NOVARTIS

aClinical Development

CFZ533/Iscalimab

CCFZ533B2201/NCT03905525

A 48-week, 6-arm, randomized, double-blind, placebo-controlled multicenter trial to assess the safety and efficacy of multiple CFZ533 doses administered subcutaneously in two distinct populations of patients with Sjögren's Syndrome (TWINSS)

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
09-Sep-2019	Prior to FPFV	Creation of final version	N/A - First version	NA
14-Mar-2022	Prior to PA	Revision	Table 2-2 updated to include Group 6, 7 and 8 for endpoints with different schedule assessments.	Section 2.1.1
			The sentence "The identification of systemic therapies for Sjögren's Syndrome and prohibited medications will be identified based on the list of medications in Appendix Table 5-1" was removed.	Section 2.4.2
			A typo for Emax=3.21 fixed	Section 2.6.2
			30 days after the last dose date defined for TEAE updated to be EOS.	Section 2.8.1
27-Jun-2022	Prior to Cohort 2 PA	[redacted]	• ESSDAI, PhGA, ESSPRI, [redacted] FACIT-F, PaGA, [redacted] and IDEEL symptom bother scores, changes from baselines and the least squared means (with two-sided 95% CIs) of changes estimated from MMRM models described in Section 2.5.2 and 2.6.2 will be presented by treatment sequences and visits from baseline up to the end of study. The least squared means (+/- SE) of changes from baseline will be plotted overtime by treatment sequences.	Section 2.13

- Values and changes from baseline in ESSDAI, PhGA, ESSPRI, [redacted] FACIT-F, PaGA, [redacted] and IDEEL symptom bother scores will be summarized by treatment sequence and planned visits of corresponding assessment.
- The difference to placebo in change from baseline at week 24 in ESSPRI, [redacted] FACIT-F, PaGA, [redacted] and IDEEL together with 95% confidence interval estimated by the MMRM model will be plotted versus the dose (CFZ533 [redacted], CFZ533 [redacted] and CFZ533 [redacted]. The best model mean curve estimated using MCPMod analysis will be added to this plot.
- Responder analysis: a responder status will be assessed at week 12 and 24. Responder with respect to secondary endpoints is defined as below.
  - ESSPRI: at least 1 point or 15% reduction from baseline
  - ESSPRI: value<=3 and change from baseline<-1.5

[redacted]

• FACIT-F: 6 or more points increase from baseline

- Missing responses for any reason will be treated as non-responders for the corresponding visit. The percentages of responder together with the 95% confidence interval (Clopper-Pearson method) will be presented by treatment and visit. The difference to placebo in percentage of responder together with the associated asymptotic 95% confidence interval will be presented. Each active treatment (CFZ533 [redacted], CFZ533 [redacted] and CFZ533 [redacted]) will be compared to placebo using a two-sided Fisher exact test. The corresponding p-value will be summarized. Similarly, responder analysis will be repeated when a responder in ESSDAI is defined as a value<5.
- Sankey plot for ESSDAI disease activity (mild, moderate and severe) and each ESSDAI subdomain at Baseline, Week 12 and Week 24 will be generated, as well as corresponding shift table.
- A bar chart for each of the 12 ESSDAI subdomains

			over time across treatments. • Updated visit window definition in table 2.2. • Updated cohort definition for period 2/3.	
27-October-2022	Prior to Cohort 2 PA	Added imputation rule:	ESSDAI date imputation For ESSDAI, the date recorded in CRF does not reflect the date of visit. Therefore, below are detailed steps to follow to derive the new date/time to be used for visit windows: a. Use the date/time of specimen collection of IGG lab data to impute the analysis date/time by merging ESSDAI PRO data with IGG data by subject and scheduled visit. b. If there is no IGG data for the corresponding scheduled visit, the start date/time of visit will be used. c. If start date/time of visit is not available, the original date/time of assessment from ESSDAI PRO questionnaire data will be used. However, for ESSPRI/FACIT, the assessment date/time of the questionnaire will still be used to derive the visit windows. The same imputation rule will be used if there are errors of date/time of the questionnaire.	Section 5.1.4

30 Jan 2023	Post PA2	Added specification of the MMRM model for the Secondary endpoints	The same MMRM model utilized for the primary analysis of Cohort 1 and Cohort 2 will be utilized also for the respective secondary endpoints.	Section 2.7.2
30 Jan 2023	Post PA2	Removed sensitive analysis	Have decided not to perform the sensitive analysis	Section 2.5.4.1
30 Jan 2023	Post PA2	Added details about the analysis of primary endpoint analysis for cohort 2	The factor of baseline ESSDAI strata in MMRM model was removed in Cohort 2	Section 2.5.2.2
27 March 2023	Post PA2	Added section for PRO data imputation rule	The rule of PRO data imputation are added.	Section 5.1.5
27 March 2023	Post PA2	Removed the supportive analysis section.	Based on the team discussion, the supportive analysis does not need to be included here in the SAP.	Section 2.5.4
27 March 2023	Post PA2	Updated Interim analysis section.	Added the specification for the first interim analysis.	Section 2.14
	Prior to final DBL	Corrections and to address dry run comments.	[redacted] Removed digital data analysis. Updated analysis plan for labs. Other updates according to dry run prior to final DBL.	Section 1.2, 2.13

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List of abbreviations

ACR	American College of Rheumatology
ADA	Anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
[redacted]	[redacted]
ANC	Absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical therapeutic classification
AZA	Azathioprine
BMI	Body Mass Index
[redacted]	[redacted]
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical study report
CTC	Common Toxicity Criteria
C-trough	Trough concentration
CTT	Clinical trial team
CV	coefficient of variation
DMARD	Disease modifying antirheumatic drugs
ECG	Electrocardiogram
eCRF	Electronic case report forms
EoP1	End of study period 1
EoP2	End of study period 2
EoS	End of study
[redacted]	
ESSDAI	EULAR Sjögren's syndrome disease activity index
ESSPRI	EULAR Sjögren's syndrome patient reported index
EULAR	European League Against Rheumatism
FACIT-F	Functional assessment of chronic illness therapy - fatigue
FAS	Full analysis set
FLC	Free Light Chains
FUP	Follow up
GGT	Gamma-glutamyl transferase
[redacted]	[redacted]
i.v.	intravenous
IDEEL	Impact of Dry Eye on Everyday Life
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IRT	Interactive Response Technology
LLN	lower limit of normal
LLOQ	Lower limit of quantification

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 SAP will be used in executing both the primary analyses after all patients complete the week 24 assessments and the final analysis of the study.

1.1 Study design

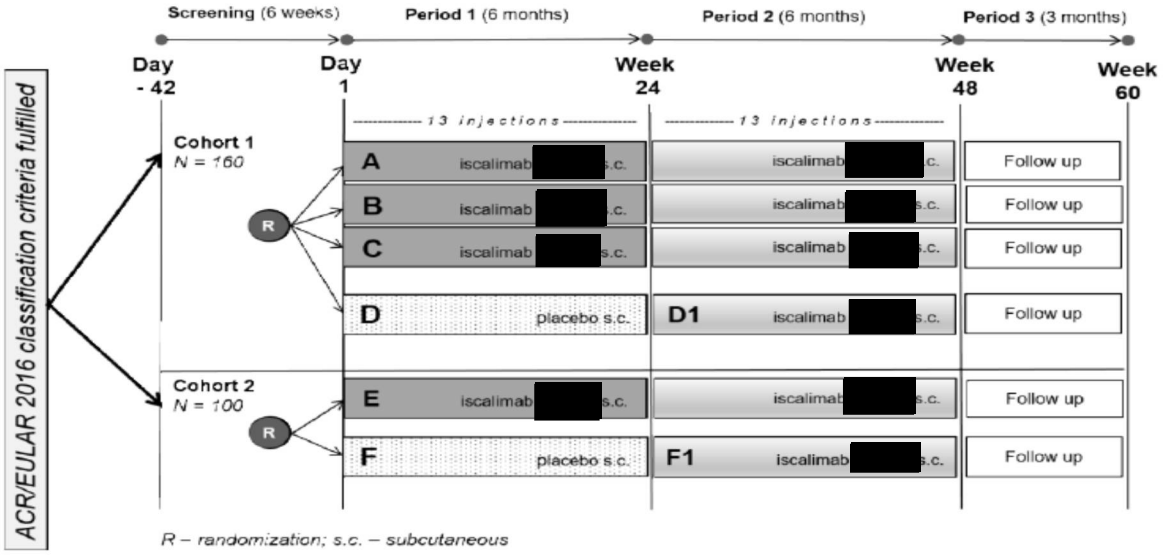
Study CFZ533B2201 (TWINSS) is a basket trial consisting of two distinct study parts termed Cohort 1 and Cohort 2. Cohort 1 is a randomized, double-blinded, placebo-controlled, parallel group, dose range finding sub-study, planned to enroll approximately 160 patients. Cohort 2 is a randomized, double-blinded, placebo-controlled proof-of-concept sub-study planned to enroll approximately 100 patients. Cohort 2 will be conducted at selected sites that have the collaboration with an ophthalmologist with current capabilities necessary to perform the ophthalmic assessments specific to the cohort.

During a 6-week screening period, all patients fulfilling the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2016 classification criteria will be assessed for all 12 ESSDAI domains.

- Patients who score ESSDAI ≥ 5 within 8 selected domains (constitutional, lymphadenopathy, glandular, articular, cutaneous, renal, hematologic and biologic) and meet additional criteria will be randomized in Cohort 1 (1:1:1:1 ratio) to one of three iscalimab arms (A, B, C) or to placebo (Arm D) with 40 patients planned for each arm.
- Patients with ESSDAI < 5 (within 8 selected domains) may be further evaluated for eligibility for the low ESSDAI (< 5) and high symptom burden (ESSPRI fatigue score ≥ 5 or ESSPRI dryness score ≥ 5) as Cohort 2. If criteria for Cohort 2 are met, patients will be randomized 1:1 to either iscalimab [redacted] (Arm E) or placebo (Arm F) with 50 patients planned for each arm.
- In both cohorts patients may continue their stable standard of care treatment (as per protocol Section 6.2.1) on top of the study treatment.

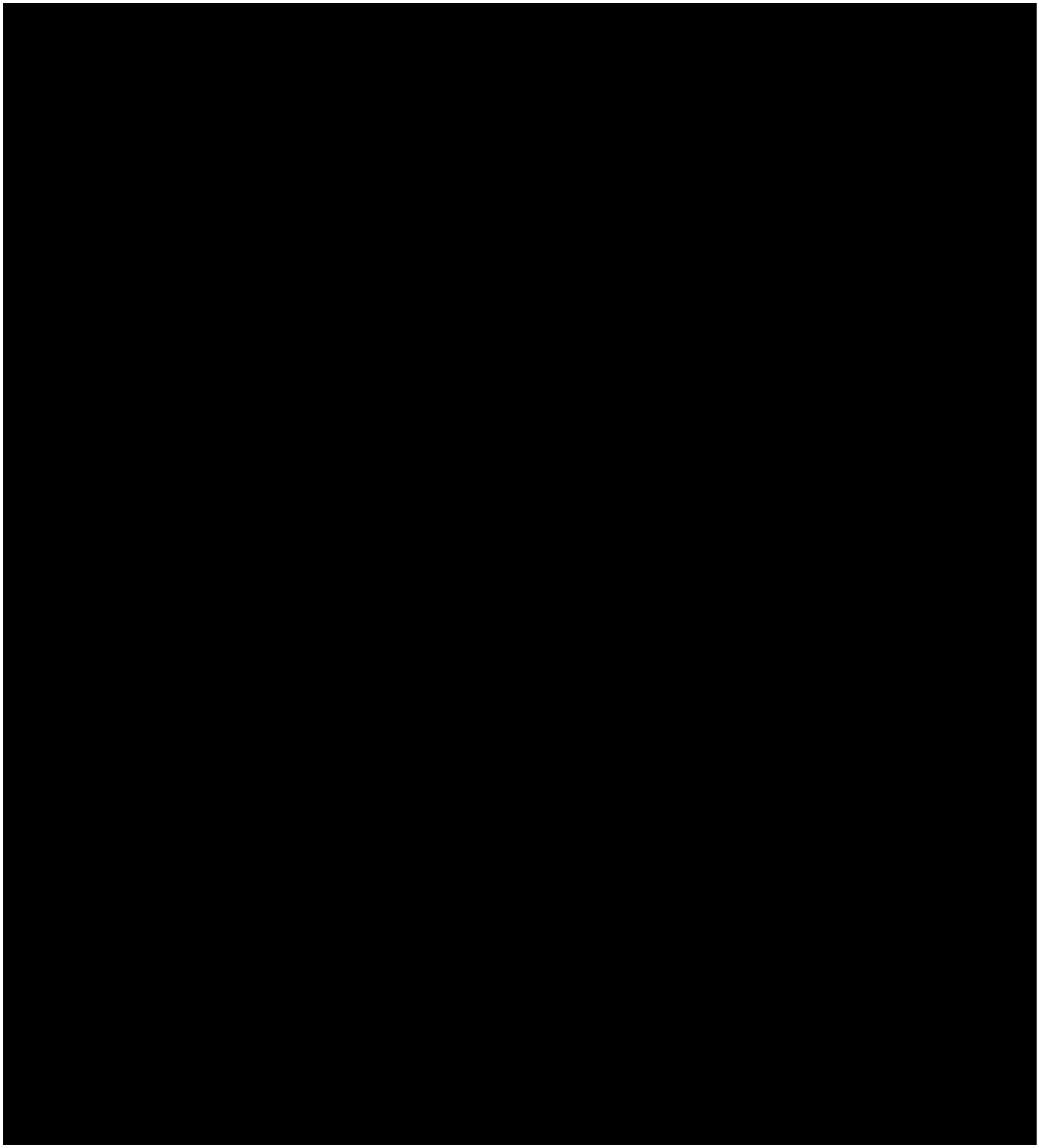
This study will consist of a 6-week screening, 2 treatment periods of 24 weeks each, and a follow-up period of 12 weeks. In Periods 1 and 2, thirteen (13) treatment administration visits are planned, including a weekly loading regimen (2 visits) at the start of each treatment period followed by Q2W dosing.

Figure 1-1 Study design



The primary analysis will occur at Week 24 including all patients and final analysis of the study will be performed after all patients have finished the study.

More details on dosing scheme during each study periods for the two cohorts are shown in Figure 1-2 and Figure 1-3.



1.2 Study objectives, endpoints and estimands

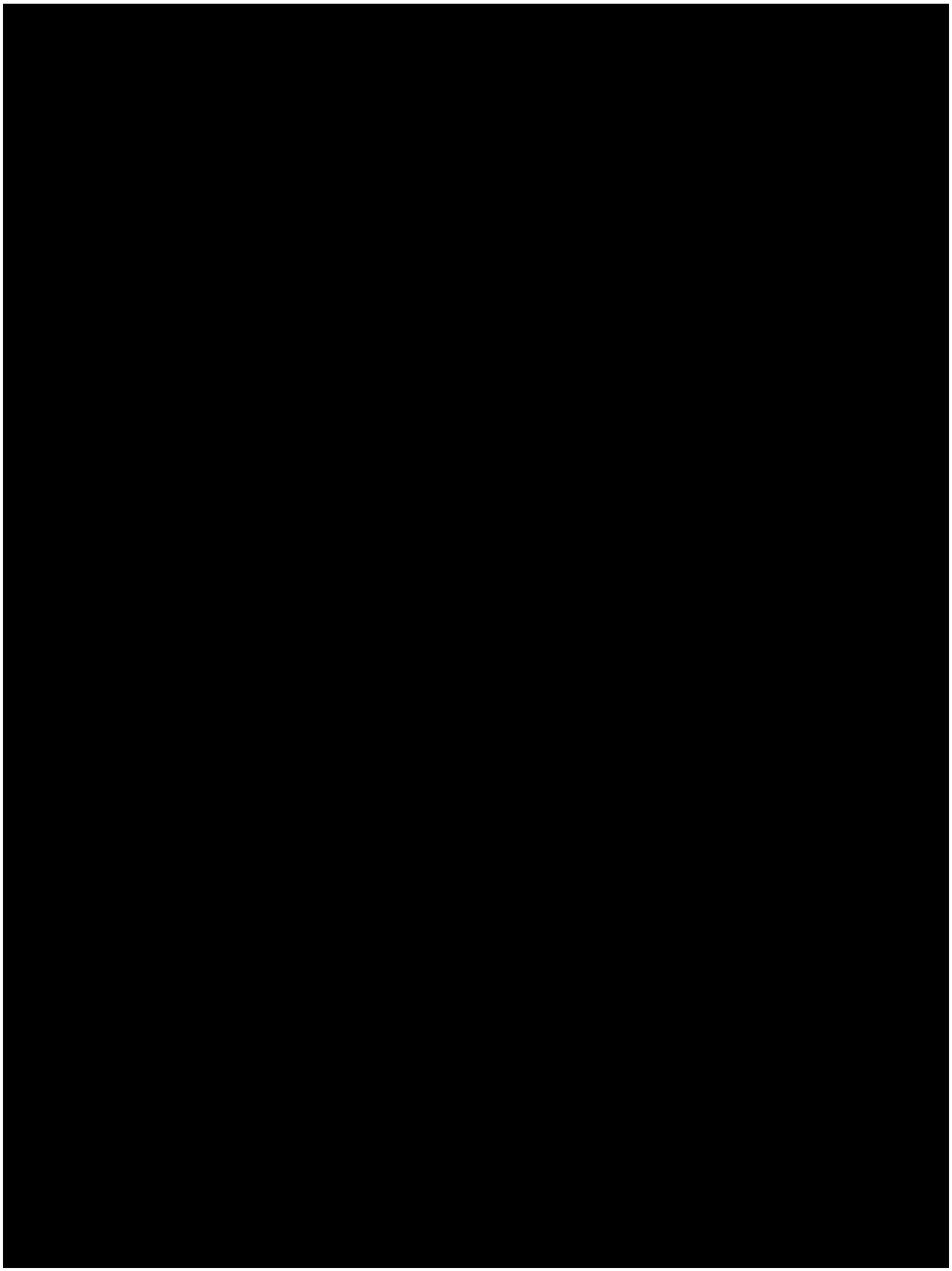
Table 1-1 Objectives and related endpoints

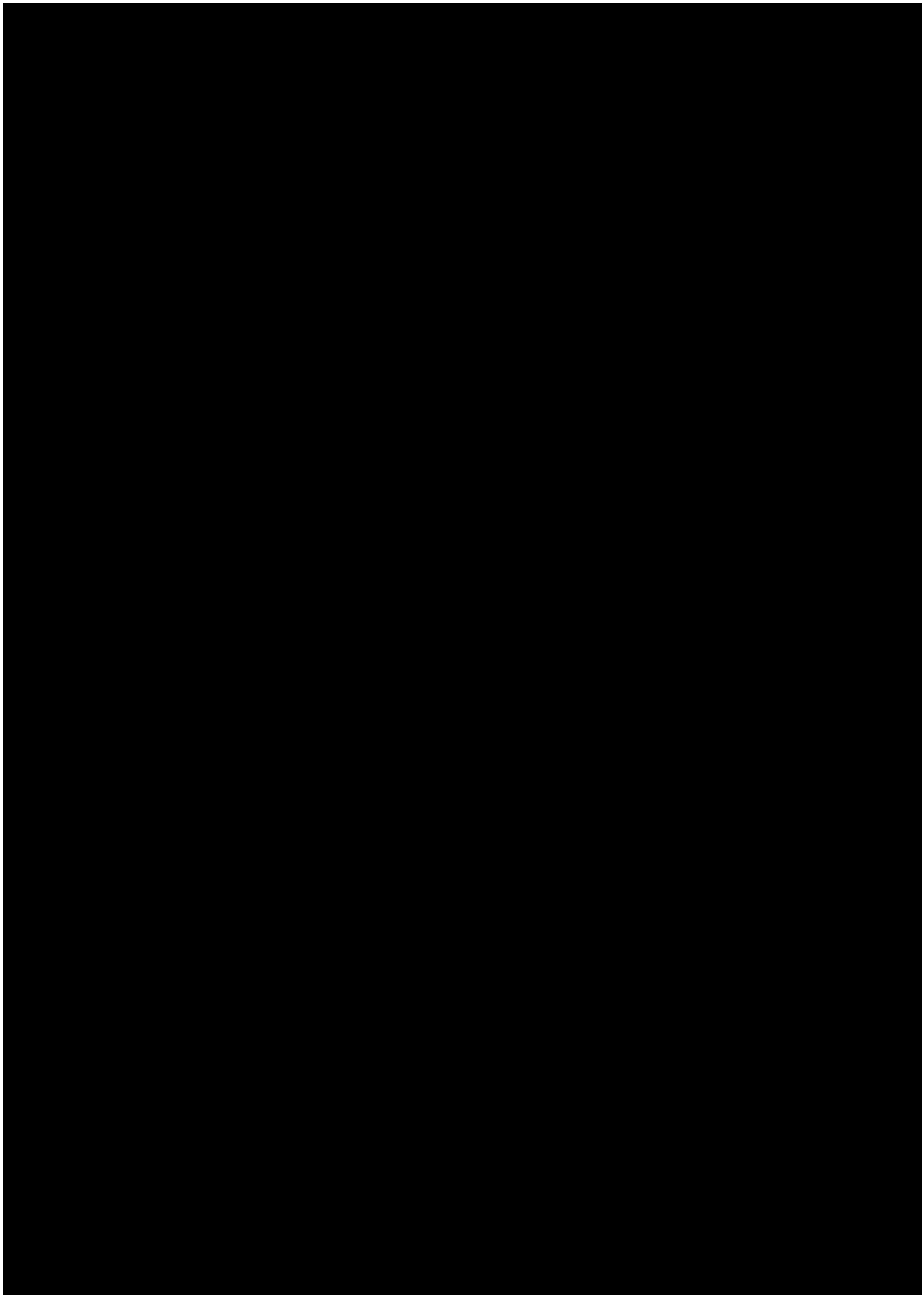
Objectives	Endpoints
Primary objectives	**Endpoints for primary objectives**

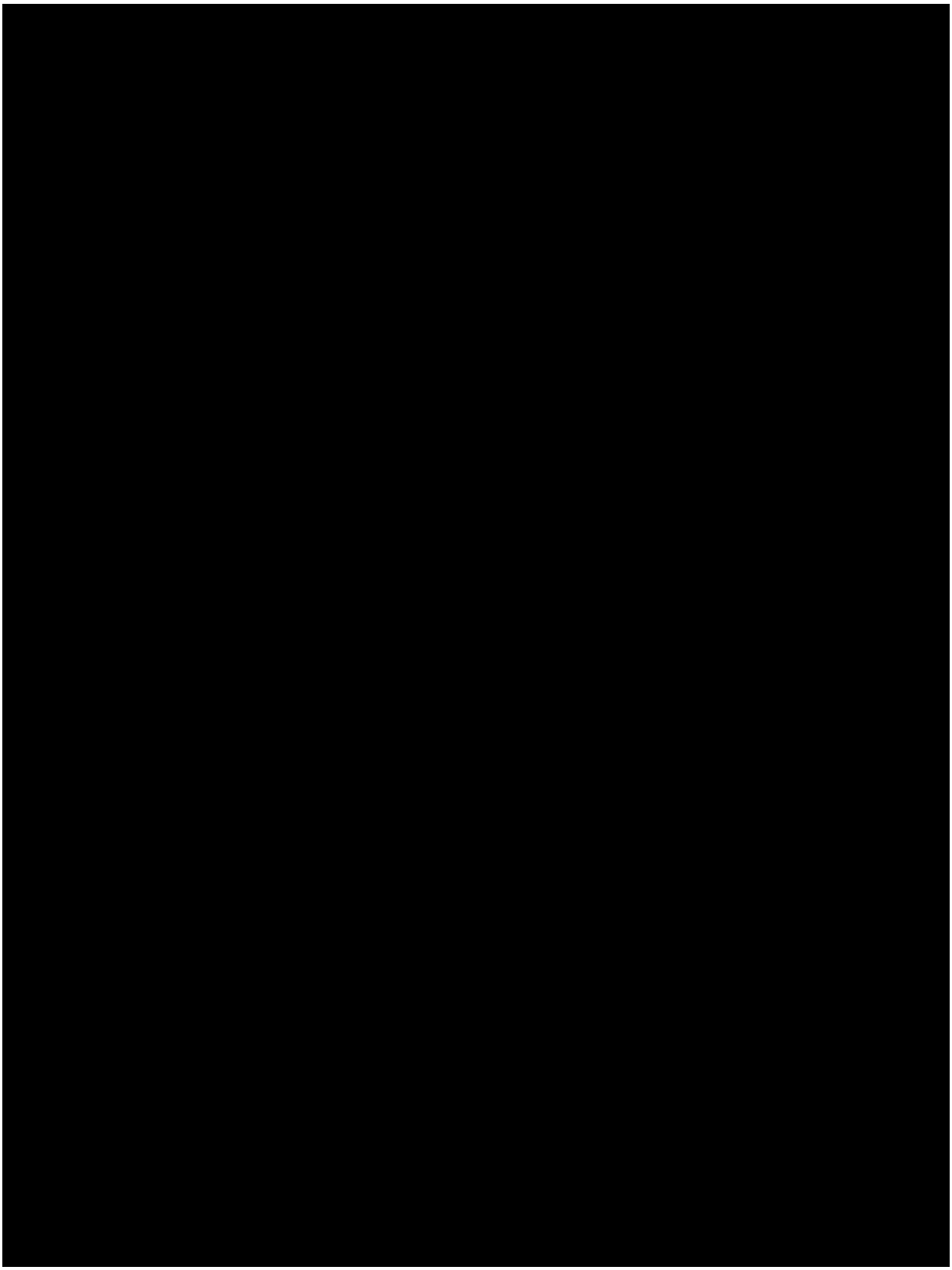
Cohort 1 To demonstrate a dose-response of CFZ533 (iscalimab) based on change in ESSDAI from baseline at Week 24	**Cohort 1** Change in ESSDAI score from baseline at Week 24 as compared to placebo
Cohort 2 To estimate the effect of CFZ533 (iscalimab) [redacted] s.c. on the change in ESSPRI at Week 24	**Cohort 2** Change in ESSPRI score from baseline at Week 24 as compared to placebo

Secondary Objectives	Endpoints for secondary objectives
Cohort 1 To demonstrate a dose response of iscalimab based on change in ESSPRI from baseline at Week 24	**Cohort 1** Change from baseline in • ESSPRI at Week 24
To estimate the effects of iscalimab based on • change in FACIT-F from baseline at Week 24 • change in physician's global assessment (PhGA) from baseline at Week 24	• FACIT-F score at Week 24 • PhGA overall disease activity scores at Week 24
To assess • the effect of iscalimab in the serum Free Light Chains (FLC) levels over time • the changes in IgG and IgM levels over time after iscalimab treatment • the effect of iscalimab on plasma CXCL-13 over time	• Serum FLC levels at analysis visit up to end of study • IgG and IgM levels at analysis visits up to end of study • Percent change from baseline in plasma CXCL-13 levels at analysis visits up to end of study
Cohort 2 To estimate the effects of iscalimab based on changes in • FACIT-F from baseline at Week 24 • physician's global assessments from baseline at Week 24 • ESSDAI from baseline at Week 24 To evaluate the efficacy of iscalimab in improving the dry eye symptoms measured by IDEEL at Week 24	**Cohort 2** Change from baseline • in FACIT-F score at Week 24 • in PhGA (VAS) at Week 24 • in ESSDAI at Week 24 Proportion of subjects with at least 12 points improvement on IDEEL dry eye symptom bother module score at Week 24 • Serum FLC levels at analysis

To assess • the effect of iscalimab in the serum FLC levels over time • the changes in IgG and IgM levels over time after iscalimab treatment • the effect of iscalimab on plasma CXCL-13 over time	visits up to end of study • IgG and IgM levels at analysis visits up to end of study • Percent change from baseline in plasma CXCL-13 levels at analysis visits up to end of study
Cohort 1 & 2 To assess	**Cohort 1 & 2**
• safety and tolerability of iscalimab	• Incidence of Treatment-emergent AEs (TEAEs) /SAEs from baseline to Week 24 • Incidence of TEAEs/SAEs from Week 24 to end of study • 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
• immunogenicity of iscalimab	• Incidence of anti-iscalimab antibodies in plasma at analysis visits up to end of study
• the pharmacokinetics 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 measure soluble CD40 in plasma	• Free or total soluble CD40 in the absence or presence of iscalimab, respectively at analysis visits up to end of study







2 Statistical methods

2.1 Data analysis general information

The primary analyses for each cohort will be conducted after all patients have finished the Week 24 visit or early discontinued from the study before Week 24.

The final analyses will be conducted at the end of study when all randomized patients have completed Week 60 or discontinued from the study earlier.

The MCP-Mod modeling in primary analysis of Cohort 1 will be implemented in R language developed by the R Foundation for Statistical Computing. The preprocessing of data (e.g. derived variables at patient level), the preparatory MMRM step and presentation of the model results from the MCP-Mod step, as well as all other efficacy and safety analyses, will be performed by Novartis statistics and statistical programming team using SAS v9.3 or later (SAS Institute, Cary NC). Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

If not otherwise specified,

- Summary statistics for continuous variables will include N, mean, standard deviation (SD), minimum, lower quartile, median, upper quartile, and maximum.
- Summary statistics for discrete variables will be presented with the number and percent of patients in each category.
- Where needed, two-sided p-values and two-sided 95% confidence intervals will be displayed.

2.1.1 General definitions

Study treatment in this document refers to the investigational drug CFZ533 (iscalimab) or placebo. Three types of study treatment labeling will be used for presenting the analysis results, depending on the specific periods or endpoints.

- "Treatment groups" or "treatment arms" refers to study treatment during Period 1 (e.g. "CFZ533 [redacted]", "CFZ533 [redacted]", "CFZ533 [redacted]" or "Placebo") and will be used for analysis of data in study Period 1, including the primary analysis, and baseline.
- "Treatment sequences" refers to study treatments during periods 1 and 2, with labels concatenated by dash (e.g. "CFZ533 [redacted] - CFZ533 [redacted]", "CFZ533 [redacted] - CFZ533[redacted] "CFZ533 [redacted] - CFZ533 [redacted]", "Placebo - CFZ53 [redacted] or "Placebo - CFZ533[redacted]) and will be used for presenting data in study period 2/3 or across the whole study.
- "Iscalimab treatment" refers to the actual iscalimab dose (excluding placebo) that a patient was most frequently exposed to during the study (e.g. "CFZ533 [redacted]", "CFZ533 [redacted] or "CFZ533 [redacted] and is used for analyzing pharmacokinetics (PK), anti-drug antibodies data and where the analysis is only meaningful if a patient was actually exposed to iscalimab.

Date of first study treatment (or first dose date) of the study or a specific period refers to the earliest date a patient is actually exposed to the study treatment (including placebo and loading dose) in the study or period. The dates will be derived based on data collected on the Dose Administration Record (DAR) page of the eCRF. The first dose date is the same for period 1 and for the study. If a patient did not receive any actual study treatment, the first dose dates of the study (period 1) and period 2 will be missing.

Date of last study treatment (or last dose date) of the study or a specific period refers to the latest date patient is exposed to the study treatment (including placebo) in the study or period. The dates will be derived based on data collected on the Dose Administration Record (DAR) page of the eCRF. The last dose date of the study would be the same as that of either Period 1 (if patient did not receive any Period 2 treatment) or Period 2 (if patient received at least one dose of study treatment for Period 2).

Study day is defined as the number of days since the Day 1 of the study. Day 1 is defined as the day of the first administration of the study treatment (defined above) or the day of randomization if a patient was randomized but never received study treatment. For dates on or after Day 1, Study day = Assessment date – Date of Day 1 + 1. For dates prior to the date of Day 1, Study day = Assessment date – Date of Day 1. The study day will be calculated for all FAS patients.

Baseline value is the last valid non-missing assessment conducted in the study prior to or on study Day 1. For example, if the scheduled baseline assessment value is missing, the screening value could be used. If date and/or time is missing for assessments, the visit number will be used to determine order of assessments. If the date of assessment is same as first dose date of the study, but time for either or both is missing for comparison, the assessment is assumed to be prior to the administration of study treatment. If not otherwise specified, the same baseline value is used for analyzing data of period 1, 2/3 or the overall study.

End of Period 1 (EoP1) of a patient is the disposition event date for study period 1. If the disposition event date is missing (e.g. lost to follow up), the date of the last visit at or before Week 24 visit will be used.

End of Period 2 (EoP2) of a patient is the disposition event date for study period 2. If the disposition event date is missing (e.g. lost to follow up), the date of the last visit at or before Week 48 visit of the patient will be used. The EoP2 date will be missing if a patient discontinued early from the study treatment at or prior to Week 24 visit.

End of study (EoS) of a patient is the date of his/her last visit or phone follow-up in the study.

Study period(s) for a patient is defined in Table 2-2 based on Day 1, EoP1, EoP2 and EoS regardless of last dose dates of study treatment.

Treatment period (TP) for a patient is defined by the actual dates of exposure to study treatment for a specific study period (e.g. TP1 or TP2).

Geographic regions to be used for descriptive summaries and inferential modeling is defined in Table 2-1.

Table 2-1 Geographic Regions

Region	Countries
1	Argentina, Chile, France, Portugal, Italy, Brazil, Columbia
2	US, UK, Canada, Australia
3	Austria, Germany, Israel, Netherlands, Sweden, Greece
4	Romania, Russia, Hungary, Turkey, Slovenia
5	Japan, South Korea

Analysis visit windows

Analyses by visits for both cohorts, including primary analysis at Week 24, will be performed based on derived analysis visits instead of the CRF visits. The data for such analyses will be mapped to analysis visits based on actual date of data collection and time windows defined in Table 2-2 for FAS/SAF or Table 2-3 for PKS (defined in Section 2.2). For example, if the scheduled Week 4 visit of a patient is delayed and occurs on Day 41 instead of on Day 29, the data collected (clinical assessment, blood sampling, etc.) at that visit will be mapped to analysis visit Week 6.

Analysis visit windows are non-overlapping and all together cover the entire study for a patient. In case that multiple assessments fall in the same analysis visit window of a parameter for a patient, the value of this analysis visit will be selected following conventions in Table 2-4. If no assessment falls into a time window for a parameter, the value at that visit will be deemed as missing unless additional imputation rules are defined in this SAP for the specific parameter.

Repeated and unscheduled visits will be mapped to analysis visits in the same way as scheduled visits for analysis purposes.

Table 2-2 Analysis visit windows for analysis based on FAS or SAF

Study Period	Analysis Visit	Target Day	Analysis Windows			[redacted]		[redacted]		[redacted]
			Group 1	Group 2	Group 3		Group 5		Group 7	
0	Baseline	1	≤ 1*	≤ 1*	≤ 1*		≤ 1*		≤ 1*	
1	Week 1	8	2-11							
	Week 2	15	12-22	2-22						
	Week 4	29	23-36	23-43	2-43				2-57	
	Week 6	43	37-50							
	Week 8	57	51-64	44-71	44-71					
	Week 10	71	65-78							

Study Period	Analysis Visit	Target Day	Analysis Windows					
			Group 1	Group 2	Group 3	[redacted]	Group 5	Group 7
	Week 12	85	79-92	72-99	72-99		2-127	58-127
	Week 14	99	93-106					
	Week 16	113	107-120	100-127	100-127			
	Week 18	127	121-134					
	Week 20	141	135-148	128-155	128-155			
	Week 22	155	149-162					
	Week 24	169	163 - EoP1	156-EoP1	156-EoP1		128-EoP1	128-EoP1
2	Week 25	176	(EoP1 +1) - 179					
	Week 26	183	180 – 190	(EoP1 +1)-190				
	Week 28	197	191 - 204	191-211	(EoP1 +1)-211			
	Week 30	211	205 – 218					
	Week 32	225	219 – 232	212-239	212-239		(EoP1 +1)-239	(EoP1 +1)-253
	Week 34	239	233 - 246					
	Week 36	253	247 – 260	240-267	240-267			
	Week 38	267	261 - 274					
	Week 40	281	275 – 288	268-295	268-295			254-309
	Week 42	295	289 - 302					
	Week 44	309	303 - 316	296-323	296-323			
	Week 46	323	317 - 330					

Study Period	Analysis Visit	Target Day	Analysis Windows						
			Group 1	Group 2	Group 3	[redacted]	Group 5	[redacted]	Group 7
	Week 48	337	331-EoP2	324-EoP2	324-EoP2		240-EoP2		310-EoP2
3	FUP 1	Max (EoP1, EoP2) +28	Days 1 – 42 after the Max (EoP1, EoP2)	Days 1 – 42 after the Max (EoP1, EoP2)	Days 1 – 42 after the Max (EoP1, EoP2)				
	FUP 2	Max (EoP1, EoP2) +56	Days 43 - 70 after the Max (EoP1, EoP2)	Days 43 - 70 after the Max (EoP1, EoP2)	Days 43 - 70 after the Max (EoP1, EoP2)				Days 1 – 70 after the Max (EoP1, EoP2)
	FUP 3	Max (EoP1, EoP2) +84	Days 71 after the Max (EoP1, EoP2) - EoS	Days 71 after the Max (EoP1, EoP2) - EoS	Days 71 after the Max (EoP1, EoP2) - EoS		Days 71 after the Max (EoP1, EoP2) - EoS		Days 71 after the Max (EoP1, EoP2) - EoS

* Study Day 1 is defined in Section 2.1.1.

Group 1: Vital signs, [redacted]

Group 2: Soluble CD40

Group 3: Routine laboratory measurements, ESSDAI, ESSPRI, FACIT-F, PhGA, PaGA, immunology

[redacted]

Group 5: [redacted] IDEEL

[redacted]

Group 7: FLC

[redacted]

Table 2-3 Analysis visit windows for analysis based on PKS

Analysis Visit	Target Day	Analysis Windows	
		Pharmacokinetics	Immunogenicity
Baseline	1	≤ 1#	≤ 1#
Week 1	8	2-11	

Analysis Visit	Target Day	Analysis Windows	
		Pharmacokinetics	Immunogenicity
Week 2	15	12-22	2-22
Week 4	29	23-36	23-43
Week 6	43	37-50	
Week 8	57	51-64	44-71
Week 10	71	65-78	
Week 12	85	79-99	72-99
Week 16	113	100-127	100-127
Week 20	141	128-155	128-155
Week 24	169	156-176	156-176
Week 26	183	177 –190	177 –190
Week 28	197	191 - 211	191 - 211
Week 32	225	212 – 239	212 – 239
Week 36	253	240 – 267	240 – 267
Week 40	281	268 – 295	268 – 295
Week 44	309	296 - 323	296 - 323
Week 48	337	324-351	324-351
Week 52	365	352 - 379	352 - 379
Week 56	393	380 - 407	380 - 407
Week 60	421	408 - EoS	408 - EoS

day 1 is the first date patient received iscalimab treatment. For patients in placebo groups during treatment period 1, the first dose of iscalimab is the first date the patient received iscalimab after study period 1.

Note that the visit windows defined in the protocol are used to guide investigators and are different from the analysis visit windows defined in this SAP for the purpose of analysis.

Table 2-4 Choosing value for analysis when there are multiple assessments within an analysis window

Timing of measurement	Type of data	Rule
Baseline	All data	The last non-missing measurement made prior to or on study Day 1. Only the date is considered if just one assessment was performed 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.

Timing of measurement	Type of data	Rule
Post-baseline efficacy	All data	• The measurement closest to the target day 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.
Post-baseline safety	Summary visit information (e.g., lab, Vital signs, etc.)	• 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.
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.

2.2 Analysis sets

The **Randomized Set (RAN)** consists of all randomized subjects. Subjects will be analyzed according to the treatment they are assigned to at randomization. Unless otherwise specified, mis-randomized patients (mis-randomized in IRT) are excluded from the randomized set.

Mis-randomized patients are patients who were screen-failures but had been randomized by the investigator before eligibility was finally assessed, however had not been treated.

The **Full Analysis Set (FAS)** comprises all subjects to whom study treatment has been assigned by randomization. The FAS will be used for all efficacy analysis, including the primary dose response analysis. According to the intent-to-treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization and the strata they actually belong to in case of misallocation of strata during the randomization process.

Subjects who were randomized but lost to follow up without a baseline visit, however, will be excluded from the FAS. Mis-randomized patients are also excluded.

Summaries of Period 1 data in FAS, including primary analysis, will be based on the treatment groups as randomized in the IRT system.

Cohort 1

- CFZ533 [redacted]
- CFZ533 [redacted]
- CFZ533 [redacted]

- Placebo

Cohort 2

- CFZ533 [redacted]
- Placebo

Analyses of data in FAS for Period 2 and overall study will be presented by treatment sequence as randomized for the study:

Cohort 1

- CFZ533 [redacted] - CFZ533 [redacted]
- CFZ533 [redacted] - CFZ533 [redacted]
- CFZ533 [redacted] - CFZ533 [redacted]
- Placebo - CFZ533 [redacted]

Cohort 2

- CFZ533 [redacted] - CFZ533 [redacted]
- Placebo - CFZ533 [redacted]

The Safety Set (SAF) 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. Analysis of PD data will also be based on safety set.

The actual treatment received in a period is defined as the treatment dose level (including placebo and 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.

Analyses of data in SAF up to Week 24 (Period 1) will be presented by actual treatment during Period 1, with data from separate cohort for the CFZ533 [redacted] and for the Placebo groups.

- CFZ533 [redacted]
- CFZ533 [redacted]
- CFZ533 [redacted]
- Placebo

Analyses of data in SAF set for period 2/3 or overall study will be presented by actual treatment sequence during periods 1 and 2, where the CFZ533 [redacted] – CFZ533 [redacted] sequence will include data from patients in separate cohort.

Cohort 1:

- CFZ533 [redacted] 24 Weeks
- CFZ533 [redacted] 48 Weeks
- CFZ533 [redacted] 48 Weeks

- CFZ533 [redacted] 48 Weeks
- Any CFZ533 [redacted]
- Any CFZ533

Cohort 2:

- CFZ533 [redacted] 24 Weeks
- CFZ533 [redacted] 48 Weeks
- Any CFZ533

The chance of dispensing error or administrative error is expected to be minimal. In a rare case that actually received treatments in periods 1 and 2 result in a treatment sequence not defined in any of the five distinct sequences planned per protocol, the patient will be grouped to the treatment sequence matching by period 1. A footnote will be added to document the patient ID.

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, soluble CD40 and 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.

- CFZ533 [redacted]
- CFZ533 [redacted]
- CFZ533 [redacted]

Frequency of receiving iscalimab treatment will be calculated using the information recorded on the Dose Administration Record (DAR) page, excluding placebo. In case a subject is exposed to more than one iscalimab treatment dose level with the same frequency, the subject will be grouped according to the dose level at the first iscalimab exposure.

2.2.1 Subgroup of interest

Subgroups of interest of Cohort 1 are FAS patients with baseline ESSDAI 12-domain total score <10 versus ≥ 10.

2.3 Patient disposition, demographics and other baseline characteristics

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

- Gender, age, race, ethnicity, weight, height, BMI (Body Mass Index), disease duration and smoking status.
- Number (%) of patients by screening ESSDAI strata used for randomization.
- Baseline values of ESSDAI, ESSPRI, FACIT-F, IDEEL, PhGA, PaGA, [redacted]

- Number (%) of patients with use of DMARDs (split by type, e.g. hydroxychloroquine, methotrexate, azathioprine) at baseline

[redacted]

- Number (%) of patients with history of prior biologics treatment for Sjögren's Syndrome.
- Number (%) if patients with use of systemic Steroids at baseline

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 and by cohorts.

2.3.1 Patient disposition

The number of patients screened, randomized, in the FAS, in the SAF, and prematurely discontinued from or completed different study periods (periods 1, 2 ,3) and the overall study will be presented in total and, except for the number of screened patients, by randomized treatment groups for each study cohort.

Except for the numbers of screened and randomized patients, percentages will be presented together with counts with the number of randomized patients as the denominator.

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

The treatment data will be presented for SAF by cohorts and study periods.

2.4.1 Study treatment / compliance

The duration of exposure to study treatment is calculated as last dose date – first dose date +1 during the study and for each period, regardless of missed or wrong dose, if any happened between the first and last dose dates. If a SAF patient did not receive any study treatment, the duration of exposure will be assigned as 0 for analysis.

Duration (days) of study treatment in SAF will be summarized for study period 1 and 2 separately.

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.

2.4.2 Prior, concomitant and post therapies

Prior and concomitant medication uses will be summarized by cohort and by treatment sequence for the overall study.

Prior medications are defined as medications taken prior to the first dose date of the study. Any medication given at least once between the first dose date and the last dose date of the study

will be a concomitant medication, including those started before the first dose date but continued into study Period 1.

The number and percentage of patients receiving prior or concomitant medications will be summarized by exposure to medications of different anatomical main group and Anatomical Therapeutic Classification (ATC).

The number and percentage of patients receiving systemic therapies for Sjögren's Syndrome or prohibited medications will be presented separately by ATC codes and by treatment groups for each cohort.

2.5 Analysis of the primary objective

The primary analysis for Cohort 1 is to characterize the dose response relationship among iscalimab doses ([redacted] s.c. Q2W) and placebo with regards to the change from baseline in ESSDAI at Week 24 for SjS patients with moderate to severe ESSDAI.

The goals of the Cohort 1 are:

- to confirm an overall dose-response signal, and
- to estimate the optimum dose

The generalized MCP-Mod (Multiple Comparison Procedure - Modelling) methodology (Bretz et al 2005; Pinheiro et al 2014) will be used to address these goals. Testing will be done at one-sided 5% alpha level.

The primary analysis in Cohort 2 is to estimate the treatment effect of [redacted] s.c. Q2W iscalimab and placebo with regards to the change from baseline in ESSPRI improvement at Week 24 among patients with high ESSPRI but low ESSDAI score at baseline.

The Week 24 data for both cohorts will be selected according to the analysis visits.

2.5.1 Primary endpoint(s)

Cohort 1

The following estimand framework is adopted for the primary analysis of Cohort 1.

- Population: Full Analysis Set (FAS)
- Variable of interest: Change from baseline in ESSDAI total score after 24 weeks of subcutaneous iscalimab administrations. This will be defined as the baseline ESSDAI value minus the Week 24 ESSDAI value with positive values indicating improvement in disease status.
- Inter-current events: Potential inter-current events in the study that may have impact on primary efficacy analysis of Cohort 1 include early discontinuation from the study treatment, interruption of study treatment, intensified symptomatic control treatment and intensified immunosuppressive treatment.
- Summary measure: Adjusted mean change from baseline in ESSDAI total score at Week 24 will be calculated from MMRM (Mixed Model for Repeated Measures) at the dose levels of 0 mg (placebo), [redacted]

[redacted]

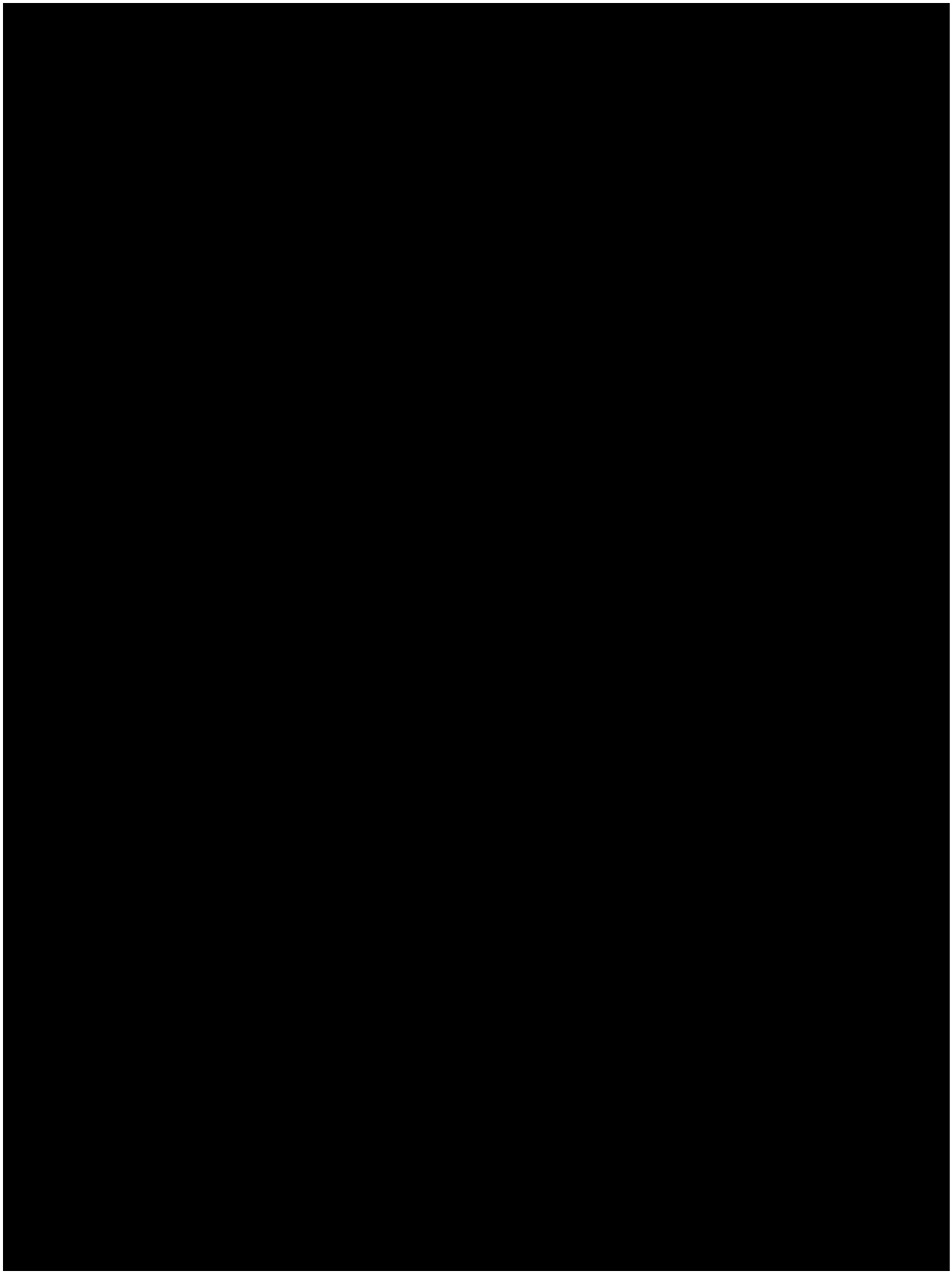
Cohort 2

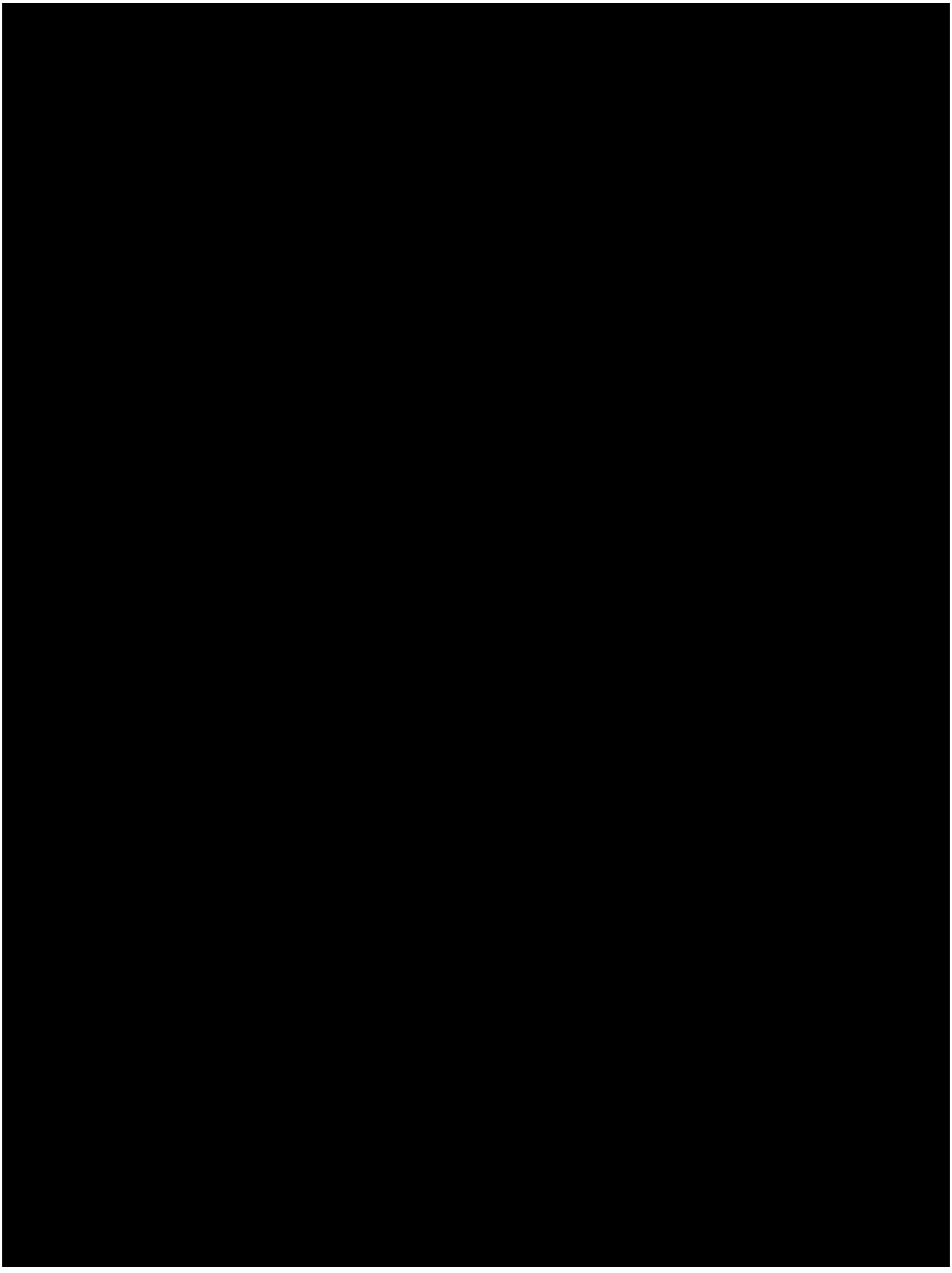
The primary analysis in Cohort 2 will be based on following estimand.

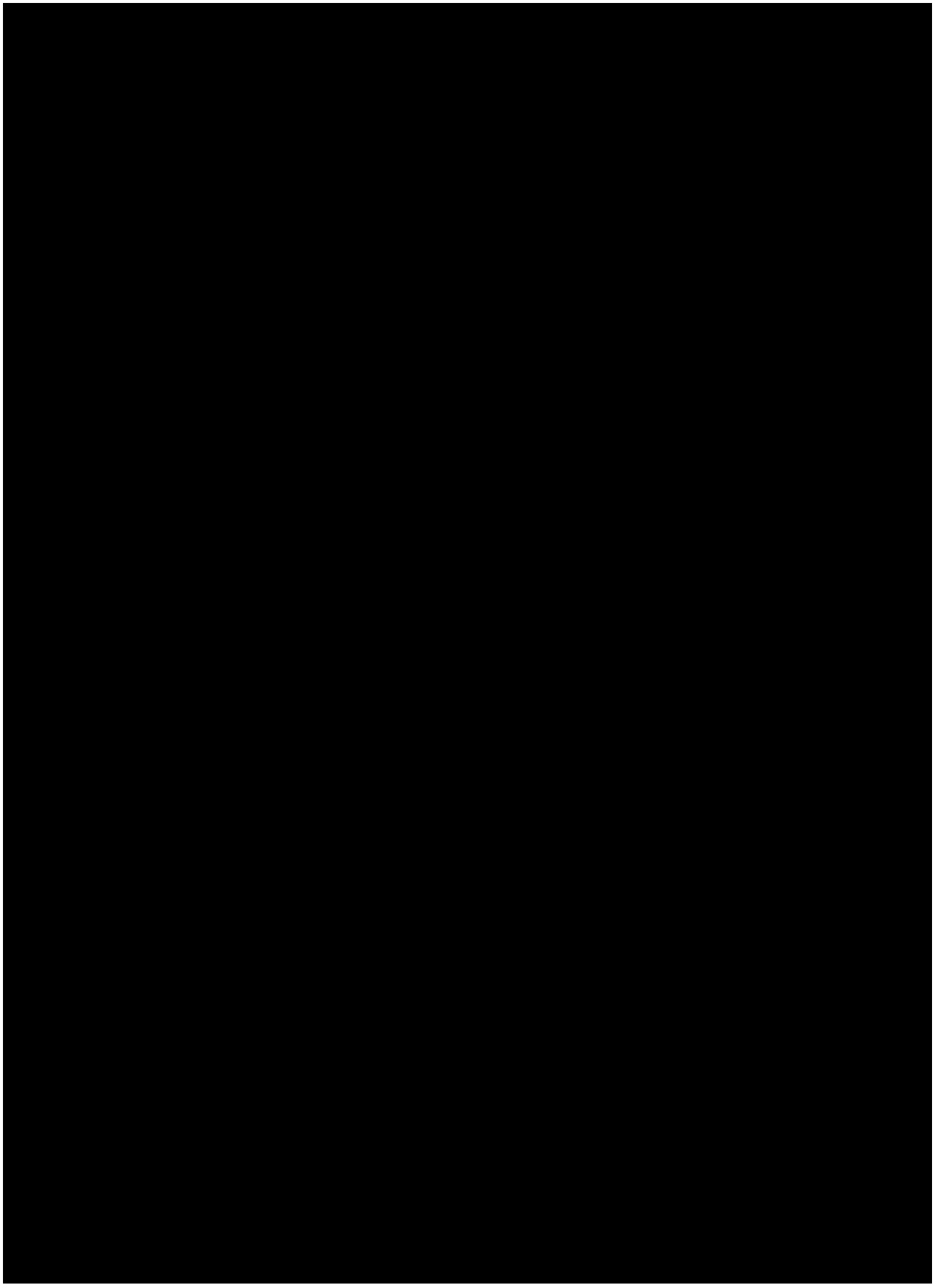
- Population: Full Analysis Set (FAS)
- Variables of interest: Response status defined as patients achieving at least 1 point or 15% improvement on ESSPRI total score at Week 24
- Inter-current events: Potential inter-current events in the study that may have impact on primary efficacy analysis of Cohort 2 includes early discontinuation from study, interruption of study treatments, intensified symptomatic control treatment and intensified immunosuppressive treatment.
- Summary measure: Proportion of responders in placebo and iscalimab [redacted] arms.

[redacted]

[redacted]







2.5.3 Handling of missing values/censoring/discontinuations

For the primary analysis of Cohort 1:

For time points with missing data in one of the ESSDAI sub-domains, the total ESSDAI score will be set to missing. If the baseline total ESSDAI score is missing, the screening value (if available) will be used to impute the baseline value. When there are post baseline assessments missing, the MMRM model utilized for the primary analysis Cohort 1 implicitly imputes missing value of change from baseline under a missing at random assumption (MAR).

Patients with non-missing total ESSDAI score for baseline and one or more post-dose time points will be included in the primary analysis.

For the primary analysis of Cohort 2:

For time points with missing data in one of the ESSPRI sub-domains, the total ESSPRI score will be set to missing. If the baseline total ESSPRI score is missing, the screening value (if available) will be used to impute the baseline value. When there are post baseline assessments missing, the MMRM model utilized for the primary analysis Cohort 2 implicitly imputes missing value of change from baseline under a missing at random assumption (MAR).

Patients with non-missing total ESSPRI score for baseline and one or more post-dose time points will be included in the primary analysis.

For the ESSPRI response at week 24 with missing observations for any reason will be treated as non-responders for the corresponding visit.

2.6 Analysis of the key secondary objective

The key secondary objective is to demonstrate a dose response of iscalimab in Cohort 1 based on change from baseline in ESSPRI and FACIT-F scores at Week 24.

2.6.1 Key secondary endpoint

The key secondary analysis will be performed in following estimand framework.

- Population: Full Analysis Set (FAS)
- Variables of interest: Change from baseline in ESSPRI and FACIT-F scores after 24 weeks of subcutaneous iscalimab administrations. Change is defined as

baseline minus Week 24 values with positive values indicating improvement.

- Inter-current events: Potential inter-current events in the study that may have impact on demonstration of dose response in ESSPRI or FACIT-F includes early discontinuation from the study treatment, interruption of study treatment, intensified symptomatic control treatment and intensified immunosuppressive treatment.
- Summary measure: Adjusted mean change from baseline at Week 24 for the dose levels of 0 mg (placebo), [redacted] will be calculated from similar MMRM model as adopted for the primary analysis.

The intention-to-treat principle and missing data handling rules for the primary analysis of cohort 1 will also be adopted for the key secondary efficacy analysis.

[redacted]

2.6.3 Handling of missing values/censoring/discontinuations

For time points with missing data in one of the ESSPRI sub-domains, the ESSPRI score will be set to missing. Patients with non-missing ESSPRI score for baseline and at least one post-dose time point will be included in this key secondary analysis.

The same MMRM model utilized for the primary analysis of Cohort 1 will be utilized also for the key secondary efficacy analysis, which implicitly imputes missing value of change from baseline under a missing at random assumption (MAR). The reasonableness of this assumption will be checked during the blinded review of the data.

2.7 Analysis of secondary efficacy objectives

Additional secondary efficacy analysis will be conducted based on the FAS.

2.7.1 Secondary endpoints

Secondary efficacy endpoints will be evaluated as follow:

Cohort 1:

- Change from baseline in ESSPRI at Week 24
- Change from baseline in PhGA at Week 24
- Change from baseline in FACIT-F at Week 24
- Change from baseline in serum FLC levels at Week 24
- Change from baseline in IgG and IgM levels at Week 24
- Change from baseline in plasma CXCL-13 levels at Week 24

Cohort 2:

- Change from baseline in ESSDAI at Week 24
- Change from baseline in PhGA at Week 24
- Change from baseline in FACIT-F at Week 24
- Change from baseline in serum FLC levels at Week 24
- Change from baseline in IgG and IgM levels at Week 24
- Change from baseline in plasma CXCL-13 levels at Week 24
- Percentage of patient who achieved >=12 points reduction on IDEEL dry eye symptom bother module score at Week 24. This will be calculated as number of patients with (week 24 – baseline value) <= -12 divided by the number of patients for a treatment group

2.7.2 Statistical hypothesis, model, and method of analysis

For analyzing the secondary endpoints related to change from baseline, an MMRM will be fitted. For analyzing Cohort 1, we will adjust for treatment, visit, treatment by visit interaction, ESSDAI stratum (<10 vs. ≥10), geographic region as fixed factors and the value of the endpoint of interest at baseline. For analyzing Cohort 2, we will adjust for treatment, visit, treatment by visit interaction, geographic region as fixed factors and the value of the endpoint of interest at baseline. The list of the endpoints of interest is reported in Section 2.7.1.

An unstructured variance-covariance matrix will be used to model the dependency between repeated observations in all MMRM.

Descriptive summaries of the absolute values at baseline and Week 24 as well as change from baselines at Week 24 will be presented with 2-sided 95% confidence intervals in Cohort 1 and 2 respectively based on the MMRM previously described.

The number and percentage of patients with >= 12 points reduction on IDEEL dry eye symptom bother module score at Week 24 will be presented by treatment arms in Cohort 2. Response analysis of IDEEL using non-responder imputation will be performed with fisher exact test comparing treatment arms to placebo.

No hypothesis testing will be performed for these additional secondary endpoints.

2.7.3 Handling of missing values/censoring/discontinuations

No imputation of missing values will be implemented for descriptive summaries of these additional secondary efficacy endpoints. For the IDEEL responder analyses, if a subject has a missing value at Week 24, this subject will be evaluated as a non-responder,

2.8 Safety analyses

All safety analysis will be on Safety set based on data from both cohorts. Safety data will be summarized separately for Period 1 and Period 2/3. The iscalimab [redacted] and placebo treatment groups in Period 1 analysis will include patients from both cohorts. For safety summaries from start of Period 2 to end of study (Period 2/3), the patients from both cohorts will be grouped according to distinct treatment sequence received during the two treatment periods of the study.

If a patient received more than one treatment during a specific treatment period (e.g. preparation or administration error), the patient is considered treated with the most frequently received treatment during the period. Such a situation, if it exists, will be identified after unblinding with information recorded on the Dose Administration Record (DAR) page of the eCRF where pack number reveals whether or not the patient received the wrong study drug.

2.8.1 Adverse events (AEs)

Treatment-emergent adverse events (TEAE) will be summarized for treatment Period 1 and treatment period 2 separately. TEAE is defined as events (based on preferred term) newly started, or presented before baseline but increased in severity, during the treatment period of interest.

The treatment period 1 (TP1) of a patient starts from the first dose date of the study and ends on the day before first dose date of period 2, if the patient received at least one dose of study treatment for period 2, or the end of study (EOS) otherwise.

The treatment period 2 (TP2) of a patient starts from the first dose date of period 2 to the end of study. The identification of TEAE for period 2 is based on the existence or severity of such AE before baseline of the study regardless of occurrence or severity of the same AE during TP1. If a patient did not receive study treatment in period 2, the patient will be excluded from the AE analysis for period 2.

The number (and percentage) of patients with TEAEs for each treatment period will be summarized in the following ways:

- 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 Period 1 and 2 on study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment.

A patient with multiple adverse events of same preferred term during a period of analysis is counted only once for that preferred term, a patient with multiple adverse events in a primary system organ class is only counted once towards the total of the primary system organ class.

A listing of all adverse events during the study will be produced with those defined as TEAE for study treatment period 1 and 2 additionally flagged.

Shift tables for newly occurring or worsening neutropenia up to Week 24 and Week 48 will be provided for both cohorts separately.

Clinical Trial Safety Disclosure

Regulatory-required safety disclosure tables will be produced with the final CSR.
For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% 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 and for the overall study period.

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.

2.8.1.1 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.

2.8.2 Deaths

Patients who died will be listed by treatment sequence and patient ID. Listing will include the start/stop dates of study treatment for each study period as well as the date, study day and reason for death.

2.8.3 Laboratory data[CL21]

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

Routine hematology (including immunoglobulins IgG and IgM) and serum chemistry (including lipids) laboratory tests results will be summarized by analysis visits during Period 1 and Period 2/3. Descriptive statistics for the value and change from baseline will be included. The number and percentage of patients with clinically notable laboratory results after baseline

will also be presented by laboratory test groups and parameters listed in section 5.3 for Period 1 and 2/3. Central and local lab results will be displayed in separate tables for clinically notable laboratory results..

An MMRM is fitted for analyzing the changes from baseline in IgG and IgM from all time points until Week 24. For analyzing Cohort 1, we will adjust for treatment, visit, treatment by visit interaction, ESSDAI stratum (<10 vs. ≥10), geographic region as fixed factors and the value of the endpoint of interest (IgG and IgM) at baseline. For analyzing Cohort 2, we will adjust for treatment, visit, treatment by visit interaction, geographic region as fixed factors and the value of the endpoint of interest (IgG and IgM) at baseline. An unstructured variance-covariance matrix will be used to model the dependency between repeated observations in all MMRM.

Urinalysis data will be listed indicating whether from central or local lab.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Not Applicable

2.8.4.2 Vital signs

The values and changes from baseline in Systolic/Diastolic blood pressure, body weight and heart rate will be summarized by analysis visits during the period 1 and period 2/3 separately.

2.9 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 2-3 to assign the values to analysis visits. If multiple measurements fall within the same analysis window, the algorithms outlined in Table 2-4 will 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; typically at Week 24 and Week 48) 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 cohort, 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.

2.10 PD and PK/PD analyses

PD analysis will be performed on SAF and PK set separately. To preserve blinding of treatment assignment, the PD data will be accessible to blinded personnel in the CTT only after unblinding for the primary analysis.

The blood samples for soluble CD40 (sCD40) concentration in plasma will be collected from all patients according to assessment schedule defined in protocol, and bioanalytical analysis will be performed on all samples.

For each sCD40 concentration, elapsed time since first dose (Elapsed Time #1 with reference to Dose Reference ID #1 defined in the Blood Log) and elapsed time since the specified dose (Elapsed Time #2 with reference to Dose Reference ID #2 defined in the Blood Log) will be derived and presented in the PK merge file.

The sCD40 concentrations will be listed by cohort, treatment sequence, patient ID, and visit/sampling time point.

Descriptive summary of sCD40 will be provided by analysis visits (derived according to Table 2-2) for Period 1 and Period 2/3 in SAF set. Summary statistics will include mean (arithmetic and geometric), SD, 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.

In addition, the descriptive summary of sCD40 in PK set will be provided by analysis visits (derived according to Table 2-3) by iscalimab treatments. Spaghetti plots of sCD40 levels vs. time since first iscalimab dose will be produced for each iscalimab treatment group.

[redacted]

As appropriate, modeling of PK (/PD) data using a population approach will be performed separately and reported in a separate, standalone modeling and simulation report.

An MMRM is fitted for analyzing the changes from baseline in sCD40 from all time points until Week 24. For analyzing Cohort 1, we will adjust for treatment, visit, treatment by visit interaction, ESSDAI stratum (<10 vs. ≥10), geographic region as fixed factors and the value sCD40 at baseline. For analyzing Cohort 2, we will adjust for treatment, visit, treatment by visit interaction, geographic region as fixed factors and the value of the sCD40 at baseline. An unstructured variance-covariance matrix will be used to model the dependency between repeated observations in all MMRM.

2.11 Patient-reported outcomes

Analysis of patient reported outcomes in the study are detailed in sections for secondary [redacted] analysis. Additional analysis on PRO data could be performed outside of the main study CSR.

2.12 Biomarkers

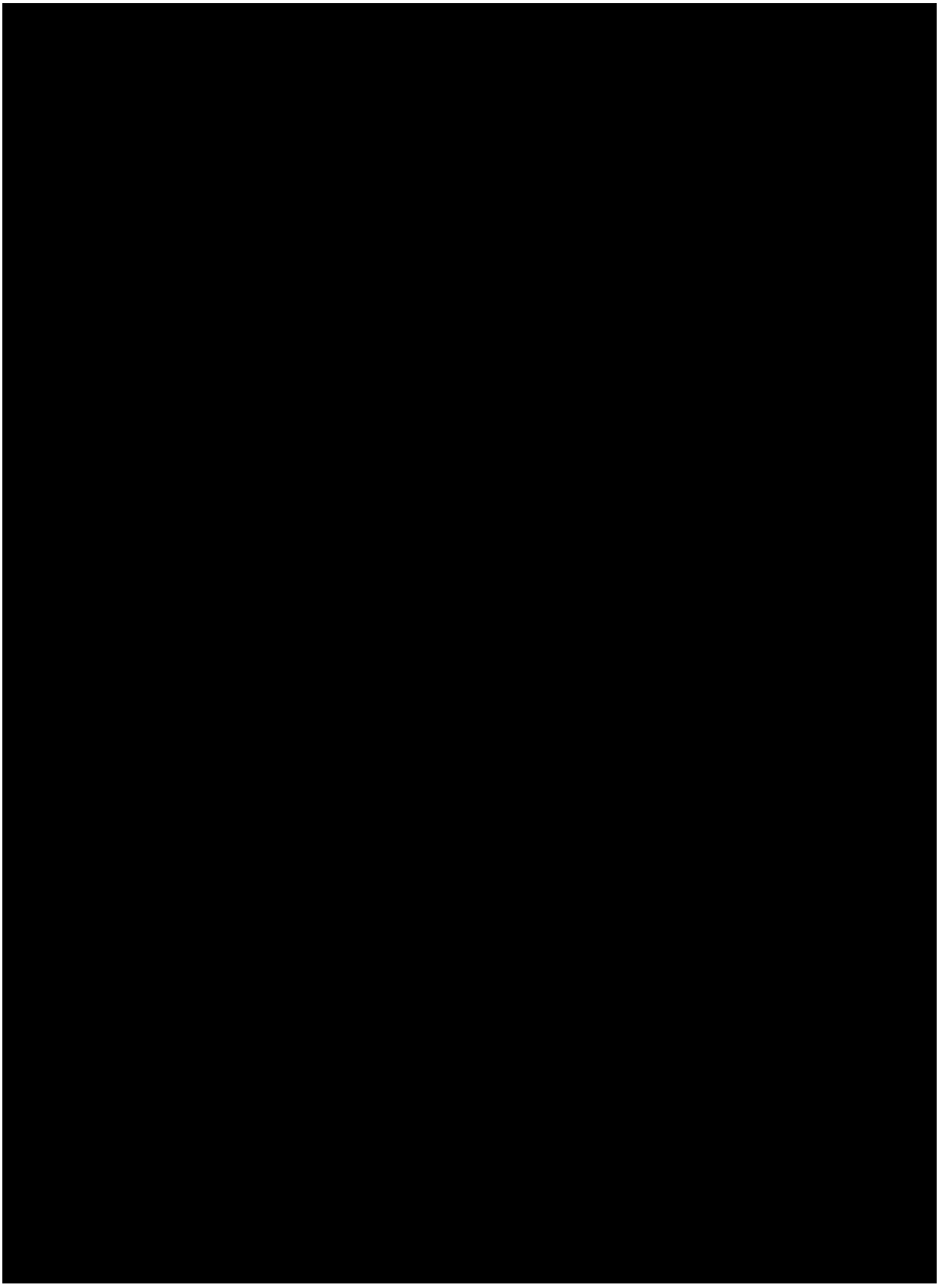
Analysis of biomarkers will be performed in FAS.

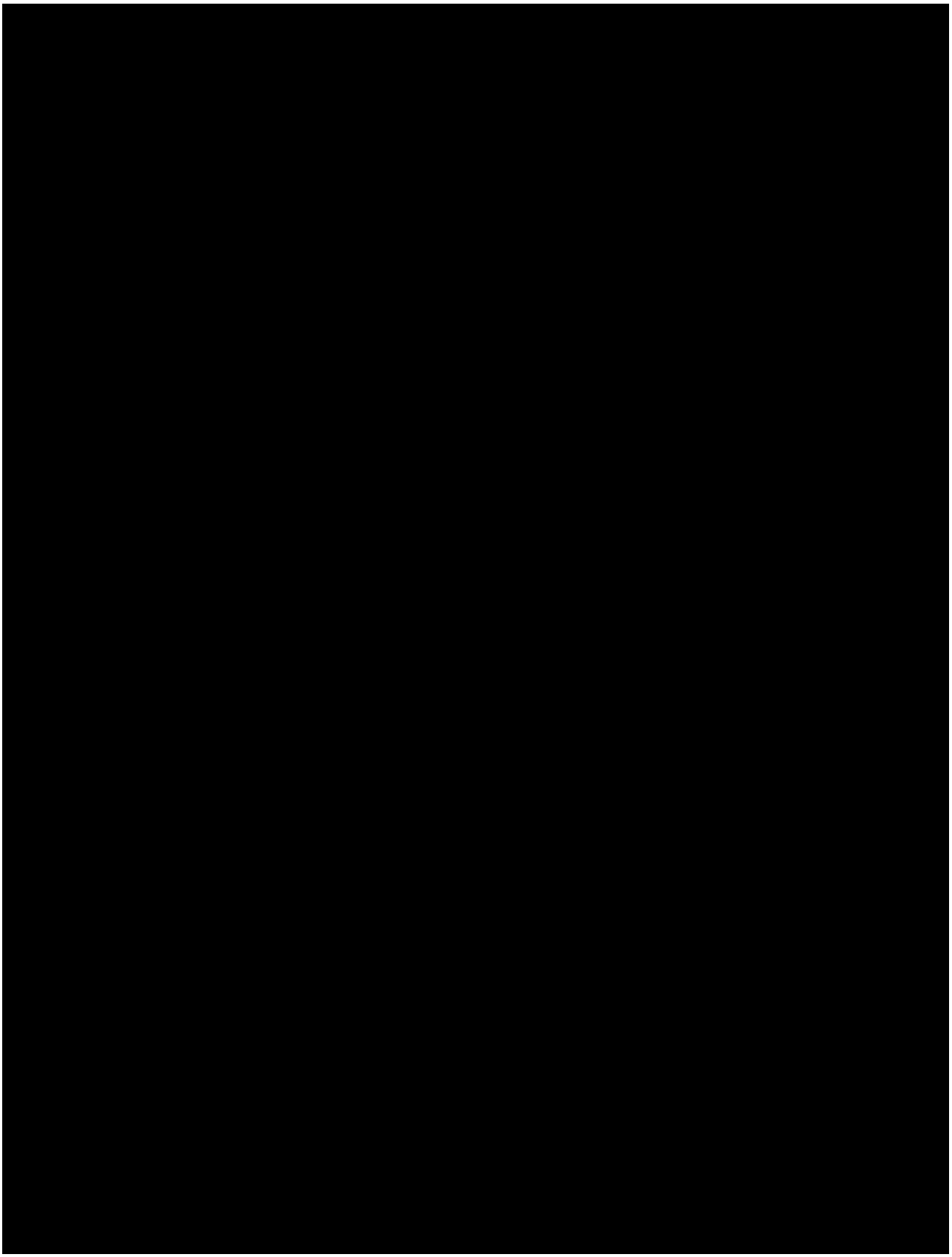
The value and percent change from baseline in serum level of FLC, IgG/IgM and CXCL-13 will be summarized by cohort and analysis visits for period 1 and for period 2/3. The summary statistics will include minimum, 25% quartile, median, 75% quartile, maximum, mean, SD and CV. Concentrations below LLOQ will be treated as zero and concentrations above ULOQ will be assign as the ULOQ for the purpose of descriptive analysis. The frequency (n, %) of values below the LLOQ and above the ULOQ, respectively, will also be provided.

[redacted]

An MMRM is fitted for analyzing for these biomarkers. For analyzing Cohort 1, we will adjust for treatment, visit, treatment by visit interaction, ESSDAI stratum (<10 vs. ≥10), geographic region as fixed factors and the value of biomarker at baseline. For analyzing Cohort 2, we will adjust for treatment, visit, treatment by visit interaction, geographic region as fixed factors and the value of biomarker at baseline. An unstructured variance-covariance matrix will be used to model the dependency between repeated observations in all MMRM.

[redacted]



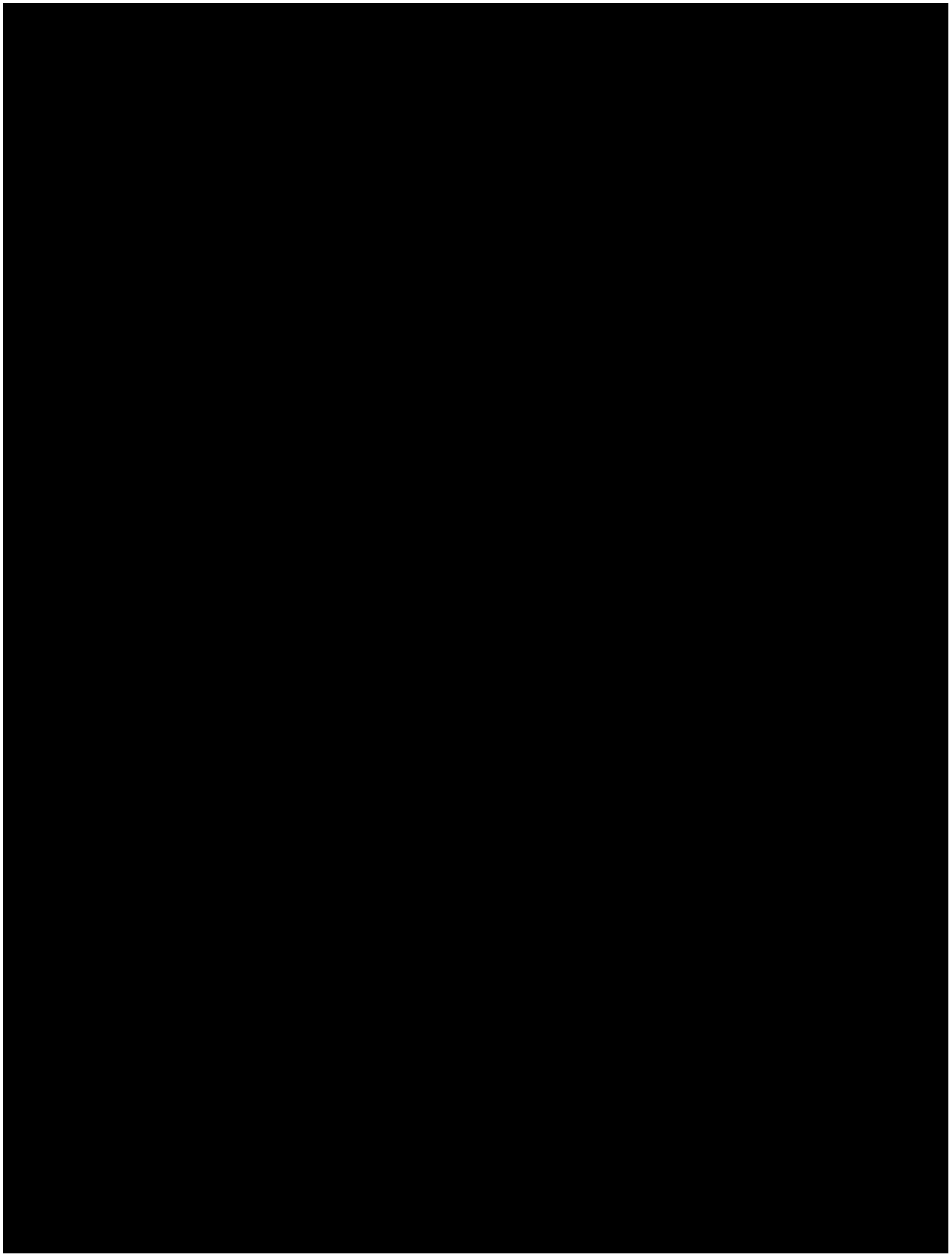


[redacted]

2.14 Interim analysis

One interim analysis are planned after at least 50% of the subjects in Cohort 1 have completed Week 24 visit or discontinued prior to Week 24 to access the dose-response relationship of the study medication. Two additional interim analyses are planned when all patients from Cohort 1 and all patients from Cohort 2 have completed Week 24 assessment or have discontinued prior to Week 24. No other interim analyses are currently planned. A final analysis will be performed after all patients have completed Week 60 (or discontinued prior to Week 60).

[redacted]



[redacted]

4 Change to protocol specified analyses

This SAP implemented following updates to the statistical analysis originally planned in study protocol V00 (15-Feb-2019).

- A PK analysis set (PKS) is additionally defined. Because patients initially assigned to the placebo treatment group will switch to iscalimab after Period 1, the PKS facilitate appropriate analysis of PK and immunogenicity, which is only relevant after a patient gets exposed to iscalimab.

- [redacted]

- MCP-Mod analysis on FACIT-F is additionally included as the third step of the hierarchical testing procedure to evaluate dose-response relationship of iscalimab on fatigue. Because the hypothesis tests (MCP) for FACIT-F will be performed only if those for both ESSDAI and ESSPRI are rejected, this update does not impact the statistical characteristics of the primary analysis (on ESSDAI) or key secondary analysis (on ESSPRI) previously planned in the study protocol, but enables the potential of obtaining stronger evidence for efficacy of iscalimab in improving fatigue.

- The additional sensitivity analysis of using alternative candidate models in MCP-Mod and nonparametric approach for Cohort 1 primary endpoint are removed. This is because the objective of the MCP step is not to confirm any specific candidate model being true. The candidate models for the primary analysis could be updated in the SAP if blinded data review or additional external data before study unblinding warrants such change. In the spirit of lean SAP, this alternative analysis method could be explored outside of the main CSR if needed.

- The definition of the estimand for the primary analysis in Cohort 2 reported in the protocol has been revised in the SAP in order to address the primary objective of the study (for Cohort 2). Indeed, to estimate the effect of CFZ533 (iscalimab) [redacted] s.c. on the change in ESSPRI at Week 24 for Cohort 2, we will not evaluate the "Response status defined as subjects achieving at least 1 point or 15% improvement on ESSPRI score at Week 24" as reported in the protocol (section 12.4.1), but we will evaluate the change of ESSPRI at Week 24 with respect to the value recorded at baseline.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

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

5.1.2 AE date imputation

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

5.1.3 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.

5.1.3.1 Prior therapies date imputation

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

5.1.3.2 Post therapies date imputation

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

5.1.3.3 Other imputations

Not applicable

5.1.4 ESSDAI date imputation

For ESSDAI, the date recorded in CRF does not reflect the date of visit. Therefore, below are detailed steps to follow to derive the new date/time to be used for visit windows:

a. Use the date/time of specimen collection of IGG lab data to impute the analysis date/time by merging ESSDAI data with IGG data by subject and scheduled visit.
b. If there is no IGG data for the corresponding scheduled visit, the start date/time of visit will be used.
c. If start date/time of visit is not available, the original date/time of assessment from ESSDAI PRO questionnaire data will be used.

5.1.5 Patient-reported Outcomes date imputation

For ESSPRI/FACIT and other PRO endpoints, the assessment date/time of the questionnaire will still be used to derive the visit windows. The similar imputation rule as specified in the section 5.1.4 will be used if there are errors of date/time of the patient-reported outcomes data.

5.2 AEs coding/grading

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

5.3 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. Any elevations of ALP >1.5x ULN
6. Gamma-Glutamyltransferase (GGT): >3x ULN
7. Creatinine (serum): ≥3x ULN
8. Creatinine clearance (CrCl) (Cockroft-Gault formula): ≥25% decrease from baseline
9. Triglycerides: >5x ULN
10. IgG and IgM: <LLN for 12 weeks

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

5.4 Statistical models

5.4.1 Primary analysis

The MCP-Mod method for primary analysis, including the framework of hypothesis testing, is specified in Section 2.7.2. Additional statistical and/or implementation details are provided in this section.

5.4.1.1 Repeated measures analysis

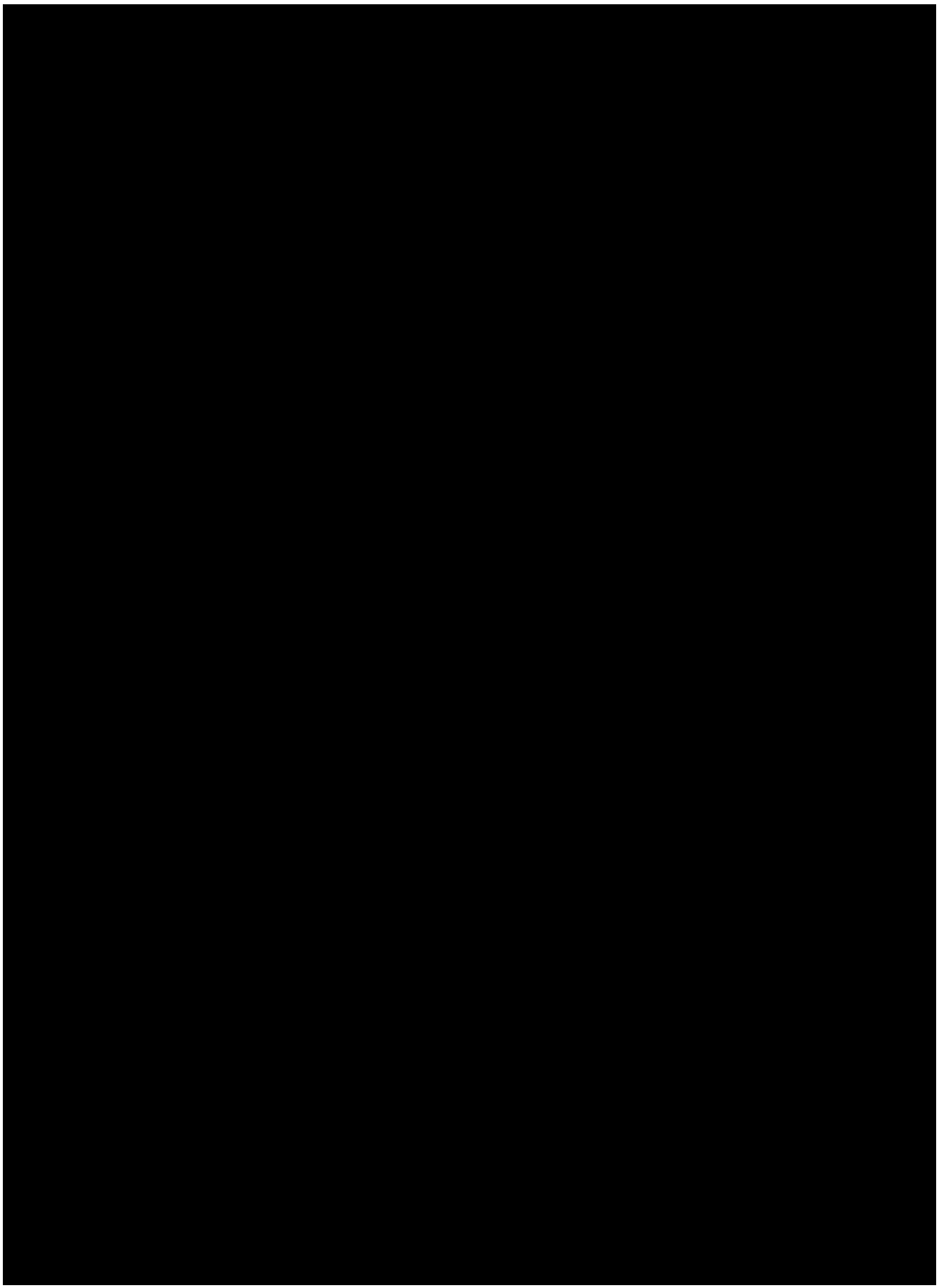
Based on the MMRM model specified in Section 2.7.2, the covariate-adjusted least square means (LSMs) of change from baseline in ESSDAI will be estimated at Week 24, with also adjustment for correlations between time points within patient. These estimates are subsequently used in dose-response modeling based on the MCP-Mod method also detailed in Section 2.7.2.

The MMRM model will be fitted using the SAS procedure "PROC MIXED". Unstructured covariance matrix will be used (TYPE = UN), which allows adjustment for correlations between time points within patient under minimal assumption on such correlation structures. To get a full rank variance-covariance matrix of treatment effects, no intercept option will be used (NOINT option in MODEL statement). Adjusted means and the corresponding variance covariance matrix will be estimated. The treatment differences for all pair-wise treatment comparisons will also be estimated along with associated 95% confidence intervals (ALPHA = 0.05). For calculation of denominator degrees of freedom, Kenwood-Rogers method would be used (DDFM=KR).

In case the MMRM model does not converge, the following steps will be sequentially used to achieve convergence:

1. change ddfm=kr to ddfm=bw. If still no convergence, perform step 2.
2. change type=un to type=cs. If still no convergence, perform step 3.
3. remove covariates in the following order until convergence:, geographic region, stratification factor(if applicable), treatment group by visit interaction.

The use of MMRM is under the assumption of missing at random (MAR) and the assumption that patients who dropouts early from the study would behave similarly to other patients in the same treatment group with similar covariate values had they not dropped out. Such assumption in clinical trials, however, has a potential of being overly optimistic. Patients with missing primary endpoint will be reviewed using blinded data during the study before primary database lock and additional sensitivity analysis based on multiple imputations could be added.



5.5 Rule of exclusion criteria of analysis sets

No patient in the Safety set will be excluded from the safety analysis.

Efficacy analysis that uses the FAS set will follow the ITT principle without data exclusion, except for the sensitivity analysis that repeat the primary analysis by excluding data after inter-current events. Inter-current events of prohibited medication (newly introduced or changes in concomitant and allowed background medication - protocol section 6.2.2) will be identified based on generic names and/or ATC code as listed in Table 5-1 along with dose intensity, indication and/or route of administration reported on the concomitant medication eCRF. This appendix Table 5-1 may be updated based on blinded study data review and finalized in SAP before primary analysis database lock.

Table 5-1 De novo or intensified medications excluding data from sensitivity analysis

generic name	ATC5 code	ATC5 class	Additional criteria
ABATACEPT	L04AA	SELECTIVE IMMUNOSUPPRESSANTS	
ALEFACEPT	L04AA	SELECTIVE IMMUNOSUPPRESSANTS	
AZATHIOPRINE	L04AX	OTHER IMMUNOSUPPRESSANTS	

generic name	ATC5 code	ATC5 class	Additional criteria
BELIMUMAB	L04AA	SELECTIVE IMMUNOSUPPRESSANTS	
CHLORAMBUCIL	L01AA	NITROGEN MUSTARD ANALOGUES	
CYCLOPHOSPHAMIDE	L01AA	NITROGEN MUSTARD ANALOGUES	Intravenous or oral administration
CICLOSPORIN			Multiple ATC class possible. Ophthalmic Cyclosporine treatment is allowed. Oral cyclosporine is prohibited
EPRATUZUMAB	L01XC	MONOCLONAL ANTIBODIES	
ETANERCEPT	L04AB	TUMOR NECROSIS FACTOR ALPHA (TNF-) INHIBITORS	
HYDROXYCHLOROQUINE	P01BA	Aminoquinolines	
INFLIXIMAB	L04AB	TUMOR NECROSIS FACTOR ALPHA (TNF-) INHIBITORS	
BETAMETHASONE	H02AB01	GLUCOCORTICOIDS	
DEXAMETHASONE	H02AB02	GLUCOCORTICOIDS	
FLUOCORTOLONE	H02AB03	GLUCOCORTICOIDS	
METHYLPREDNISOLONE	H02AB04	GLUCOCORTICOIDS	
PARAMETHASONE	H02AB05	GLUCOCORTICOIDS	
PREDNISOLONE	H02AB06	GLUCOCORTICOIDS	
PREDNISONE	H02AB07	GLUCOCORTICOIDS	
TRIAMCINOLONE	H02AB08	GLUCOCORTICOIDS	
HYDROCORTISONE	H02AB09	GLUCOCORTICOIDS	
CORTISONE	H02AB10	GLUCOCORTICOIDS	
PREDNYLIDENE	H02AB11	GLUCOCORTICOIDS	
RIMEXOLONE	H02AB12	GLUCOCORTICOIDS	
DEFLAZACORT	H02AB13	GLUCOCORTICOIDS	
CLOPREDNOL	H02AB14	GLUCOCORTICOIDS	
MEPREDNISONE	H02AB15	GLUCOCORTICOIDS	
CORTIVAZOL	H02AB17	GLUCOCORTICOIDS	
MYCOPHENOLATE MOFETIL	L04AA	SELECTIVE IMMUNOSUPPRESSANTS	
OCRELIZUMAB	L04AA	SELECTIVE IMMUNOSUPPRESSANTS	
RITUXIMAB	L01XC	MONOCLONAL ANTIBODIES	

6 Reference

6.1 Internal references

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6.2 External references

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