone	1

2.2 Scoring of the CHAQ©

The following coding was used for the 8 categories of the outcome dimension:

- Without ANY Difficulty = 0
- With SOME Difficulty = 1
- With MUCH Difficulty = 2
- UNABLE to do = 3

Within each of the 8 categories only the item indicating the most severe impairment will contribute to the category score. If the patient required the use of aids, devices, or help from another to accomplish any of the activities in an associated category, then the score for that category will be assigned a value of 2, unless the score is already 3 (i.e. the scores of 0 or 1 will be increased to 2).

From the scores for each category, a Standard Disability Index (SDI) will be computed by summing up the computed scores for each category and dividing by the number of categories answered. The SDI will not be computed if the patient did not have the scores for at least 6 categories. This SDI is the CHAQ score, which will be used in the statistical analyses of this instrument. The range for this score will be (0, 3).

The 'Other' option will be excluded in the calculation of the CHAQ score.

2.3 Clinically notable laboratory values and vital signs

Laboratory Criteria

The following criteria will be used for newly occurring notable laboratory abnormalities. These criteria are based on the clinically notable laboratory values described in the protocol and the BIOS FEN liver Safety guidance.

Biochemistry

- Alanine transaminase (ALT)(SGPT):
  - > Upper Limit of Normal (ULN)
  - >3 x ULN
  - >5 x ULN
  - >8 x ULN
  - >10 x ULN
  - >20 x ULN
- Aspartate transaminase (AST) (SGOT):
  - >ULN
  - >3 x ULN
  - >5 x ULN
  - >8 x ULN
  - >10 x ULN
  - >20 x ULN
- Total Bilirubin (TBL)
  - >ULN,
  - >1.5xULN,
  - > 2xULN
- ALP
  - >ULN
  - >1.5xULN,
  - >2xULN,
  - >3x ULN
  - >5xULN
- ALT or AST >3x-, 5x-, 8x-, 10x-, 20x ULN
- ALT and/or AST >3x-, 5x-, 10x ULN accompanied by TBL >1.5x-, 2xULN
- ALT or AST >3x ULN and TBL >2x ULN and ALP ≤ 2 x ULN.
- ALP >3x-, 5x ULN and TBL >2x ULN

- Gamma-Glutamyltransferase (GGT):
  - >ULN
  - >3 x ULN
  - >5 x ULN
- Creatinine (serum): ≥1.5 x ULN
- Creatinine clearance (Schwartz formula§): ≥ 25% decrease from baseline, ≥3 months in duration *
- Protein urine dipstick:
  New protein ≥1+, ≥3 months in duration
- Creatinine clearance (Schwartz formula§): ≥ 25% decrease from baseline, ≥3 months in duration* in combination with protein urine dipstick resulting in new protein ≥1+, ≥3 months in duration *
- Total Cholesterol: ≥1.5xULN
- Triglycerides: ≥5.7 mmol/L.

§Schwartz formula- Creatinine clearance (mL/min/1.73 m^2) was derived using the following formula 0.413 x length (cm) / (serum creatinine (mg/dl) (Schwartz et al. 2009).

* The notable laboratory abnormalities will be assessed for each assessment and presented in the table. The duration will be picked up manually.

For creatinine clearance only, baseline value for the decrease from baseline criterion will be calculated as the average of all values prior to the first dose (i.e. screening and baseline values).

Hematology

- Hemoglobin:
  ≥ 20 g/L decrease from baseline,
  or < 85 g/L for < 16 years of age
  < 100 g/L for ≥ 16 years of age
- Criteria based on CTC grades for hemoglobin:
  Grade 1: <LLN – 100 g/L
  Grade 2: <100 – 80 g/L
  Grade 3: <80 – 65 g/L
  Grade 4: <65 g/L
- Absolute neutrophils:
  Grade 1: <LLN – 1.5 x 10E9/L
  Grade 2: <1.5 – 1.0 x 10E9/L
  Grade 3: <1.0 – 0.5 x 10E9/L
  Grade 4: <0.5 x 10E9/L
- Criteria based on CTC grades for platelet count:

Grade 1: <LLN – 75.0 x 10E9/L
Grade 2: <75.0 – 50.0 x 10E9/L
Grade 3: <50.0 – 25.0 x 10E9/L
Grade 4: <25.0 x 10E9/L

- Criteria based on CTC grades for WBC:
  G1:<LLN – 3.0 x10E9/L
  G2:<3.0 – 2.0 x10E9/L
  G3:<2.0 – 1.0 x10E9/L
  G4: <1.0 x10E9/L
- Absolute Lymphocytes: < LLN
- Absolute Eosinophils:
  ≥ 1.1 x ULN
  ≥0.45 x 10E9/L

Vital Signs

The following criteria will be used.

Note: The age is the age at the time of the visit.

Systolic blood pressure (mmHg):

- High: >ULN and Increased >20 in change from baseline
- Low: <LLN and Decreased >20 in change from baseline
  Reference Ranges:
  - Age 1-5 : LLN=100, ULN=115
  - Age 6-12 : LLN=110, ULN=125
  - Age 13-19: LLN=120, ULN=135

Diastolic blood pressure (mmHg):

- High: >ULN and Increased >20 in change from baseline
- Low: <LLN and Decreased >20 in change from baseline
  Reference Ranges:
  - Age 1-5 : LLN=65, ULN=75
  - Age 6-12 : LLN=70, ULN=80
  - Age 13-19: LLN=75, ULN=85

Pulse (bpm):

- High: >ULN and Increased >20 in change from baseline
- Low: <LLN and Decreased >20 in change from baseline
  Reference Ranges:
  - Age 1-5 : LLN=80, ULN=130
  - Age 6-12 : LLN=70, ULN=115

- Age 13-19: LLN=60, ULN=100

Note: Only post-baseline values will be flagged as notable abnormalities

2.4 Normal range for hematology differential counts of leucocytes

The following normal range for hematology differential counts of leucocytes will be used. The age is the age at the time of the visit.

Table 2-2 Normal range for hematology differential counts of leucocytes

Parameter	Unit	Gender	Age	LLN	ULN
Neutrophils (absolute)	GI/L	F	=<5	1.00	9.00
			6-11	1.35	8.15
			12-17	1.65	8.15
			18=<	1.96	7.23
		M	=<5	1.35	8.65
			6-11	1.35	8.15
			12-17	1.65	8.15
			18=<	1.96	7.23
Lymphocytes (absolute)	GI/L	F	=<2	1.50	10.00
			3-5	1.50	8.00
			6-11	1.15	6.65
			12-17	0.95	5.25
			18=<	0.91	4.28
		M	=<2	1.50	10.00
			3-5	1.50	8.00
			6-11	1.15	6.65
			12-17	0.95	5.25
			18=<	0.91	4.28
Monocytes (absolute)	GI/L	F	=<5	0.50	1.10
			6-11	0.40	0.90
			12-17	0.40	0.90
			18=<	0.12	0.92
		M	=<5	0.30	1.20
			6-11	0.30	0.90
			12-17	0.40	1.30
			18=<	0.12	0.92
Eosinophils (absolute)	GI/L	F	=<5	0.00	0.20
			6-11	0.00	0.20
			12-17	0.00	0.20
			18=<	0.00	0.57
		M	=<5	0.00	0.20
			6-11	0.00	0.30

Parameter	Unit	Gender	Age	LLN	ULN
			12-17	0.00	0.30
			18=<	0.00	0.57
Basophils (absolute)	GI/L			0.00	0.20