NOVARTIS

Clinical Development

ACZ885/Canakinumab

CACZ885N2301E2

An extension study of CACZ885N2301, multi-center, open label study of canakinumab in patients with Periodic Fever Syndromes (TRAPS, HIDS, or crFMF)

Statistical Analysis Plan (SAP)

Author: Statistician, [redacted]

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Table of contents

List of abbreviations

AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Area Under the Curve
AST	Aspartate Aminotransferase
crFMF	colchicine resistant Familial Mediterranean Fever
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
HIDS	Hyper IgD Syndrome
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PGA	Physician's Global Assessment of Disease Activity
PSW	Premature Subject Withdrawal
q4w	Every 4 weeks
q8w	Every 8 weeks
SAE	Serious Adverse Event
TBL	Total Bilirubin
TD	Study Treatment Discontinuation
TRAPS	TNF-receptor Associated Periodic Syndrome
SAP	Statistical Analysis Plan

1 Introduction

This Statistical Analysis Plan (SAP) describes the plan for producing specific listings for study CACZ885N2301E2, which was planned to provide specific paients with opportunity to have access with canakinumab until approval in Japan.

The details about the study can be found in the latest version of the study protocol.

1.1 Study design

Japanese patients are allowed to enter this extension study after completion of Epoch 4 (an open-label treatment epoch) in CACZ885N2301 study. This study consists of two study epochs (Screening epoch and Extension-treatment epoch). This study will be continued until approval of Canakinumab in Japan or the termination of the development of the Canakinumab in Periodic Fever Syndromes in Japan.

In this study, all patients will receive the same dose and regimen as administered at the end of study CACZ885N2301 consisting of 1 or 2 subcutaneous injections every 4 or 8 weeks. Safety will be evaluated every 8 weeks.

1.1.1 Screening epoch (Epoch 1)

At Visit 1, patients will be assessed for eligibility for study participation after completion of Epoch 4 of the CACZ885N2301 study.

Visit 1 of this extension study and Visit 399 of the CACZ885N2301 study are conducted on the same day.

1.1.2 Extension-treatment epoch (Epoch 2)

Patients who meet entry criteria at Visit 1 will enter the extension-treatment epoch (epoch 2). Since eligible patients initiate the extension- treatment epoch on the same day of screening, their first two visits (Visit 1 and Visit 101) can be on the same day.

Patients will continue the study drug based on the final dose and regimen administered at the end of the CACZ885N2301 study. All patients will receive 1 or 2 ACZ885 subcutaneous injections every 4 or 8 weeks. Stepwise up-titration up to a dosing regimen of ACZ885 300 mg (or 4 mg/kg for patients weighing ≤ 40 kg) every 4 weeks (q4w) will be allowed. In case of re-flare [Physician's global assessment of disease activity (PGA) ≥ 2 AND CRP ≥ 30 mg/L], patients will be allowed to increase the dose as follows accordingly to the same up-titration scheme in study CACZ885N2301: If flare occurs at the last visit (V399) or visit between V309 and V399 of CACZ885N2301 study, up-titration will be allowed at visit 101.

- If patients receive ACZ885 150 mg (or 2 mg/kg for patients weighing ≤ 40 kg) every 8 weeks (q8w), they will increase the dose to ACZ885 150 mg q4w.
- If patients receive ACZ885 150 mg (or 2 mg/kg for patients weighing ≤ 40 kg) q4w, they will increase the dose to ACZ885 300 mg q4w.
- If patients receive ACZ885 300 mg (or 4 mg/kg for patients weighing ≤ 40 kg) q8w, they will increase the dose to ACZ885 300 mg q4w.

If flare occurs at the last visit (V399) it will be recorded in the CACZ885N2301 study. Safety will be evaluated every 8 weeks in the extension-treatment epoch (epoch 2). Patients receiving ACZ885 q4w or up-titrated to q4w administration, will come back every 4 weeks for unscheduled visits in addition to the scheduled visits.

For all patients, a safety follow-up visit should be conducted (e.g. by telephone) 30 days after study treatment discontinuation (TD)/ premature subject withdrawal (PSW), or 8 weeks after last injection of investigational drug, whichever is later.

1.1.3 Sample size calculation

See section 3 “Sample size calculation”.

1.1.4 Primary analysis time point

No specific time point is considered as the one for primary analysis.

1.1.5 Interim analysis

No interim analysis is planned.

1.2 Study objectives and endpoints

The primary objective of this study is to evaluate safety and tolerability of ACZ885 in this extension study.

2 Statistical methods

2.1 Data analysis general information

All analyses for this study will be performed by Novartis using SAS version 9.4 or later.

For this study, only specific listings will be produced, and there will be no statistical summary presented.

All data will be presented for each individual cohorts, TRAPS, HIDS, and crFMF.

2.1.1 General definitions

Table 2-1 General definitions

Terms	Definiton
Study treatment	The treatment by dosing the investigational drug, canakinumab.
Date of first administration of extension treatment	The first visit date that the study treatment is given *for this extension study*.
Date of last administration of study treatment	The last visit date that the study treatment is given.
Extension Day 1	Date of first administration of extension treatment
Extension Study Day	Extension Study Day is defined as (Event start date) – (Extension Day 1) + 1 for any event dated on or after Extension Day 1, or (Event start date) – (Extension Day 1) for any event dated before Extension Day 1.
Baseline	The last assessments obtained before the first dose of study treatment. This definition will be applied to percent change for creatinine clearance.

2.2 Analysis sets

The **Safety Set** will consist of all patients receiving at least one dose of study medication in the extension study.

2.2.1 Subgroup of interest

Not applicable.

2.3 Patient disposition, demographics and other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race, ethnicity, relevant medical history/ current medical condition present before signing informed consent. Where possible, diagnoses but not symptoms will be recorded.

Demographic and baseline characteristics will be listed.

Any significant prior or active medical condition at the time of signing informed consent will be also listed.

2.3.1 Patient disposition

The following listings will be presented:

- Subjects who discontinued prior to Epoch 2 on Safety Set
- Study completion during Epoch 2 on Safety Set

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Exposure to study treatment will be listed. Also, the number of doses will be listed for individual patients.

For each patient, duration of exposure will be defined as (date of last visit in study) – (date of first administration of extension treatment) + 1.

2.4.2 Prior, concomitant and post therapies

Listings will be provided to display prior/concomitant medications or therapies, and medical surgeries and procedures. Specifically, rescue medications will be listed.

Prior medications will be defined as treatments taken and stopped prior to date of first administration of study treatment. Any medication will be defined as a concomitant medication, if it is given at least once on or after date of first administration of study treatment.

Rescue medications will be defined as corticosteroids or NSAIDS provided as concomitant medications.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary variable is adverse event. Details will be discussed in section 2.8.1.

2.5.2 Statistical hypothesis, model, and method of analysis

Not applicable.

2.5.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.5.4 Supportive analyses

Not applicable.

2.6 Analysis of the key secondary objective

2.6.1 Key secondary endpoint

Not applicable.

2.6.2 Statistical hypothesis, model, and method of analysis

Not applicable.

2.6.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

Not applicable.

2.7.2 Statistical hypothesis, model, and method of analysis

Not applicable.

2.7.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.8 Safety analyses

All safety analysis will be based on Safey Set.

2.8.1 Adverse events (AEs)

A listing will be presented to display individual adverse events reported in Epoch 1 and 2.

Also, SAEs will be listed.

2.8.1.1 Adverse events of special interest / grouping of AEs

Due to very much limited number of patients, no listing will be produced to display any grouping of AE.

2.8.2 Deaths

Deaths will be listed.

2.8.3 Laboratory data

All laboratory evaluations will be conducted locally.

Laboratory evaluations will be listed by patient. Additionally, notable abnormalities will be listed. Notable criteria will be defined as listed in section 5.3.1.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Not applicable.

2.8.4.2 Vital signs

Not applicable.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

Not applicable.

2.12 Biomarkers

Not applicable.

2.13 Other Exploratory analyses

Not applicable.

2.14 Interim analysis

No interim analysis is planned.

3 Sample size calculation

Patients who completed Epoch 4 of the preceding CACZ885N2301 study in Japan will be entered into this extension study. Therefore the maximum number of patients is 10.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

Not applicable.

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

Not applicable.

5.1.3 Concomitant medication date imputation

Not applicable.

5.1.3.1 Prior therapies date imputation

Not applicable.

5.1.3.2 Post therapies date imputation

Not applicable.

5.1.3.3 Other imputations

Not applicable.

5.2 AEs coding/grading

Adverse events will be coded using MedDRA dictionary.

5.3 Laboratory parameters derivations

5.3.1 Clinically notable laboratory values

Notable laboratory abnormalities in adult patients (≥ 18 years of age)

Post-baseline values will be flagged as notable abnormalities as follows:

Biochemistry

1. ALT (SGPT): > 3 x, 5 x, 10 x, and 20 x Upper Limit of Normal (ULN) [1]
2. AST (SGOT): > 3 x, 5 x, 10 x, and 20 x ULN [1]
3. Elevation of AST and/ or ALT (> 3 x ULN) accompanied by elevated bilirubin (> 1.5 x ULN, > 2 x ULN) [1]
4. Any elevations of bilirubin; elevated total bilirubin (TBL) to > 2 x ULN [1]
5. Any elevations of ALP > 1.5 x ULN [1]
6. Gamma-Glutamyltransferase (GGT): > 3 x ULN

7. Creatinine (serum): ≥ 3 x ULN
8. Creatinine clearance (CrCl) (Cockroft-Gault formula) [2]: ≥ 25% decrease from baseline
9. Triglycerides: > 5 x ULN

Hematology

1. Hemoglobin: ≥ 20 g/L decrease from baseline or < 100 g/L
2. Platelet count [3]
   - CTC Grade 1: < Lower Limit of Normal (LLN) – 75 x 10^9/L
   - CTC Grade 2: < 75 – 50 x 10^9/L
   - CTC Grade 3: < 50 – 25 x 10^9/L
   - CTC Grade 4: < 25 x 10^9/L
3. White blood cell count [3]
   - CTC Grade 1: < LLN – 3 x 10^9/L
   - CTC Grade 2: < 3 – 2 x 10^9/L
   - CTC Grade 3: < 2 – 1 x 10^9/L
   - CTC Grade 4: < 1 x 10^9/L
4. Absolute neutrophils [3]
   - CTC Grade 1: < LLN – 1.5 x 10^9/L
   - CTC Grade 2: < 1.5 – 1 x 10^9/L
   - CTC Grade 3: < 1 – 0.5 x 10^9/L
   - CTC Grade 4: < 0.5 x $10E^9$/L
5. Absolute lymphocytes: < LLN
6. Absolute eosinophils: ≥ 2.5 x, ≥ 3 x ULN

Urinalysis

Protein urine dipstick: ≥ ++

Notable laboratory abnormalities in pediatric patients (< 18 years of age)

Post-baseline values in pediatric patients (at the time of the assessment) will be flagged as notable abnormalities as follows:

Biochemistry

1. ALT (SGPT): > 3 x, 5 x, 10 x, and 20 x Upper Limit of Normal (ULN) [1]
2. AST (SGOT): > 3 x, 5 x, 10 x, and 20 x ULN [1]
3. Elevation of AST and/ or ALT (> 3 x ULN) accompanied by elevated bilirubin (> 1.5 x ULN, > 2 x ULN) [1]
4. Any elevations of bilirubin; elevated total bilirubin (TBL) to > 2 x ULN [1]
5. Any elevations of ALP > 1.5 x ULN [1]
6. GGT: ≥ 3 x, 5 x ULN
7. Creatinine (serum): ≥ 1.5 x ULN
8. Creatinine clearance (Schwartz formula [4]): ≥ 25% decrease from baseline, ≥ 2 consecutive visits
9. Total Cholesterol: ≥ 1.5 x ULN
10. Triglycerides: ≥ 5.7 mmol/L
11. Creatinine clearance (Schwartz formula [4]): ≥ 25% decrease from baseline for ≥ 3 months in duration in combination with protein urine dipstick resulting in new protein ≥ 1+, ≥ 3 months in duration

Hematology

1. Hemoglobin: ≥ 20 g/L decrease from baseline or < 85 g/L (patients < 16 years of age) or < 100 g/L (patients ≥ 16 years of age)
2. Platelet count [3]
   - CTC Grade 1: < Lower Limit of Normal (LLN) – 75 x 10^9/L
   - CTC Grade 2: < 75 – 50 x 10^9/L
   - CTC Grade 3: < 50 – 25 x 10^9/L
   - CTC Grade 4: < 25 x 10^9/L
3. White blood cell count [3]
   - CTC Grade 1: < LLN – 3 x 10^9/L
   - CTC Grade 2: < 3 – 2 x 10^9/L
   - CTC Grade 3: < 2 – 1 x 10^9/L
   - CTC Grade 4: < 1 x 10^9/L
4. Absolute neutrophils [3]
   - CTC Grade 1: < LLN – 1.5 x 10^9/L
   - CTC Grade 2: < 1.5 – 1 x 10^9/L
   - CTC Grade 3: < 1 – 0.5 x 10^9/L
   - CTC Grade 4: < 0.5 x $10E^9$/L
5. Absolute lymphocytes: < LLN

6. Absolute Eosinophils: ≥ 1.1 x ULN, ≥ 0.45 x 10^9/L

Urinalysis

Protein urine dipstick: ≥+ for ≥ 3 months in duration

[1] Adapted from FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009)

[2] Cockroft-Gault formula (Men): CrCl (mL/min) = [((140-age (years)) x weight (kg))/(serum creatinine (µmol/L)/88.4) (mg/dL) x 72]

[2] Cockroft-Gault formula (Women): CrCl (mL/min) = [((140-age (years)) x weight (kg))/(serum creatinine (µmol/L)/88.4) (mg/dL) x 72] x 0.85

[3] Common Terminology Criteria for Adverse Events, US Department of Health and Human Services (v4.03: 14-Jun-2010)

[4] Creatinine clearance was derived using the following formula: CrCl (mL/min/1.73 m2) = [0.413 x length (cm)/(serum creatinine mg/dl)] (Schwartz et al 2009)

5.4 Statistical models

5.4.1 Primary analysis

Not applicable.

5.4.2 Key secondary analysis

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

Table 5-1 Protocol deviations that cause subject to be excluded

Deviation ID	Description of deviation	Exclusion from analysis
INCL02	No written informed consent was obtained before any asessments were performed	Excluded from all analysis
TRT01	Patient was not exposed to study medication at any visit	Excluded from analysis based on Safety Set

6 Reference

Schwartz GJ, Munoz A, Schneider MF, et al (2009) New Equations to Estimate GFR in Children with CKD. J Am Soc Nephrol; 20(3):629-37.