NOVARTIS

Clinical Development

ACZ885/ canakinumab /Ilaris®

ACZ885GFR01 / NCT02334748

A French open-label extension study of canakinumab in patients who participated in international phase III studies CACZ885G2301E1 or CACZ885G2306 in Systemic Juvenile Idiopathic Arthritis and CACZ885N2301 in Hereditary Periodic Fevers (TRAPS, HIDS, or crFMF)

Statistical Analysis Plan (SAP)

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Document type: SAP Documentation

Document status: Final *1.0*

Release date: 31-08 -2018

Number of pages: 18

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
None				
….				

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List of abbreviations

AE	Adverse event
TEAE	Treatment emergent adverse event
CRF	Case Report/Record Form
CPO	Country Pharma Organization
CRO	Contract Research Organization
CSR	Clinical Study Report
DS&E	Drug Safety and Epidemiology
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
RAP	Report and Analysis Process
SAE	Serious adverse event
SAP	Statistical Analysis Plan

Introduction

This document contains details of the statistical methods which will be used in the phase IV clinical trial CACZ885GFR01. This is an extension study to collect additional safety data (serious and non-serious adverse events) and to provide continuous Ilaris® (canakinumab) to patients in France who completed study CACZ885G2301E1, CACZ885N2301 or CACZ885G2306 until canakinumab (Ilaris®) is commercially available and reimbursed in France for these indications.

Data will be analyzed by Novartis and/or by the designated CRO and *statistical software SAS* version 9.4 according to the data analysis section 9 of the study protocol version 04 which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

Unless otherwise specified, the statistical methodologies including the analysis sets, analysis models, algorithms and conventions are following then interventional study protocol ACZ885GFR01.

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

1.1 Study design

This is an open-label (single treatment arm) extension period for patients in France who have completed the international studies CACZ885G2301E1, CACZ885N2301 or CACZ885G2306. The last visit of CACZ885G2301E1, CACZ885N2301 or CACZ885G2306 studies will be the first visit of this extension study.

Patients follow up previously included in studies:

1. CACZ885G2301E1 (SJIA): These patients will continue the same dosing regimen as at the end of CACZ885G2301E1.
2. CACZ885N2301 (HPF indications: TRAPS, HIDS or crFMF): These patients will continue the maintenance dose as determined at the open-label period/ epoch 4(i.e the lowest clinically efficacious does to maintain clinical efficacy in individual patients with a good tolerability).
3. CACZ885G2306 (SJIA indication): These patients will continue on their dosing regimen considered to constitute the lowest clinically efficacious does to maintain clinical efficacy in individual patients.

Visits will take place at scheduled administration dates, approximately every 4, 8 or 12 weeks. The safety of canakinumab (Ilaris®) will be evaluated (adverse events and serious adverse events collection). Patients will followed up according to SmPC with possible

adaptation based on investigators judgment related to specific patient medical consideration.

The study duration will depend on the date of reimbursement of canakinumab (Ilaris®) in France for the new indications and will be extended until the medication is commercially available for each indication. However, as the commercialization of the different indications may be effective at different dates, the patients will discontinue indication by indication (see section 5; end of treatment).

1.2 Study objectives and endpoints

The objective of this protocol is to collect additional safety data (serious and non-serious adverse events) and to provide continuous Ilaris® (canakinumab) treatment to patients in France who completed CACZ885G2301E1, CACZ885N2301 or CACZ885G2306 study.

The end of study is defined as premature termination or end of the study according to protocol: in the month following the availability of repaid product in France.

Visits will take place at scheduled administration date every 4, 6, 8 or 12 weeks (section 5). If no visit is performed within 12 weeks of previous injection, a control visit will be performed at week 13 +/- 7 days after the last administration in order to evaluate safety and need for the patient to continue the treatment and study.

Patients may voluatarily withdraw from study for any reason at any time. If premature withdrawal occurs, the investigator must make every effort to complete End of study visit in the CRF and to determine the primary reason for patient's premature withdrawal from the study and record this information.

2 Statistical methods

2.1 Data analysis general information

All categorical data will be presented in terms of frequencies and percentages. Summaries of continuous data will be presented in terms of mean, median, lower and upper quartile (for most variables), minimum and maximum, and the number of missing data points (for most variables) and the number of non- missing data points.

For descriptive statistics, the following number of decimal places will used: arithmetic mean, and median to 1 more decimal places than the raw data; minimum and maximum to the same number of decimal places as the raw data and SD to 2 more decimal places than the raw data. Percentages will be presented to 1 decimal place. Patient disposition, background and demographic characteristics.

2.1.1 General definitions

Study treatment: refers to: Illaris = ACZ885

Study treatment start and end date: Study treatment start date is defined as the first date of study drug is administered and recorded on the Study Medication Dosing Record in CRF page. Similarly, study drug end date is defined as the last date of study drug is administered.

Study day: Study day will be calculated as (event date – study drug start date + 1 day) for events that occurred on or after study drug start date (e.g. visit, adverse events). For events prior to study drug start date (e.g., time of diagnosis), study day will be negative and calculated as (event date – study drug start date).

Baseline and post baseline: In general, a *baseline* value refers to the last measurement made prior to administration of the first dose of study treatment or the average values taken prior to administration of the first dose of study treatment. A post-baseline value refers to a measurement taken after the first dose of study treatment.

2.2 Analysis sets

Safety Set: Consists of all patients who received at least one dose of study drug and had at least one post-treatment safety assessment in the study. The statement that a patient had no adverse event (AE) also constitutes a safety assessment.

Analysis set	Population codes that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
Safety	1	Did not provide informed consent, No treatment taken

Population code: 0=Include in everything, 1=Exclude from safety set

2.2.1 Subgroup of interest

All planned table will be repeated on following subgroup.

- Pathology: SJIA, HIDS/ MKD and FMF

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The eligible subjects in study protocol ACZ885GFR01 have to fulfill inclusion and exclusion criteria. Inclusion and exclusion information will collected in CRF ACZ885GFR01. Frequency and percentage of patients passing and failing Screening will be presented for all screened patients. Percentage will be computed using the total number of screened patients as denominator.

The total number of patients who were completed the study and discontinued the study (and/or treatment) will be presented by number and percentage along with reason of discontinuation for safety set. Patient identification number and whether they completed the study or discontinued from the study will be listed, along with date of last dose and primary reason for premature discontinuation for safety set. Separate listing of all screened failure patients will also be provided for safety set.

2.3.2 Protocol deviations

The number and percentage of patients with protocol deviations will be tabulated by category and deviation for the safety set. Protocol deviations will be listed with date and study day of occurrence, deviation code and severity code for the safety set.

The number of patients included in safety set will be tabulated for all screened patients by number and percentage. Subject exclusion from analysis sets will be listed for all patients with reasons of exclusion (i.e., both protocol and non-protocol deviation).

2.3.3 Background and demographic characteristics

Demographics data (except sex and age) and baseline characteristics are collected from the CACZ885G2301E1, CACZ885N2301 or CACZ885G2306 study. Sex and date of birth will be re-collected in the CRF. The following demographic characteristics collected in the CRF at screening will be summarized using the Safety set.

Continuous variables:

- Age (years)

Categorical variables:

- Age group (years) (≥2 - <4, ≥4 - <6, ≥6 - <12, ≥12 - <20)
- Sex (Male, Female)
- Race (Caucasian, Black, Asian, Native American, Pacific Islander, Other)

The following baseline disease characteristics will be summarized using the Safety set.

- Steroid (oral) free at baseline(Yes, No)
- Median dose of steroid
- MTX free at baseline(Yes, No)
- C-reactive protein (mg/L)

The below information will be included for (SJIA)

- Number of active joints
- Number active joints(≤ 26, >26)
- Number of joints with limitation of motion

2.3.4 Medical history and current medical condition

Medical history will be coded using the Medical Dictionary for Regulatory Activities terminology (MedDRA version 18.1 and above). History/conditions will be summarized for the safety set by primary system organ class and preferred term. Verbatim recorded history/conditions will be listed together with the coded terms, date of diagnosis/surgery and whether the problem was ongoing at start of the study ACZ885FR01.

All medical history data will be taken from the the CACZ885G2301E1, CACZ885N2301 or CACZ885G2306 study.

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

2.4.1 Study treatment / compliance

The maximal total single dose of canakinumab (ACZ885) allowed is 300 mg, which is administered as two subcutaneous 150 mg injections once every 4 weeks.

The canakinumab dose interval (i.e. every 6, 8 or 12 weeks) may also be prolonged in patients with adequate response according to the clinical response and investigators judgment.

The extent of exposure will be examined to determine the degree to which safety can be assessed for canakinumab (ACZ885). The extent of exposure to study drug will be characterized according to the duration of exposure and the number of patients exposed.

Duration of exposure to the treatment will be calculated as the number of days between the first dose date and the last dose date exposed to that treatment over the specified period in Ilaris (ACZ885GRR01) study, expressed as: Duration of exposure = ((Date of last known dose of study drug – Date of first dose of study drug) – Number of days interrupted) + 1.

The duration of exposure (in days) and the cumulative volume administered (in mL) will be summarized with descriptive statistics (n, mean, median, standard deviation, minimum, maximum, Q1, Q3) for the safety set.

The total number of doses (injections) administered, number of 2 mg/kg doses administered, number of 4 mg/kg doses administered will be summarized with number and percentage for overall, 2mg/kg and 4 mg/kg dose group for safety set. By subject listing along with dose date will be provided for safety set.

The duration of exposure (in days) and number of injection will be summarized for the safety set as

- a continuous variable with the standard descriptive statistics
- a categorical variable for number of does (injections) administered classified into 1-4, 5-8, 9-12, 13-16, 17-20, 21-24 with number and percentage for below group.
    - Number of doses (injections) administered
    - Number of 1 mg/kg q4w doses administered
    - Number of 2 mg/kg q4w doses administered
    - Number of 4 mg/kg q4w doses administered
    - Number of 2 mg/kg q8w doses administered
    - Number of 4 mg/kg q12w doses administered
    - Other dose administered
    - No dose administered
- Number of subject and percentage at baseline, reduction in dose at end of study, increase in dose at end of study and stable dose with all dose amount.

- a continuous variable total cumulative volume injected with the standard descriptive statistics.

2.4.2 Prior, concomitant and post therapies

Prior medications are those medications which were taken and stopped prior to the first dose of study drug in this study.

Concomitant medications are those medications which were taken prior to and continued after the first dose of the study drug or those medication which were given at least once between the day of first dose of study treatment and the date of the last study visit.

All prior and concomitant medications will be summarized for steroid, MTX and NSAIDS table seperataly. Medications started and stopped prior to study drug, and then taken again concomitantly will be included in both prior and concomitant summaries separately.

All prior and concomitant medication will be coded using WHO drug dictionary with most updated version. The number and percentage of patients taking concomitant medications prior to start and after start of study drug will presented by ATC class and preferred term. Separate tables showed the frequencies and percentages of patients who took Methotrexate and Oral corticosteroids medications, also by ATC class and preferred term.
All information collected will be listed by patient and visit using safety set.

2.5 Analysis of the primary objective

Not applicable

2.5.1 Primary endpoint

2.5.2 Statistical hypothesis, model, and method of analysis

2.5.3 Handling of missing values/censoring/discontinuations

2.5.4 Supportive analyses

2.6 Analysis of the key secondary objective

Not applicable

2.6.1 Key secondary endpoint

2.6.2 Statistical hypothesis, model, and method of analysis

2.6.3 Handling of missing values/censoring/discontinuations

2.7 Analysis of secondary efficacy objective(s)

Not applicable

2.7.1 Secondary endpoints

2.7.2 Statistical hypothesis, model, and method of analysis

2.7.3 Handling of missing values/censoring/discontinuations

2.8 Safety analyses

Safety measurements include, Extent of exposure and adverse events. All safety endpoints will be summarized for the safety set. All data will be used in safety analyses; however, no imputation will be carried out for missing data.

2.8.1 Adverse events (AEs)

Adverse events starting on or after the time of the first dose of study drug but not later than 7 days (30 days in the case of a SAE) after the date of last dose of study drug taken or those AE present at baseline with increased severity will be classified as a TEAE and will be included in all summaries. AEs which started and ended prior to baseline and AEs which started prior to baseline but whose severity does not change post baseline will not be included in treatment emergent adverse event. In addition, all the treatment emergent AEs will also be listed.

The by-patient listing includes, SOC/PT/Verbatim term, start date, end date, the severity of an AE, Seriousness ,whether or not an AE is related to study drug, and whether or not it is a serious AE, action taken with study drug, outcome, duration, discontinue from study. Duration will be calculated as end date – start date +1 and for ongoing last visit date – start date +1.

2.8.1.1 Adverse events of special interest / grouping of AEs

AEs by primary system organ class and preferred term

The number and percentage of patients who reported treatment emergent adverse events will be summarized for each primary system organ class and preferred term. Primary system organ classes will be sorted alphabetically and, within each primary system organ class, the preferred terms will be sorted in descending order of frequency.

If a patient reported more than one adverse event with the same preferred term, the adverse event will be counted only once at the preferred term level. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once at the system organ class level.

Treatment emergent adverse events will be presented in two parts:

- Adverse events (including infections)
- Infectious adverse events

AEs by severity

All treatment emergent adverse events will be summarized by maximum severity for each primary system organ class and preferred term. If a patient reports more than one adverse event within the same primary system organ class, only one adverse event will be counted for that patient at the highest severity level in the total row for each primary system organ class. If a patient reported more than one adverse event with the same preferred term, the highest (maximum) severity will be presented.

AEs suspected to be related to study drug

The treatment emergent adverse events suspected to be related to the study drug (according to the investigators) will be summarized by primary system organ class and preferred term. Relationship to study drug is considered as suspected for those events where "Relationship to study drug" is answered by the investigator as "Suspected".

AEs leading to permanent study drug discontinuation

Treatment emergent adverse events leading to permanent study drug discontinuation will be summarized by primary system organ class and preferred term.

Serious Adverse Event (SAE)

Number and percentage of patients with serious adverse events, regardless of study drug relationship, will be presented by primary system organ class and preferred term.

2.8.2 Deaths

All the deaths in the clinical database will be listed with the last dose date/visit, date of death and investigator-reported principal cause. Deaths occurring after the first dose of study treatment until 30 days after the date of last treatment will be summarized with numbers and percentages for safety set.

2.8.3 Laboratory data

Baseline measurements for laboratory evaluations will be taken from the last visit of the CACZ885G2301E1, CACZ885N2301 or CACZ885G2306 study.

All laboratory parameter will be listed and summarized with standard descriptive statistics.

- All lab value by laboratory test category and parameter name
  - BIOCHEM (BUN, GLUC etc)
  - HEMA (BAS,EOS etc)
  - URINE (UGLUCST, USPGR etc)

2.8.4 Other safety data

Not applicable

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

Not applicable

3 Sample size calculation

No sample size calculation was performed for this extension study which will include all eligible subjects who complete CACZ885G2301E1 or CACZ885N2301 study and meet the eligibility criteria.

4 Change to protocol specified analyses

Not applicable

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

No imputation for study drug.

5.1.2 AE date imputation

AE date imputation is based only on a comparison of the partial AE start date to the treatment start date.

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If the AE year is less than the treatment year and the AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Else if the AE year is less than the treatment year and the AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE year is greater than the treatment year and the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. Else if the AE year is greater than the treatment year and the AE month is not missing, the imputed AE start date is set to the month start point (01MONYYYY).
4. If the AE start date year value is equal to the treatment start date year value:
    a. And the AE month is missing or the AE month is equal to the treatment start month, the imputed AE start date is set to one day after treatment start.
    b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
    c. Else if the AE month is greater than the treatment start month, the imputed AE start date is set to the start month point (01MONYYYY).

Table 1-2: AE date imputation

	MON	**MON < CFM**	**MON = CFM**	**MON > CFM**
	MISSING			
YYYY MISSING	NULL	NULL	NULL	NULL
	Uncertain	Uncertain	Uncertain	Uncertain
YYYY < CFY	(D) = 01JULYYYY	(C)= 15MONYYYY	(C)= 15MONYYYY	(C)= 15MONYYYY
	Before Treatment Start	Before Treatment Start	Before Treatment Start	Before Treatment Start
YYYY = CFY	(B)= TRTSTD+1	(C)= 15MONYYYY	(A)= TRTSTD+1	(A)= 01MONYYYY
	Uncertain	Before Treatment Start	Uncertain	After Treatment Start
YYYY > CFY	(E)= 01JANYYYY	(A)= 01MONYYYY	(A)= 01MONYYYY	(A)= 01MONYYYY
	After Treatment Start	After Treatment Start	After Treatment Start	After Treatment Start
Before Treatment Start		Partial indicates date prior to Treatment Start Date		
After Treatment Start		Partial indicates date after Treatment Start Date		

Uncertain	Partial insufficient to determine relationship to Treatment Start Date
LEGEND:	
(A)	MAX(01MONYYYY,TRTSTD+1)
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

5.1.3 Concomitant medication date imputation

Concomitant medication (CMD) date imputation uses both a comparison of the partial CMD start date to the treatment start date, and the value of the CMDTYP1C flag (1, 2, or 3). Event date comparisons to treatment start date are made based on the year and month values only (any day values are ignored) in Table 1-3 below.

1. If the CMD start date year value is missing, the date will be imputed based on the CMDTYP1C flag value. If the flag value is 1 or 3, the imputed CMD start date is set to one day before the treatment start date. Else, if the flag value is missing or 2, the imputed CMD start date is set to one day after the treatment start date. (Note that for some legacy data, the CMDTYP1C variable may not exist in the data. When this happens and the CMD start date year value is missing, the imputed date value will be NULL.)
2. If the CMD start date year value is less than the treatment start date year value, the CMD started before treatment. Therefore:
    a. if the CMD year is less than the treatment year and the CMD month is missing, the imputed CMD start date is set to the mid-year point (01JulYYYY).
    b. Else if the CMD year is less than the treatment year and the CMD month is not missing, the imputed CMD start date is set to the mid-month point (15MONYYYY).

If the CMD start date year value is greater than the treatment start date year value, the CMD started after treatment. Therefore:

    a. If the CMD year is greater than the treatment year and the CMD month is missing, the imputed CMD start date is set to the year start point (01JanYYYY).
    b. Else if the CMD year is greater than the treatment year and the CMD month is not missing, the imputed CMD start date is set to the month start point (01MONYYYY).

3. If the CMD start date year value is equal to the treatment start date year value:
    a. and the CMD month is missing or the CMD month is equal to the treatment start month,
        i. If the flag value is 1 or 3, the imputed CMD start date is set to one day before the treatment start date.

ii. Else, if the flag value is missing or 2, the imputed CMD start date is set to one day after the treatment start date.

a. Else if the CMD month is less than the treatment start month, the imputed CMD start date is set to the mid-month point (15MONYYYY).

b. Else if the CMD month is greater than the treatment start month, the imputed CMD start date is set to the start month point (01MONYYYY).

Table 1-3: CMD date imputation

	MON MISSING	**MON < CFM**	**MON = CFM**	**MON > CFM**
YYYY MISSING	**(F)**	**(F)**	**(F)**	**(F)**
	Uncertain	Uncertain	Uncertain	Uncertain
YYYY < CFY	**(D)=01JULYYYY**	**(C)=15MONYY**	**(C)=15MONYY**	**(C)=15MONYY**
	Before Treatment Start	Before Treatment Start	Before Treatment Start	Before Treatment Start
YYYY = CFY	**(B)**	**(C)=15MONYY**	**(B)**	**(A)=01MONYYYY**
	Uncertain	Before Treatment Start	Uncertain	After Treatment Start
YYYY > CFY	**(E)= 01JANYYYY**	**(A)=01MONYYYY**	**(A)=01MONYYYY**	**(A)=01MONYYYY**
	After Treatment Start	After Treatment Start	After Treatment Start	After Treatment Start

Before Treatment Start	Partial indicates date prior to Treatment Start Date
After Treatment Start	Partial indicates date after Treatment Start Date
Uncertain	Partial insufficient to determine relationship to Treatment Start Date
LEGEND:	
(A)	MAX(01MONYYYY,TRTSTD+1)
(B)	IF CMDTYP1C IN (1,3) THEN TRTSTD-1 ELSE IF CMDTYP1C in(. , 2) THEN TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY
(F)	IF CMDTYP1C IN (1,3) THEN TRTSTD-1 ELSE IF CMDTYP1C in (. , 2) THEN TRTSTD+1

5.2 AEs coding/grading

The verbatim term recorded on CRF will be identified as adverse event and will be coded by primary system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 and above.

5.3 Laboratory parameters derivations

Not applicable

5.4 Statistical models

This is an open-label single arm safety trial for patients and the data will be presented in descriptive manner.

5.5 Rule of exclusion criteria of analysis sets

All protocol deviations defined at the start of the study are listed with associated population codes in below table. The list will be updated before CDBL.

Protocol Deviation ID	Protocol Deviation Description	Population code
I01	Written informed consent was not obtained before performing any assessment.	1
M01	Patient took prohibited concomitant medication	0
E01	Pregnant or nursing female patients,where pregnancy is defined as state of a female after conception and until termination of gestation,confirmed by +ve hCG laboratory test or urinary pregnancy test	0
S01	Canakinumab not administered as per protocol dosage different than 2mg/kg or 4 mg/kg	0
S02	Canakinumab not aministered per protocol schedule. Difference between the dose on consecutive visits (dd-mmm-yyyy) and (dd-mmm-yyyy) is not between 6 weeks to 8 weeks.	0
	No treatment is taken.	1

6 Reference

Clinical Study Protocol CACZ885G2301E1: An open-label extension study of canakinumab (ACZ885) in patients with Systemic Juvenile Idiopathic Arthritis (SJIA) and active systemic manifestations who participated in studies ACZ885G2301 and ACZ885G2305; and response characterization study in canakinumab treatment-naïve patients with active SJIA with and without fever