NOVARTIS

Clinical Development

CFZ533 (iscalimab)

CCFZ533B2201E1 / NCT04541589

A TWINSS extension trial to evaluate the safety and tolerability of CFZ533 (iscalimab) at two dose levels administered subcutaneously in patients with Sjögren's Syndrome

Statistical Analysis Plan (SAP)

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5-September-2024	[redacted]	Added paragraph in section 2.1.1.3	Section 2.1.1.3
	Updated Definition of exposure duration	Added paragraph in section 2.3.1	Section 2.3.1
25-September-2024	[redacted]	[redacted]	[redacted]

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List of abbreviations

ADA	Anti-drug antibody
AE	adverse event
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
ANA	Antinuclear antibody
AST	aspartate aminotransferase
ATC	Anatomical therapeutic classification
BMI	Body Mass Index
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical study report
CTCAE	Common Terminlolgy Criteria for Adverse Events
C-trough	Trough concentration
CV	coefficient of variation
DMARD	Disease modifying antirheumatic drugs
ECG	Electrocardiogram
EoP3	End of study period 3
EoS	End of study
[redacted]	[redacted]
ESSDAI	EULAR Sjögren's syndrome disease activity index
ESSPRI	EULAR Sjögren's syndrome patient reported index
EULAR	European League Against Rheumatism
[redacted]	[redacted]
FAS	Full analysis set
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
IRT	Interactive Response Technology
LLN	lower limit of normal
LLOQ	Lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
[redacted]	[redacted]
PD	Pharmacodynamic(s)
PFS	Pre-filled syringe
[redacted]	[redacted]
[redacted]	[redacted]
SAE	serious adverse event
SAF	Safety Set
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SD	standard deviation
SjS	Sjögren's Syndrome

SMQ	Standardized MedDRA Query
SSA	Sjögren's-syndrome-related antigen A
TBL	Total Bilirubin
TEAE	Treatment emergent adverse events
ULN	upper limit of normal
VAS	Visual analog scale

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis planned in section 12 of the study protocol.

This document covers the statistical and analytical plans for the analysis of all data collected up to the end of the study.

1.1 Study design

Study CCFZ533B2201E1 (TWINSS extension) is a continuation of the core study CCFZ533B2201 and is planned as a multicenter trial. This study will offer continuation of treatment for participants who have completed the core study and are deemed by the Investigator to clinically benefit from continued iscalimab therapy. The primary purpose of this 1-year extension study is to provide additional safety and tolerability information of the two doses of iscalimab (iscalimab 600 mg and 300 mg) administered via prefilled syringes (PFS).

A total of 206 participants from both Cohort 1 and Cohort 2 of the core study were enrolled. Study blinding for the extension study will be maintained until final database lock of the core study, upon which the participants and Investigators will be unblinded, making it an open-label study through Week 120 (end of study visit). All visit numbers (in weeks) used in the extension study are relative to the baseline visit of the core study CCFZ533B2201. The baseline visit for the extension study (Week 60E1) will be carried out on the same day as the Week 60 visit of the core study.

The extension study is a 48-week treatment study, with a safety follow-up period of 12 weeks (Figure 1-1). Participants who complete 48 weeks of treatment and the mandatory 12 weeks of follow-up in the core study CCFZ533B2201 are eligible to participate in the extension study. The 12 weeks of follow-up in the core study is considered mandatory to obtain PK data. The extension study will help to evaluate the sustainability of response (ESSDAI) after a year of treatment in the core study.

Upon completion of treatment Period 2 (Week 48) of the core study, Investigators will use their clinical judgment to decide if it is beneficial for participants to continue with the extension study based upon response to therapy at the end of the treatment period. All participants will be considered for participation in the extension study. A new Informed Consent must be signed before proceeding into the extension study. The participant should provide their informed consent prior to the start of the Week 60 assessments of the core study.

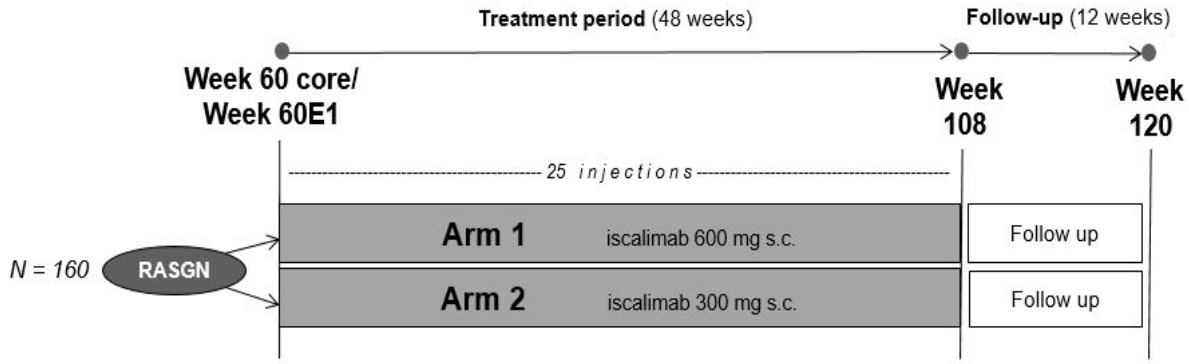
The treatment will be administered via pre-filled syringe (PFS) in the extension study. This is a change from the core study, which used s.c. injections prepared from vials. During the treatment period, 25 treatment administration visits are planned, including a weekly loading regimen. All participants enrolled in the extension study will receive a weekly loading regimen (Week 60E1, Week 61, Week 62) at the start of the treatment period followed by a s.c. maintenance regimen (600 or 300 mg s.c. every 2 weeks (Q2W)). One administration equals two s.c. injections.

To maintain extension study blinding until final database lock of the core study, an Interactive Response Technology (IRT) algorithm will be used to re-assign participants to either iscalimab

600 mg (Arm 1) or 300 mg (Arm 2) s.c. Q2W in the extension study using ESSDAI (Cohort 1 of core study) or ESSDAI and ESSPRI (Cohort 2 of core study) scores at predefined time points (Weeks 4 (or Week 0 in case of a missed visit) and 48 (or Week 40 in the case of a missed visit)) in the TWINSS core study.

Participants will be instructed in detail how to self-administer the s.c. injection using the PFS formulation. Each injection will be administered into an appropriate injection site of the body (thighs, arms, or abdomen). For the first four visits of the study (through Week 64), all injections will be performed at the study site. If a participant had good safety and tolerability, with no indication of hypersensitivity or other acute reactions from the previous doses, starting from Week 66, the participant is allowed to self-administer the study treatment at home according to the assessment schedule. The participant may continue to present at 2 week intervals to the study site for injection administrations, based on the participant's preference and the Investigator's judgment. Site staff will administer the injection to participants who are not able or unwilling to self-administer the PFS injection. The treatment period is from Week 60E1 to Week 108.

Figure 1-1 Study design



RASGN – new treatment reassignment; s.c. – subcutaneous

Treatment period		Follow-up
48 weeks		12 weeks
Loading regimen weekly	Maintenance Q2W	
2 weeks (weekly visits)	46 weeks every 2 wks (alternating monthly site visits with home administrations)	

1.2 Study objectives and endpoints

The objectives and related endpoints planned in the Clinical Study Report (CSR) are listed in Table 1-1.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the safety and tolerability of iscalimab at two dose levels (600 mg and 300 mg) in patients with SjS, who participated in the TWINSS core study, CCFZ533B2201	• Incidence of Treatment-emergent adverse events (TEAEs)/ serious adverse events (SAEs) Routine hematology and clinical chemistry laboratory test results at analysis visits up to end of study Vital signs at analysis visits up to end of study
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the pharmacokinetics (PK trough levels) and dose-exposure relationship of iscalimab	• Free iscalimab concentration in plasma during the treatment (Ctrough) and follow-up (up to end of study) periods
• To assess immunogenicity of iscalimab	• Incidence of anti-iscalimab antibodies in plasma at analysis visits up to end of study

[redacted]

2 Statistical methods

2.1 Data analysis general information

Novartis will perform the analyses for this study. Statistical software SAS version 9.4 or later will be used.

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies.

If not otherwise specified, two-sided confidence intervals will be displayed. Unless otherwise stated, the level of significance will be set to 5% (two-sided).

All safety listings will be presented by treatment sequence from extension study.

All efficacy/PRO listing will be presented by core study cohort and extension treatment group

Only descriptive statistics will be provided, no inferential statistics will be conducted.

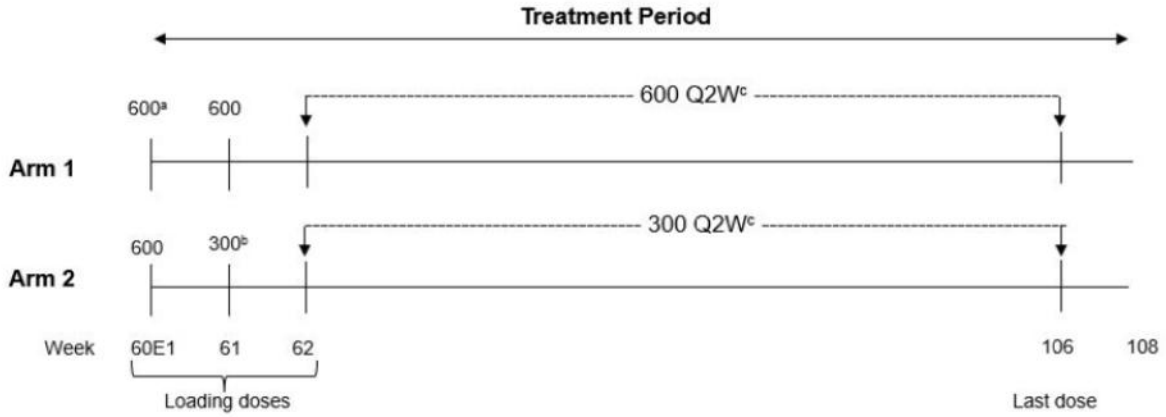
2.1.1 General definitions

2.1.1.1 Study treatment

CFZ533 (iscalimab) 600 mg or 300 mg will be administered s.c., weekly for the first 3 doses (Weeks 60E1, 61 and 62); then, from Week 64, iscalimab will be administered s.c. bi-weekly (every other week or Q2W). This is illustrated in Figure 2-1 for Arm 1 (iscalimab 600 mg maintenance regimen) and Arm 2 (iscalimab 300 mg maintenance regimen).

- For participants assigned to the iscalimab 600 mg maintenance regimen (Arm 1), the loading doses are 600 mg on Week 60E1, 61 and 62, followed by a bi-weekly maintenance regimen at 600 mg.
- For participants assigned to the iscalimab 300 mg maintenance regimen (Arm 2), the loading doses are 600 mg on Week 60E1, and 300 mg on Week 61 and Week 62, followed by a bi-weekly maintenance regimen at 300 mg.

Figure 2-1 Iscalimab doses and regimen



[a] 600 mg s.c.: 2 injections of 2 mL iscalimab (300 mg/2 mL); [b] 300 mg s.c.: 1 injection of 2 mL iscalimab (300 mg/2 mL) and 1 injection of 2 mL placebo; [c] every other week (bi-weekly) s.c. administration

2.1.1.2 Study Day 1 and other study days

The first day of administration of study treatment in extension study is defined as Study Day 1 or Day 1.

All other study days will be labeled relative to Day 1. For event dates on or after Day 1, study day for a particular event date is calculated as [Date of event] – [Date of first dose]+1, i.e., Day 2, Day 3, etc., will be one day, two days, etc., after Day 1, respectively. For the dates before Day 1, study day for an event date is calculated as [Date of event] – [Date of first dose], i.e., Day -1, Day -2, etc., will be one day, two days, etc., before Day 1, respectively. Duration of an event will be calculated as (Event end date – Event start date + 1).

The descriptor "Day 0" will not be used.

2.1.1.3 Baseline and post-baseline definitions

Baseline (Week 60E1) is defined as the last assessment (including unscheduled visits) obtained before the first dose of study treatment in extension study. All assessments obtained after first dose of study treatment at extension study are considered as post-baseline unless otherwise specified.

[redacted]

2.1.1.4 Day of last dose of study treatment

The dates will be derived based on data collected on the Dose Administration Record (DAR) page of the eCRF. The subject's exposure will be calculated considering the last dosing visit plus 14 days.

2.1.1.5 Last day of study period

The last date of study period will be collected via the CRF. The subject's study period will be calculated considering the end of study period visit (e.g., study completion visit).

2.1.1.6 Visit window

Visit-windows will be used for the summary by visit, which are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. The visit windows are shown in Table 2-1. In this table, the days are counted since the first dose of study treatment (study days) for both efficacy and safety assessments in the extension study. These visit windows apply to measurements taken at every visit. For assessments collected less often, different visit windows will be applied as detailed below.

When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the *Week 62* visit of a subject is delayed and occurs on Day 449 (Day 29 relative to the first dose date of the extension study) instead of on Day 435 (Day 15 relative to the first dose date of the extension study), it will be re-aligned to visit window *Week 64*. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

Table 2-1 Assessment windows for scheduled visits in the extension study

Study Period	Analysis Visit	Target Day	Analysis Windows					
			[redacted]	Group2	[redacted]	Group 4	[redacted]	Group7	Group 8	[redacted]
Extension	Week 60E1 (Baseline)	1		<= 1*		<= 1*		<= 1*	<= 1*	
	Week 61	8		2 – 11						
	Week 62	15		12 – 22						
	Week 64	29		23 – 43		2 - 43				
	Week 66	43								
	Week 68	57		44 – 71		44 – 71				
	Week 70	71								
	Week 72	85		72 - 99		72 – 99			2 – 127	

	Week 74	99						
	Week 76	113		100 - 127		100 – 127		
	Week 78	127						
	Week 80	141		128 - 155		128 – 155		
	Week 82	155						
	Week 84	169		156 – 183		156 – 183		128-211
	Week 86	183						
	Week 88	197		184 - 211		184 – 211		
	Week 90	211						
	Week 92	225		212 - 239		212 – 239		
	Week 94	239						
	Week 96	253		240 - 267		240 – 267		212-295
	Week 98	267						
	Week 100	281		268 - 295		268 - 295		
	Week 102	295						
	Week 104	309		296 - 323		296 - 323		
	Week 106	323						
	Week 108	337		324 – EoP3		324 – EoP3	2 – EoP 3	296 – EoP3
Post-Treatment Follow-Up	Week 112	365		(EoP3 +1)- 393		(EoP3 +1) - 393		
	Week 120	421		394-EoS		394-EoS		(EoP3 +1) - EoS

* The first dose date of the extension study is defined as Day 1.

Group 2: Vital signs,

[redacted]
Group 4: Hematology, Clinical Chemistry, Urinalysis Dipstick pregnancy, Physical Examinations, SSSD
[redacted]
Group 7: ECG
Group 8: Cryoglobulins, Hepatitis and CMV monitoring
[redacted]
Group 11: Immunology
[redacted]

The visit window will not be used for the listings.

2.1.1.7 Multiple assessments within visit windows

When there are *multiple assessments* in a particular visit window, the following rules are applied to select one value "representing" the subject in summary statistics in a visit window (See Table 2-2).

Table 2-2 Rules for selecting values for analysis within a given visit window

Timing of measurement	Type of data	Rule
Baseline	All data	The last non-missing measurement made prior to or on the date of administration of the first dose of study treatment in the extension study (the reference start date / Day 1). If a patient did not receive any dose of study treatment then the IFC date in the extension study will be used. Only date part is considered if just one assessment on Day 1. If there are multiple assessments on Day 1, following rules will apply: (a) If assessment time exists, - select the last available measurement prior to reference start date/time considering time; - if no measurement prior to reference start date/time considering time, select the earliest measurement post reference start date/time considering time . (b) If assessment time does not exist, select the available measurement from the lowest CRF visit number.
[redacted]		

Timing of measurement	Type of data	Rule
[redacted]		
Post-baseline safety	Summary visit information (e.g. lab, Vital signs, etc.)	For quantitative variables: • The measurement closest to the target will be used. In the event two measurements are taken equally apart (e.g. 1 before target date and 1 after) the first one will be used. • Cases where the same parameter is recorded more than once on the same date will be handled as follows: o If time of completion exists the earliest measurement will be used; o If time does not exist the measurement from the lowest CRF visit number will be used. For qualitative variables: the worst record is selected. It is noted that in the analyses performed, worst case is always well defined (e.g., for urine protein values "+" and "++", the worst case is defined as "++"). In the case qualitative variables are based on quantitative variables, e.g. [redacted] response, the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.
Post-baseline safety	Notable abnormalities (e.g. lab)	The most extreme measurement in the window will be used. Note this means a patient can have a notably high and notably low measurement within a window.

Analysis sets

Full Analysis Set (FAS): The FAS comprises all participants to whom study treatment for the extension study has been assigned by the re-assignment algorithm. For analysis on FAS, participants will be analyzed according to the treatment group to which they have been assigned. Only data in the extension study will be included in the analysis.

Summaries of extension data in FAS will be based on the core study cohort assignment and re-assigned treatment groups.

- Cohort 1 - CFZ533 600 mg
- Cohort 1- CFZ533 300 mg
- Cohort 2 - CFZ533 600 mg
- Cohort 2 - CFZ533 300 mg

Safety Set (SAF): The Safety Set includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the actual treatment received. The safety set will be used in the analysis of all safety variables.

The actual treatment received in a period is defined as the treatment dose level (including loading dose) that a subject was most frequently exposed to during the period. The frequency will be calculated using data collected on the Dose Administration Record (DAR). In case a subject is exposed to more than one dose level for the same number of times during a period, the actual treatment is the earliest one administered to the subject in that period.

Summaries of extension data in SAF will be based on the re-assigned treatment groups.

- CFZ533 600 mg
- CFZ533 300 mg

The PK Set (PKS) includes all subjects who received at least one dose of iscalimab treatment and have quantifiable PK measurements of iscalimab. Analysis of plasma PK, [redacted] will be based on PKS and by the iscalimab treatment dose level a subject is most frequently exposed to, including the loading dose, during the study. Only data in the extension study will be included in the analysis.

Summaries of extension data in PKS will be based on the re-assigned treatment groups.

- CFZ533 600 mg
- CFZ533 300 mg

The IM Set (IMS) includes all subjects who received at least one dose of iscalimab treatment and have quantifiable immunogenicity measurements of iscalimab. Analysis of immunogenicity data will be based on PKS and by the iscalimab treatment dose level a subject is most frequently exposed to, including the loading dose, during the study. Only data in the extension study will be included in the analysis.

Summaries of extension data in IMS will be based on the re-assigned treatment groups.

- CFZ533 600 mg
- CFZ533 300 mg

2.2 Patient disposition, demographics and other baseline characteristics

Analyses will be based on the FAS.

2.2.1 Patient disposition

The number and percentage of subjects in the FAS who completed study periods and who discontinued the study prematurely (including the reason for discontinuation) after Week 60E1 will be presented for each treatment group and all subjects.

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

2.2.2 Demographics and baseline characteristics

Demographic and other baseline data, including disease characteristics, will be summarized by treatment groups for FAS.

- Gender, age, race, ethnicity, weight, height, BMI (Body Mass Index), disease duration and smoking status.
- [redacted]

- Number (%) of patients with use of DMARDs (split by type, e.g. hydroxychloroquine, methotrexate, azathioprine, prednisone or other corticosteroid) at baseline.
- [redacted]
- Number (%) of patients with history of prior biologics treatment for SjS.

Relevant medical histories and current medical conditions at baseline will be coded according to MedDRA dictionary version that is current at time of database lock and summarized by system organ class and preferred term for each treatment group.

Unless otherwise specified, summary statistics will be presented for continuous variables for each treatment group and total. The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and total.

2.2.3 Medical history

Any condition entered on the *Relevant medical history / current medical conditions* CRF (including family history, concomitant asthma diagnosis, food allergies etc.) will be coded using the MedDRA dictionary. They will be summarized by System Organ Class (SOC) and Preferred Term (PT) of the MedDRA dictionary.

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

2.3.1 Study treatment / compliance

The analysis of study treatment data will be based on the safety set.

Duration of exposure will be defined as the time from first dose of study medication to the last dose date plus 14 days.

For subjects who completed treatment, there is a visit window of +/- 5 days for the 14 days. For subjects who discontinued treatment, the EoT disposition date is the last assessment date in treatment period. Therefore, the EoT visit was not considered ideal for the end of exposure calculation and the current exposure calculation method is proposed:

Duration of exposure (days) = (last dose date + 14 days) – first dose date +1

Duration of exposure (weeks) = duration of exposure (days) / 7

The number and percentage of patients in SAF who are exposed to study treatment for pre-specified time intervals (every two weeks) will be summarized for the overall study. Patients who receive any wrong study medications will be listed.

2.3.2 Prior, concomitant and post therapies

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system (ATC).). Prior and concomitant treatments will be

summarized by treatment group for the safety set unless otherwise specified. Concomitant treatments will be displayed for the treatment period.

Medications will be presented by ATC code and preferred term. ATC codes will be displayed in alphabetical order, and grouped by *anatomical main group* (the 1st level of the ATC codes). Tables will also show the overall number and percentage of subjects receiving at least one drug of a particular ATC code and at least one drug in a particular anatomical main group.

Prior medications are defined as drugs taken and stopped prior to the first dose of study treatment in core study. Any medication given at least once between the day of first dose of study treatment during extension period, and the last dose during extension period will be a **concomitant** medication, including those which were started pre-week 60 and continued into the extension treatment period. Any medication given at least once between the day of first dose of study treatment, and the last dose during core study period, which is stopped before end of extension study will be a **concomitant** medication only for core study.

2.4 Safety analyses

All safety endpoints (i.e., adverse events, laboratory data, and vital signs in extension study will be summarized by treatment for all subjects of the safety set.

Adverse events (AEs)

All adverse events in extension study are summarized based on treatment emergent only. The definition for "treatment emergent" is as below:

TEAE includes all events up to the last dose date plus 14 weeks (98 days) or the end of the entire study period (including the safety follow-up period), whichever occurred earlier. A listing of all adverse events during the study will be produced, with those defined as TEAE for the study treatment period with "treatment emergent" flag displayed.

The number and percentage of patients with treatment emergent adverse event (TEAE) will be summarized for the following:

- by treatment, primary system organ class and preferred term
- by treatment, primary system organ class, preferred term and maximum severity
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Summaries will also be provided for study treatment related adverse events, serious adverse events, treatment related serious adverse events, deaths, and adverse events leading to permanent discontinuation of study-drug.

If a particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

The most common adverse events reported (≥ 5% in any group for each preferred term in the table by PT or ≥ 5 % in any group for each SMQ table) will be presented in descending frequency according to its incidence in all subjects starting from the most common event.

2.4.1 Disclosure reporting

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent AEs: non-SAEs with an incidence greater than 5%, and deaths and SAEs including events suspected to be related to study treatment, will be provided by treatment, SOC and PT on the Safety Set.

If, for the 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 after all participants have completed the study.

Adverse events of special interest / grouping of AEs

Adverse events of special interest for the treatment will also be summarized. AEs of special

interest for CFZ533 treatment include the following, specified as compound-level risk factors defined in the Case Retrieval Strategy (eCRS). The search criteria in the latest eCRS corresponding the MedDRA version at the database lock will be used and reported in the CSR.

2.4.2 Deaths

Separate summary and listing will be provided for deaths.

2.4.3 Laboratory data

Only data from the central labs will be used for analysis in this section unless otherwise specified.

The summary of laboratory evaluations in extension study will be presented for two groups of laboratory tests (hematology and serum chemistry).

Descriptive summary statistics for the change from baseline to each study visit in extension study will be presented by laboratory test [redacted] and treatment group. Change

from baseline will only be summarized for subjects with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline value – extension baseline value

For laboratory test values below Lower Level of Quantification (LLQ) or above Upper Level of Quantification (ULQ) will be imputed as LLQ or ULQ value, respectively. These laboratory values will be displayed in listings using the standard unit with the reported sign ("<" or ">")."

The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in Table 2-3: hemoglobin, platelets, white blood cell count, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and others.

The number and percentage of patients with clinically notable laboratory results after baseline (Week 60E1) will also be presented by laboratory test groups and parameters listed in section 4.2. These summaries will be split into hematology and chemistry. Central and local lab results will be displayed in separate tables for clinically notable laboratory results

Table 2-3 CTCAE grades for laboratory parameters to be analyzed

CTCAE v5.00 Term	Grade 1	Grade 2	Grade 3	Grade 4
HGB decreased (Anemia)	<LLN – 100 g/L	<100 – 80 g/L	<80 g/L	Life-threatening consequences; urgent intervention indicated
Platelet count decreased	<LLN – 75.0 x10e9 /L	<75.0 - 50.0 x10e9 /L	<50.0 – 25.0 x10e9 /L	<25.0 x 10e9 /L
White blood cell decreased	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 - 1.0 x 10e9 /L	<1.0 x 10e9 /L
Neutrophil count decreased	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L
Lymphocyte count decreased	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L
Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
TBL increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
ALT increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
AST increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALP increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
INR increased	>1.2 - 1.5 x	>1.5 - 2.5	>2.5	-

Shift tables will be presented comparing baseline laboratory result (CTCAE grade) with the worst results (expressed in CTCAE grade) during the treatment phase analyzed.

2.4.4 Other safety data

2.4.4.1 ECG

A listing of all newly occurring or worsening abnormalities (based on the treatment period/study period) will be provided, as well as a by-subject listing of all quantitative ECG parameters. Notable abnormal QTc will be defined as:

QTc > 500 msec

QTc > 480 msec

QTc > 450 msec

QTc changes from baseline > 30 msec

QTc changes from baseline > 60 msec

PR > 250 msec

2.4.4.2 Vital signs

Analysis in vital sign measurement using descriptive summary statistics for the change from baseline for each post-baseline visit will be performed by vital sign and treatment group. Change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline value – extension baseline value

The number and percentage of subjects with newly occurring notable vital signs will be presented. Criteria for notable vital sign abnormalities are provided in Table 2-5 below. A listing of subjects with newly occurring notably abnormal vital signs will be provided.

Table 2-5 Criteria for notable vital sign abnormalities

Vital sign (unit)	Notable abnormalities
Systolic blood pressure (mmHg)	Either an increase of ≥ 30 that results in ≥ 180 or > 200 (mm/Hg) OR a decrease of ≥30 that results in ≤ 90 or < 75 (mm/Hg)
Diastolic blood pressure (mmHg)	Either an increase of ≥ 20 that results in ≥ 105 or > 115(mm/Hg) OR a decrease of ≥20 that results in ≤ 50 or < 40 (mm/Hg)
Pulse (bpm)	> 100 bpm or <40 bpm

2.5 Pharmacokinetic and immunogenicity endpoints

PK data will be analyzed in PK set by iscalimab treatment. To preserve blinding of treatment assignment, the PK data will be accessible to blinded personnel in the CTT only after unblinding for the primary analysis.

Trough free plasma concentration (C-trough in microg/mL) of iscalimab will be directly derived from the bioanalytical data and loaded into clinical database.

Time (days) elapsed since the first dose (Elapsed Time #1 with reference to the Dose Reference ID #1 – as defined in the Blood Log) of iscalimab will be derived (date of PK blood sampling – date of first dose of iscalimab treatment) + 1) and compared to the analysis windows defined in Table 2-1 to assign the values to analysis visits. If multiple measurements fall within the same analysis window, the algorithms outlined in Table 2-1will be used to choose the value for the visit.

Also, with reference to the Dose Reference ID #2 (as defined in the Blood Log), Elapsed Time #2, the time (days) elapsed since the specified dose, will be derived and reported as well in the merged file.

Descriptive summaries of C-trough will be presented by iscalimab treatment and analysis visit. Summary statistics will include mean (arithmetic and geometric), SD, coefficient of variation (CV) (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and the frequency (n, %) of concentrations below the LLOQ will be provided.

Trough plasma iscalimab concentrations overtime (elapsed time since first dose) for patients will be presented with spaghetti plots for each iscalimab treatment group. All concentration measurements will be plotted based on the actual day/time of assessment after the first dose date of iscalimab treatment.

A listing by cohorts, iscalimab treatment, patient number and CRF visit will also be produced.

The Ctrough,ss (steady state Ctrough) will be directly extracted from the bioanalytical data and summarized by iscalimab treatment groups for mean (arithmetic and geometric), SD, coefficient of variation (CV) (arithmetic and geometric), median, minimum and maximum.

Immunogenicity results will be listed by treatment arm, subject, and visit for subject who received at least one dose of iscalimab. Incidence of anti-drug antibody positive subjects (ADA+) may be calculated by iscalimab dose level and analysis visit defined based on time since first dose of iscalimab. Subjects' data from both cohorts will be pooled according to the iscalimab dose levels.

[redacted]

- [redacted]
- [redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

2.7 Interim analysis

There is no interim analysis planned for the study.

3 Change to protocol specified analyses

- New broader definition of TEAE than defined in the protocol

4 Appendix

4.1 Imputation rules

4.1.1 Study drug

No imputation will be made to the start date and end date of study treatment.

4.1.2 AE date imputation

Imputation for missing AE start and end dates will be defined in Programming Data set Specifications (PDS) document with details.

4.1.3 Concomitant medication date imputation

Imputation for missing start and end dates of concomitant medication will be defined in Programming Data set Specifications (PDS) document with details.

4.1.3.1 Prior therapies date imputation

Imputation will be defined in Programming Data set Specificiations (PDS) document.

4.1.3.2 Post therapies date imputation

Imputation will be defined in Programming Data set Specificiations (PDS) document.

4.1.3.3 Other imputations

Not applicable

4.2 AEs coding/grading

Adverse events will be coded according to MedDRA version 22.0 or later

Laboratory parameters derivations

Clinically notable laboratory values

Biochemistry

1. ALT (SGPT): ≥3xULN
2. AST (SGOT): ≥3xULN
3. Elevation of AST and/ or ALT (>3xULN) accompanied by elevated bilirubin (>1.5xULN, >2xULN)
4. Any elevations of bilirubin; elevated total bilirubin (TBL) to >2x ULN
5. Gamma-Glutamyltransferase (GGT): >3x ULN
6. Creatinine (serum): ≥3x ULN
7. Creatinine clearance (CrCl) (Cockroft-Gault formula): ≥25% decrease from baseline
8. [redacted]

Hematology

1. Hemoglobin: ≥20 g/L decrease from baseline or <100 g/L
2. Platelet count (per CTCAE v5.0)
   a. CTC Grade 1: <Lower Limit of Normal (LLN) – 75 x 10^9/L
   b. CTC Grade 2: <75 – 50 x 10^9/L
   c. CTC Grade 3: <50 – 25 x 10^9/L
   d. CTC Grade 4: <25x 10^9/L
3. White blood cell count (per CTCAE v5.0)
   a. CTC Grade 1: <LLN – 3 x 10^9/L
   b. CTC Grade 2: <3 – 2 x 10^9/L
   c. CTC Grade 3: <2 – 1 x 10^9/L
   d. CTC Grade 4: <1 x 10^9/L
4. Absolute neutrophils (per CTCAE v5.0)
   a. CTC Grade 1: <LLN – 1.5 x 10^9/L
   b. CTC Grade 2: <1.5 – 1 x 10^9/L
   c. CTC Grade 3: <1 – 0.5 x 10^9/L
   d. CTC Grade 4: <0.5 x $10E^9$/L
5. Absolute lymphocytes: <LLN
6. Absolute eosinophils: ≥2.5x, ≥3x ULN

4.3 Statistical models

4.3.1 Analysis of binary (and categorical) data

4.3.1.1 Summary statistics

Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies. If applicable, confidence intervals will be derived as well based on the score method including continuity correction [Newcombe (1998)]:

With z as (1-alpha/2)-quantile of the standard normal distribution (SAS: z=PROBIT(1-alpha/2), n as total number of subjects (i.e. number of subjects in the denominator), and p as estimated crude incidence (number of subjects with event / n) it is $q = 1 - p$

Then the lower limit is for $p > 0, (L = 0 \text{ for } p = 0)$,

$$L = \max\left(0, \frac{2np + z^2 - 1 - z\sqrt{z^2 - 2 - 1/n + 4p(nq + 1)}}{2(n + z^2)}\right)$$

and the upper limit is for $p < 1, (U = 1 \text{ for } p = 1)$,

$$U = \min\left(1, \frac{2np + z^2 + 1 + z\sqrt{z^2 + 2 - 1/n + 4p(nq - 1)}}{2(n + z^2)}\right).$$

For response variables the placebo adjusted response rates (risk difference) including 95% confidence interval will be derived by visit.

5 Reference

Newcombe RG (1998) Two-sided confidence intervals for the single proportion: comparison of seven methods. Statistics in Medicine; 17: 857-872.