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Novartis Research and Development

CFZ533 (Iscalimab)

Clinical Trial Protocol 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)

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Table of contents

[redacted]

[redacted]

[redacted]

[redacted]

List of tables

[redacted]

List of figures

[redacted]

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
BUN	blood urea nitrogen
[redacted]	[redacted]
CFR	Code of Federal Regulation
CK	creatinine kinase
ClinRo	Clinician reported outcomes
CMO	Chief medical office
CMV	Cytomegalovirus (Human- Cytomegalovirus)
CNS	Central nervous system
CO	Country Organization
COA	Clinical outcome assessments
COVID-19	Coronavirus Disease 2019
CRA	Clinical research associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CTC	Common Toxicity Criteria
CTLA4	cytotoxic T-lymphocyte-associated protein 4
Ctrough	Trough concentration
CTT	Clinical trial team
CV	coefficient of variation
DMARD	Disease modifying antirheumatic drug
DMC	Data Monitoring Committee
dsDNA	double-stranded deoxyribonucleic acid
EC	Ethics committee
ECG	Electrocardiogram
eCOA	electronic Clinical Outcome Assessments
eCRF	Electronic case report forms
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EMA	European medicines agency
[redacted]	[redacted]
ESR	Erythrocyte sedimentation rate
ESSDAI	EULAR Sjögren's syndrome disease activity index
ESSPRI	EULAR Sjögren's syndrome patient reported index

[redacted]

EU	European Union
EULAR	European League Against Rheumatism
FACIT-F	Functional assessment of chronic illness therapy - fatigue
FAS	Full analysis set
FDA	Food and Drug Administration
FLC	Free Light Chains
FLCκ	Free Light Chains kappa
FLCλ	Free Light Chain lambda
FSH	Follicle stimulating hormone
FUP	Follow up
GCP	Good Clinical Practice
GCS	Global clinical supply
GGT	Gamma-glutamyl transferase
HA	Health authority
[redacted]	
HBc	HB core antigen
HBs	HB surface antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HC	Hepatitis C
hCG	Human chorionic gonadotropin
HCQ	Hydroxychloroquine
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
i.v.	intravenous
IA	Interim Analysis
IB	Investigators brochure
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDEEL	Impact of Dry Eye on Everyday Life
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IN	Investigator notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
LDH	lactate dehydrogenase
LFT	Liver function test
LLN	lower limit of normal
LLOQ	Lower limit of quantification
LN	lupus nephritis
LVV	Large vessel vasculitis
mAb	Monoclonal antibody

[redacted]

MAR	Missing at random
MCP	Measure-Correlate-Predict
MedDRA	Medical dictionary for regulatory activities
MMF	Mycophenolate Mofetil
MMRM	Mixed-Effect Model Repeated Measure
MNAR	Missing Not at Random
MOA	Mechanism of Action
MTX	Methotrexate
NHP	Non-human primates
NSAID	Nonsteroidal anti-inflammatory drugs
[redacted]	
PCR	Polymerase chain reaction
PD	pharmacodynamic(s)
PhGA	Physician's Global Assessment of disease activity
PHQ	Patient Health Questionnaire
PI	Principal investigator
PK	pharmacokinetic(s)
PNS	Peripheral nervous system
PoC	Proof of Concept
PRO	Patient reported outcome
PS	Patient Safety
pSS	primary Sjögren's syndrome
PTLD	Post-transplantation proliferative disorder
PTT	Partial thromboplastin time
Q2W	every 2 weeks, bi-weekly
QMS	Quality Management System
QTcF	QT correction formula
RA	Regulatory Authority
RCT	Randomized controlled trial
[redacted]	[redacted]
RNA	Ribonucleic acid
s.c.	subcutaneous
SAE	serious adverse event
SAF	Safety Set
SAP	Statistical Analysis Plan
sCD40	Serum Cluster of differentiation
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SjS	Sjögren's Syndrome
SLE	Systemic lupus erythematosus
SMQ	Standardized MedDRA Query
SoC	Standard-of-care
SOP	Standard operating procedures
SSA	Sjögren's-syndrome-related antigen A

[redacted]

SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
[redacted]	[redacted]
TD	Treatment discontinuation
TEAE	Treatment emergent adverse events
TMDD	Target mediated drug disposition
TP1	Treatment period 1
TP2	Treatment period 2
ULN	upper limit of normal
ULOQ	Upper limit of quantification
US	United States
VAS	Visual analog scale
WBC	white blood cell(s)
WHO	World Health Organization
WOCBP	Women of child-bearing potential

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.)
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.

[redacted]

Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points.
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Amendment 2 (27-Apr-2021)

Amendment rationale

The key purpose of this amendment is to introduce an interim analysis to assess the dose-response relationship of CFZ533, after at least 50% of the subjects in Cohort 1 have completed Week 24 visit or discontinued prior to that. The results from the interim analysis may inform future clinical development planning. Specific guidance concerning public health emergency situations as declared by local or regional authorities (i.e., pandemic, epidemic or natural disaster) has been included in Section 4.6, as well as mitigation procedures to ensure participant safety and trial integrity in the relevant sections. At the time of this amendment, Novartis has performed a study-specific medical and safety risk assessment and concluded that based on the current data, the benefit/risk of iscalimab due to COVID-19 pandemic remains unchanged in the target population.

Additionally, this protocol amendment includes the correction of typographical and formatting errors and minor editorial changes for increased clarity of the text. Consequently, a small number of changes were implemented throughout the protocol.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The following sections have been changed in the amended protocol:

List of abbreviations:

The list of abbreviations has been updated.

Section 3: Updated to include the option of interim analysis.Section 4.2: Removed study is ongoing for CCFZ533X2203 and removed preliminary for PK data as per Investigators Brochure (IB) Edition 10.

Removed preliminary for PK data of Figure 4-3 description as per IB Edition 10.

Section 4.4: Included interim analysis.Section 4.5: Removed preliminary for safety and efficacy data from PoC study as per IB Edition 10.

Section 4.6: Section 4.6 added for Public Health Emergency mitigation procedures.Section 5.2: Added bilateral to the tubal ligation for clarity.

Section 6.4: Section 6.4 and Table 6-4 updated to clarify the treatment blinding/unblinding plan in relation to the introduced interim analysis.Section 8: Section 8, Section 8.3, Section 8.4 and Section 8.4.3 have been updated for Public Health Emergency mitigation procedures accordingly based on addition of Section 4.6.

Section 8.1: Re-added Hepatitis C (HC) to list of tests due to a typo from previous version.Section 8.2: Provided further clarification for CMV testing eligibility criteria.Section 9.1.2: Added clarification on withdrawal of consent/opposition to use data/biological samples.

Section 12.7: Updated to include the interim analysis.

[redacted]

IRBs/IECs

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 1 (21 Feb 2020)

Amendment rationale

The key purpose of this amendment is to introduce screening for human cytomegalovirus (CMV) and monitoring for active CMV infection in at risk subjects. Briefly, as reported in an Investigator Notification (IN) (Case ID: NVSC2019TN015399), a patient in CCFZ533X2202 being treated with CFZ533 (under clinical investigation for the treatment of lupus nephritis) developed a gastrointestinal infection which subsequently required hospitalization. Despite treatment with broad-spectrum antibiotics followed by ganciclovir for suspected CMV disease based on positive IgM serology, the patient also developed a respiratory infection that progressed to a fatal outcome. While the CMV infection was, according to Novartis assessment, not related to study drug (as the serum IgM positivity preceded study drug initiation), the events in this CFZ533 treated patient leading to fatal outcome were likely triggered by a primary CMV infection. The clinical course of events is unclear, and could have been associated with bacterial superinfection. In view of complex clinical course the role of study medication remains unclear. Therefore, Novartis has implemented enhanced screening, monitoring and treatment recommendations to mitigate the risks of CMV infection in patients receiving CFZ533 together with other immunosuppressants.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The following sections have been changed in the amended protocol:

Protocol Summary:

The protocol summary was updated to reflect the modification of the main protocol.

[redacted]

Section 4.4: The below lines were deleted

There is no interim analysis planned before the primary analysis.

The below lines were inserted to provide more clarity.

The analysis for Cohort 1 and analysis for Cohort 2 may occur at different time points depending on patient recruitment and preparation timelines (please refer to Section 6.4).

Section 4.5: Table 4-1 was added that describes the various risks of CFZ533

Risks and benefit section was updated with below lines describing the safety information on CMV.

[redacted]

"One fatal event (potential CMV infection) was reported in the CCFZ533X2202 clinical trial in Lupus nephritis, suspected to be related to the study medication by the Investigator.

The event was confounded by CMV infection present before first intake of the study medication. The ultimate cause of death remains unclear; however, the events leading to fatal outcome could have been associated with the CMV infection and/or with a bacterial superinfection, and a role of study drug cannot be excluded.

Currently the causal effect of CFZ533 remains unclear, however, active viral infections do remain a potential risk. Therefore, specific detection measures have been implemented with amendment 1# to monitor the risk of CMV infection across the clinical development program for CFZ533.

The infections including CMV are considered as an important potential risk for CFZ533 and continue to be adequately monitored and mitigated in CFZ533B2201 study. Therefore, the fatal case with potential CMV infection from CCFZ533X2202 study is not considered to impact the overall risk-benefit ratio."

Section 5.2: Exclusion Criterion #13 was updated to reflect the use of live attenuated vaccine during treatment and for at least 14 weeks thereafter.

Exclusion criterion #20 is a new addition, post which renumbering of existing exclusion criteria was done chronologically.

"Evidence of active CMV infection in the form of a positive serology for CMV IgM (in the absence or presence of positive CMV IgG) and/or quantifiable CMV DNA by PCR at screening.

Note: patients with detectable but NOT quantifiable CMV DNA titers may be eligible for the study".

Section 6.2.1: A clarification sentence was added on CMV medication.

"Similarly CMV antiviral medication used as pre-emptive therapy is allowed for patients with detectable virus by PCR".

Table 6-3: Prohibited medication list updated with addition of Oral MMF and Vaccines.

Section 6.4: A clarification sentence was added on the time point for primary database lock. "The primary database lock at Week 24 for the two cohorts may happen at different times depending on the recruitment rates".

Section 7: The following below text was deleted.

Male subjects must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

Table 8-1, 8-2, 8-3, and 8-4:

Anti-RO/SSA

Footnote number 3 (Table 8-1, 8-3) was updated to reflect the mandatory Anti-RO/SSA testing at screening.

[redacted]

CMV Monitoring

Footnote number 6 (Table 8-1, 8-2, 8-3) and Footnote number 8 (Table-8-4) was updated to reflect that CMV IgG, IgM and DNA (by PCR) will be done for all subjects at screening. Local lab testing of CMV IgG, IgM and DNA (by PCR) performed every 4 weeks for the first 6 months and every 3 months thereafter until end of study.

Ophthalmic Assessment

[redacted]

Table 8-6 Table 8-6 laboratory evaluation was updated to reflect the CMV monitoring requirements.

[redacted]

Section 8.2: CMV Guidance to Investigators was added.

Section 8.3.2: Based on the EULAR ESSDAI user guide (Seror et al 2015), an inconsistency was observed under pulmonary domain of the questionnaire. The description column of the questionnaire states "persistent cough **or** bronchial involvement" instead of "persistent cough **due to** bronchial involvement". A communication will be sent to all Investigators informing the sites about this inconsistency and referring to the version of the EULAR ESSDAI user guide (Seror et.al 2015) that needs to be considered while evaluating the patients.

[redacted]

Section 9.2.1: The following below text was deleted.

Pregnancy outcomes should be collected for the pregnant partner of any male who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

Section 12: The below lines were inserted to provide more clarity

"The analysis for cohort 1 and analysis for cohort 2 may occur at different time points depending on patient recruitment and preparation timelines (please refer to Section 6.4)."

Section 12.5: The below lines were inserted for to provide more clarity.

"If primary database locks (week 24) for the two cohorts happen at different times, the safety, immunogenicity and PK analysis at the time of database lock for first cohort will include only data of one cohort. The corresponding analysis at the time of database lock for the second cohort and final analysis will include data pooled from both cohorts".

Section 12.7: The below lines were inserted to provide more clarity.

[redacted]

"The analysis for cohort 1 and analysis for cohort 2 may occur at different time points depending on patient recruitment and preparation timelines (please refer to Section 6.4)".

Table 16.7 and 16.9 Blood volume required for Hepatitis, CMV and HIV at screening increased from 3.5ml to 12ml. Total blood volume at screening was increased to 25.5 ml from exiting 17 ml due to CMV screening procedure.

Section 16.7 Appendix 7 UK ESSPRI English version was replaced with US ESSPRI version for consistency.

Additionally, this protocol amendment includes the correction of typographical and formatting errors and minor editorial changes for increased clarity of the text. Consequently, a small number of changes were implemented throughout the protocol.

IRBs/IECs

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Protocol summary

Protocol number	CCFZ533B2201
Full Title	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)
Brief title	Study of safety and efficacy of multiple doses of CFZ533 in two distinct populations of patients with Sjögren's Syndrome
Sponsor and Clinical Phase	Novartis Phase IIb
Investigation type	Biological
Study type	Interventional

Purpose and rationale	The purpose of this trial is to
	• determine the dose-response of iscalimab in a population of patients with moderate-to-severe Sjögren's Syndrome (SjS), defined by ESSDAI ≥5 and ESSPRI ≥5 (Cohort 1)
	• evaluate the preliminary efficacy and safety of iscalimab administered in a population of patients with low ESSDAI (<5) but high symptom burden (Cohort 2) defined by:
	  • ESSPRI fatigue ≥5 or ESSPRI dryness ≥5 and
	  • Moderate ocular disease burden as measured by the Impact of Dry Eye on Everyday Life (IDEEL) questionnaire.
	The dual cohort design of this trial allows the concurrent study of two clinically distinct patient populations with Sjögren's Syndrome, both characterized by high unmet need.

Primary Objectives	The primary objectives of the study are defined separately for each cohort. **Cohort 1**: To demonstrate a dose-response of CFZ533 (iscalimab) based on change in ESSDAI from baseline at Week 24. **Cohort 2**: To estimate the effect of CFZ533 (iscalimab) [redacted] s.c. on the change in ESSPRI at Week 24.

Secondary Objectives	**Cohort 1**
	• To demonstrate a dose response of iscalimab based on change in ESSPRI from baseline 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
	• 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.
	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
	• 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

[redacted]

	• the effect of iscalimab on plasma CXCL-13 over time.
	Cohort 1 & 2
	• To assess
	  • safety and tolerability of iscalimab
	  • immunogenicity of iscalimab
	  • the pharmacokinetics and dose-exposure relationship of iscalimab
	• To measure soluble CD40 in plasma

Study design	Study CFZ533B2201 (TWINSS) is a double-blind, randomized, placebo-controlled, multicenter study to evaluate the safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of multiple doses of CFZ533 in 2 distinct populations of patients with 1) moderate-to-severe SjS (systemic and symptomatic involvement) and 2) low systemic involvement but high symptom burden.
Population	The study population will consist of 2 Cohorts: **Cohort 1**: adult male and female patients with moderate-to-severe SjS (systemic involvement (ESSDAI ≥5) and symptomatic (ESSPRI ≥5). It is planned to randomize approximately 160 patients into this cohort. **Cohort 2**: adult male and female patients with low systemic involvement (ESSDAI <5) but high symptom burden (ESSPRI fatigue ≥5 or ESSPRI dryness ≥5). It is planned to randomize approximately 100 patients into this cohort.
Key Inclusion criteria	**Both cohorts:** • Male or female patient ≥ 18 years of age • Classification of Sjögren's Syndrome according to ACR/EULAR 2016 criteria (Shiboski et al 2017) • Seropositive for anti-Ro/SSA antibodies • Stimulated whole salivary flow rate of ≥ 0.1 mL/min. **Inclusion criteria specific for Cohort 1:** • Screening ESSDAI score ≥ 5 within the following 8 organ domains: constitutional, lymphadenopathy, glandular, articular, cutaneous, renal, hematologic and biologic. • Screening ESSPRI score of ≥ 5. **Inclusion criteria specific for Cohort 2:** • Screening ESSDAI value < 5 within 8 predefined domains • Screening ESSPRI fatigue subscore ≥ 5 or ESSPRI dryness subscore ≥ 5

Key Exclusion criteria	**Exclusion criteria**
	• Sjögren's Syndrome overlap syndromes where another autoimmune rheumatic disease constitutes the principle illness, specifically:
	  • Moderate-to-severe active systemic lupus erythematosus (SLE) with anti-dsDNA positivity and renal involvement, or other organ involvement that impedes on ability to score ESSDAI domains
	  • Active rheumatoid arthritis (RA) that impedes on the ability to score the ESSDAI articular domain
	  • Systemic sclerosis
	  • Any other concurrent connective tissue disease (e.g. lupus nephritis (LN), large vessel vasculitis (LVV), Sharp syndrome (mixed connective tissue disease) that is active and requires immunosuppressive treatment outside the scope of this trial and would impede on Sjögren's Syndrome organ domain assessments
	• Prior treatment with any of the following within 6 months prior to randomization:
	  • B-cell depletors (e.g. rituximab, ianalumab (VAY736)) unless CD19+ B cell count have returned to ≥ 50 cells/µL; abatacept (CTLA4-Fc Ig), anti-tumor

[redacted]

	necrosis factor alpha (TNFα) mAb, intravenous/subcutaneous Ig; plasmapheresis; i.v. or oral cyclophosphamide, i.v. or oral cyclosporine A any other immunosuppressants (e.g. JAK inhibitors or other kinase inhibitors) unless explicitly allowed. • Use of steroids (predniso(lo)ne or equivalent corticosteroids) at dose >10 mg/day. • Use of steroids and synthetic disease-modifying antirheumatic drugs (DMARDS) at inconsistent dose within 3 months prior to randomization. • Uncontrolled ocular rosacea (affecting the eye adnexa), posterior blepharitis or Meibomian gland disease (this criterion applies only to patients considered for Cohort 2) • Active viral, bacterial or other infections requiring systemic treatment at the time of screening or enrollment, or history of recurrent clinically significant infection or of bacterial infections with encapsulated organisms. • Receipt of live/attenuated vaccine within a 2-month period prior to randomization, during treatment and for at least 14 weeks thereafter. • Chronic infection with hepatitis B (HBV) or hepatitis C (HCV) • Evidence of active CMV infection in the form of a positive serology for CMV IgM (in the absence or presence of positive CMV IgG) and/or quantifiable CMV DNA by PCR at screening. • Note: patients with detectable but NOT quantifiable CMV DNA titers may be eligible for the study. • Evidence of active tuberculosis (TB) infection.
Study treatment	CFZ533 (iscalimab) or placebo, administered as two 2 mL bi-weekly subcutaneous (Q2W s.c.) injections. Overall duration of study treatment is 48 weeks, divided into treatment periods 1 (TP1) and 2 (TP2) of 24 weeks each. **Cohort 1 (n=160)** • **Arm A** – iscalimab [redacted] s.c. for 48 weeks (TP1 + TP2) • **Arm B** – iscalimab [redacted] s.c. for 48 weeks (TP1 + TP2) • **Arm C** – iscalimab [redacted] .c. for 48 weeks (TP1 + TP2) • **Arm D/D1** – placebo s.c. for 24 weeks (TP1). Switch to iscalimab [redacted] s.c. for 24 weeks in TP2. • **Cohort 2** (n=100) • **Arm E** – iscalimab [redacted] s.c. for 48 weeks (TP1 + TP2) • **Arm F/F1** – placebo s.c. for 24 weeks TP1. Switch to iscalimab [redacted] s.c. for 24 weeks in TP2.
Efficacy assessments	• ESSDAI • ESSPRI • FACIT-Fatigue • IDEEL (symptom bother module) • Physicians Global Assessment (PhGA)
Pharmacodynamic assessments	Soluble CD40 in plasma
Pharmacokinetic assessments	Trough iscalimab plasma concentrations
Key safety assessments	Adverse event monitoring, physical examinations, vital signs, monitoring of laboratory markers in blood and urine, monitoring of IgM and IgG levels.
[redacted]	

[redacted]

	[redacted]
Data analysis	Analysis on efficacy endpoints and evaluation of potential biomarkers for the study will be performed separately for each cohort, while safety, immunogenicity and PK analysis will be performed on data pooled from both cohorts. If primary database locks (week 24) for the two cohorts happen at different times, the safety, immunogenicity and PK analysis at the time of database lock for first cohort will include only data of one cohort. The corresponding analysis at the time of database lock for the second cohort and final analysis will include data pooled from both cohorts. **Cohort 1:** The dose response relationship of CFZ533 in regard to the change from baseline in ESSDAI at Week 24 will be characterized based on the data collected for the four CFZ533 dose levels of 0 mg (Placebo), [redacted] The generalized MCP-Mod method will be implemented using ESSDAI measurements from all time points up to Week 24 to confirm an overall dose-response signal and to estimate the optimum dose for achieving clinically relevant benefits of CFZ533 over placebo. Statistical testing will be performed at one-sided 5% alpha level. If the dose response relationship of CFZ533 in ESSDAI is statistically evidenced, a secondary analysis to demonstrate dose response of iscalimab based on change from baseline in ESSPRI at Week 24 will be performed using the same MCP-Mod method. This hierarchical testing procedure ensures an overall type I error rate of 5%. The change from baseline in ESSPRI, FACIT-F and PhGA at Week 24 will also be analyzed using mixed effect model for repeated measurement (MMRM). The adjusted mean change from baseline and the differences of iscalimab arms with placebo, along with 95% confidence intervals, will be estimated. Additional sensitivity analyses for the primary endpoint may be performed. **Cohort 2:** The difference between the iscalimab [redacted] s.c. and placebo arms in the change from baseline in ESSPRI total score, FACIT-F and PhGA at Week 24 will be estimated along with the 95% confidence interval. The difference between the two arms in the proportions of subjects achieving at least 12 points improvement on IDEEL dry eye symptom bother module score after 24 weeks will also be summarized. No hypothesis testing for the analysis in Cohort 2. A supportive analysis for the primary analysis of Cohort 2 will be performed by pooling subjects with ESSPRI fatigue ≥ 5 or ESSPRI dryness ≥ 5 from Cohort 1 with the Cohort 2 subjects.
Key words	Sjögren's Syndrome, sicca syndrome, dryness, fatigue, autoimmune disease, ESSDAI, ESSPRI, monoclonal antibody, anti-CD40, CFZ533, iscalimab, TWINSS

[redacted]

1 Introduction

1.1 Background

Sjögren's Syndrome (SjS) is a chronic autoimmune disease of unknown etiology, characterized by lymphoid infiltration and progressive destruction of exocrine glands. Although primarily organ-specific for the lacrimal and salivary glands, the inflammatory process can target any organ (Asmussen et al 1996). Thus, the clinical features range from dryness, pain and fatigue affecting nearly all patients, to severe, extra-glandular and systemic involvement in a more limited subset. The increased B-cell activity underlying SjS also results in an increased risk for malignant transformation, with lymphoma development occurring in up to 5% of SjS patients (Ramos-Casals et al 2005, Theander et al 2011). SjS is second only to rheumatoid arthritis (RA) in prevalence as a systemic autoimmune disease, with an estimated prevalence of 0.2%-0.5%. The disease affects mainly women with a female/male ratio of 9:1 and can occur at any age (Qin et al 2015).

Current standard of care (SoC) treatment for SjS patients is limited to symptomatic care for the mucosal signs and symptoms (dryness). Steroids and conventional disease-modifying antirheumatic drugs (DMARDs), although used in selected patients, have not been proven efficacious, and no pharmacologic intervention is effective against the severe, disabling fatigue. Hence, there are no approved treatments available for active, systemic disease.

CFZ533 (iscalimab), a fully human Fc-silenced, non-depleting, Immunoglobulin G1 (IgG1) anti-CD40 monoclonal antibody (mAb) blocking the CD154-induced activation of CD40 pathway signaling, thereby preventing CD40 pathway signaling and activation of all $CD40^{+}$ cell types (B-cells, activated parenchymal cells, antigen presenting cells). The relevance of the CD40/CD154 pathway for autoimmunity and inflammation in multiple cell types and functions is well established (Karnell et al 2018). In the context of SjS, the most important molecular and cellular action of iscalimab is expected to be inhibition of T cell-dependent antibody response (TDAR) responses and disruption of germinal center formation in secondary lymphoid tissues in the affected salivary glands.

The therapeutic hypothesis was successfully tested in a first proof-of-concept (PoC) study of iscalimab in patients with primary Sjögren's Syndrome (pSS). Briefly, in this randomized controlled trial, the primary endpoint of European Sjögren's Syndrome Disease Activity Index (ESSDAI) improvement was met, along with improvements in patient reported outcomes (PRO) including fatigue (Fisher et al 2017); also please see Investigator's Brochure Edition 9 for details. The overall risk/benefit profile was favorable, warranting continued development in this indication.

1.2 Purpose

The purpose of this trial is two-fold:

1. to determine the dose-response of CFZ533 (iscalimab) in a population of patients with moderate-to-severe SjS, defined by (i) ESSDAI ≥ 5 and (ii) complementary EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) ≥5
2. to evaluate the preliminary efficacy and safety of iscalimab administered on top of standard treatment in a population of low ESSDAI (< 5) but high symptom burden,

[redacted]

defined by (i) ESSPRI fatigue ≥ 5 or ESSPRI dryness ≥ 5, and (ii) moderate ocular disease burden (measured by the Impact of Dry Eye on Everyday Life (IDEEL) tool) compared to placebo on top of standard treatment.

Both ESSDAI and ESSPRI are validated outcome measures in SjS and currently accepted by Health Authorities (HA) as complementary endpoints in registration trials. Key efficacy and safety data from both cohorts will be used to define the most appropriate dose(s) of iscalimab for subsequent clinical studies (i.e. Phase 3).

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objectives	Endpoints
Primary objectives	**Endpoints for primary objective(s)**
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 24 weeks 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 24 weeks 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
• 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
• 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
	Cohort 1
	• Change from baseline in
	  • ESSPRI at Week 24
	  • FACIT-F score at Week 24
	  • PhGA overall disease activity scores at Week 24
	  • 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
  • PhGA 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
• To assess
  • the effect of iscalimab in the serum FLC levels over time
	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 visits up to end of study

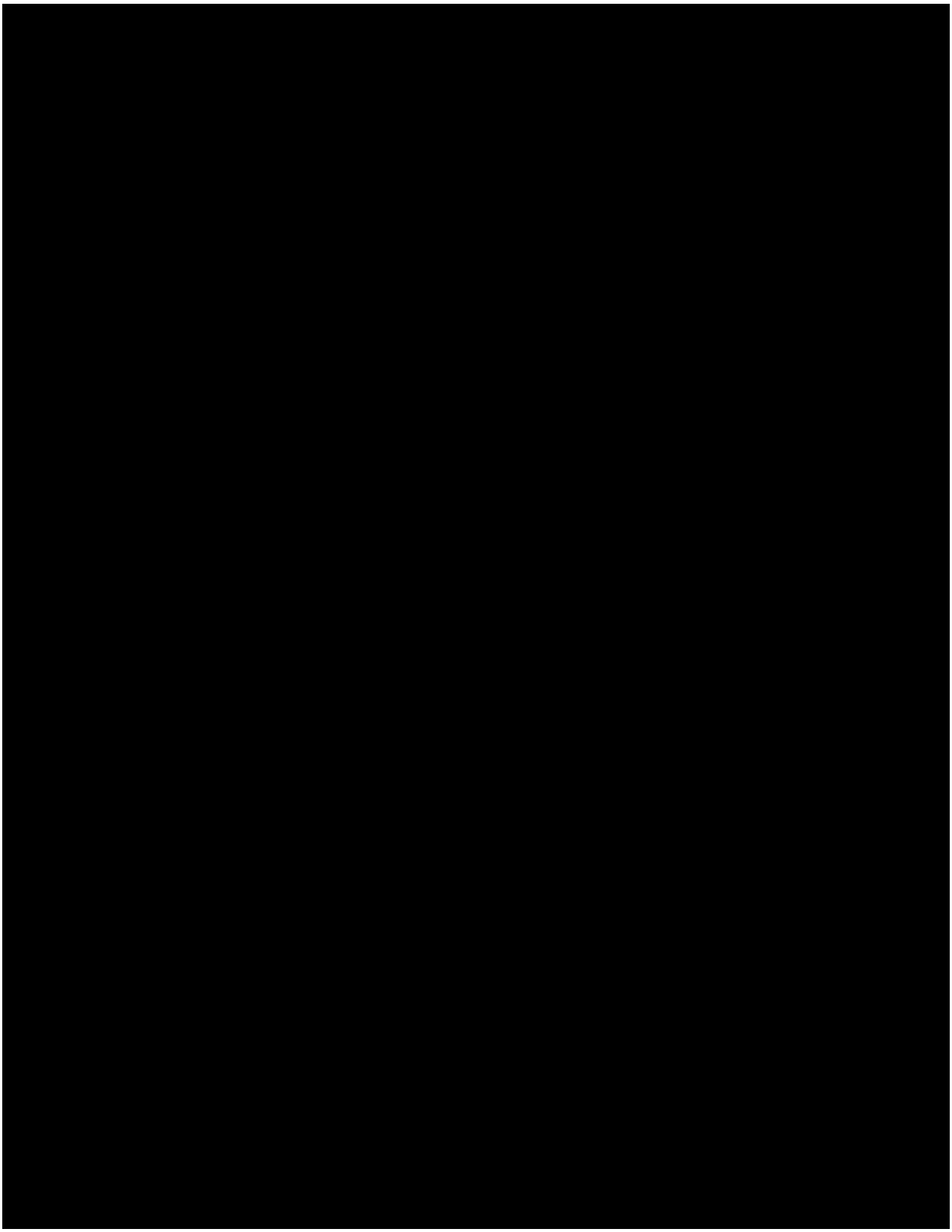
[redacted]

Objectives	Endpoints
• the changes in IgG and IgM levels over time after iscalimab treatment • the effect of iscalimab on plasma CXCL-13 over time	• 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
  • safety and tolerability of iscalimab
  • immunogenicity of iscalimab
  • the pharmacokinetics and dose-exposure relationship of iscalimab
• To measure soluble CD40 in plasma
	Cohort 1 & 2
	• Incidence of Treatment-emergent AEs (TEAEs) /Serious Adverse Events (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
	• Incidence of anti-iscalimab antibodies in plasma at analysis visits up to end of study
	• Free iscalimab concentration in plasma during the treatment (Ctrough) and follow-up (up to end of study) periods
	• Free or total soluble CD40 in the absence or presence of iscalimab, respectively at analysis visits up to end of study

[redacted]

[redacted]



3 Study design

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 study, planned to enroll approximately 160 patients. Cohort 2 is a randomized, double-blinded, placebo-controlled proof-of-concept study, planned to enroll approximately 100 patients. Cohort 2 part will be conducted at selected sites that have the collaboration with an ophthalmologist/qualified ophthalmic professional and current capabilities necessary to perform the ophthalmic assessments specific to that cohort (e.g., the ability to obtain required ocular dyes).

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.

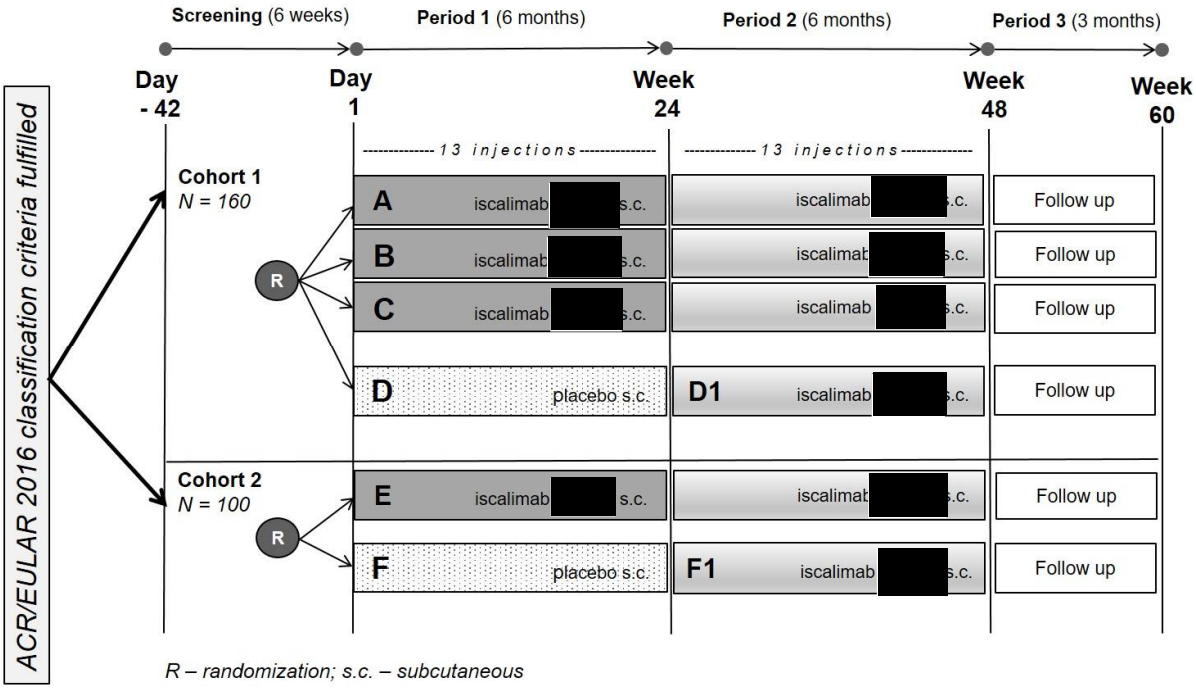
- Patients who score ESSDAI ≥ 5 within 8 selected domains (constitutional, lymphadenopathy, glandular, articular, cutaneous, renal, hematologic and biologic) and meet additional criteria, will be randomized to Cohort 1 (1:1:1:1 ratio) into one of three iscalimab arms (A, B, C) or to placebo (Arm D). In each of these four Cohort 1 treatment arms, approximately 40 patients will be randomized.
- Patients with ESSDAI < 5 (within 8 selected domains) may be further evaluated for eligibility for the low ESSDAI (< 5) and high symptom burden 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). In each of these two Cohort 2 treatment arms, approximately 50 patients will be randomized.
- In both cohorts patients can continue their stable standard of care treatment (as per 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 weekly loading regimen (2 visits) at the start of each treatment period. One administration equals two s.c. injections.An interim analysis (IA) may be performed to assess the dose-response relationship of CFZ533 after at least 50% of patients in Cohort 1 have completed their Week 24 visit or discontinued prior to that. The results from the interim analysis (IA) may inform future clinical development planning.

Primary analysis will occur at Week 24 including all patients but the analysis for cohort 1 and analysis for cohort 2 may occur at different time points depending on patient recruitment and preparation timelines (please refer to Section 6.4). While maintaining the blinding at Week 24, patients in the placebo arms D and F will be automatically switched to iscalimab (Arms D1 and F1, respectively) for treatment Period 2. All other patients (Arms A, B, C and E) will continue with their randomized iscalimab treatment from Period 1 into Period 2 (additional 24 weeks). The purpose of this second treatment period is to collect longer-term efficacy and safety data in a controlled, double-blinded fashion, while minimizing the number of patients who will continue to receive only placebo.

[redacted]

Figure 3-1 TWINSS Study design



Screening	Double-blind treatment Period 1		Double-blind treatment Period 2		Follow-up
6 weeks	24 weeks		24 weeks		12 weeks
	Loading regimen weekly	Maintenance Q2W	Loading regimen weekly	Maintenance Q2W	
	2 weeks (weekly visits)	22 weeks (visits every 2 wks)	2 weeks (weekly visits)	22 weeks (visits every 2 wks)	

4 Rationale

4.1 Rationale for study design

The dual cohort design chosen for this trial allows the concurrent study of two patient populations with SjS, both characterized by high unmet need: (i) patients with moderate-to-severe systemic involvement (defined by ESSDAI score ≥ 5) and (ii) patients with low systemic involvement (ESSDAI < 5) but high symptom burden, defined by high scores of fatigue and dryness in patient reported outcomes (ESSPRI and IDEEL).

The 24-week randomized, placebo-controlled design was previously used in interventional phase 2 SjS studies (Devauchelle-Pensec et al 2014, Mariette et al 2015). The 24-week blinded treatment period is justified in this indication because SjS is a slow progressing disease, placebo is given on top of standard treatments, and no approved, systemic therapy for SjS exists. Further, all patients receiving placebo in treatment Period 1 will be switched to active treatment in Period 2. Standard treatments for SjS include local remedies such as pilocarpine to control sicca

symptoms. According to local practice in some patients systemic medications such as low-dose steroids, hydroxycholoroquine or methotrexate (MTX) are used.

Treatment Period 2 is also designed as a 24-week period to allow the adequate assessment of continued treatment effects and risk/benefit at steady state.

A follow-up period of 14 weeks after last dose is required and calculated based on the non-linear drug elimination (target mediated disposition) of iscalimab – see Section 4.2 below for detailed pharmacokinetics (PK) considerations.

4.1.1 Rationale for choice of background therapy

Local remedies for symptom relief and systemic background medication as per local practice is allowed, as long as patients are on stable dose and in accordance with the inclusion exclusion criteria (see Section 6.2.1).

4.2 Rationale for dose/regimen and duration of treatment

Dosing regimen for Cohort 1

CFZ533 (iscalimab) or placebo will be administered subcutaneously (s.c.), weekly for the first 3 doses in Period 1 (P1; Weeks 0, 1 and 2) and in Period 2 (P2; Weeks 24, 25 and 26), then, from Week 2 (P1) or from Week 26 (P2), iscalimab or placebo will be administered s.c. bi-weekly (every other week or Q2W). This is illustrated in Figure 4-1 for Arms A, B, C and D/D1.

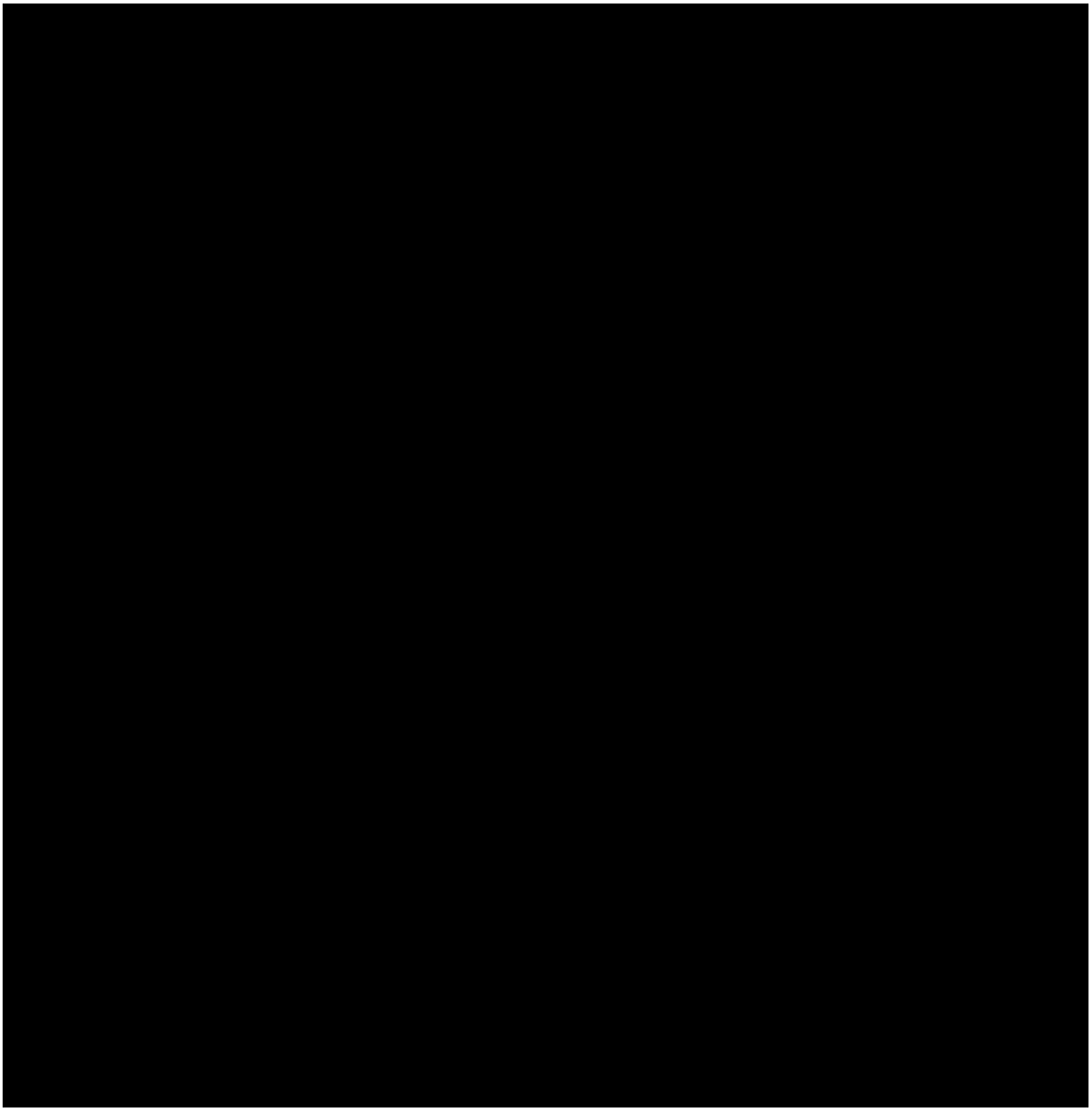
[redacted]

[redacted]

- In **Arm A** the 3 weekly s.c. loading doses of iscalimab are [redacted] on Weeks 0, 1 and 2. From Week 2 and up to Week 46 (last dose), iscalimab is administered s.c. bi-weekly at [redacted] To maintain blinding in Period 2, placebo is administered at Week 25.
- In **Arm B** the 3 weekly s.c. loading doses of iscalimab are [redacted] on Week 0, and [redacted] on Week 1 and Week 2. From Week 2 and up to Week 46 (last dose), iscalimab is administered s.c. bi-weekly at [redacted]. To maintain blinding in Period 2, placebo is administered at Week 25.
- In **Arm C** the 3 weekly s.c. loading doses of iscalimab are [redacted] on Week 0, [redacted] on Week 1 and Week 2. From Week 2 and up to Week 46 (last dose), iscalimab is administered s.c. bi-weekly at [redacted]. To maintain blinding in Period 2, placebo is administered at Week 25.
- In **Arm D** placebo treatment is administered s.c. weekly for the first 3 doses, then bi-weekly from Week 2 to Week 22 in P1. In P2 (**Arm D1**), patients receive 3 weekly s.c. loading doses of [redacted] iscalimab on Week 24, 25 and 26. After Week 26 and up to Week 46 (last dose), iscalimab is administered bi-weekly at [redacted]

The pharmacokinetic profiles for SjS patients in Arms A, B and C are presented in Figure 4-2.

[redacted]



Predicted time-course for the median iscalimab (CFZ533) concentrations in plasma for the typical SjS subject in Arm A (s.c. loading doses followed by a s.c. bi-weekly (Q2W) maintenance regimen), Arm B (s.c. loading doses and s.c. Q2W maintenance regimen) and Arm C (s.c. loading doses and s.c. Q2W maintenance regimen).

Rationale for the loading doses

Iscalimab is subject to CD40-mediated elimination (or target mediated drug disposition (TMDD)), and the level of expression of CD40 receptors in target tissues has the potential to affect exposure to iscalimab, and ultimately target engagement. High CD40 expression may be associated with high elimination rate of iscalimab and loss of CD40-CD40L pathway blockade if CD40 receptors are not fully saturated. The loading doses are aiming to achieve, at start of

treatment, CD40 receptor saturation and minimal CD40-mediated elimination, in conditions where CD40 expression is enhanced. In each arm, the loading doses are also aiming to rapidly obtain close to steady state conditions for iscalimab concentration in plasma.

The 3 weekly loading doses of iscalimab in SjS patients are guided by PK data collected in the proof-of-concept (PoC) Study CCFZ533X2203 in pSS (Figure 4-3).

In Cohort 1 of the PoC study, iscalimab was administered at 3 mg/kg s.c. (on Days 1, 15, 29, and 57 in the placebo-controlled period, and on Days 85, 99, 113, and 141 in the open labelled period). PK data in this cohort indicated sub-optimal iscalimab plasma concentrations, and only few patients had iscalimab concentrations above 10 µg/mL (not shown). Iscalimab concentrations in this cohort were well below the threshold of 40 µg/mL which has been associated, in non-human primates (NHP), with complete suppression of germinal center development in cortical B cell areas of lymph nodes (26-week toxicity study in cynomolgus monkey; 1 mg/kg weekly), and of T cell dependent antibody response (recall antibody responses to immunization challenge; more details in the Investigator's Brochure). PK and soluble CD40 plasma data in this cohort suggested an efficient pre-systemic CD40-mediated elimination of iscalimab (efficient first pass effect), possibly in the interstitium, lymphatic capillaries and/or lymph nodes. This is supported by the fact that pSS patients with an EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) ≥ 6 generally have a systemic disease with extraglandular/systemic manifestations and lymph node enlargement in addition to glandular manifestations. As CD40 has been reported to be upregulated on parenchyma in inflamed tissues, an increased level of CD40 receptors could be responsible for the efficient CD40-mediated elimination of iscalimab under sub-optimal doses or regimen.

In Cohort 2 of the PoC study, iscalimab was administered at 10 mg/kg i.v. (on Days 1, 15, 29, and 57 in the placebo-controlled period, and on Days 85, 99, 113, and 141 in the open labelled period). With the exception of Day 15/Day 99, mean trough iscalimab plasma concentrations were generally between about 100 and 200 µg/mL. Based on efficacy data, clear improvements in the primary endpoint (EULAR SjS Disease Activity Index - ESSDAI) were seen after 12 weeks of treatment in the 10 mg/kg CFZ533 group as compared to placebo (difference in change from baseline ESSDAI of at least 5). Trends in most secondary endpoints also favored CFZ533 with more pronounced effects seen in the 10 mg/kg i.v. vs the 3 mg/kg s.c. group. In the open labelled period, sustained efficacy was seen in patients who were initially randomized to the 10 mg/kg CFZ533 arm and some improvement were observed when placebo patients were switched to 10 mg/kg i.v. iscalimab. Based on interim data, multiple doses of 10 mg/kg i.v. iscalimab (for a total of eight doses over 21 weeks) have been well-tolerated in patients with pSS. Collectively these data support the idea that an efficient dosing regimen in pSS patients may require a loading regimen (i.v. or s.c.), providing early full CD40 saturation and minimal target-mediated disposition followed by a s.c. maintenance regimen.

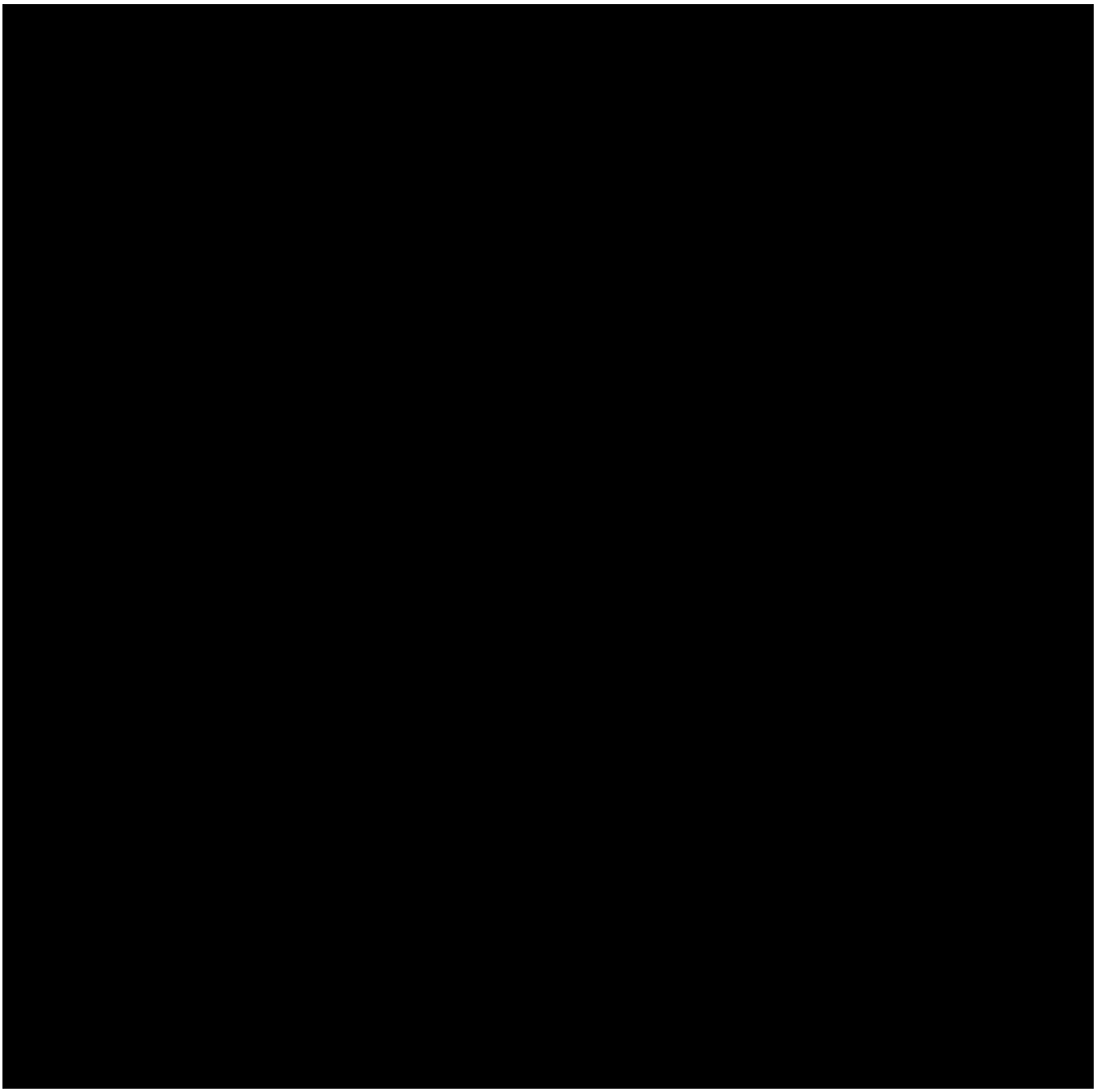
Cohort 3 of the PoC study tested 2 dosing regimens, to explore whether either an i.v. or a s.c. loading regimen (both followed by a s.c. maintenance regimen) had the ability to overcome the CD40-mediated elimination of CFZ533 observed in Cohort 1 (3 mg/kg s.c.) and to deliver steady state trough plasma concentrations similar to the 10 mg/kg i.v. regimen in Cohort 2.

- In Cohort 3/Arm 1 (n = 13), iscalimab was administered at [redacted] s.c. weekly on 4 occasions (loading doses), followed by [redacted] s.c. weekly on 9 occasions (maintenance regimen starting on study Day 29).

[redacted]

- In Cohort 3/Arm 2 (n = 12), the loading dose consisted of a single i.v. dose of 10 mg/kg iscalimab on Day 1, followed by [redacted] s.c. weekly doses of iscalimab on 12 occasions (maintenance regimen starting on Day 8).

PK data from Cohort 2 and Cohort 3 of the PoC study CCFZ533X2203 are presented in Figure 4-3.



In Cohort 2 iscalimab was administered at 10 mg/kg i.v. (on Day 1, 15, 29, and 57 in the placebo-controlled period, and on Day 85, 99, 113, and 141 in the open labelled period).

[redacted]

In Cohort 3 / Arm 1, iscalimab was administered at [redacted] s.c. weekly on 4 occasions (loading regimen), followed by [redacted] s.c. weekly on 9 occasions (maintenance regimen starting on study Day 29). In Cohort 3 / Arm 2, the loading dose consisted of a single i.v. dose of 10 mg/kg iscalimab on Study Day 1, followed by [redacted] s.c. weekly doses of iscalimab on 12 occasions (maintenance regimen starting on Day 8).

PK data from Cohort 3-Arm 1 indicated that,

- A s.c. loading regimen was able to overcome the CD40-mediated elimination of iscalimab (and efficient first-past effect) observed in Cohort 1 (3 mg/kg s.c.), and that an i.v. loading regimen is not necessary
- A single s.c. dose of [redacted] iscalimab at Day 1 was able to deliver plasma concentrations that were generally above 40 µg/mL after 1 week (a threshold associated with pharmacodynamic effects in tissues in NHPs).

Also, these data indicated that a [redacted] s.c. weekly maintenance regimen was able to deliver trough CFZ533 plasma concentrations between about 100 and 200 µg/mL, provided good observance of the weekly dosing schedule.

In the TWINSS study,

- The [redacted] s.c. loading dose in applied on Day 1/Week 0 for Arm A, B, and C in P1, and on Week 24 for Arm D1 in P2, to overcome CD40-mediated elimination of iscalimab at start of treatment.
- Subsequent weekly doses on Week 1 and 2 in Arm A, B, C and on Week 25 and 26 in Arm D1 are aiming (i) to maintain CFZ533 plasma levels above 40 µg/mL, and (ii) to deliver iscalimab trough levels that are close to expected steady state conditions, while ensuring that iscalimab concentrations during the first 3 weeks do not exceed too much steady state conditions (no 'overshooting') and do not skew the clinical readout at Week 24.
- Based on our predictions, at Week 24, Arm A ([redacted] Q2W) and Arm B [redacted] Q2W) will be in steady state conditions, and Arm C ([redacted] Q2W) in close-to-steady state conditions.

Rationale for the maintenance regimen

In **Arm A**, the [redacted] s.c. Q2W regimen is expected to deliver a median steady state trough plasma level at about 144 µg/mL (90% of the population within 282 - 46 µg/mL), in the upper range of trough levels observed in the PoC Study CCFZ533X2203-Cohort 2 (i.v. regimen; these concentrations were associated with clinical efficacy and suppression of a biologically relevant biomarker CXCL13 - a marker of germinal center activity).

In **Arm B**, the [redacted] s.c. Q2W regimen is in between the [redacted] s.c. [redacted] s.c. Q2W regimen. It is expected to deliver a median steady state trough plasma level at about 54 µg/mL (90% of the population within 125 - 0.1 µg/mL), with a reasonable chance to show efficacy in SjS.

In **Arm C**, considering the between subject variability in PK observed in Cohort 3 of the PoC study ([redacted] s.c. weekly; Figure 4-3), the [redacted] s.c. Q2W regimen is expected to deliver a median steady state trough plasma level at about 12 µg/mL (range 50 to < 0.1 µg/mL), and may

[redacted]

represent a sub-optimal regimen. The [redacted] s.c. Q2W regimen is expected to be on the lower end of the exposure-efficacy relationship.

The between subject variability in exposure within Arm B and Arm C (to a lesser extent in Arm A) is likely to depend on the biology of CD40 in target tissues (expression level, turnover) and its potential modulation during the treatment period.

Dosing regimen for Cohort 2

Similar to Cohort 1, in Cohort 2 iscalimab or placebo will be administered s.c. weekly for the first 3 doses in P1 (Week 0, 1 and 2) and in P2 (Week 24, 25 and 26), then, from Week 2 (P1) or from Week 26 (P2), iscalimab or placebo will be administered s.c. bi-weekly. This is illustrated in Figure 4-4 for Arm E and F/F1.

[redacted]

- In **Arm E,** the 3 weekly s.c. loading doses of iscalimab are [redacted] on Week 0, 1 and 2. From Week 2 and up to Week 46 (last dose), iscalimab is administered s.c. bi-weekly at [redacted] To maintain blinding in P2, placebo is administered at Week 25.
- In **Arm F,** placebo treatment is administered s.c. weekly for the first 3 doses, then bi-weekly from Week 2 to Week 22 in P1. In P2 (**Arm F1**), patients receive 3 weekly s.c. loading doses of iscalimab: [redacted] on Week 24, and [redacted] on Week 25 and Week 26. After Week 26, iscalimab is administered s.c. bi-weekly at [redacted]

The weekly schedule at start of P2 (Weeks 24, 25 and 26) is maintained as in P1 to preserve blinding in Cohort 2.

The loading doses in Cohort 2 (all arms) are justified for the same reasons as for Cohort 1.

In **Arm E**, the [redacted] s.c. Q2W maintenance regimen is expected to deliver steady state trough plasma levels that are associated with clinical efficacy in SjS.

In Period 2 **Arm F1** (patients previously treated with placebo in P1), the [redacted] s.c. Q2W maintenance regimen has a reasonable chance to show efficacy in SjS.

[redacted]

The [redacted] s.c. Q2W maintenance regimen tested in Cohort 1 will not be tested in Cohort 2, to avoid exposing too many patients from this study to iscalimab levels that are expected to be sub-optimal for efficacy.

Rationale for the duration of the safety follow-up period (target engagement after the last dose)

Based on predicted median CFZ533 plasma concentration-time profile at [redacted] s.c. Q2W regimen, at about 14 weeks after the last dose, iscalimab plasma concentrations are expected to drop below 20 µg/mL with no expected pharmacodynamic activity in target tissues (e.g. germinal centers; data from non-human primates - please see current Investigator's Brochure).

A 14-week follow-up period after the last dose of iscalimab has been selected for the study and is justified to monitor for any related serious adverse events (SAE).

4.3 Rationale for choice of control drug (placebo)

Placebo will be comparator treatment for iscalimab. Current standard of care treatment for SjS patients is limited to a symptomatic care for the mucosal signs and symptoms (dryness). Steroids and conventional DMARDs are largely ineffective, and no pharmacologic intervention is effective against the severe, disabling fatigue. There are no approved treatments available for moderate-to-severe (i.e. systemic) SjS.

4.4 Purpose and timing of interim analyses/design adaptations

An interim analysis may be conducted when at least 50% of subjects in Cohort 1 have completed the Week 24 visit or discontinued prior to that. Site staff, investigators and subjects will remain blinded until final database lock. Additional information is presented in Section 12.7 (Interim analysis) and Section 6.4 (Treatment blinding).

The primary analysis for both cohorts of the study will be performed after all subjects of each cohort finish the Week 24 visit or are early terminated from the study before that. The analysis for cohort 1 and analysis for cohort 2 may occur at different time points depending on patient recruitment and preparation timelines (please refer to Section 6.4).

The final analysis of the study will be performed at the end of the study. The end of study is defined when all randomized patients have completed Week 60 or discontinued earlier.

4.5 Risks and benefits

The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring.

Risks:

In the indication of SjS there are no identified risks beyond those described in detail in Section 7 of the current edition of the CFZ533 Investigator's Brochure (IB).

The potential safety concerns in humans and the investigator guidance related to administration of CFZ533 are based on the data from the available clinical trials with CFZ533, preclinical and toxicological data, as well as experience with other compounds of the same class.

[redacted]

Important Potential Risks for CFZ533 are summarized in Table 4-1 below:

Table 4-1 Potential risks associated with CFZ533

Risk 1 Vaccination Failure
Vaccination of subjects during treatment with CFZ533 and prior to clearance of the antibody is likely to result in therapeutic failure (i.e., non-protective antibody titers) due to the pharmacologic activity of the antibody.
Risk 2 Infections
Subjects treated with CFZ533 may be at an increased risk of infection. CD40 ligation is linked to the functional activity of antigen presentation, as well as T-cell priming, B-cell differentiation, antibody production and immune memory. Administration of CFZ533 is expected to result in general immunosuppression with a decreased capacity to mount a response to novel immunogens, including those of bacterial, viral, fungal and parasitic origin when full receptor occupancy has been achieved. Although the ability to mount a primary immune response will be affected by CFZ533, the memory B-cell repertoire should remain intact and protective. In addition, subjects will have adequate preformed antibody to maintain protective humoral response for extended periods of time (months). The patients will be monitored for any signs and symptoms of the infection including serology tests for CMV infection.
Risk 3 Thrombosis
There is a hypothetical risk for thromboembolic complications when targeting this co-stimulatory pathway. This risk is based on clinical results from previous compounds (e.g. BG9588, IDEC-131) which have targeted CD154 (CD40 ligand) and resulted in a fatal hyper-coagulation phenotype. Although the risk is theoretical, hematologic and coagulation parameters will be monitored in the current study. Furthermore, patients with conditions such as antiphospholipid syndrome, who are at a higher risk for thromboembolism, will be excluded unless they are receiving antithrombotic prophylaxis. Both preclinical and clinical data from an extensive Phase 2 clinical program across healthy subjects and patients across different indications have not indicated a risk of thrombosis with CFZ533.
Risk 4 Immunogenicity
There is a risk of developing anti-CFZ533 antibodies. However, it is likely that CFZ533 doses will achieve complete receptor occupancy during the treatment period. In these conditions, it is expected that CFZ533 will retain its capacity to block immune responses, including those directed against the drug itself, neutralizing or not. Samples will be collected during study to assess immunogenicity. Immunogenicity will be monitored during clinical development and the consequences of an immune response to CFZ533 could be correlated with, a loss of exposure (PK), a loss of peripheral CD40 receptor occupancy (PD), and/or the appearance of immune related adverse events.
Risk 5 Malignancy including Lymphoproliferative disease
With immunosuppression there is a risk of developing lymphoproliferative disorders. Of note, lymphomas are also known to occur more frequently in patients with pSS as compared to the age- and sex-matched control population. No signs of Lymphoproliferative disorders have been observed in NHP studies, or in clinical trials in healthy volunteers or patients where CFZ533 was evaluated. Hematology will be regularly monitored for changes consistent with a lymphoproliferative disorder. A physical examination will be performed to check for unusual lymphadenopathy in the absence of infection.

One fatal event (potential CMV infection) was reported in the CCFZ533X2202 clinical trial in Lupus nephritis, suspected to be related to the study medication by the investigator.

The event was confounded by CMV infection present before first intake of the study medication. The ultimate cause of death remains unclear; however, the events leading to fatal outcome could have been associated with the CMV infection and/or with a bacterial superinfection, and a role of study drug cannot be excluded.

Currently the causal effect of CFZ533 remains unclear, however, active viral infections do remain a potential risk. Therefore, specific detection measures have been implemented with

[redacted]

amendment 1# to monitor the risk of CMV infection across the clinical development program for CFZ533.

The infections including CMV are considered as an important potential risk for CFZ533 and continue to be adequately monitored and mitigated in CFZ533B2201 study. Therefore, the fatal case with potential CMV infection from CCFZ533X2202 study is not considered to impact the overall risk-benefit ratio.

Lastly, women of childbearing potential (WOCBP) must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study. In order to participate in the study, they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

For further information on the above specific risks and other potential adverse effects of the compound please refer to Section 7 of the CFZ533 Investigator's Brochure.

Benefits:

The study design allows that all patients are treated with standard treatment for SjS, including systemic treatments such as hydroxychloroquine or immunosuppressive medicines where indicated, as long as the dose is kept stable (Section 6.2.1). Thus, there is some benefit expected also for patients randomized to the control arms, and the potential risks and benefits from these medicines are known. Based on the safety and efficacy data from the exploratory PoC study of iscalimab in pSS, it is possible that a number of patients in some or all iscalimab dose arms experience clinically important benefit from iscalimab treatment in the current study.

Systemic treatment of patients with lower ESSDAI scores, who nevertheless have active disease as evidenced by measures of disease burden has precedence (Devauchelle-Pensec et al 2014, Bowman et al 2017). In general, there is a positive risk-benefit expected for systemic treatment with a MOA-targeted biologic such as iscalimab also in this subgroup of low ESSDAI patients. Moreover, some evidence of presence of systemic SjS disease is required in Cohort 2. However, this patient population has not been studied with iscalimab before and therefore, it cannot be ruled out that patients belonging to the low ESSDAI subgroup may have limited or no benefit from iscalimab treatment.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities (i.e., pandemic, epidemic or natural disaster), mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Population

The study population will consist of male and female patients ≥ 18 years, with SjS defined according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2016 classification criteria (Shiboski et al 2017).

[redacted]

Approximately 260 patients will be enrolled in both Cohorts: approximately 160 patients in Cohort 1, and approximately 100 patients in Cohort 2.

In Cohort 1, each of the four treatment arms will consist of approximately 40 patients (160 in total), in Cohort 2 each of the two treatment arms will consist of approximately 50 patients (100 in total).

Subjects eligible for Cohort 1 must have ESSDAI score ≥ 5 (within 8 predefined organ domains) and a mean ESSPRI score of ≥ 5. Subjects with ESSDAI score of < 5 within the 8 domains but with high symptom burden, defined as score ≥ 5 points on ESSPRI fatigue or ESSPRI dryness scale, will be eligible for Cohort 2. Subjects screened for, and enrolled in Cohort 2 at selected sites will also undergo additional ophthalmological examinations to determine severity of their ocular dryness.

The justification for the above ESSDAI restrictions on the study population is a widely accepted proposal advocated by the scientific community to define SjS patients with ESSDAI ≥ 5 as having moderate-to severe disease, and patients with ESSDAI ≥ 14 having severe disease (Seror et al 2016). Further, the restriction to 8 domains is justified based on (i) previous clinical experience that several ESSDAI domains are insensitive to change (e.g the polyneuropathy domain), irrespective of the study medication chosen (Ramos-Casals et al 2015), and (ii) based on interrogation of patient level results in the Novartis PoC studies, where certain domains appeared infrequent and/or less likely to respond.

Subjects eligible for Cohort 2 are representative of a large sub-population of SjS patients, not yet widely investigated in the randomized clinical trial (RCT) setting, who suffer from active disease defined by substantial symptom burden, who have some features of systemic autoimmune disease such as presence of autoantibodies and hypergammaglobulinemia, but do not meet the ESSDAI threshold of moderate-to-severe disease. These patients have a reduced health-related quality of life due to a profound, and frequently disabling fatigue, as well as complications resulting from oral and/or ocular, and/or vaginal dryness. Moreover, patients with low ESSDAI scores may also develop lymphoma (Papageorgiou et al 2015, Brito-Zerón et al 2017, De Vita et al 2018).

5.1 Inclusion criteria

Subjects eligible for inclusion into both cohorts must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Male or female patient ≥ 18 years of age
3. Classification of Sjögren's Syndrome according to ACR/EULAR 2016 criteria (Shiboski et al 2017)
4. Seropositive for anti-Ro/SSA antibodies
5. Stimulated whole salivary flow rate of ≥ 0.1 mL/min
6. Able to communicate well with the Investigator to understand and comply with the requirements of the study

Inclusion criteria specific for Cohort 1:

7. Screening ESSDAI value ≥ 5 within the following 8 organ domains: constitutional, lymphadenopathy, glandular, articular, cutaneous, renal, hematologic and biologic

[redacted]

- Patients with involvement of one or more of the remaining 4 domains are eligible but scores of these domains will not contribute to the assessment for eligibility for Cohort 1
- At selected sites participating in Cohort 2, patients who based on the above criterion 7, do not qualify for Cohort 1, should be further evaluated for Cohort 2

8. Screening ESSPRI score of ≥5

Inclusion criteria specific for Cohort 2:

9. Screening ESSDAI value < 5 within 8 domains scored for inclusion criterion #7 Cohort 1
10. Screening ESSPRI fatigue subscore ≥ 5 or ESSPRI dryness subscore ≥ 5
11. Hypergammaglobulinemia defined by IgG greater than upper limit of normal (ULN) or lymphocytopenia (less than lower limit of normal (LLN)) or hypocomplementemia (low C3, or low C4 - when considered due to disease activity and not due to genetic factors)
12. Score of ≥ 30 on IDEEL symptom bother questionnaire at Screening

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study:

1. Sjögren's Syndrome overlap syndromes where another autoimmune rheumatic disease constitutes the principle illness, specifically:

- Moderate-to-severe active systemic lupus erythematosus (SLE) with anti-dsDNA positivity and renal involvement, or other organ involvement that impedes on ability to score ESSDAI domains
- Active rheumatoid arthritis (RA) that impedes on the ability to score the ESSDAI articular domain
- Systemic sclerosis
- Any other concurrent connective tissue disease (e.g. lupus nephritis (LN), large vessel vasculitis (LVV), Sharp syndrome (mixed connective tissue disease) that is active and requires immunosuppressive treatment outside the scope of this trial and would impede on Sjögren's Syndrome organ domain assessments

2. Use of other investigational drugs within 5 half-lives of enrollment or within 30 days whichever is longer, or longer if required by local regulations
3. Prior treatment with any of the following within 6 months prior to randomization:
    - B-cell depletors (e.g. rituximab, ianalumab (VAY736)) unless $CD19^+$ B cell count have returned to ≥ 50 cells/µL
    - abatacept (CTLA4-Fc Ig)
    - anti-tumor necrosis factor alpha (TNFα) mAb
    - intravenous/subcutaneous Ig; plasmapheresis; i.v. or oral cyclophosphamide
    - i.v. or oral cyclosporine A
    - any other immunosuppressants (e.g. JAK inhibitors or other kinase inhibitors) unless explicitly allowed in criterion #5
4. Use of steroids (predniso(lo)ne or equivalent corticosteroid) at dose > 10 mg/day

[redacted]

5. Use of steroids and synthetic disease-modifying antirheumatic drugs (DMARDS) at inconsistent dose and within 3 months prior to randomization

NOTE:

Subjects treated with predniso(lo)ne or hydroxychloroquine (HCQ) or methotrexate (MTX) or azathioprine (AZA) at a consistent dose within predefined dose limits for ≥ 3 months prior to randomization are eligible, if a stable dose is maintained throughout the study

If azathioprine is discontinued prior to enrollment, a minimum washout period of 30 days prior to randomization is required

6. Any one of the following laboratory values at screening:
   - Hemoglobin levels below 8.0 g/dL
   - White blood cells (WBC) count < 2.0 x 10^3/μL
   - Platelet count < 100.0 x 10^3/μL
   - Absolute neutrophil count (ANC) < 1.5 x 10^3/μL (one re-test is allowed during the screening period)
7. Uncontrolled ocular rosacea (affecting the eye adnexa), posterior blepharitis or Meibomian gland disease (this criterion applies only to patients considered for Cohort 2)

NOTE:

Controlled is defined as a stable condition, not as an asymptomatic condition. If the patient is doing lid scrubs and/or warm compresses to control these conditions, they must continue with their normal regimen. However, patients must have been utilizing these therapies for at least 30 days prior to screening, no new regimens should be added, and no current regimens should be discontinued during the study

8. Active viral, bacterial or other infections requiring systemic treatment at the time of screening or enrollment, or history of recurrent clinically significant infection or of bacterial infections with encapsulated organisms
9. History of major organ, hematopoietic stem cell or bone marrow transplant
10. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes (e.g. mAb of IgG1 class) or to any of the constituents of the study drug (sucrose, L-Arginine hydrochloride, L-histidine, polysorbate 80, hydrochloric acid)
11. Required regular use of medications known to cause dry mouth/eyes as a regular and major side effect, and which have not been on a stable dose for at least 30 days prior to Screening, or any anticipated change in the treatment regimen during the course of the study
12. Use of topical ocular prescription medications (excluding artificial tears, gels, lubricants) that have not been on a stable dose for at least 90 days prior to Screening, or any anticipated change in the treatment regimen during the course of the study
13. Receipt of live/attenuated vaccine within a 2-month period prior to randomization, during treatment and for at least 14 weeks thereafter.
14. History of primary or secondary immunodeficiency, including a positive human immunodeficiency virus (HIV) (ELISA and Western blot) test result

[redacted]

15. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin, in situ cervical cancer or SjS-related lymphoma), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
16. History of sarcoidosis
17. Patients who are at significant risk for thromboembolic events based on the following:
    - History of either thrombosis or 3 or more spontaneous abortions
    - Presence of lupus anticoagulant or significantly prolonged partial thromboplastin time (PTT) consistent with co-existent anti-phospholipid syndrome and without concurrent prophylactic treatment with aspirin or anticoagulants as per local standard of care
18. Any surgical, medical (e.g., uncontrolled hypertension, heart failure or diabetes), psychiatric or additional physical condition that the Investigator feels may jeopardize the patient in case of participation in this study
19. Chronic infection with hepatitis B (HBV) or hepatitis C (HCV). Positive serology for hepatitis B surface antigen (HBsAg) excludes the subject. HBsAg negative patients who are hepatitis B core antibody (HBcAb) positive are also excluded except if both following criteria are met: 1) HBV DNA is negative and 2) hepatitis B monitoring is implemented (i.e. HBsAg and HBV DNA tested monthly for the first six months and every three months thereafter). Subjects with a positive HCV antibody test should have HCV ribonucleic acid (RNA) levels measured. Subjects with positive (detectable) HCV RNA must be excluded.
20. Evidence of active CMV infection in the form of a positive serology for CMV IgM (in the absence or presence of positive CMV IgG) and/or quantifiable CMV DNA by PCR at screening.

Note: patients with detectable but NOT quantifiable CMV DNA titers may be eligible for the study.

21. Evidence of active tuberculosis (TB) infection (after anti-TB treatment, patients with history of or latent TB may become eligible according to national guidelines)
22. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human Chorionic Gonadotropin (hCG) laboratory test
23. Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 14 weeks after stopping of investigational drug

Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
- Male sterilization (at least 6 months prior to screening and confirmed as successful). For female patients in the study, the vasectomized male partner should be the sole partner for

[redacted]

that patient. In case the vasectomized male partner is not the sole partner of the female patient, highly effective method of contraception must be applied (double barrier contraception is not sufficient)

- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment she is considered not of childbearing potential.

In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the Informed Consent Form (ICF).

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

The following drugs will be used in this study and will be administered in accordance with this protocol and where applicable, current local labeling. CFZ533 (iscalimab) in a liquid is provided in vials of [redacted]/1 mL as a solution for subcutaneous administration. Placebo liquid is also provided in vials of 0 mg/1 mL as a solution for subcutaneous administration. Novartis Global Clinical Supply (GCS) will supply the following investigational products:

Table 6-1 Investigational and control drug

Investigational/Control Drug (name and strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
CFZ533 [redacted] mL	Solution for injection	Subcutaneous Use	Open-label; vials	Novartis Pharma AG (global)
CFZ533 Placebo 1mL	Solution for injection	Subcutaneous Use	Open-label; vials	Novartis Pharma AG (global)
Instructions for preparation and administration of CFZ533 (iscalimab) and matching placebo are described in a separate pharmacy manual.				

6.1.2 Additional study treatments

Not applicable.

[redacted]

6.1.3 Treatment arms/group

Study subjects will be screened by the Investigator to one of the two Cohorts (Cohort 1 or Cohort 2), within which they will be randomized to one of the treatment arms as follows (for sake of simplicity, only the maintenance regimen is indicated below; for a full description of the dosing regimens in Cohort 1 and Cohort 2, please see Section 4.2):

Cohort 1

Treatment Period 1

- **Arm A** - iscalimab [redacted] s.c. every 2 weeks (Q2W)
- **Arm B** - iscalimab [redacted] s.c. Q2W
- **Arm C** - iscalimab [redacted] s.c. Q2W
- **Arm D** - placebo s.c. Q2W

Treatment Period 2

At Week 24, subjects will be automatically assigned double-blinded treatment for Period 2 as follows:

Patients in the 3 iscalimab treatment arms will continue with their originally assigned doses:

- **Arm A** - iscalimab [redacted] s.c. Q2W
- **Arm B** - iscalimab [redacted] s.c. Q2W
- **Arm C** - iscalimab [redacted] s.c. Q2W

Patients in **Arm D** (placebo) will be switched to:

- **Arm D1** - iscalimab [redacted] s.c. Q2W

Cohort 2

Treatment Period 1

- **Arm E** - iscalimab [redacted] s.c. Q2W
- **Arm F** - placebo s.c. Q2W

Treatment Period 2

At Week 24, subjects will be automatically assigned double-blinded treatment for Period 2 as follows:

Patients in the iscalimab treatment arm will continue with their originally assigned dose:

- **Arm E** - iscalimab [redacted] s.c. Q2W

Patients in **Arm F** (placebo) will be switched to:

- **Arm F1** - iscalimab [redacted] s.c. Q2W

6.1.4 Treatment duration

The overall planned duration of study treatment is 48 weeks, split between Period 1 (24 weeks) and Period 2 (24 weeks). Patients may be discontinued from treatment earlier (see Section 9.1.1).

[redacted]

Every effort will be made to continue provision of study treatment for subjects, who derive clinical benefit from iscalimab (after completing the 48 weeks of treatment). An extension study may be considered. Details of such a study including length, eligibility criteria, dose and dosing frequency, assessment schedule and monitoring requirements will be defined in a separate protocol or a protocol amendment.

6.2 Other treatment(s)

Patients experiencing disease signs and symptoms may receive short-term symptomatic care with over-the-counter, anti-inflammatory/analgesic agents such as nonsteroidal anti-inflammatory drugs (NSAID) and paracetamol. Patients whose SjS disease signs and symptoms are not adequately controlled by symptomatic care, and/or who suffer from more severe SjS disease manifestations not suitable for such treatment, may receive rescue therapy with corticosteroids, if determined by the Investigator to be medically necessary (Section 6.2.3). However, any increases in corticosteroid dosing during the blinded treatment period to treat increased SjS disease activity may result in the patient labeled as a non-responder for primary endpoint (see Table 6-2 and Table 6-3 for allowed and prohibited concomitant medications, respectively).

There is currently no consensus on the definition of flare in SjS. With reference to the recently completed JOQUER trial in pSS (Gottenberg et al 2014) that reported 12 flares among 120 patients during 12 months, it is conceivable that < 10% of all patients in the current iscalimab trial will experience a deterioration (or 'flare') that warrants treatment escalation. Treatment escalation would, for example, be increasing the steroid dose, or introducing de novo an immunosuppressant agent like azathioprine. Patients who require escape treatment (other than allowed rescue medications – see Section 6.2.3) must be discontinued from study medication, enter the safety follow-up period and follow the local standards for treatment of SjS worsening. In the absence of consensus guidelines for treatment of systemic manifestations in SjS, it is recommended to consult the SLE treatment guidelines as far as they pertain to the respective organ involvement observed in the trial (for example renal, nervous system or skin vasculitis).

Any medication used to treat Adverse Events (AE) must be recorded on the Case Report Form (CRF).

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded on the appropriate Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the Investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

Concomitant treatment may include standard of care for dry eye and dry mouth symptoms, such as the use of artificial tears and artificial saliva/salivary stimulants (e.g., cevimeline, pilocarpine) at the discretion of the treating physician. Amount and frequency of use should be recorded at each visit. Please refer to Table 6-2 for guidance on suggested treatment time pause prior to

[redacted]

assessment of clinical disease outcome measurements. Artificial tears and artificial saliva are to be provided by the study center or personal physician.

Table 6-2 Dry eye/dry mouth treatment time pause prior to study assessments

Treatment Type	Time Interval
Artificial tears or other topical ophthalmic medications	4 hrs
Artificial saliva	4 hrs
Pilocarpine (oral or topical)	12 hrs
Cevimeline or other salivary stimulants	24 hrs or 5x times half-life whichever is longer

Short term use of oral analgesics (NSAIDs, paracetamol) is permitted. Azathioprine (up to [redacted]day), methotrexate (≤ 25 mg/week) and hydroxychloroquine (≤ 400 mg/day) are allowed as stable background medication defined as continued treatment ≥ 3 months without dose adjustments. Steroids (prednisone or equivalent ≤ 10 mg/day) are allowed and patients must be on a stable dose for at least 3 months prior to randomization and during the Period 1. After 24 weeks of study treatment tapering is allowed at intervals not exceeding prednisone 2.5 mg/2 weeks.

Pre-emptive therapy with Lamivudine or Entecavir is allowed for patients with HBsAg seroreversion while on study treatment. Similarly, CMV antiviral medication used as pre-emptive therapy is allowed for patients with detectable virus by PCR.

Note: Background and concomitant medications will not be provided by Novartis and must be supplied by the study center.

6.2.2 Prohibited medication

Use of treatments displayed in the below table is not allowed in study periods as indicated.

Table 6-3 Prohibited medication

Medication	Prohibited in Study Period	Action to be taken
Other experimental therapies	All	Study discontinuation required, patients should remain in the study and follow visit schedule of respective treatment period
Other biologics (for treatment of autoimmune diseases e.g. SjS, SLE, RA)	All	Study discontinuation required, patient should remain in study and follow visit schedule of respective treatment period
DMARDs or other immune suppressive agents or changes in concomitant and allowed DMARD regimen (hydroxychloroquine, methotrexate, azathioprine)	Period 1, Period 2	Study treatment discontinuation may be required on a case-by-case basis
Prednisone >10 mg (or equivalent other corticosteroid)	Period 1, Period 2	Study treatment discontinuation may be required on a case-by-case basis

[redacted]

Medication	Prohibited in Study Period	Action to be taken
Intravenous or oral cyclophosphamide; oral cyclosporine; oral MMF	All	Study treatment discontinuation required in periods 1 and 2. Patient should remain in the study and follow visit schedule of respective treatment period
Existing co-medications observed to cause in an individual patient a major side effect of dry mouth/eyes. Examples include antihistamines, antidepressants, anticholinergics, sedatives, antipsychotic drugs, anti-Parkinson agents A comprehensive guide to medications with documented effects on salivary gland function or symptoms has been published by Wolff et al 2017 (please see the footnote)	Period 1, Period 2	Study treatment discontinuation may be required on a case-by-case basis
Live/attenuated vaccine	Screening (within a 2 month period before baseline, during treatment and for at least 14 weeks thereafter), Period 1, Period 2, and for 5 half-lives after discontinuation of investigational treatment	Study treatment discontinuation. Patient should remain in the study and follow visit schedule of respective treatment period

Wolff A, Joshi RK, Ekström J, et al (2017) A guide to medications inducing salivary gland dysfunction, xerostomia, and subjective sialorrhea: A systemic review sponsored by the World Workshop on Oral Medicine VI; Drugs R D.; 17(1):1-28.

6.2.3 Rescue medication

There is no established, approved immunosuppressive treatment for SjS. Patients may receive NSAIDs, paracetamol, or symptomatic care at the discretion of the treating physician as outlined in Section 6.2.1. Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication (Table 6-3). When in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started. If any of the medications listed in Table 6-3 is deemed a necessary rescue therapy, the investigator must follow the actions to be taken outlined in this table. Rescue treatment is to be provided by the study center or personal physician. Patients must be encouraged to continue the follow-up visits even when discontinued permanently from the study treatment.

Corticosteroids may be administered to patients for SjS clinical disease flares after enrollment into this study as determined necessary by the responsible Investigator. However, patients receiving steroids in addition to the baseline steroid dosing levels will be considered non-responders for primary endpoint if after Week 12 of study treatment:

- the incremental daily steroid dose is > 2.5 mg/day prednisone or equivalent, or
- the increased daily steroid dose is administered > 2 days within a 4-week period.

[redacted]

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) as assigned by Novartis to the investigative site with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available. Once assigned to a subject the subject number will not re-used. The re-screened subject will receive a new Subject Number.

6.3.2 Treatment assignment, randomization

The following methods are used to minimize bias in the assignment:

After completing screening, all eligible subjects will be randomized via Interactive Response Technology (IRT). The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion and does not fulfill any of the exclusion criteria for the specific cohort. Subjects eligible for Cohort 1 are randomized at 1:1:1:1 ratio to the placebo Arm D, iscalimab [redacted] Arm C, iscalimab [redacted] Arm B or iscalimab [redacted] Arm A. Subjects eligible for Cohort 2 will be randomized at 1:1 ratio to either placebo Arm F or iscalimab [redacted] Arm E. IRT will assign a randomization number to the subject, which is then used to link the subject to a treatment arm, and will specify a unique medication number for the first package of study treatment to be dispensed to the subject.

At Week 24, patients who have been randomized to placebo (Cohort 1 Arm D; Cohort 2 Arm F) and who have completed treatment Period 1 will be switched to receive iscalimab during Period 2 (24 weeks). Cohort 1 Arm D subjects will be assigned to iscalimab [redacted] s.c. (Arm D1) and Cohort 2 Arm F subjects will be assigned to iscalimab [redacted] s.c. (Arm F1).

To maintain double blinding, the 3 weekly doses at start of treatment Period 1 will be repeated at start of treatment in Period 2 for all patients.

The randomization numbers are generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list for each cohort is produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers based on the specific cohort the subject was enrolled into. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

For Cohort 1, the randomization will be stratified by screening ESSDAI total score (< 10 or ≥ 10 based on weighted scores). If applicable, separate blocks of randomization numbers will be generated for subjects in Japan to ensure that Japanese patients are equally distributed across all treatment groups in the study.

[redacted]

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office at Novartis.

6.4 Treatment blinding

For the interim analysis (IA), when at least 50% of the subjects in Cohort 1 have completed the Week 24 visit or discontinued prior to that, site staff, investigators and subjects will remain blinded until final database lock (see Section 4.4). Roles and responsibilities of blinded/unblinded sponsor personnel will be described in a separate charter. Sponsor staff responsible for decision-making at the clinical program development level may receive aggregated unblinded results at the time of the interim analysis.

The primary database lock at Week 24 for the two cohorts may happen at different times depending on the recruitment rates. Subjects, investigator, site staff, persons performing the assessments, and the Novartis study team directly involved in the conduct of the trial will remain blinded to the identity of the treatment from the time of randomization until primary database lock for a specific Cohort at Week 24. Specifically, (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study except for staff in Novartis Global Clinical Supply who assigns medications numbers to true study treatment (2) the identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

The randomization codes associated with subjects from whom PK samples are taken will be disclosed to the PK sample analyst(s) who will keep the PK results confidential until primary database lock (Week 24). Blood samples for PK, immunogenicity and CD40 assessment will be collected for all subjects in order to maintain blinding even though only those with iscalimab exposure will be subsequently tested.

In addition, to allow for the development of suitable exposure-response models in time for development decisions triggered by the IA results, the randomization codes will be made available to the PK sample analyst(s) and independent pharmacometrician in a restricted area of the statistical server before the IA.

Unblinding to investigators, site staff and patients will occur in the case of subject emergencies and at the conclusion of the study.

Unblinding of the Clinical Trial Team (CTT) will occur at the time of the primary database lock at Week 24 for each Cohort. Also, the PK data should not be accessible to the CTT other than PK sample analyst(s) before primary database lock at Week 24.

[redacted]

Table 6-4 Blinding and unblinding plan for each cohort

	Time or Event					
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety event (single subject unblinded)**	**Interim Analysis**	**Primary DB lock at Week 24**	**Period 2 Week 48**
Subjects	B	B	B	B	B	B
Site staff	B	B	UI	B	B	B
Unblinded site staff e.g. pharmacy staff (specify)	B	U	NA	U	U	U
Global Clinical Supply and Randomization Office	U	U	U	U	U	U
PK sample analyst(s)	B	U	UI	UI	UI	U
Unblinded Pharmacovigi-lance sponsor staff	B	UI	UI	UI	UI	U
CTT and other sponsor team members (except unblinded sponsor personnel, as described in the row below, and unblinded Pharmacovigilance sponsor staff)	B	B	B	B	U	U
Unblinded sponsor personnel as defined in a separate charter	B	U	UI	U	U	U
Data Monitoring Committee (DMC)	B	U	U	U	U	U
Key:UI: Allowed to be unblinded on individual subject level U: Unblinded B: Remains blinded NA: Not applicable to this study						

6.5 Dose escalation and dose modification

Dose escalation is not applicable in this study.

6.5.1 Dose modifications

Dose modifications of the investigational drug are not permitted.

[redacted]

6.5.2 Dose interruptions

Considering the between subject **variability** of iscalimab plasma concentrations after the [redacted] s.c. weekly regimen in the PoC study CCFZ533X2203 (Cohort 3, Section 4.2, Figure 4-3), and predicted variability in the [redacted] and [redacted] Q2W regimen in this study, **every efforts should be made to respect the weekly dosing schedule (loading doses) and the bi-weekly maintenance dosing regimen in all arms in this trial.**

This is of particular importance,

- To obtain an early saturation of CD40 receptors at start of treatment
- To keep trough plasma levels within expected targets for efficacy and for an appropriate description of the dose (exposure)-efficacy relationship. This trial is evaluating a low dose regimen [redacted] Q2W) that is expected, in some patients, to be sub-optimal. If sustained trough levels are not established, target engagement in tissues is at risk.

Nevertheless, for subjects who are not able to follow the protocol-specified dosing schedule due to unresolved AEs, or for any other reason cannot attend a visit within a time window specified in Section 8, dose interruptions may be occasionally permitted. A **maximum** of 2 doses of study treatment may be missed in each treatment period, as specified below. In case of an AE or for any reason (e.g. non-compliance, operational hurdle) resulting in additional interruptions of the dosing scheme, consultation and agreement with Novartis will be necessary to decide whether the patient can continue or needs to be withdrawn from the treatment.

[redacted]

These changes must be recorded on the appropriate eCRF.

In all cases the **original visit schedule should be maintained** (no recalculation from the last visit).

6.5.3 Follow-up for toxicities

Subjects whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more

[redacted]

frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary. All subjects must be followed up for adverse events and serious adverse events for 14 weeks following the last dose of CFZ533.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The site staff will administer the study treatment assigned by IRT to the subjects during onsite visits. Kit numbers are collected in the IRT and the site staff will record study drug administration in the eCRF. The compliance will also be assessed by means of site and patient-specific drug accountability by Novartis monitors during site monitoring visits using medication pack numbers, drug label information and information from IRT. In this study, the compliance to the planned administration schedule is expected to be high since the study treatment will be administered onsite by trained site staff.

6.6.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken. Subjects unblinded following an intentional emergency code breaking should be discontinued from the study.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- subject number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that unblinding can be performed at any time.

6.7 Preparation and dispensation

Each study site will be supplied with study drug CFZ533 (iscalimab) and placebo by Novartis, in packaging as described under investigational and control drugs section.

A unique medication number is printed on the study medication label.

[redacted]

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document. In addition, the unblinded pharmacist or designee at the Investigator's site will prepare the medication for administration to patients based on a separate pharmacy manual.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

The investigational drug iscalimab will be provided in vials of [redacted] 1mL as a solution for subcutaneous administration. The matching placebo will be provided in vials of 0 mg/1 mL as a solution for subcutaneous administration. Two injections of 2 mL each will be prepared and administered to the patient at every dosing visit, as follows:

- **Arms A, D1 and E**: two 2 mL syringes, each containing [redacted] of iscalimab
- **Arm B and F1**: one 2 mL syringe of placebo and one 2 mL syringe containing [redacted] of iscalimab
- **Arm C**: one 2 mL syringe of placebo and one 2 mL syringe containing [redacted] of iscalimab
- **Arms D and F**: two 2 mL syringes of placebo

An unblinded pharmacist or qualified site personnel needs to be assigned at study site to prepare the study drug for administration. Details will be provided in the Pharmacy Manual.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the subject except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

[redacted]

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

See Figure 4-1 (Cohort 1) and Figure 4-4 (Cohort 2) in Section 4.2 for a detailed description and schematic representation of the dosing events in this trial.

Cohort 1

Treatment Period 1

Patients will be randomized at baseline in ratio 1:1:1:1 into one of the following 4 treatment arms:

Arm A (iscalimab [redacted] s.c. Q2W), n = 40

- Iscalimab loading doses will be [redacted] s.c. (2 injections of 2 mL iscalimab at [redacted]/1mL) on Week 0 (Day 1), Week 1 (Day 8) and Week 2 (Day 15)
- From Week 2 the patient will receive [redacted] s.c. Q2W iscalimab until Week 22.

Arm B (iscalimab [redacted] s.c. Q2W), n = 40

- Iscalimab loading doses will be [redacted] s.c. (2 injections of 2 mL iscalimab at [redacted]1mL) on Week 0 (Day 1), [redacted]s.c. (1 injection of 2 mL iscalimab at [redacted]1mL and 1 injection of 2 mL of the placebo) on Week 1 (Day 8), and [redacted]s.c. k 2 (Day 15)
- From Week 2 the patient will receive [redacted]s.c. Q2W iscalimab until Week 22.

Arm C (iscalimab [redacted] s.c. Q2W), n = 40

- Iscalimab loading doses will be [redacted] s.c. (2 injections of 2 mL iscalimab at [redacted]1mL) on Week 0 (Day 1),[redacted]s.c. (1 injection of 2 mL iscalimab diluted at 75 mg/1mL, and 1 injection of 2 mL of the placebo) on Week 1 (Day 8), and [redacted] s.c. on Week 2 (Day 15)
- From Week 2 the patient will receive [redacted] s.c. Q2W iscalimab until Week 22.

Arm D (placebo s.c. Q2W), n = 40

- Placebo loading doses (2 injections of 2 mL placebo) will be given s.c. on Week 0 (Day 1), Week 1 (Day 8) and Week 2 (Day 15)
- From Week 2 the patient will receive placebo s.c. Q2W until Week 22.

Treatment Period 2

Patients in iscalimab treatment arms will continue on their initially randomized dose level starting from Week 24.

To maintain blinding within Cohort 1 the 3 weekly dose administrations at start of treatment Period 1 (Week 0, 1 and 2) are also maintained at start of treatment Period 2 (Week 24, 25 and 26).

[redacted]

Arm A (iscalimab [redacted] s.c. Q2W)

- Iscalimab loading doses will be [redacted] s.c. (2 injections of 2 mL iscalimab at [redacted] 1mL) on Week 24 (Day 169), placebo s.c. (2 injections of 2 mL placebo) at Week 25 (Day 176) and iscalimab [redacted] s.c. at Week 26 (Day 183)
- From Week 26 the patient will receive [redacted] s.c. Q2W iscalimab until Week 46 (last dose).

Arm B (iscalimab [redacted] s.c. Q2W)

- Iscalimab loading doses will be [redacted] s.c. (1 injection of 2 mL iscalimab at [redacted] 1mL and 1 injection of 2 mL of the placebo) on Week 24 (Day 169), placebo s.c. (2 injections of 2 mL placebo) at Week 25 (Day 176) and iscalimb [redacted] s.c. on Week 26 (Day 183)
- From Week 26 the patient will receive [redacted] s.c. Q2W iscalimab until Week 46 (last dose).

Arm C (iscalimab [redacted] s.c. Q2W)

- Iscalimab loading doses will be [redacted] s.c. (1 injection of 2 mL iscalimab diluted at 75 mg/1mL, and 1 injection of 2 mL of the placebo) on Week 24 (Day 169), placebo s.c. (2 injections of 2 mL placebo) at Week 25 (Day 176) and iscalimab [redacted] s.c. on Week 26 (Day 183).
- From Week 26 the patient will receive [redacted] s.c. Q2W iscalimab until Week 46 (last dose).

Arm D (placebo s.c. Q2W in Period 1) will be switched to:

Arm D1 (iscalimab [redacted] s.c. Q2W)

- Iscalimab loading doses will be [redacted] s.c. (2 injections of 2 mL iscalimab at [redacted] 1mL) on Week 24 (Day 169), Week 25 (Day 176) and Week 26 (Day 183)
- From Week 26 the patient will receive [redacted] s.c. Q2W iscalimab until Week 46 (last dose).

Cohort 2

Treatment Period 1

Patients will be randomized at baseline in ratio 1:1 into one of the following 2 treatment arms:

Arm E (iscalimab [redacted] s.c. Q2W), n=50

- Iscalimab loading doses will be [redacted] s.c. (2 injections of 2 mL iscalimab at [redacted] mL) on Week 0 (Day 1), Week 1 (Day 8) and Week 2 (Day 15)
- From Week 2 the patient will receive [redacted] s.c. Q2W iscalimab until Week 22.

Arm F (placebo s.c. Q2W), n=50

- Placebo loading doses (2 injections of 2 mL placebo) will be given s.c. on Week 0 (Day 1), Week 1 (Day 8) and Week 2 (Day 15)
- From Week 2 the patient will receive placebo s.c. Q2W until Week 22.

[redacted]

Treatment Period 2

Patients in iscalimab treatment arm will continue on their initially randomized dose level starting from Week 24.

To maintain blinding within Cohort 2 the 3 weekly dose administrations at start of treatment Period 1 (Week 0, 1 and 2) are also maintained at start of treatment Period 2 (Week 24, 25 and 26).

Arm E (iscalimab [redacted] s.c. Q2W)

- Iscalimab loading doses will be [redacted] s.c. (2 injections of 2 mL iscalimab at [redacted] mL) on Week 24 (Day 169), placebo s.c. (2 injections of 2 mL placebo) at Week 176) and iscalimab [redacted] s.c. at Week 26 (Day 183).
- From Week 26 the patient will receive [redacted] s.c. Q2W iscalimab until Week 46 (last dose).

Arm F (placebo s.c. Q2W in Period 1) will be switched to:

Arm F1 (iscalimab [redacted] s.c. Q2W)

- Iscalimab loading doses will be [redacted] s.c. (2 injections of 2 mL iscalimab at [redacted] mL) on Week 24 (Day 169), and [redacted] s.c. (1 injection of 2 mL iscalimab at [redacted] mL and 1 injection of 2 mL of the placebo) on Week 25 (Day 176) and Week 26 (Day 183)
- From Week 26 the patient will receive [redacted] s.c. Q2W iscalimab until Week 46 (last dose).

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board/Independent Ethics Committee (IRB/IEC)-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject

[redacted]

informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

[redacted]

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

[redacted]

8 Visit schedule and assessments

Assessment schedule (Table 8-1, Table 8-2, Table 8-3 and Table 8-4) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day as possible.

Every efforts should be made to adhere to the weekly dosing schedule (loading doses) and the bi-weekly maintenance dosing regimen in all arms in this trial.

Visits can be performed with the following time windows:

Treatment Period 1

- +/- 1 calendar day: Week 1 (Day 8) and Week 2 (Day 15)
- +/- 2 calendar days: from Week 4 (Day 29) to Week 8 (Day 57)
- +/- 3 calendar days: from Week 10 (Day 71) to Week 14 (Day 99)
- +/- 5 calendar days: from Week 16 (Day 113) to Week 24 (Day 169)

Treatment Period 2

- +/- 1 calendar day: Week 25 (Day 176) and Week 26 (Day 183)
- +/- 2 calendar days: from Week 28 (Day 197) to Week 32 (Day 225)

[redacted]

- +/- 3 calendar days: from Week 34 (Day 239) to Week 38 (Day 267)
- +/- 5 calendar days: from Week 40 (Day 281) to Week 48 (Day 337)

Follow-up Period

+/- 5 calendar days: from Week 52 (Day 365) to Week 60 (Day 421)

Note: All efforts need to be made to maintain the actual duration of 48-week study treatment period. Therefore, a study visit subsequent to a visit, which has been delayed or brought forward needs to be planned as per original visit schedule (e.g. if a visit Week 16 (Day 113) has been delayed by 3 days, visit Week 18 should not be shifted by 3 days, but scheduled for Day 127).

Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the eCRF.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities (i.e., pandemic, epidemic or natural disaster) that limits or prevents on-site study visits, alternative methods of providing continuing care except study drug administration may be implemented by the investigator as the situation dictates. If allowed by local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consult) or visits by site staff/home nursing staff to the participant´s home can replace certain components of on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

[redacted]

Table 8-1 Assessment Schedule, Cohort 1- Screening and Treatment Period 1

Period	Screening	Cohort 1 - Treatment Period 1													
Visit Name	**Screening**	**Baseline**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**	**Wk 12**	**Wk 14**	**Wk 16**	**Wk 18**	**Wk 20**	**Wk 22**	**Wk 24/ End of TP1/TD[1,2]**
Days	**-42 to -1**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**
Weeks	**-6 to -1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Informed consent	X														
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X													
Study drug administration		X	X	X	X	X	X	X	X	X	X	X	X	X	
Inclusion / Exclusion criteria	X														
Demography	X														
Medical history/current medical conditions	X														
Prior therapy for Sjögren's Syndrome	X														
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	S	S			S		S		S		S		S		S
Vital signs and body measurements	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X														

[redacted]

[redacted]

Period	Screening	Cohort 1 - Treatment Period 1													
Visit Name	**Screening**	**Baseline**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**	**Wk 12**	**Wk 14**	**Wk 16**	**Wk 18**	**Wk 20**	**Wk 22**	**Wk 24/ End of TP1/TD[1,2]**
Days	**-42 to -1**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**
Weeks	**-6 to -1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Tuberculosis test[5]	X														
Hepatitis CMV and HIV screen	X														
Hepatitis and CMV monitoring (local)[6]		S			S		S		S		S		S		S
Hematology	X	X			X		X		X		X		X		X
Clinical Chemistry	X	X			X		X		X		X		X		X
Coagulation Panel[7]	X								X						X
Immunology	X	X			X		X		X		X		X		X
Cryoglobulins[8]	X								X						X
Pregnancy test[9]	X	X			X		X		X		X		X		X
Serum Free Light Chain		X			X				X						X
PK blood collection[10]		X	X	X	X	X	X	X	X		X		X		X
Immunogenicity[10]		X		X	X		X		X		X		X		X
Soluble CD40[10]		X		X	X		X		X		X		X		X
[redacted]															
Urinalysis dipstick	X	X			X		X		X		X		X		X
ESSDAI	X	X			X		X		X		X		X		X
PhGA	X	X			X		X		X		X		X		X

[redacted]

Period	Screening	Cohort 1 - Treatment Period 1													
Visit Name	**Screening**	**Baseline**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**	**Wk 12**	**Wk 14**	**Wk 16**	**Wk 18**	**Wk 20**	**Wk 22**	**Wk 24/ End of TP1/TD[1,2]**
Days	**-42 to -1**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**
Weeks	**-6 to -1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
ESSPRI	X	X			X		X		X		X		X		X
FACIT-Fatigue	X	X			X		X		X		X		X		X
[redacted]															
IDEEL	X	X							X						X
[redacted]															

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
1 The visit week 24 in Treatment Period 1 (TP1) is the first dosing visit of Treatment Period 2 (TP2). Treatment administration for this time point applies as per protocol design.
2 In case of premature discontinuation, subjects will enter the follow up after completing assessments for this visit.
[redacted]
5 Quantiferon-TB Gold or PPD
6 CMV IgG, IgM and DNA (by PCR) will be done for all subjects at screening. Local lab testing of CMV IgG, IgM and DNA (by PCR) performed every 4 weeks for the first 6 months and every 3 months thereafter until end of study. Hepatitis B monitoring applicable to HBsAg (–) patients who are HBcAb (+) and HBV DNA (-) at screening. Local lab testing of HBsAg and HBV DNA must be performed monthly for the first 6 months and every 3 months thereafter until end of study.
7 Testing required at screening for all patients. While on treatment, coagulation monitoring applies only to patients who have antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin antibodies) and/or who are on pre-existing antithrombotic therapy/prophylaxis, as reflected in the exclusion criteria.
8 Cryoglobulins will be tested for all patients at screening. During treatment the analysis will be done only for patients who were positive at screening.
9 Serum pregnancy test will be done at screening and baseline. For remaining visits urine pregnancy test will be performed.
10 Blood sample is collected pre-dose
[redacted]

[redacted]

Period	Screening	Cohort 1 - Treatment Period 1													
Visit Name	Screening	Baseline	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24/ End of TP1/TD[1,2]
Days	-42 to -1	1	8	15	29	43	57	71	85	99	113	127	141	155	169
Weeks	-6 to -1	0	1	2	4	6	8	10	12	14	16	18	20	22	24
[redacted]															

[redacted]

Table 8-2 Assessment Schedule, Cohort 1- Treatment Period 2 and Follow up

Period	Cohort 1 - Treatment Period 2														Post-Treatment Follow-Up		
Visit Name	**Wk 24[1]**	**Wk 25**	**Wk 26**	**Wk 28**	**Wk 30**	**Wk 32**	**Wk 34**	**Wk 36**	**Wk 38**	**Wk 40**	**Wk 42**	**Wk 44**	**Wk 46**	**Wk 48/TD[2]**	**FUP1**	**FUP2**	**FUP3/ End of Study[3]**
Days	**169**	**176**	**183**	**197**	**211**	**225**	**239**	**253**	**267**	**281**	**295**	**309**	**323**	**337**	**365**	**393**	**421**
Weeks	**24**	**25**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**52**	**56**	**60**
Contact IRT		X	X	X	X	X	X	X	X	X	X	X	X	X			
Study drug administration	X	X	X	X	X	X	X	X	X	X	X	X	X[4]				
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination				S		S				S				S	S	S	S
Vital signs and body measurements		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)														X			
[redacted]																	
Hematology				X		X		X		X		X		X	X	X	X
Clinical Chemistry				X		X		X		X		X		X	X	X	X
Coagulation Panel[5]								X						X			
Immunology				X		X				X				X	X	X	X
Hepatitis and CMV monitoring (local)[6]								S						S			S
Cryoglobulins[7]						X				X				X			X
Pregnancy test[8]				X		X		X		X		X		X	X	X	X
serum Free Light Chain						X				X				X		X	X

[redacted]

Period	Cohort 1 - Treatment Period 2														Post-Treatment Follow-Up		
Visit Name	Wk 24[1]	Wk 25	Wk 26	Wk 28	Wk 30	Wk 32	Wk 34	Wk 36	Wk 38	Wk 40	Wk 42	Wk 44	Wk 46	Wk 48/TD[2]	FUP1	FUP2	FUP3/ End of Study[3]
Days	169	176	183	197	211	225	239	253	267	281	295	309	323	337	365	393	421
Weeks	24	25	26	28	30	32	34	36	38	40	42	44	46	48	52	56	60
[redacted]																	
PK blood collection[10]			X	X		X		X		X		X		X		X	X
Immunogenicity[10]			X	X		X		X		X		X		X		X	X
Soluble CD40[10]			X	X		X		X		X		X		X		X	X
[redacted]																	
Urinalysis dipstick				X		X		X		X		X		X	X	X	X
ESSDAI				X		X				X				X	X	X	X
PhGA				X		X				X				X			
ESSPRI				X		X				X				X			
FACIT-Fatigue				X		X				X				X			
[redacted]																	
IDEEL								X						X			
[redacted]																	

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Assessments for visit week 24 are recorded under Treatment Period 1
[2] In case of premature discontinuation, subjects will enter the follow up after completing assessments for this visit.
[3] Mandatory to all subjects, including those who have discontinued the study prematurely.
[4] Week 46 is the last dose administration visit in Period 2.
[5] Testing required at screening for all patients. While on treatment, coagulation monitoring applies only to patients who have antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin antibodies) and/or who are on pre-existing antithrombotic therapy/prophylaxis, as reflected in the exclusion criteria.

[redacted]

Period	Cohort 1 - Treatment Period 2														Post-Treatment Follow-Up		
Visit Name	Wk 24[1]	Wk 25	Wk 26	Wk 28	Wk 30	Wk 32	Wk 34	Wk 36	Wk 38	Wk 40	Wk 42	Wk 44	Wk 46	Wk 48/TD[2]	FUP1	FUP2	FUP3/ End of Study[3]
Days	169	176	183	197	211	225	239	253	267	281	295	309	323	337	365	393	421
Weeks	24	25	26	28	30	32	34	36	38	40	42	44	46	48	52	56	60

[6] CMV IgG, IgM and DNA (by PCR) will be done for all subjects at screening. Local lab testing of CMV IgG, IgM and DNA (by PCR) performed every 4 weeks for the first 6 months and every 3 months thereafter until end of study. Hepatitis B monitoring applicable to HBsAg (–) patients who are HBcAb (+) and HBV DNA (-) at screening. Local lab testing of HBsAg and HBV DNA must be performed monthly for the first 6 months and every 3 months thereafter until end of study.
[7] Cryoglobulins will be tested for all patients at screening. During treatment the analysis will be done only for patients who were positive at screening.
[8] Serum pregnancy test will be done at screening and baseline. For remaining visits urine pregnancy test will be performed.
[redacted]
[10] Blood sample is collected pre-dose
[redacted]

[redacted]

Table 8-3 Assessment Schedule, Cohort 2- Screening and Treatment Period 1

Period	Screening	Cohort 2 - Treatment Period 1													
Visit Name	**Screening**	**Baseline**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**	**Wk 12**	**Wk 14**	**Wk 16**	**Wk 18**	**Wk 20**	**Wk 22**	**Wk 24/ End of TP1/TD[1,2]**
Days	**-42 to -1**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**
Weeks	**-6 to -1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Informed consent	X														
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X													
Study drug administration		X	X	X	X	X	X	X	X	X	X	X	X	X	
Inclusion / Exclusion criteria	X														
Demography	X														
Medical history/current medical conditions	X														
Prior therapy for Sjögren's Syndrome	X														
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	S	S			S		S		S		S		S		S
Vital signs and body measurements	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X														
[redacted]															
Tuberculosis test[5]	X														
[redacted]															

Period	**Screening**	**Cohort 2 - Treatment Period 1**													
Visit Name	**Screening**	**Baseline**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**	**Wk 12**	**Wk 14**	**Wk 16**	**Wk 18**	**Wk 20**	**Wk 22**	**Wk 24/ End of TP1/TD[1,2]**
Days	**-42 to -1**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**
Weeks	**-6 to -1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Hepatitis, CMV and HIV screen	X														
Hepatitis and CMV monitoring (local)[6]		S			S		S		S		S		S		S
Hematology	X	X			X		X		X		X		X		X
Clinical Chemistry	X	X			X		X		X		X		X		X
Coagulation Panel[7]	X								X						X
Immunology	X	X			X		X		X		X		X		X
Cryoglobulins[8]	X								X						X
Pregnancy test[9]	X	X			X		X		X		X		X		X
Serum Free Light Chain		X			X				X						X
PK blood collection[10]		X	X	X	X	X	X	X	X		X		X		X
Immunogenicity[10]		X		X	X		X		X		X		X		X
[redacted]															
Urinalysis dipstick	X	X			X		X		X		X		X		X
[redacted]															

Period	Screening	Cohort 2 - Treatment Period 1													
Visit Name	**Screening**	**Baseline**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**	**Wk 12**	**Wk 14**	**Wk 16**	**Wk 18**	**Wk 20**	**Wk 22**	**Wk 24/ End of TP1/TD[1,2]**
Days	**-42 to -1**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**
Weeks	**-6 to -1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
[redacted]															
ESSDAI	X	X			X		X		X		X		X		X
PhGA	X	X			X		X		X		X		X		X
ESSPRI	X	X			X		X		X		X		X		X
FACIT-Fatigue	X	X			X		X		X		X		X		X
[redacted]															
IDEEL	X	X							X						X
[redacted]															

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
1 The visit week 24 in Treatment Period 1 (TP1) is the first dosing visit of Treatment Period 2 (TP2). Treatment administration for this time point applies as per protocol design.
2 In case of premature discontinuation, subjects will enter the follow up after completing assessments for this visit.
[redacted]
5 Quantiferon TB-Gold or PPD

[redacted]

Period	Screening	Cohort 2 - Treatment Period 1													
Visit Name	**Screening**	**Baseline**	**Wk 1**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**	**Wk 12**	**Wk 14**	**Wk 16**	**Wk 18**	**Wk 20**	**Wk 22**	**Wk 24/ End of TP1/TD[1,2]**
Days	**-42 to -1**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**
Weeks	**-6 to -1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**

[6] CMV IgG, IgM and DNA (by PCR) will be done for all subjects at screening. Local lab testing of CMV IgG, IgM and DNA (by PCR) performed every 4 weeks for the first 6 months and every 3 months thereafter until end of study. Hepatitis B monitoring applicable to HBsAg (–) patients who are HBcAb (+) and HBV DNA (-) at screening. Local lab testing of HBsAg and HBV DNA must be performed monthly for the first 6 months and every 3 months thereafter until end of study.

[7] Testing required at screening for all patients. While on treatment, coagulation monitoring applies only to patients who have antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin antibodies) and/or who are on pre-existing antithrombotic therapy/prophylaxis, as reflected in the exclusion criteria.

[8] Cryoglobulins will be tested for all patients at screening. During treatment the analysis will be done only for patients who were positive at screening.

[9] Serum pregnancy test will be done at screening and baseline. For remaining visits urine pregnancy test will be performed.

[10] Blood sample is collected pre-dose

[redacted]

[redacted]

Table 8-4 Assessment Schedule, Cohort 2- Treatment Period 2 and Follow up

Period	Cohort 2 - Treatment Period 2													Post-Treatment Follow-Up		
Visit Name	**Wk 24[1]**	**Wk 25**	**Wk 26**	**Wk 28**	**Wk 30**	**Wk 32**	**Wk 34**	**Wk 36**	**Wk 38**	**Wk 40**	**Wk 42**	**Wk 44**	**Wk 46**	**Wk 48/TD[2]**	**FUP1**	**FUP2**	**FUP3/ End of Study[3]**
Days	**169**	**176**	**183**	**197**	**211**	**225**	**239**	**253**	**267**	**281**	**295**	**309**	**323**	**337**	**365**	**393**	**421**
Weeks	**24**	**25**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**52**	**56**	**60**
Contact IRT		X	X	X	X	X	X	X	X	X	X	X	X	X			
Study drug administration	X	X	X	X	X	X	X	X	X	X	X	X	X[4]				
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination				S		S		S		S		S		S	S	S	S
Vital signs and body measurements		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)														X			
[redacted]																	
Hematology				X		X		X		X		X		X	X	X	X
Clinical Chemistry				X		X		X		X		X		X	X	X	X
Coagulation Panel[7]								X						X			
Immunology				X		X				X				X	X	X	X
[redacted]																	

Period	Cohort 2 - Treatment Period 2														Post-Treatment Follow-Up		
Visit Name	**Wk 24[1]**	**Wk 25**	**Wk 26**	**Wk 28**	**Wk 30**	**Wk 32**	**Wk 34**	**Wk 36**	**Wk 38**	**Wk 40**	**Wk 42**	**Wk 44**	**Wk 46**	**Wk 48/TD[2]**	**FUP1**	**FUP2**	**FUP3/ End of Study[3]**
Days	**169**	**176**	**183**	**197**	**211**	**225**	**239**	**253**	**267**	**281**	**295**	**309**	**323**	**337**	**365**	**393**	**421**
Weeks	**24**	**25**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**52**	**56**	**60**
Hepatitis and CMV monitoring (local)[8]								S						S			S
Cryoglobulins[9]						X				X				X			X
Pregnancy test[10]				X		X		X		X		X		X	X	X	X
Serum Free Light Chain						X				X				X		X	X
[redacted]																	
PK blood collection[12]			X	X		X		X		X		X		X		X	X
Immunogenicity[12]			X	X		X		X		X		X		X		X	X
Soluble CD40[12]			X	X		X		X		X		X		X		X	X
[redacted]																	
Urinalysis dipstick				X		X		X		X		X		X	X	X	X
ESSDAI				X		X				X				X	X	X	X
PhGA				X		X				X				X			
ESSPRI				X		X				X				X			
FACIT-Fatigue				X		X				X				X			
[redacted]																	
IDEEL								X						X			
[redacted]																	

[redacted]

Period	Cohort 2 - Treatment Period 2														Post-Treatment Follow-Up		
Visit Name	Wk 24[1]	Wk 25	Wk 26	Wk 28	Wk 30	Wk 32	Wk 34	Wk 36	Wk 38	Wk 40	Wk 42	Wk 44	Wk 46	Wk 48/TD[2]	FUP1	FUP2	FUP3/ End of Study[3]
Days	169	176	183	197	211	225	239	253	267	281	295	309	323	337	365	393	421
Weeks	24	25	26	28	30	32	34	36	38	40	42	44	46	48	52	56	60

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Study assessments for visit week 24 are defined in Table for Treatment Period 1
[2] In case of premature discontinuation, subjects will enter the follow up after completing assessments for this visit.
[3] Mandatory to all subjects, including those who have discontinued the study prematurely.
[4] Week 46 is the last dose administration visit in Period 2.
[redacted]
[7] Testing required at screening for all patients. While on treatment, coagulation monitoring applies only to patients who have antiphospholipid antibodies (lupus anticoagulant, anti-cardiolipin antibodies) and/or who are on pre-existing antithrombotic therapy/prophylaxis, as reflected in the exclusion criteria.
[8] CMV IgG, IgM and DNA (by PCR) will be done for all subjects at screening. Local lab testing of CMV IgG, IgM and DNA (by PCR) performed every 4 weeks for the first 6 months and every 3 months thereafter until end of study. Hepatitis B monitoring applicable to HBsAg (–) patients who are HBcAb (+) and HBV DNA (-) at screening. Local lab testing of HBsAg and HBV DNA must be performed monthly for the first 6 months and every 3 months thereafter until end of study.
[9] Cryoglobulins will be tested for all patients at screening. During treatment the analysis will be done only for patients who were positive at screening.
[10] Serum pregnancy test will be done at screening and baseline. For remaining visits urine pregnancy test will be performed.
[redacted]
[12] Blood sample is collected pre-dose
[redacted]

[redacted]

8.1 Screening

It is permissible to re-screen a subject if she/he fails the initial screening. Patients can be re-screened only once and no study-related re-screening procedure should be performed prior to written re-consent by the patient.

- Tests for tuberculosis, HIV, Hepatitis B (HB), Hepatitis C (HC) and CMV do not need to be repeated if they satisfied eligibility criteria in the initial screening, and have been conducted within 12 weeks prior to planned date of randomization.

[redacted]

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and are subsequently found to be ineligible prior to randomization, will be considered a screen failure. The reason for screen failure will be recorded on the appropriate Case Report Form. In addition, only the eCRFs related to the following assessments should be completed: informed consent, demography, and inclusion/exclusion criteria. The eCRF for adverse events (AEs) should be completed for any serious adverse events (SAEs) that occurred during the screening period. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

If the subject fails to be randomized, the IRT must be notified within 2 days of the screen fail that the subject was not randomized. Subjects who are randomized and fail to start treatment, e.g. subjects randomized in error, will be considered early terminators. The reason for early termination will be recorded on the appropriate eCRF.

8.2 Subject demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with eCRF.

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race, ethnicity, source of patient referral, relevant medical history/current medical condition present before signing informed consent where possible, diagnoses instead of symptoms will be recorded.

Investigators will have the discretion to record abnormal test findings on the medical history eCRF if, in their judgment, the test abnormality occurred prior to the informed consent signature.

The following assessments are to be done at screening only and will not be repeated after the patient starts the study treatment.

[redacted]

Screening for Hepatitis, CMV and HIV

Hepatitis B

- All patients will be screened for hepatitis B surface antigen (HBsAg), anti-HBs and anti-HBc antibodies.
  - Subjects tested positive for HBsAg will not be eligible for randomization.
  - Patients HBsAg negative, who are hepatitis B core antibody (HBcAb) positive will be further tested for HBV-DNA. If HBV-DNA is negative the patient can be enrolled in the study, providing local monitoring is implemented: HBsAg and HBV-DNA tested monthly for the first 6 months, and every 3 months thereafter until end of study participation, and should be consulted with an expert in hepatitis. Results must be available as source data in patient's medical notes. In case of seroreversion (i.e. if either HBsAg or HBV-DNA turn positive) treatment with Lamivudine or Entecavir must be initiated immediately.
  - Patients positive for anti-HBs due to previous vaccination against HBV are eligible.

Table 16-4 in (Appendix 4) provides detailed HBV serology result interpretations.

Hepatitis C

- Screening for hepatitis C will be based on HCV antibodies. Subjects with a positive HCV antibody test will need to have HCV RNA levels measured. Subjects with positive (detectable) HCV RNA must be excluded.
- **CMV**

Guidance to investigators:

CMV infections will be recorded as Adverse Events. CMV infection is identified by assessments of laboratory and/or clinical signs/symptoms. Active CMV infection is defined as a detectable cytomegalovirus viral load in the absence of signs or symptoms attributable to cytomegalovirus, resulting from either reactivation or primary infection (Ljungman 2017).

Detection during screening and monitoring:

- Subjects are not eligible for participation in the study if they have positive serology for CMV IgM (in the absence or presence of positive CMV IgG) and/or quantifiable CMV DNA by PCR at screening. Note that a patient with detectable but NOT quantifiable CMV DNA test result may be eligible.
- CMV IgM, CMV IgG and DNA tests by PCR will be performed at screening, every 4 weeks for the first 6 months and then every 3 months thereafter until end of study.

Management of asymptomatic, confirmed or probable disease:

- For asymptomatic subjects with active infection reaching a viral load threshold of 1000 CMV DNA copies/mL or higher, consider (1) initiating preemptive anti-CMV therapy in consultation with experts and (2) consider stopping study medication and stopping or reducing the dose of other immunosuppressive agents, (3) increasing CMV monitoring to at least weekly intervals of DNA monitoring by serial PCR assessments as well as clinical monitoring for early signs of CMV end organ disease until resolution, and (4) repeating CMV IgG serology after resolution of primary infection and after completion of study

[redacted]

treatment, if primary CMV infection is suspected based on confirmed prior negative serology CMV IgG.

- In case of probable or proven disease, in consultation with experts, (1) initiate treatment with approved anti-viral agents according to local practice, (2) stop the study medication and consider stopping or reducing the dose of other immunosuppressive agents.

HIV

- Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique.

Appropriate counseling will be made available by the Investigator in the event of a positive finding. Results will be available as source data and will not be recorded within the eCRF.

Screening for Tuberculosis

Determination of the tuberculosis (TB) status will be required before administration of study treatment and should be performed as defined by local guidelines. The TB status must be determined by medical history, signs, symptoms, TB testing (QuantiFERON-TB Gold assay or, if per local requirement only, a purified protein derivative [PPD] test may be performed instead of Quantiferon).

Quantiferon

If the test result is negative, the patient may be randomized.

If the test result is positive, the investigator should perform workup for the test result as per local procedures. If a TB workup was conducted prior to screening the patient, results of the workup can be used to assess eligibility if the workup was conducted within 12 weeks prior to randomization.

If the test result is indeterminate, the investigator may repeat the test once or may proceed directly to perform workup for the test result as per local procedures. This action is at the discretion of the investigator. If the second test is negative, the patient may be randomized.

If the second test is positive or indeterminate, the investigator should perform workup as per local guidelines.

PPD skin test

PPD skin test will be performed as an alternative to Quantiferon in accordance with local guidelines and read at screening or within 6 months prior to randomization in order to evaluate an eventual infection with tuberculosis. The test dose is bioequivalent to 5 tuberculin units (or as according to local standard practice) of standard PPD injected intradermally into usually the volar surface of the forearm. The site is cleansed and the PPD extract is then injected into the most superficial dermal layer of the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

Because the reaction (induration) will take 48-72 hours to develop, the patient must return to the investigators' site within that time for a proper evaluation of the test site. This will determine whether the patient have had a significant reaction to the PPD test. A reaction is measured in millimeters of induration (hard swelling) at the site. A PPD skin induration $\geq$ 5 mm is interpreted as positive result.

[redacted]

Precautions against tuberculosis should be handled according to the best medical practice consistent to the local standards in each country with prior consultation with Novartis.

Patients requiring administration of antibiotics against latent tuberculosis should complete their treatment and should be considered cured prior to being re-considered for entry into this study (consultation with Novartis must occur before allowing the patient to enter the study).

Patients testing positive for latent TB per workup may be randomized to the trial if sufficient treatment has been completed according to local routine clinical practice. Patients testing positive for active TB per workup are not eligible for the study. Patients testing negative for TB (no signs of latent or active TB) per workup may be randomized to the trial.

Sjögren's Syndrome medical history and prior therapies

The date of first diagnosis of SjS will be collected from the patient's medical history. History of any other connective tissue disorders must be recorded on the eCRF.

If the patient had previously received biologics for treatment of SjS, the medications received must be recorded on the appropriate eCRF. These may include infliximab, etanercept, rituximab, ocrelizumab, epratuzumab, belimumab, alefacept and abatacept and investigational drugs (CFZ533 and VAY736). If the patient has been treated previously with a B-cell depleting therapy, then in order to be eligible the B-cell count must be evaluated ($CD19^+$ B-cells must be $\geq$ 50 cells/µL) and a minimum time to last dose must be observed.

If the patient was previously treated with another disease modifying or immunosuppressive therapy for SjS, these must be recorded on the dedicated eCRF. These treatments may include: hydroxychloroquine, methotrexate, azathioprine, mycophenolate, cyclophosphamide and chlorambucil.

8.3 Efficacy

Clinical efficacy measurements related to primary and secondary objectives are outlined in the subsections below.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities (i.e., pandemic, epidemic or natural disaster) that limits or prevents on-site study visits, electronic Clinical Outcome Assessments (eCOA) data may be collected on paper depending on local regulations, technical capabilities, and following any applicable training in the required process. The efficacy assessments and PROs may be completed using the paper back-up option (for details, refer to the eCOA vendor user guide).

8.3.1 Appropriateness of efficacy assessments

Clinical efficacy measurements related to primary and secondary objectives are outlined in the subsections below and include established outcome measures of Sjögren's Syndrome ESSDAI and ESSPRI, [redacted] of the Physician Global Assessment (PhGA) of overall disease activity and patient reported outcomes of FACIT-F and IDEEL.

[redacted]

8.3.2 EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI)

ESSDAI (Appendix 6) is a validated disease outcome measure for SjS that will be applied to the study patients. The instrument contains 12 organ-specific domains contributing to disease activity. For each domain, features of disease activity are scored in 3 or 4 levels according to their severity. These scores are then summed across the 12 domains in a weighted manner to provide the total score. The domains (weights) are as follows: constitutional (3), lymphadenopathy (4), glandular (2), articular (2), cutaneous (3), pulmonary (5), renal (5), muscular (6), peripheral nervous system (PNS) (5), central nervous system (CNS) (5), hematological (2) and biological (1). The maximum possible score is 123.

To calculate ESSDAI, all 12 organ domains must be individually assessed at every scheduled timepoint (from screening visit until end of study). Domain assessments will be entered into a tablet (provided by a central vendor) and ESSDAI score will be calculated by the software. At screening, the ESSDAI subscore from 8 pre-selected domains listed in the inclusion criterion #7, will be calculated to determine patient's eligibility.

Based on the EULAR ESSDAI user guide (Seror et.al 2015), an inconsistency was observed under pulmonary domain of the questionnaire. The description column of the questionnaire states "persistent cough **or** bronchial involvement" instead of "persistent cough **due to** bronchial involvement". A communication will be sent to all Investigators informing the sites about this inconsistency and referring to the version of the EULAR ESSDAI user guide (Seror et.al 2015) that needs to be considered while evaluating the patients.

8.3.3 EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI)

ESSPRI (Appendix 7) is an established disease outcome measure for SjS (Seror et al 2011). It consists of three domains of dryness, pain and fatigue. The subject will assess severity of symptoms they experience on a single 0-10 numerical scale for each of the three domains. The ESSPRI score is defined as mean of scores from the three scales: (dryness + pain + fatigue) /3. ESSPRI will be applied to the study patients at screening, baseline and during study treatment as per study assessment schedule.

8.3.4 Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)

The Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F version 4) is a short, 13-item, easy-to-administer tool that measures an individual's level of fatigue during their usual daily activities over the past week (Webster et al 2003). The level of fatigue is measured on a 5-point Likert scale (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much).

8.3.5 Impact of Dry Eye on Everyday Life (IDEEL)

The Impact of Dry Eye on Everyday Life (IDEEL) questionnaire is a comprehensive dry eye specific questionnaire to evaluate treatment satisfaction, symptom-related bother and impact on daily life in a population with dry eye. This study will only utilize the Dry Eye Symptom-Bother module.

The Dry Eye Symptom-Bother module of IDEEL (Appendix 8) is composed of a single dimension (20 items), A 4-point Likert-like scale is used: from "not at all" to "very much".

[redacted]

Patients can also answer “I did not have this symptom / Not applicable”. One item is scored on a 5-point Likert-like scale from “none of the time” to “all of the time”. The range for the symptom-bother score is 0 to 100, with higher scores indicating greater symptom bother.

8.3.6 Physicians global assessment (PhGA)

Physician's global assessment (PhGA) of disease activity will be performed using a Visual Analog Scale (VAS) - an unnumbered 100 mm horizontal line ranging from "no disease activity" to "maximal disease activity". The assessment of patient's condition on the day is made by placing a vertical mark across the line. To increase objectivity, this assessment must be done prior to viewing the patient’s global assessment of overall disease activity.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities (i.e., pandemic, epidemic or natural disaster) that limits or prevents on-site study visits, instead regular phone or virtual calls can occur (every 2 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

For details on AE collection and reporting, refer to AE section.

Table 8-5 Assessments & Specifications

Assessment	Specification
Physical	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed. A short physical exam will include the examination of general appearance and vital signs (blood pressure and pulse). A short physical exam will be at all visits where ESSDAI assessments are not required. The investigator should ask the patient for and pay attention to presence of signs and symptoms of infection. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	If possible, vital sign assessments should be performed by the same study site staff member using the same validated device throughout the study. Vital signs include blood pressure (BP) and pulse measurements. After the subject has been sitting for five

[redacted]

Assessment	Specification
	minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, with an appropriately sized cuff. Clinically notable vital signs are defined in Appendix 1.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured. Body mass index (BMI) will be calculated using the following formula:BMI = Body weight (kg) / [Height (m)]^2

8.4.1 Laboratory evaluations

Clinically notable laboratory findings are defined in Appendix 1.

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an AE and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

In all cases, the investigator must document in the source documents, the clinical considerations (i.e. result was/was not clinically significant and/or medically relevant) in allowing or disallowing the subject to continue in the study.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate. All listed below laboratory evaluations will be performed by a central laboratory with exception of erythrocyte sedimentation rate (ESR), urinalysis, urine pregnancy test, cryoglobulins and post-screening hepatitis monitoring (HBsAg and HBV-DNA) applicable to HBsAg-negative, anti-HBc positive patients and post screening CMV monitoring.

Table 8-6 Laboratory Evaluations

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other), Erythrocyte sedimentation rate (ESR - local testing).
Clinical chemistry	Albumin, Alkaline phosphatase, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (non-fasting), C-reactive protein (CRP). Estimated creatinine clearance will be calculated using MDRD formula.

[redacted]

Test Category	Test Name
Urinalysis (locally)	Macroscopic Panel: (Dipstick) pH, Glucose, Protein, Blood, Bilirubin, Urobilinogen, Ketones, Urine nitrite, Leukocytes, Specific Gravity. If the dipstick result is positive for protein, nitrite, leucocytes and/ or blood, the sample will be analyzed locally for culture and for microscopic analysis of white blood cells, red blood cells and casts.
Coagulation	Prothrombin time (PT), Partial Thromboplastin Time (PTT), International normalized ratio (INR)
Immunology	IgG, IgM, Complement (C3, C4)
Serology	Hepatitis serology: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody(anti-HBs), hepatitis B core antibody (anti-HBc), hepatitis B DNA (HBV-DNA); antibodies to hepatitis C virus (anti-HCV), hepatitis C RNA (HCV-RNA) CMV). Human immunodeficiency virus antibody (HIV Ab) and if positive confirmation by the second technique (e.g PCR).
CMV , Hepatitis monitoring (locally, as applicable)	HBsAg, HBV-DNA, CMV serology (CMV IgG, IgM) and CMV DNA by PCR
Additional tests	FSH, Cryoglobulins (local testing), PK, PD (soluble CD40) and immunogenicity [redacted] blood samplings, [redacted]
Pregnancy Test	Serum (beta hCG) / Urine pregnancy test (please see Section 8.4.3)

8.4.2 Electrocardiogram (ECG)

Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, blood sampling, and then all other assessments. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12 lead ECGs are collected. The original ECGs on non-heat-sensitive paper and a certified copy on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site. Each ECG tracing must be labeled with study number, patient number, date and time, and filed in the study site source documents. Any identifier details must be redacted e.g. subject initials, date of birth. Results must be entered into the eCRF.

For any ECGs with subject safety concerns (e.g., severe arrhythmia, conduction abnormality of QTcF > 500 ms), two additional ECGs must be performed to confirm the safety finding. If the subject is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion). Clinically significant ECG findings at screening must be discussed with the sponsor before administration of study treatment.

Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical conditions or adverse events as appropriate.

[redacted]

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum β-hCG test (serum pregnancy test) performed at the screening and baseline visits, and local urine pregnancy tests monthly, as indicated in Table 8-1 , Table 8-2 , Table 8-3 and Table 8-4 . Additional pregnancy testing might be performed if requested by local requirements. A positive urine test requires immediate interruption of study drug and needs to be confirmed with a serum test. If positive, the subject must be discontinued from the study treatment. Highly effective method of birth control must be used for women of childbearing potential (see exclusion criteria definitions, Section 5.2). In consideration of the patient population and overall iscalimab risk benefit profile, women of child-bearing potential must utilize highly effective contraception methods to avoid becoming pregnant while receiving iscalimab and for 14 weeks after the last dose or until data from the reproductive toxicity studies suggest otherwise. Women who are nursing may not participate in this trial. The washout period of 14 weeks after the last dose is justified based on predicted PK profiles at 10 mg/kg, where iscalimab is predicted to be fully cleared from plasma and tissues, with no residual pharmacodynamic activity.

Assessments of Fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of childbearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, Follicle Stimulating Hormone (FSH) testing is required of any female subject regardless of reported reproductive/menopausal status at screening.

If participants cannot visit the site to have pregnancy tests, urine pregnancy test kits may be used. Relevant subjects can perform the urine pregnancy test at home and report the result to the site. A communication process should be established with the participant so that the site is informed and can verify the pregnancy test results (e.g., following country-specific measures).

8.4.4 Other safety evaluations

Malignancies

For subjects on study treatment and in follow-up, any type of malignancies (including skin neoplasms, leukemia, post-transplantation proliferative disorder (PTLD)) should be reported as an SAE and recorded on the appropriate eCRFs. A SAE report should be completed for malignancies occurring until the last visit (for subjects in follow-up) or for 14 weeks after the last dose of study treatment taken (for subjects in the treatment period or who completed the treatment period).

[redacted]

Infections

Infections should be recorded with start and end date, type of infection, and medications used on the appropriate eCRFs. If medications are used to treat the infection, the name of the medication must be entered on the appropriate eCRF. If the subject is hospitalized a SAE report must be completed and reported.

8.4.5 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/subject population.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

8.5.1.1 Clinician Reported Outcomes (ClinRO)

The impact of study treatment on subject's disease acvitivity will be assessed by the following measures:

- EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) - please see Section 8.3.2 for details
- Physician's global assessment of disease activity (PhGA, VAS) - please see Section 8.3.6 for details

[redacted]

[redacted]

Trial Feedback

This trial will include an option for patients to complete an anonymized questionnaire, 'Trial Feedback Questionnaire' (TFQ) for subjects to provide feedback on their experience in a Novartis clinical trial.The TFQ is a validated web-based questionnaire. The TFQ has been tested and validated by research conducted by Adelphi, PatientsLikeMe and HRM using established PRO methodology and is based on feedback from 400 adult patients across different therapeutic areas.

TFQ questions relate to both protocol-specified and site-specific components, including study burden and interaction with site staff. Feedback is anonymous. Individual subject level responses will not be reviewed by investigators. Responses will be used by Novartis to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the subject's disease, symptoms, treatment effect or adverse events and therefore the TFQ data is not trial data.

The TFQ data will be stored in the HealthiVibe's database, separate from the clinical trial database.

8.5.2 Pharmacokinetics

Free CFZ533 (iscalimab) plasma concentrations will be measured in all iscalimab-treated subjects (only).

PK samples will be collected at the visits defined in the assessment schedule. All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Details of sample processing, handling, storage and shipment will be described in a separate laboratory manual.

All samples will be given a unique sample number and a dose reference identification number (as listed in the Table 16-5 and Table 16-6). The actual sample collection date and time will be entered on the appropriate eCRF.

Free CFZ533 (iscalimab) plasma concentrations will be determined using a validated target-based sandwich ELISA method. The data and details of the analytical methods will be provided in a standalone Bioanalytical Data Report.

Concentrations below the lower limit of quantification (LLOQ) will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report.

For each PK sample, the actual recorded sampling time will be captured, and the elapsed time since the first and since the last dose will be calculated.

8.5.3 Immunogenicity

The presence of anti-CFZ533 (iscalimab) antibodies will be determined in all iscalimab-treated subjects (only), using a validated assay.

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Details of sample processing, handling, storage and shipment are described the Laboratory Manual.

All samples will be given a unique sample number (as listed in the Table 16-5 and Table 16-6).

The detailed methods and analysis will be described in the Bioanalytical Data Report.

8.5.4 Soluble CD40 in plasma

Blood samples will be collected for the determination of free (in the absence of iscalimab) or total (in the presence of iscalimab) soluble CD40 concentrations in plasma, to assess the biology of the target (free soluble CD40) and target engagement in whole blood (total soluble CD40 during treatment and follow-up).

Together with PK measures in plasma, total soluble CD40 measures are contributing to the immunogenicity strategy.

Soluble CD40 plasma concentrations will be measured in all subjects (iscalimab- and placebo-treated subjects).

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Details of sample processing, handling, storage and shipment will be described in a separate Laboratory Manual.

[redacted]

All samples will be given a unique sample number (as listed in Table 16-5 and Table 16-6). The actual sample collection date and time will be entered on the appropriate eCRF.

The data and details of the analytical methods will be provided in a standalone Bioanalytical Data Report.

8.5.5 Biomarkers

Biomarkers are aligned across the CFZ533 program and focus on disease status and progression. Beside the digital approach to evaluate fatigue and cognition, the plan includes specific markers like serum immunoglobulins G (IgG) and M (IgM), CXCL-13, [redacted] and free light chain (FLC) that have been shown to be modulated by disease activity or in response to treatment. Free light chain levels have been suggested to be useful to monitor the effect of immunomodulatory treatment on B cell activity (Verstappen et al 2018). Serum samples will be analyzed by a central laboratory for free light kappa (FLCκ) and free light lambda (FLCλ) chains. In addition to absolute levels of FLC, the κ/λ ratio will be assessed.

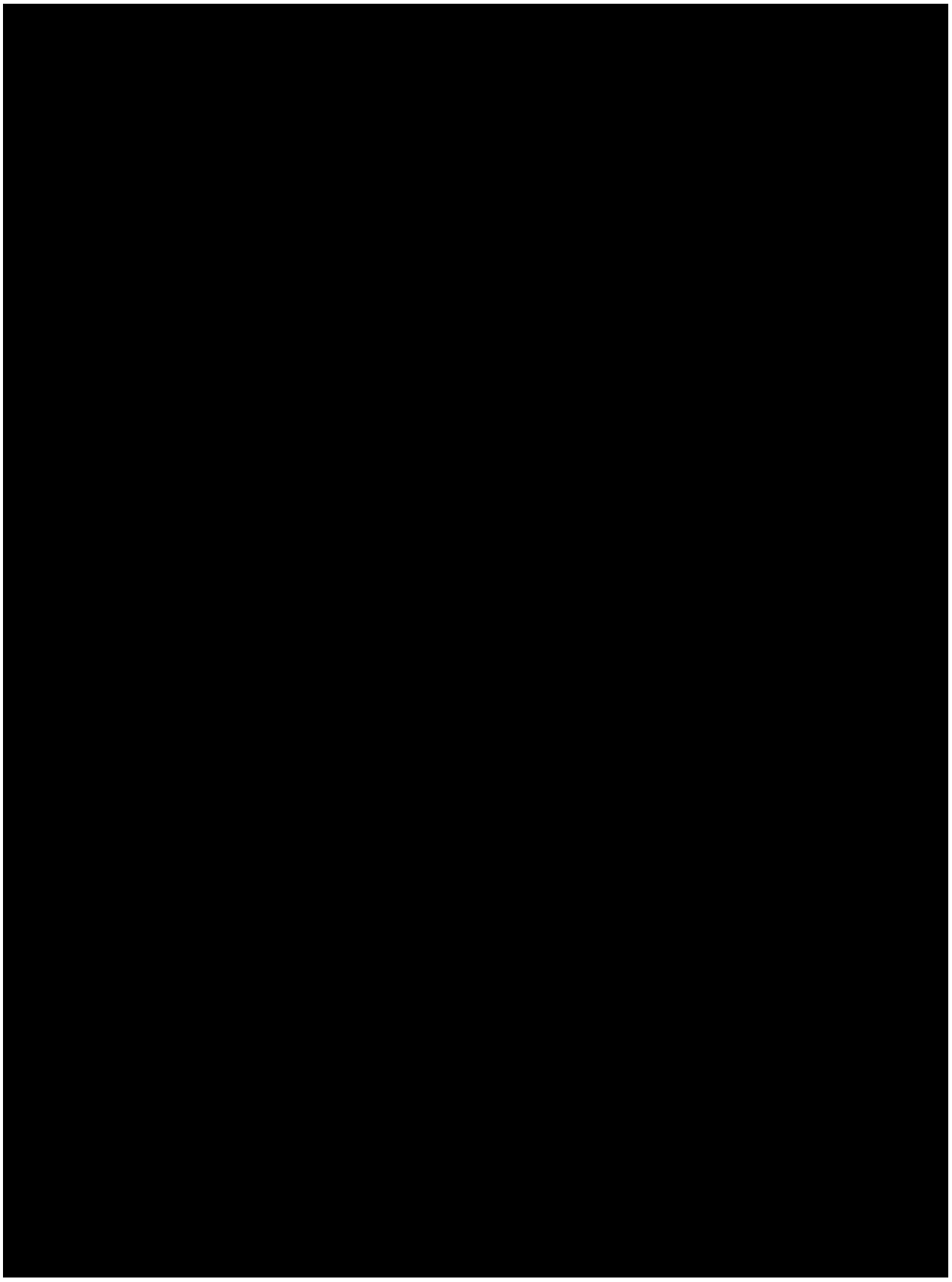
We are including the potential of profiling of proteins, RNA, or other markers to be able to answer questions in response to the clinical outcome or new developments in the disease area.

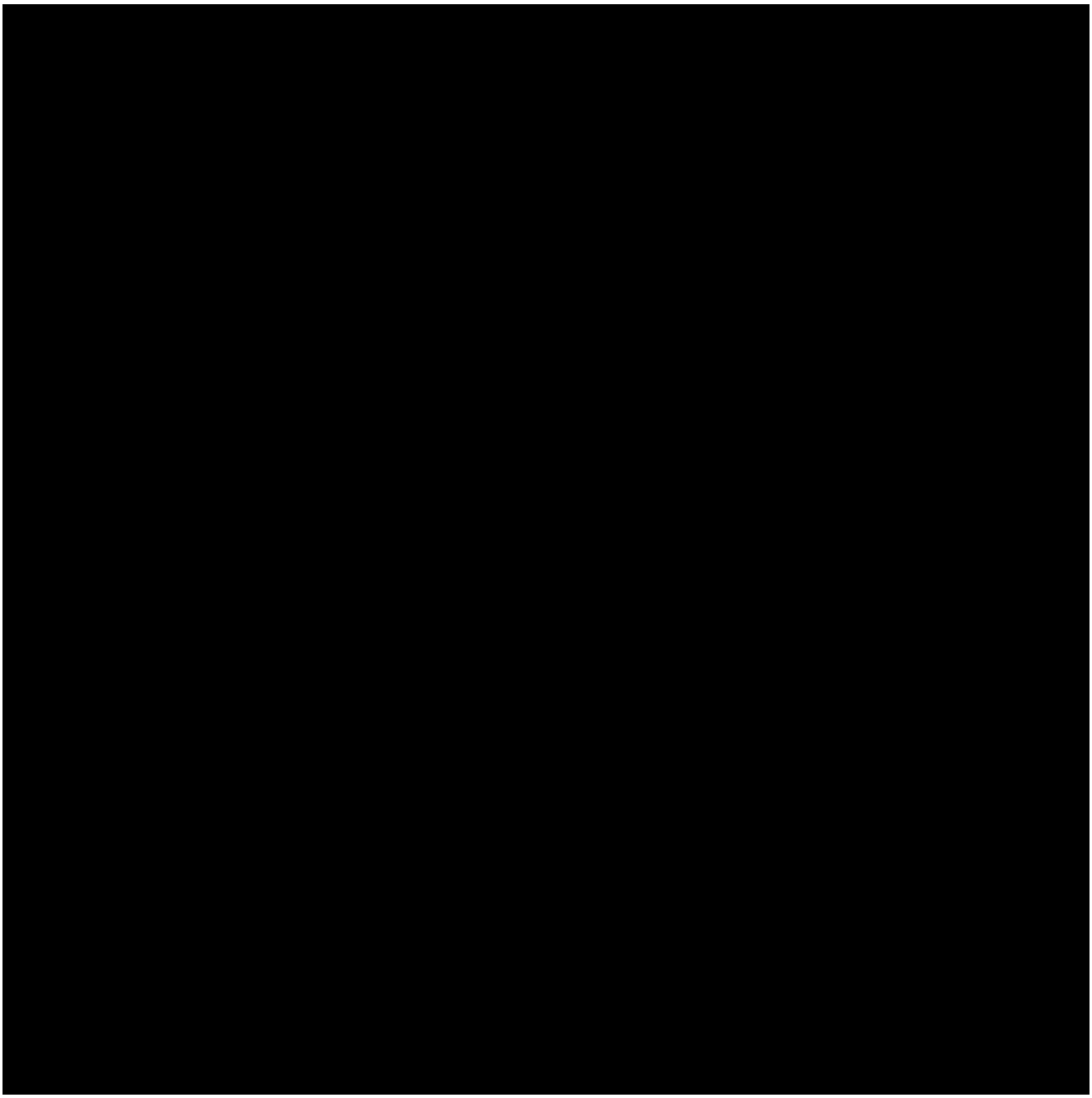
Sample(s) will be collected at the time point(s) defined in the Assessment Schedule (Section 8).

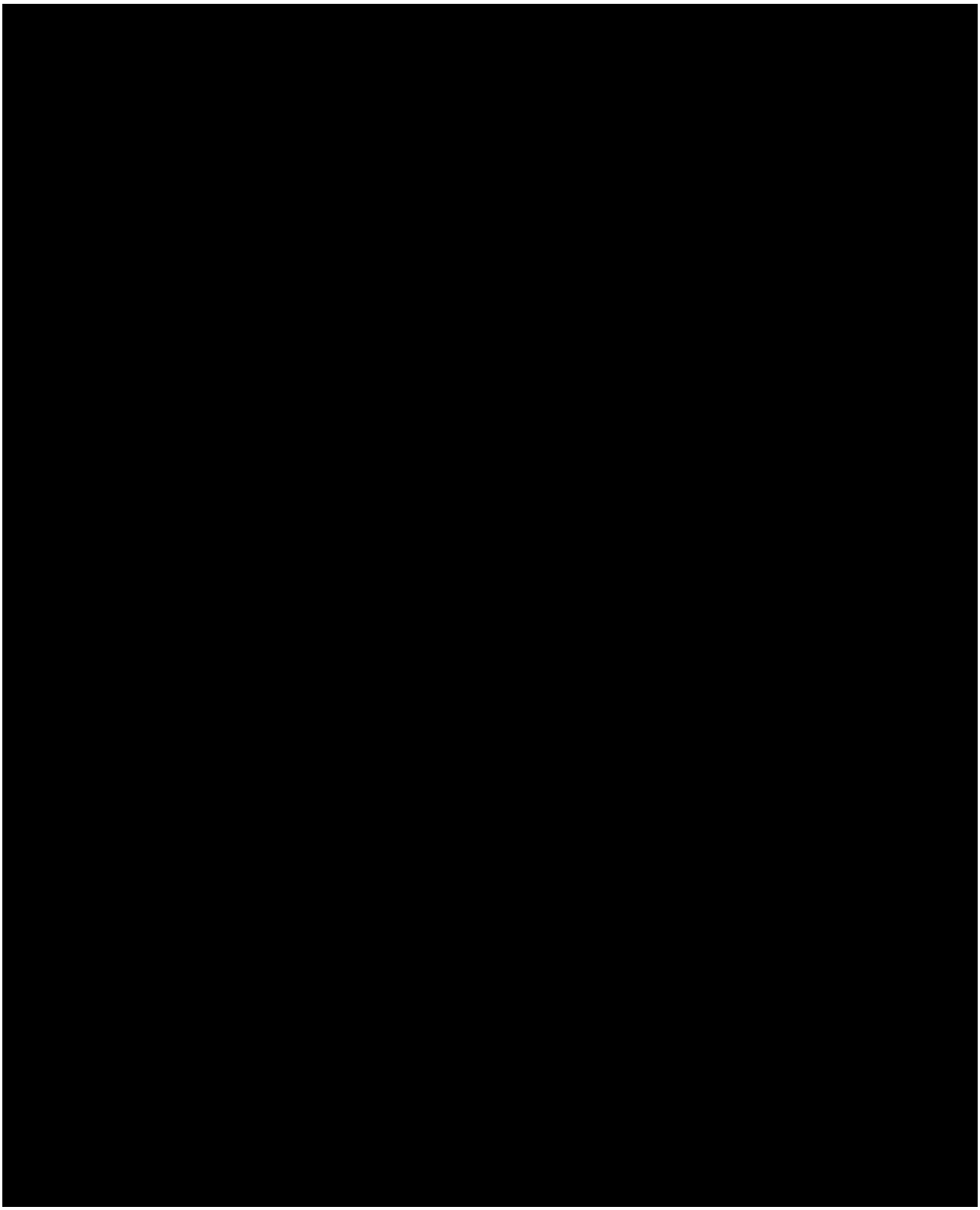
Follow instructions for sample collection, numbering, processing, and shipment provided in the laboratory manual.

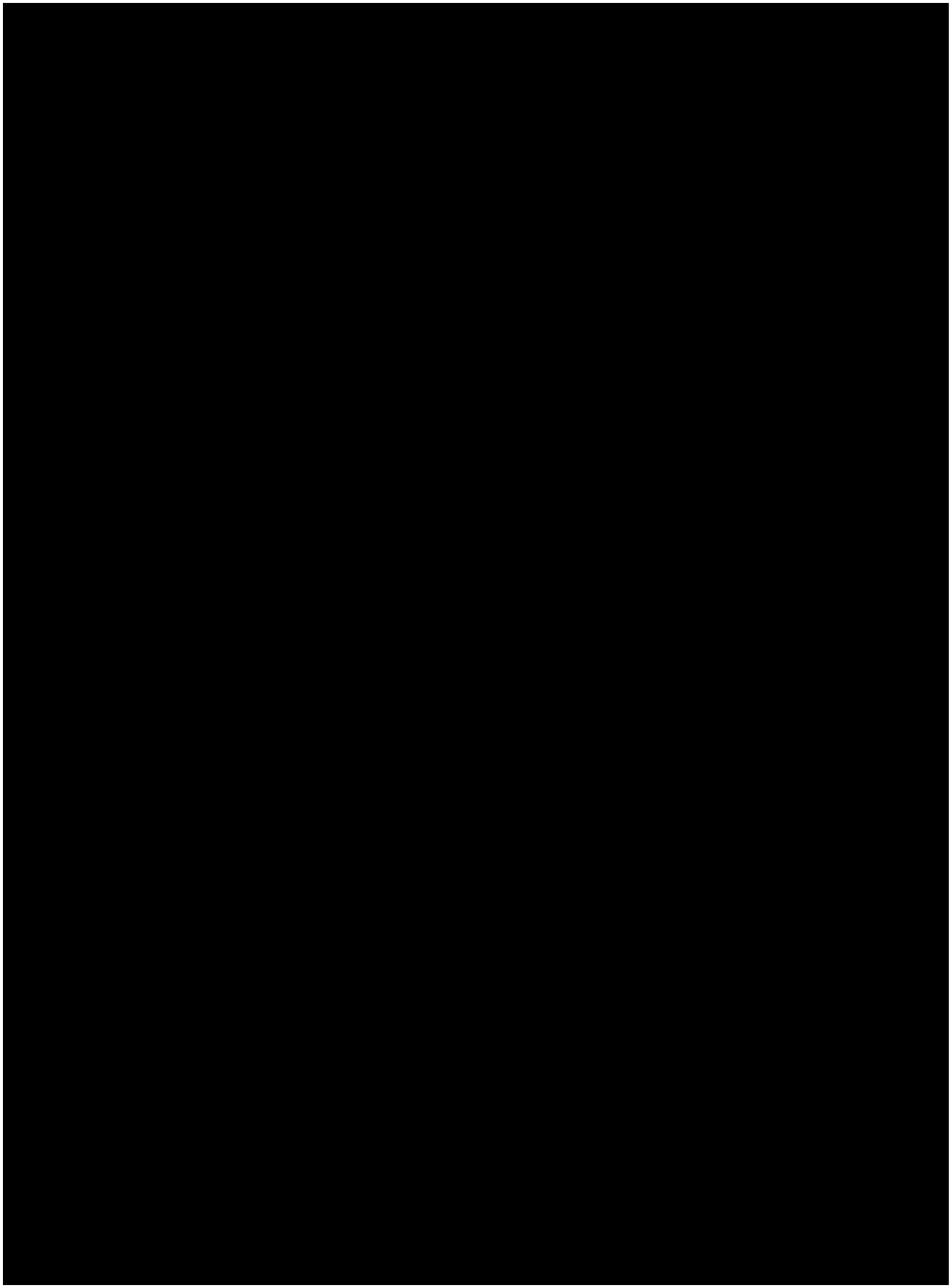
[redacted]

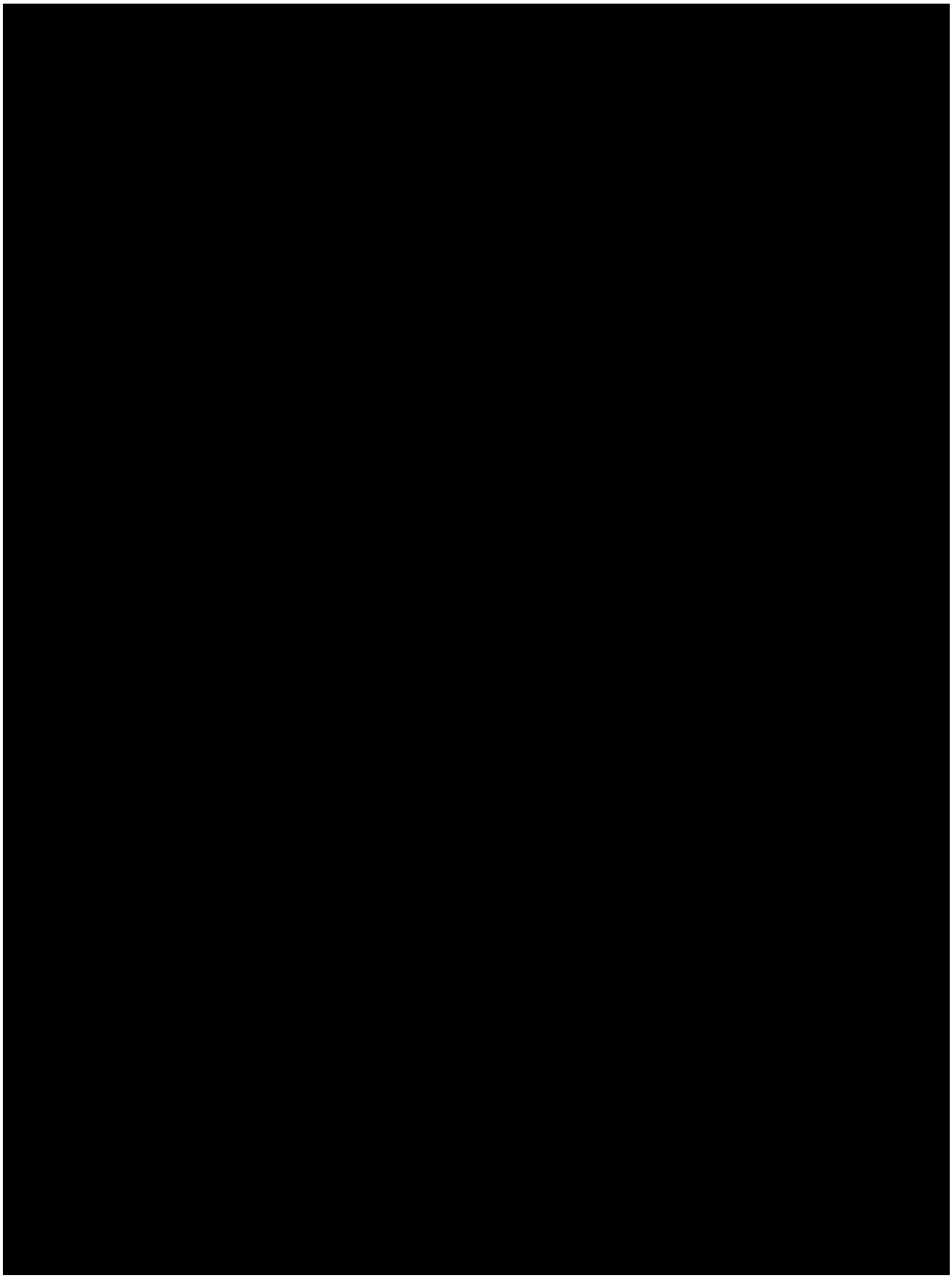
[redacted]











[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Subject/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the subject
- Following emergency unblinding of the treatment arm
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject’s overall status, prevents the subject from continuing participation in the study.

In addition, in case of emergence of the following adverse events discontinuation must be considered jointly by the investigator and Novartis:

- Persistent neutropenia Common Terminology Criteria (CTC) grade 3 or higher
- SAEs or severe AEs of infection

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject’s premature discontinuation of study treatment and record this information.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' section). **Where possible, they should return for the follow up assessments indicated** in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

[redacted]

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse events / serious adverse events

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

9.1.1.1 Replacement policy

Subjects who are randomized but do not come to baseline visit and are not treated may be replaced by next subjects in the same stratum at the site by assigning the same treatment arm utilizing a separate replacement randomization list. Other discontinued subjects will not be replaced.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent/opposition to use data/biological samples occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

For United States (US) and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For European Union (EU) and other countries: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the time point of his/her scheduled last study visit has passed.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

Continuing care should be provided by investigator and/or referring physician based on patient availability for follow-up. This care may include enrollment in an extension study, if any.

9.2.1 Pregnancy reporting

Pregnancies

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed- up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment. Any

[redacted]

SAE experienced during pregnancy must be reported. Information will be collected at three time points after the estimated date of delivery and for a period of 12 months.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values, which are considered non-typical in subject with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities

[redacted]

- severe: prevents normal activities

2. its relationship to the study treatment (Yes/ No)
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment

All adverse events must be treated appropriately. Action taken with the study medication must be recorded. It may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdraw

6. Its outcome

- not recovered/not resolved;
- recovered/resolved;
- recovering/resolving,
- recovered/resolved with sequelae;
- condition deteriorated
- fatal, or unknown.

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 14 weeks following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the subject.

The investigator must also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject’s personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator’s

[redacted]

source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

10.1.2 Serious adverse events

A SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent (e.g., liver allograft biopsy, hospitalization for rejection treatment, revision of an incisional hernia, etc.)
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

[redacted]

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 14 weeks following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Any SAEs experienced after this period should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medial Office & Patient Safety (CMO & PS) department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

10.1.4 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

[redacted]

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE CRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

There has been no safety signal for liver toxicity with iscalimab to date in all healthy volunteers and patients exposed, and from a mechanism of action standpoint there is no known effect on the liver (refer to the current Investigator's Brochure). Standard liver function tests (LFT) will be obtained at regular intervals.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 16-2 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 16-2 of Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Appendix 2.

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation.

These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate

[redacted]

- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed must be recorded on appropriate CRF pages, including the liver event overview CRF pages.

10.2.2 Renal safety monitoring

The available data does not suggest a risk of renal injury with iscalimab. Standard renal function tests will be obtained at regular intervals.

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

1. Serum event:
   - confirmed (after ≥ 24h) increase in serum creatinine of ≥ 25% compared to baseline during normal hydration status
2. Urine event
   - new onset (≥ 1+) proteinuria; confirmed by doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable)
   - new onset (≥ 1+), hematuria or glycosuria

Every renal laboratory trigger or renal event as defined in Appendix 3 should be followed-up by the investigator or designated personnel at the trial site as summarized.

10.2.3 Data Monitoring Committee

This study will include a DMC which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will be comprised of a group of physicians with experience in the disease area and an independent statistician. The DMC will assess at defined intervals the progress of a clinical trial, review the unblinded safety data variables and recommend to the sponsor whether or not changes need to be made to the conduct of the study. The first DMC data review meeting will be triggered after approx. 10% of patients have completed 4 weeks of treatment. The subsequent review meetings will occur quarterly.

Decisions based on the recommendations of the DMC will take into account the potential risks and benefits associated with continuing the enrollment of patients in the study or continued randomization into all dosing arms. Such information and recommendations will be used in the best interest of patients enrolled in the trial. The final decision with respect to any modification of the protocol will be made by Novartis.

Specific details regarding composition, responsibilities, organization and function of the DMC will be described in a separate charter established between the sponsor and the DMC.

[redacted]

11 Data Collection and Database management

11.1 Data collection

Data not requiring a separate written record will be defined in the protocol and the Assessment Schedule (Table 8-1, Table 8-2, Table 8-3, Table 8-4) and can be recorded directly on the eCRFs. All other data captured for this study will have an external originating source (either written or electronic) with the eCRF not being considered as source.

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR (Code of Federal Regulation) Part 11 requirements, Investigator site staff will not be given access to the Electronic Data Capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs. The EDC system allows modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

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. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Randomization codes and data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made

available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitoring will be performed according to relevant sections of the monitoring plan. Blinded monitors will visit the site to check the completeness and appropriate storage of investigator site files, subject records, the accuracy of data capture / data entry, the adherence to the protocol, to the study procedures and to Good Clinical Practice. The monitor is also responsible to report any deviation from the protocol or defined procedures and to follow the progress of enrollment. Unblinded monitors are responsible to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Blinded and unblinded monitors are responsible to ensure deviations or issues are reported in a manner that maintains blinding, as described in the monitoring plan. Key study personnel must be available to assist the field monitors during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/CRA (Clinical Research Associate) organization. Additionally, a central analytics organization may analyze data and identify risks and trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent forms signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents in paper or electronic format to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

The primary analyses for each cohort will be conducted after all subjects have finished the Week 24 visit or early terminated before Week 24. The final analyses will be conducted after all subjects in both cohorts have finished the study. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

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 in the number and percent of patients in each category.

[redacted]

If not otherwise specified, p-values will be presented as two-sided p-values and two-sided confidence intervals will be displayed.

The baseline value is defined as the last assessment value prior to first dose administration. In case the scheduled baseline assessment value is missing, the screening value if available will be used instead.

The values for analysis visits will be selected based on study periods and time windows in which the data are observed. Derivation of analysis visits will be detailed in SAP (Study Analysis Plan). The analysis for cohort 1 and analysis for cohort 2 may occur at different time points depending on patient recruitment and preparation timelines (please refer to Section 6.4).

12.1 Analysis sets

The following analysis sets will be defined for each cohort of the study:

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 procedure and the strata they actually belong to in case of misallocation of strata during the randomization process.

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

12.2 Subject demographics and other baseline characteristics

The analyses described in this section will be presented by cohort and by the treatment groups.

Demographics and baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by Cohort and treatment group for the FAS.

The following demographic variables and baseline disease characteristics will be summarized by treatment group for each cohort:

- Gender, age, race, ethnicity, weight, height, BMI (Body Mass Index), disease duration and smoking status.
- ESSDAI and number of patients per ESSDAI stratum, ESSPRI, PhGA, [redacted] use of DMARDs (split by type), [redacted] and percentage of patients with history of prior biologics treatment use.

Relevant medical histories and current medical conditions at baseline will be summarized combined by system organ class and preferred term and by treatment group and Cohort.

12.3 Treatments

The treatment data will be analyzed based on the safety set by cohorts and study period.

Study treatment

[redacted]

Duration (days) of study treatment will be summarized. In addition, the number and percentage of patients being exposed for pre-specified time intervals (Any, >= 4 weeks, >= 12 weeks, >= 24 weeks) may be summarized.

Prior and concomitant medication

Prior medications for a study period are defined as treatments taken and stopped prior to first dose of study medication in the period. Any medication given at least once between the date of first dose of study treatment and the last date of the study period will be a concomitant medication, including those which were started before the study period but continued into the period. Prior and concomitant medications will be summarized in separate tables in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will show the overall number and percentage of patients receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group. The number and percentage of patients receiving systemic therapies for SjS as prior and concomitant background medication will be presented separately by preferred term.

12.4 Analysis of the primary endpoint(s)

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 subjects 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 ESSP ovement at Week 24 among subjects with high ESSPRI but low ESSDAI score.

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

12.4.1 Definition of primary endpoint(s)

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.
- Intercurrent events: Potential intercurrent events in the study that may have impact on primary efficacy analysis of Cohort 1 include early termination from the study, interruption of study treatment, intensified symptomatic control treatment and intensified immunosuppressive treatment.

[redacted]

- 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]

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

- Population: Full Analysis Set (FAS)
- Variables of interest: Response status defined as subjects achieving at least 1 point or 15% improvement on ESSPRI total score at Week 24
- Intercurrent events: Potential intercurrent events in the study that may have impact on primary efficacy analysis of cohort 2 includes early termination 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]

[redacted]

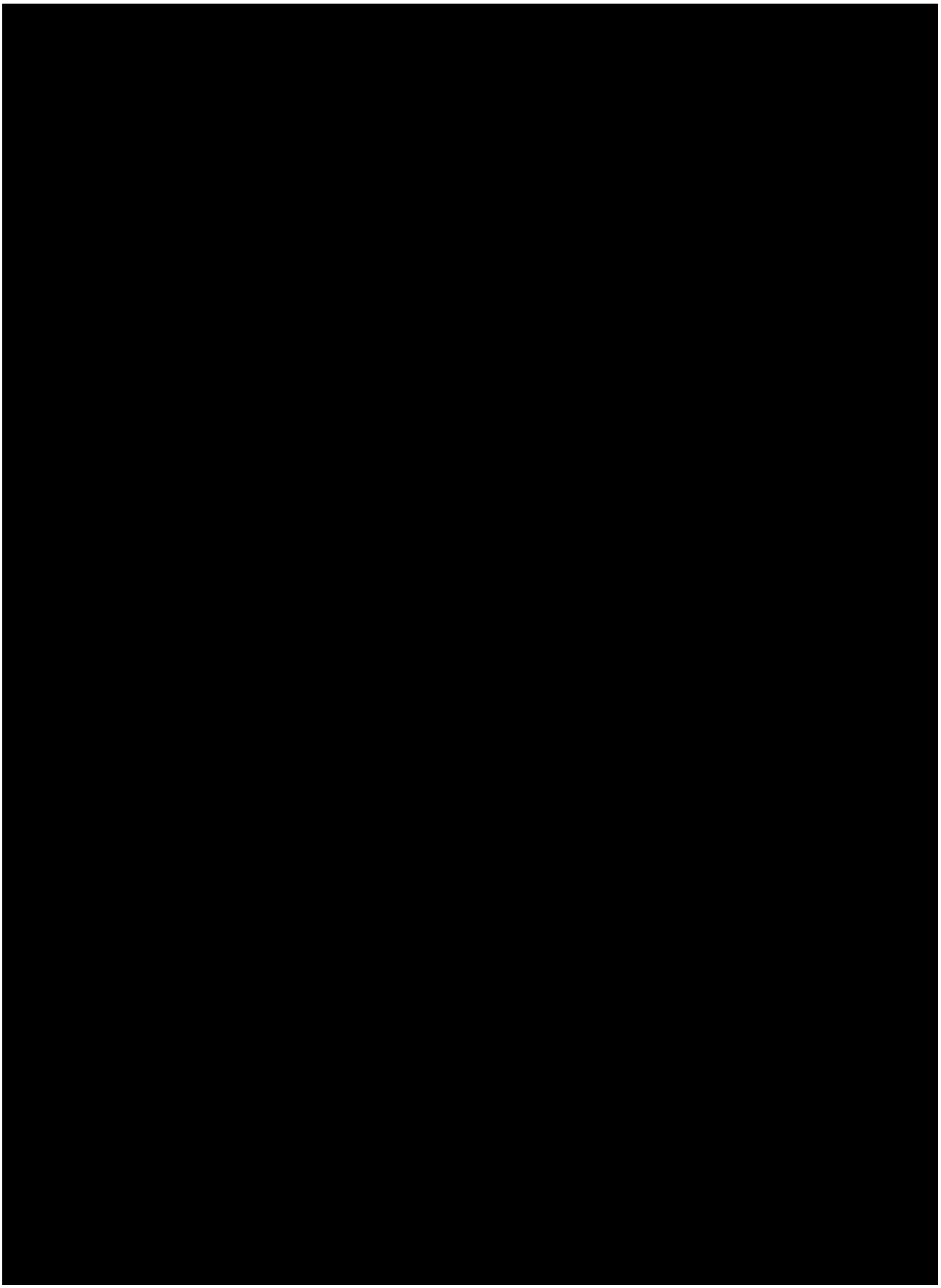
12.4.2 Statistical model, hypothesis, and method of analysis

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

12.4.4 Sensitivity and Supportive analyses

Sensitivity analyses

The primary analysis for both cohorts may be repeated based on different data imputation rules for subjects with missing data at Week 24 and subjects with inter-current events before Week 24. The detailed imputation rules will be decided based on blinded data review and detailed in the study SAP.

Clinical flares could happen among subjects with pSS. The JOQUER study (Gottenberg et al 2014) reported 12 flares among 120 patients during 12 months. While the effect of iscalimab on the incidence of flares is still unknown, a systemic flare could temporarily lead to a much-elevated ESSDAI and ESSPRI total score, resulting in high variability of the sample mean as well as violation of normality assumption on error terms for statistical analysis models. Due to the lack consensus clinical definition of flares in SjS, the incidence of flares and its impact on the primary analysis of both cohorts will be investigated based on statistical outliers, which is defined as values higher than the third quartile by more than 1.5 times the interquartile range within each treatment arm. Number of statistical outliers by treatment arm will be summarized and the primary analysis for both cohorts will be repeated on FAS with such statistical outliers removed.

Based on blinded data review before primary database lock, the primary analysis for Cohort 1 may be repeated based on alternative sets of pre-specified candidate models for the MCP-Mod procedure, in addition, Non-parametric analysis based on ranking of data across all treatment arms and robust regression analysis could be performed.

Supportive analyses

The primary analysis of Cohort 2 will be repeated based on pooled data from both subjects in Cohort 2 and subjects who were in Cohort 1 with ESSPRI fatigue ≥ 5 or ESSPRI dryness ≥ 5.

12.5 Analysis of secondary endpoints

The secondary efficacy endpoints and potential biomarkers will be analyzed separately for each cohorts.

For the secondary objective of demonstrating dose-response relationship at Week 24 based on ESSPRI in cohort 1, the following estimand framework is adopted.

[redacted]

- Population: Full Analysis Set (FAS)
- Variables of interest: Change from baseline in ESSPRI total score after 24 weeks of subcutaneous iscalimab administrations. This will be defined as the baseline ESSPRI minus the Week 24 ESSPRI value with positive values indicating improvement.
- Intercurrent events: Potential intercurrent events in the study that may have impact on demonstration of dose response in ESSPRI includes early termination from the study, interruption of study treatment, intensified symptomatic control treatment and intensified immunosuppressive treatment.
- Summary measure: Adjusted mean change from baseline in ESSPRI total score 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 same intention-to-treat principle and missing data handling rules for the primary analysis will be adopted also for the secondary demonstration of dose response relationship based on ESSPRI at Week 24.

The pharmacokinetics and immunogenicity for the iscalimab [redacted] arm will be summarized with pooled data from both cohorts. Safety analysis for the placebo and iscalimab [redacted] arms will also be based on pooled data from both cohorts unless where additionally specified otherwise. If primary database locks (week 24) for the two cohorts happen at different times, the safety, immunogenicity and PK analysis at the time of database lock for first cohort will include only data of one cohort. The corresponding analysis at the time of database lock for the second cohort and final analysis will include data pooled from both cohorts.

12.5.1 Efficacy endpoints

Analysis of secondary efficacy endpoints in Cohort 1

The demonstration for a dose-response relationship of iscalimab at Week 24 based on ESSPRI total scores will be based on the same MCP-Mod methods adopted for the primary analysis and the adjusted mean change from baseline calculated with similar MMRM model fitted to observed ESSPRI data from baseline to Week 24. The choice of candidate models for the MCP step will be finalized in the study SAP. This secondary analysis for dose response relationship will be performed hierarchically after the primary analysis based on ESSDAI. The graphical approach (Bretz et al 2009) for sequentially rejective testing procedures will be used to control the overall Type I error rate at 5%, for which the details will be provided in the SAP.

Summary statistics for the change from baseline in ESSPRI, FACIT-F and PhGA at Week 24 will be presented for original results and mean change from baseline. The adjusted mean change from baseline and the differences of iscalimab arms with placebo, along with 95% confidence intervals, will be estimated from the similar MMRM model for primary analysis of Cohort 1.

[redacted]

Analysis of secondary efficacy endpoints in Cohort 2

Original value and change from baseline in FACIT-F and PhGA at Week 24 will be summarized. Differences in the change from baseline between iscalimab [redacted] and placebo arms and associated confidence intervals will be calculated using the same method as for the primary analysis of Cohort 2.

Number and percentage of subjects with at least 12 points improvement on IDEEL dry eye symptom bother module score at Week 24 will be summarized by treatment. The difference in the percentages with 95% Wald confidence limits calculated with continuity correction (Fleiss, Levin, and Paik, 2003) will also be presented.

12.5.2 Safety endpoints

All safety analysis will be on Safety set based on data from both cohorts. Safety data will be summarized separately for study period 1 and from start of period 2 to the end of study. The iscalimab [redacted] and placebo arms in period 1 analysis will include subjects from both cohorts. For safety summaries from start of period 2 to end of study, the subjects from both cohorts will be grouped by distinct treatment sequence during the first two periods of the study.

Adverse event

Treatment-emergent adverse events (TEAE) is defined as events (based on preferred term) newly started, or presented before but increased in severity, during the period of analysis.

The number (and percentage) of subjects with TEAE 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 study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment.

A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

A listing will be produced for any adverse events newly observed during study Period 3.

Vital signs

The values and change from baseline for post-baseline of vital sign measurements (Systolic/Diastolic blood pressure, body weight and heart rate) will be summarized by analysis visits.

12-lead ECG

Not Applicable

[redacted]

Clinical laboratory evaluations

Routine hematology (with immunoglobulins IgG and IgM) and serum chemistry (including lipids) laboratory tests results will be summarized by analysis visits. Descriptive summary statistics for the original value and change from baseline will be included. Shift tables based on the normal laboratory ranges will also be provided. The number and percentage of patients with clinically notable laboratory results after baseline will also be presented.

Resource utilization

Not applicable

12.5.3 Pharmacokinetics

PK data will be analyzed on safety set.

Trough free iscalimab plasma concentrations will be listed by cohort, treatment arm, subject, and visit/sampling time point.

Descriptive summary statistics will be provided by iscalimab dose level and analysis visits, including the frequency (n, %) of concentrations below the LLOQ. 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.

The following PK parameters will be determined: trough concentration (Ctrough), Ctrough,ss (steady state), and will be directly derived from the bioanalytical data (summary statistic tables; no non-compartmental analysis will be performed).

For each iscalimab concentration (or sample), an elapsed time since first (and last) dose of iscalimab will be calculated based on a Dose Reference ID (provided in the Blood Log). The time window for deriving the elapsed time will be defined in the SAP.

Graphical presentation of the data will be provided.

12.5.4 Biomarkers

The biomarkers to be evaluated include serum FLC, IgG/IgM, CXCL-13. [redacted] Absolute value and percent change from baseline of biomarker levels will be summarized for each cohort at scheduled visits of biomarker assessment by treatment as randomized (for Period 1) or by treatment sequence (for Period 2). The frequency (n, %) of values below the LLOQ and above the ULOQ, respectively, will be summarized. Correlations between biomarkers and clinical efficacy endpoints in both cohorts may be assessed.

12.5.5 PK/PD relationships

The relationship between PK, PD, efficacy or biomarker endpoints may be explored graphically. Modeling of PK data using a population approach may be performed, as appropriate, and may be reported in a separate, standalone modeling and simulation report.

[redacted]

12.5.6 Immunogenicity

Blood samples for immunogenicity testing will be collected from all subjects (to protect blinding) and analysis will be performed in samples collected from iscalimab-treated subjects only.

The presence of anti-iscalimab antibodies in plasma samples will be assessed using screening and confirmatory assays.

An integrated PK/PD/immunogenicity approach, focusing on the clinical and functional consequences of anti-drug antibodies will be applied. The consequences of an immune response to iscalimab may be correlated with a loss of exposure (free iscalimab concentrations in plasma), a loss of target engagement (soluble CD40 concentrations in plasma), and/or the appearance of immune related adverse events.

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.

12.5.7 Soluble CD40 in plasma

Blood samples for soluble CD40 (sCD40) concentration in plasma will be collected from all subjects (at selected time points, as defined in the Assessment Schedule), and analysis will be performed in samples collected from all subjects.

sCD40 concentrations will be listed by cohort, treatment arm, subject, and visit/sampling time point. Descriptive summary statistics will be provided by iscalimab dose level and analysis visits, including the frequency (n, %) of concentrations below the LLOQ.

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.

For each sCD40 concentration (or sample), an elapsed time since first (and last) dose of iscalimab will be calculated based on the corresponding PK Dose Reference ID (as provided in the Blood Log). The time window for deriving the elapsed time will be defined in the SAP.

Graphical presentation of the data will be provided.

[redacted]

12.7 Interim analyses

An interim analyses (IA) may be performed prior to the primary efficacy analysis in addition to regularly scheduled safety reviews of data performed by the DMC. The results from the IA may facilitate strategic planning of future development steps. The IA results will be unblinded to designated vendor and designated Novartis personnel as described in Section 6.4. Subjects, site

[redacted]

personnel, Novartis CO and/or local Contract Research Organization (CRO) representatives involved in the study conduct, however, will stay blinded.

The IA will occur when at least 50% of the subjects in Cohort 1 complete Week 24 visit or discontinue prior to that. MCP-Mod as planned for the primary analysis (Section 12.4) will be performed to estimate a dose-response trend over placebo in the CFZ533 dose groups. There is no plan to change the study design or study conduct based on this interim analysis. Therefore, no multiplicity adjustment will be made to account for this IA. Results on the primary and selected secondary efficacy endpoints will be assessed in addition to patient disposition, demographics and disease history, AEs and SAEs.

The primary analysis will be performed after all subjects of each cohort have completed Week 24 or discontinued prior to Week 24. The analysis for cohort 1 and analysis for cohort 2 may occur at different time points depending on patient recruitment and preparation timelines (please refer to Section 6.4). A final analysis will be performed after all subjects have completed Week 60 (or discontinued prior to Week 60). Formal testing of the primary endpoint with full level alpha will be performed at the primary analysis time point.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Council on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and

procedures found in this protocol, and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion and finalization of the study report the results of this trial might be submitted for publication and will be posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. clinicaltrials.gov, EudraCT etc).

For details on the Novartis publication policy including authorship criteria, one can refer to the Novartis publication policy training materials provided at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal standard operating procedures (SOPs), and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case-by-case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

[redacted]

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

[redacted]

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests.

Table 16-1 Clinically notable laboratory values and vital signs

Laboratory variable	Standard units	SI units
Liver function and related variables	≥ 3 × ULN	≥ 3 × ULN
SGOT (AST)	≥ 3 × ULN	≥ 3 × ULN
SGPT (ALT)	≥ 3 × ULN	≥ 3 × ULN
Bilirubin	≥ 3 × ULN	≥ 3 × ULN
Alkaline phosphatase	≥ 5 × ULN	≥ 5 × ULN
GGT	≥ 5 × ULN	≥ 5 × ULN
Renal function, metabolic and electrolyte variables		
Urea	≥ 5 × ULN	≥ 5 × ULN
Creatinine	≥ 3 mg/dL	≥ 265 µmoFl/L
Uric acid	M ≥ 12 mg/dL	M ≥ 714 µmol/L
	F ≥ 9 mg/dL	F ≥535 µmol/L
Glucose	< 45 mg/dL	< 2.5 mmol/L
	> 250 mg/dL	> 13.9 mmol/L
Cholesterol	≥ 350 mg/dL	≥ 9.1 mmol/L
Triglycerides	≥ 750 mg/dL	≥ 8.5 mmol/L
CK (MB)	None	None
Potassium	≤ 3.0 mEq/L	≤ 3 mmol/L
	≥≤ 6.0 mEq/L	≥≤ 6 mmol/L
Calcium	≤ 6 mg/dL	≤ 1.5 mmol/L
	≥ 13 mg/dL	≥ 3.2 mmol/L
Magnesium	< 1.0 mg/dL	< 0.4 mmol/L
	> 3.6 mg/dL	> 1.5 mmol/L
Amylase	≥ 2 x ULN	≥ 2 x ULN
Lipase	≥ 2 x ULN	≥ 2 x ULN
Hematology variables		
Hemoglobin	< 7 g/dL	< 4.39 mmol/L
Platelets (thrombocytes)	< 50 k/mm^3	< 50 × 10^9/L
	≥ 700 k/mm^3	≥ 700 × 10^9/L
Leukocytes (WBCs)	≤ 2.0 k/mm^3	≤ 2.0 × 10^9/L
	≥ 16 k/mm^3	≥ 16 × 10^9/L

[redacted]

Laboratory variable	Standard units	SI units
Hematology variables: differential		
Granulocytes (poly, neutrophils)	≤ 1,000/mm^3	≤ 1 x 10^9/L
Eosinophils	≥ 12%	≥ 12%
Lymphocytes	≤ 1,000/mm^3	≤ 1 × 10^9/L
Vital sign variables	**Notable criteria**	
Systolic BP (mm/Hg)	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 BP (mm/Hg)	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)	

[redacted]

16.2 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-2 Liver event and laboratory trigger definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal

Table 16-3 Follow up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALT or AST > 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

[redacted]

Criteria	Actions required	Follow-up monitoring
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

[redacted]

Criteria	Actions required	Follow-up monitoring
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

[redacted]

16.3 Appendix 3: Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥1+ Albumin- or Protein-creatinine ratio increase ≥2-fold Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥3 mg/mmol; Protein-creatinine ratio (PCR) ≥150 mg/g or >15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick glycosuria ≥1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.	

16.4 Appendix 4: Hepatitis B serology results, interpretation and patient eligibility

Table 16-4 Hepatitis B serology results, interpretation and patient eligibility

Test	Test result	Interpretation	Patient Eligibility
HBsAg Anti-HBc Anti-HBs	Negative Negative Negative	Susceptible	Patient eligible
HBsAg Anti-HBc Anti-HBs HBV DNA	Negative Positive Positive Negative	Immune due to natural infection. Regular monitoring of HBsAg is required. If HBsAg becomes positive, immediately start anti-HBV therapy with either Lamivudine or Entecavir.	Eligible
HBsAg Anti-HBc Anti-HBs	Negative Negative Positive	Immune due to hepatitis B vaccination	Patient eligible
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Positive Negative	Acutely infected	Not eligible
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Negative Negative	Chronically infected	Not eligible
HBsAg Anti-HBc Anti-HBs HBV DNA	Negative Positive Negative Negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. “Low level” chronic infection 4. Resolving acute infection Regular monitoring of HBsAg is required. If HBsAg becomes positive, immediately start anti-HBV therapy with either Lamivudine or Entecavir	Eligible

[redacted]

16.5 Appendix 5: Blood Logs

Table 16-5 Cohort 1: blood sampling schedule for pharmacokinetics (CFZ533), immunogenicity and pharmacodynamics (soluble CD40)

COHORT 1	Visit Name	Days	Time point	Pharmacokinetics (CFZ533)			Immuno-genicity	Pharmaco-dynamics (soluble CD40)
				Sample ID	Dose Reference ID (Series #1)	Dose Reference ID (Series #2)	Sample ID	Sample ID
Treatment Period 1	Baseline	1	Pre-dose	**101**	1	1	**201**	**301**
	Wk 1			**102**	1	2	-	
	Wk 2	15		**103**	1	3	**202**	**302**
	Wk 4	29		**104**	1	4	**203**	**303**
	Wk 6			**105**	1	5	-	
	Wk 8	57		**106**	1	6	**204**	**304**
	Wk 10			**107**	1	7		
	Wk 12	85		**108**	1	8	**205**	**305**
	Wk 14			*No sampling*				
	Wk 16	113		**109**	1	10	**206**	**306**
	Wk 18			*No sampling*				
	Wk 20	141		**110**	1	12	**207**	**307**
	Wk 22			*No sampling*				
	Wk 24 / End of TP1	169		*Please see Treatment Period 2*				
Treatment Period 2	Wk 24	169	Pre-dose	**111**	1	14	**208**	**308**
	Wk 25			*No sampling*				
	Wk 26	183		**112**	1	16	**209**	**309**
	Wk 28	197		**113**	1	17	**210**	**310**
	Wk 30			*No sampling*				
	Wk 32	225		**114**	1	19	**211**	**311**
	Wk 34			*No sampling*				
	Wk 36	253		**115**	1	21	**212**	**312**
	Wk 38			*No sampling*				
	Wk 40	281		**116**	1	23	**213**	**313**
	Wk 42			*No sampling*				
	Wk 44	309		**117**	1	25	**214**	**314**
	Wk 46			*No sampling*				
	Wk 48	337	NA	**118**	1	26	**215**	**315**
Post-Treatment Follow-Up	**FUP1**		NA	*No sampling*				
	FUP2	393		**119**	1	26	**216**	**316**
	FUP3/End of Study	421		**120**	1	26	**217**	**317**

[redacted]

Table 16-6 Cohort 2: blood sampling schedule for pharmacokinetics (CFZ533), immunogenicity and pharmacodynamics (soluble CD40)

COHORT 2 Period	Visit Name	Days	Time point	Pharmacokinetics (CFZ533)			Immuno-genicity	Pharmaco-dynamics (soluble CD40)
				Sample ID	Dose Reference ID (Series #1)	Dose Reference ID (Series #2)	Sample ID	Sample ID
reatment Period 1	Baseline	1	Pre-dose	**101**	1	1	**201**	**301**
	Wk 1			**102**	1	2	**-**	
	Wk 2	15		**103**	1	3	**202**	**302**
	Wk 4	29		**104**	1	4	**203**	**303**
	Wk 6			**105**	1	5	-	
	Wk 8	57		**106**	1	6	**204**	**304**
	Wk 10			**107**	1	7		
	Wk 12	85		**108**	1	8	**205**	**305**
	Wk 14			*No sampling*				
	Wk 16	113		**109**	1	10	**206**	**306**
	Wk 18			*No sampling*				
	Wk 20	141		**110**	1	12	**207**	**307**
	Wk 22			*No sampling*				
	Wk 24 / End of TP1	169		*Please see Treatment Period 2*				
Treatment Period 2	Wk 24	169	Pre-dose	**111**	1	14	**208**	**308**
	Wk 25			*No sampling*				
	Wk 26	183		**112**	1	16	**209**	**309**
	Wk 28	197		**113**	1	17	**210**	**310**
	Wk 30			*No sampling*				
	Wk 32	225		**114**	1	19	**211**	**311**
	Wk 34			*No sampling*				
	Wk 36	253		**115**	1	21	**212**	**312**
	Wk 38			*No sampling*				
	Wk 40	281		**116**	1	23	**213**	**313**
	Wk 42			*No sampling*				
	Wk 44	309		**117**	1	25	**214**	**314**
	Wk 46			*No sampling*				
	Wk 48/TD	337	NA	**118**	1	26	**215**	**315**
Post-Treatment Follow-Up	FUP1		NA	*No sampling*				
	FUP2	393		**119**	1	26	**216**	**316**
	FUP3/End of Study	421		**120**	1	26	**217**	**317**

[redacted]

Table 16-7 Cohort 1: Treatment Period 1 - Time schedule for blood sampling

A

Period	Visit Name	Days	[redacted]	Hepatitis, CMV and HIV screen	Hematology	Clinical Chemistry	Coagulation Panel	Immunology	Total (mL)
				Size (mL)	Size (mL)	Size (mL)	Size (mL)	Size (mL)	
Screening	Screening	-42 to -1		12	3	3.5	2	2.5	25.5
Cohort 1 Treatment Period 1	Baseline	1		-	3	3.5	-	2.5	11.5
	Wk 4	29		-	3	3.5	-	2.5	9
	Wk 8	57		-	3	3.5	-	2.5	9
	Wk 12	85		-	3	3.5	2	2.5	16
	Wk 16	113		-	3	3.5	-	2.5	9
	Wk 20	141		-	3	3.5	-	2.5	9
	Wk 24/End of TP1/TD	169		-	3	3.5	2	2.5	16

B

Period	Visit Name	Days	Cryoglobulins	serum Free Light Chain	PK (CFZ533)	Immuno-genicity	Soluble CD40	[redacted]	Total (mL)
			Size (mL)	Size (mL)	Size (mL)	Size (mL)	Size (mL)		
Screening	Screening	-42 to -1	2	-	-	-	-		2
Cohort 1 Treatment Period 1	Baseline	1	-	3	3	3.5	2		18.5
	Wk 1	8	-	-	3	-	-		3
	Wk 2	15	-	-	3	3.5	2		8.5
	Wk 4	29	-	3	3	3.5	2		16.5
	Wk 6	43	-	-	3	-	-		3
	Wk 8	57	-	-	3	3.5	2		8.5
	Wk 10	71	-	-	3		-		3
	Wk 12	85	2	3	3	3.5	2		20.5

[redacted]

Period	Visit Name	Days	Cryoglobulins	serum Free Light Chain	PK (CFZ533)	Immuno-genicity	Soluble CD40	[redacted]	Total (mL)
			Size (mL)	Size (mL)	Size (mL)	Size (mL)	Size (mL)		
	Wk 16	113	-	-	3	3.5	2		8.5
	Wk 20	141	-	-	3	3.5	2		8.5
	Wk 24/End of TP1/TD	169	2	3	3	3.5	2		20.5

C

[redacted]

Table 16-8 Cohort 1: Treatment Period 2 and Follow up - Time schedule for blood sampling

A

Period	Visit Name	Days	Hematology	Clinical Chemistry	Coagulation Panel	Immunology	Cryoglobulins	serum Free Light Chain	[redacted]	Total (mL)
			Size (mL)	Size (mL)	Size (mL)	Size (mL)	Size (mL)	Size (mL)		
Cohort 1 Treatment Period 2	Wk 28	197	3	3.5	-	2.5	-	-		9
	Wk 32	225	3	3.5	-	2.5	2	2		15.5
	Wk 36	253	3	3.5	2		-	-		8.5
	Wk 40	281	3	3.5	-	2.5	2	2		13
	Wk 44	309	3	3.5	-	-	-	-		6.5
	Wk 48/TD	337	3	3.5	2	2.5	2	2		17.5

[redacted]

Period	Visit Name	Days	Hematology	Clinical Chemistry	Coagulation Panel	Immunology	Cryoglobulins	serum Free Light Chain	[redacted]	Total (mL)
			Size (mL)	Size (mL)	Size (mL)	Size (mL)	Size (mL)	Size (mL)		
Post-Treatment Follow-Up	FUP1	365	3	3.5	-	2.5	-	-		9
	FUP2	393	3	3.5	-	2.5	-	2		11
	FUP3/End of Study	421	3	3.5	-	2.5	2	2		13

B

Period	Visit Name	Days	[redacted]	PK (CFZ533)	Immuno-genicity	Soluble CD40	[redacted]	Total (mL)
				Size (mL)	Size (mL)	Size (mL)		
Cohort 1 Treatment Period 2	Wk 26	183		3	3.5	2		8.5
	Wk 28	197		3	3.5	2		8.5
	Wk 32	225		3	3.5	2		18
	Wk 36	253		3	3.5	2		8.5
	Wk 40	281		3	3.5	2		8.5
	Wk 44	309		3	3.5	2		8.5
	Wk 48/TD	337		3	3.5	2		18
Post-Treatment Follow-Up	FUP2	393		3	3.5	2		8.5
	FUP3/End of Study	421		3	3.5	2		15.5

[redacted]

Table 16-9 Cohort 2: Treatment Period 1 - Time schedule for blood sampling

A

Period	Visit Name	Days	[redacted]	Hepatitis CMV and HIV screen	Hematology	Clinical Chemistry	Coagulation Panel	Immunology	Total (mL)
				Size (mL)	Size (mL)	Size (mL)	Size (mL)	Size (mL)	
Screening	Screening	-42 to -1		12	3	3.5	2	2.5	25.5
Cohort 2 Treatment Period 1	Baseline	1		-	3	3.5	-	2.5	11.5
	Wk 4	29		-	3	3.5	-	2.5	9
	Wk 8	57		-	3	3.5	-	2.5	9
	Wk 12	85		-	3	3.5	2	2.5	16
	Wk 16	113		-	3	3.5	-	2.5	9
	Wk 20	141		-	3	3.5	-	2.5	9
	Wk 24/End of TP1/TD	169		-	3	3.5	2	2.5	16

B

Period	Visit Name	Days	Cryoglobulins	serum Free Light Chain	PK (CFZ533)	Immuno-genicity	Soluble CD40	[redacted]	Total (mL)
			Size (mL)	Size (mL)	Size (mL)	Size (mL)	Size (mL)		
Screening	Screening	-42 to -1	2	-	-	-	-		2
Cohort 2 Treatment Period 1	Baseline	1	-	3	3	3.5	2		18.5
	Wk 1	8	-	-	3	-	-		3
	Wk 2	15	-	-	3	3.5	2		8.5
	Wk 4	29	-	3	3	3.5	2		16.5
	Wk 6	43	-	-	3	-	-		3
	Wk 8	57	-	-	3	3.5	2		8.5
	Wk 10	71	-	-	3	-	-		3

[redacted]

Period	Visit Name	Days	Cryoglobulins	serum Free Light Chain	PK (CFZ533)	Immuno-genicity	Soluble CD40	[redacted]	Total (mL)
			Size (mL)	Size (mL)	Size (mL)	Size (mL)	Size (mL)		
	Wk 12	85	2	3	3	3.5	2		20.5
	Wk 16	113	-	-	3	3.5	2		8.5
	Wk 20	141	-	-	3	3.5	2		8.5
	Wk 24/End of TP1/TD	169	2	3	3	3.5	2		20.5

C

[redacted]

[redacted]

Table 16-10 Cohort 2: Treatment Period 2 and Follow up - Time schedule for blood sampling

A

Period	Visit Name	Days	Hematology	Clinical Chemistry	Coagulation Panel	Immunology	Cryoglobulins	serum Free Light Chain	[redacted]	Total (mL)
			Size (mL)	Size (mL)	Size (mL)	Size (mL)	Size (mL)	Size (mL)		
Cohort 2 Treatment Period 2	Wk 28	197	3	3.5	-	2.5	-	-		9
	Wk 32	225	3	3.5	-	2.5	2	2		15.5
	Wk 36	253	3	3.5	2	-	-	-		8.5
	Wk 40	281	3	3.5	-	2.5	2	2		13
	Wk 44	309	3	3.5	-	-	-	-		6.5
	Wk 48/TD	337	3	3.5	2	2.5	2	2		17.5
Post-Treatment Follow-Up	FUP1	365	3	3.5	-	2.5	-	-		9
	FUP2	393	3	3.5	-	2.5	-	2		11
	FUP3/End of Study	421	3	3.5	-	2.5	2	2		13

B

Period	Visit Name	Days	[redacted]	PK (CFZ533)	Immuno-genicity	Soluble CD40	[redacted]	Total (mL)
				Size (mL)	Size (mL)	Size (mL)		
Cohort 2 Treatment Period 2	Wk 26	183		3	3.5	2		8.5
	Wk 28	197		3	3.5	2		8.5
	Wk 32	225		3	3.5	2		18
	Wk 36	253		3	3.5	2		8.5
	Wk 40	281		3	3.5	2		8.5
	Wk 44	309		3	3.5	2		8.5
	Wk 48/TD	337		3	3.5	2		18
Post-Treatment Follow-Up	FUP2	393		3	3.5	2		8.5
	FUP3/End of Study	421		3	3.5	2		15.5

[redacted]

16.6 Appendix 6: ESSDAI

EULAR SJÖGREN'S SYNDROME DISEASE ACTIVITY INDEX (ESSDAI)

Table 1-1: Domain and item definitions and weights

Please circle the number in each category that best reflects your response.

Domain [weight]	Activity level	Description
Constitutional [3] Exclusion of fever of infectious origin and voluntary weight loss	No = 0	Absence of the following symptoms
	Low = 1	Mild or intermittent fever (37.5–8.5°C)/night sweats and/or involuntary weight loss of 5-10% of body weight
	Moderate = 2	Severe fever (> 38.5°C)/night sweats and/or involuntary weight loss of > 10% of body weight
Lymphadenopathy [4] Exclusion of infection	No = 0	Absence of the following features
	Low = 1	Lymphadenopathy ≥ 1 cm in any nodal region or ≥ 2 cm in inguinal region
	Moderate = 2	Lymphadenopathy ≥ 2 cm in any nodal region or ≥ 3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging)
	High = 3	Current malignant B-cell proliferative disorder
Glandular [2] Exclusion of stone or infection	No = 0	Absence of glandular swelling
	Low = 1	Small glandular swelling with enlarged parotid (≤ 3 cm), or limited submandibular or lachrymal swelling
	Moderate = 2	Major glandular swelling with enlarged parotid (> 3 cm), or important submandibular or lachrymal swelling

[redacted]

Domain [weight]	Activity level	Description
Articular [2] Exclusion of osteoarthritis	No = 0	Absence of currently active articular involvement
	Low = 1	Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (> 30 min)
	Moderate = 2	1–5 (of 28 total count) synovitis
	High = 3	≥ 6 (of 28 total count) synovitis
Cutaneous [3] Rate as 'no activity' stable long-lasting features related to damage	No = 0	Absence of currently active cutaneous involvement
	Low = 1	Erythema multiforma
	Moderate = 2	Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus
	High = 3	Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis
Pulmonary* [5] Rate as 'no activity' stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use, etc)	No = 0	Absence of currently active pulmonary involvement
	Low = 1	Persistent cough or bronchial involvement with no radiographic abnormalities on radiography or radiological or HRCT evidence of interstitial lung disease with no breathlessness and normal lung function test
	Moderate = 2	Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NYHA II) or abnormal lung function tests restricted to 70% > DL_{CO} ≥ 40% or 80% > FVC ≥ 60%
	High = 3	Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NYHA III, IV) or with abnormal lung function tests DL_{CO} < 40% or FVC < 60%

[redacted]

Domain [weight]	Activity level	Description
Renal [5] Rate as 'no activity' stable long-lasting features related to damage and renal involvement not related to the disease. If biopsy has been performed, please rate activity based on histological features first	No = 0	Absence of currently active renal involvement with proteinuria < 0.5 g/day, no haematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage
	Low = 1	Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/day) and without haematuria or renal failure (GFR ≥ 60 ml/min)
	Moderate = 2	Moderately active renal involvement, such as tubular acidosis with renal failure (GFR < 60 ml/min) or glomerular involvement with proteinuria between 1 and 1.5 g/day and without haematuria or renal failure (GFR ≥ 60 ml/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate
	High = 3	Highly active renal involvement, such as glomerular involvement with proteinuria > 1.5 g/day or haematuria or renal failure (GFR < 60 ml/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinaemia-related renal involvement
Muscular* [6] Exclusion of weakness due to corticosteroids	No = 0	Absence of currently active muscular involvement
	Low = 1	Mild active myositis shown by abnormal EMG or biopsy with no weakness and creatine kinase (N < CK ≤ 2N)
	Moderate = 2	Moderately active myositis confirmed by abnormal EMG or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N < CK ≤ 4N)
	High = 3	Highly active myositis shown by abnormal EMG or biopsy with weakness (deficit ≤ 3/5) or elevated creatine kinase (> 4N)

[redacted]

Domain [weight]	Activity level	Description
PNS* [5] Rate as 'no activity' stable long-lasting features related to damage or PNS involvement not related to the disease	No = 0	Absence of currently active PNS involvement
	Low = 1	Mild active peripheral nervous system involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia
	Moderate = 2	Moderately active peripheral nervous system involvement shown by NCS, such as axonal sensorimotor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinamic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (maximal motor deficit of 4/5 or mild ataxia) Or cranial nerve involvement of peripheral origin (except trigeminal (V) neuralgia)
	High = 3	Highly active PNS involvement shown by NCS, such as axonal sensorimotor neuropathy with motor deficit ≤ 3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex, etc.), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment: motor deficit ≤ 3/5 or severe ataxia
CNS* [5] Rate as 'no activity' stable long-lasting features related to damage or CNS involvement not related to the disease	No = 0	Absence of currently active CNS involvement
	Moderate = 2**	Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or confirmed cognitive impairment
	High = 3	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischaemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit

[redacted]

Domain [weight]	Activity level	Description
Haematological [2] For anaemia, neutropenia, and thrombopenia, only autoimmune cytopenia must be considered Exclusion of vitamin or iron deficiency, drug-induced cytopenia	No = 0	Absence of auto-immune cytopenia
	Low = 1	Cytopenia of auto-immune origin with neutropenia (1000 < neutrophils < 1500/mm3), and/or anaemia (10 < haemoglobin < 12 g/dl), and/or thrombocytopenia (100000 < platelets < 150000/mm3) Or lymphopenia (500 < lymphocytes < 1000/mm3)
	Moderate = 2	Cytopenia of auto-immune origin with neutropenia (500 ≤ neutrophils ≤ 1000/mm3), and/or anaemia (8 ≤ haemoglobin ≤ 10 g/dl), and/or thrombocytopenia (50000 ≤ platelets ≤ 100000/mm3) Or lymphopenia (≤ 500/mm3)
	High = 3	Cytopenia of auto-immune origin with neutropenia (neutrophils < 500/mm3), and/or anaemia (haemoglobin < 8 g/dl) and/or thrombocytopenia (platelets < 50000/mm3)
Biological [1]	No = 0	Absence of any of the following biological features
	Low = 1	Clonal component and/or hypocomplementaemia (low C4 or C3 or CH50) and/or hypergammaglobulinaemia or high IgG level between 16 and 20 g/l
	Moderate = 2	Presence of cryoglobulinaemia and/or hypergammaglobulinaemia or high IgG level > 20 g/l, and/or recent onset hypogammaglobulinaemia or recent decrease of IgG level (< 5 g/l)

CIDP, chronic inflammatory demyelinating polyneuropathy; CK, creatine kinase; CNS, central nervous system; DL_{CO}, diffusing CO capacity; EMG, electromyogram; EULAR, European League Against Rheumatism; FVC, forced vital capacity; GFR, glomerular filtration rate; Hb, haemoglobin; HRCT, high-resolution computed tomography; IgG, immunoglobulin G; NCS, nerve conduction studies; NYHA, New York Heart Association classification; Plt, platelet; PNS, peripheral nervous system.
*Clinical investigator subjective scoring based on availability of concurrent clinical data.
**Seror R et al, 2011

[redacted]

16.7 Appendix 7: ESSPRI

EULAR SJÖGREN'S SYNDROME PATIENT REPORTED INDEX (ESSPRI)

PATIENT CASE REPORTED FORM

Your physician has asked you to answer several questions relating to your disease. To answer to these questions, please take into account how bad your symptoms have been at their worst during the last two weeks only.

Please **check one box only** that best reflects your response.

Please make sure to answer **all the questions**.

Example:

No pain ☐ ☐ ☐ ☐ ☐ ☐ ☒ ☐ ☐ ☐ ☐ **Worst imaginable pain**

0 1 2 3 4 5 6 7 8 9 10

EVALUATION SCALES

1. How severe has your **dryness** been during the last 2 weeks?

No dryness ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ **Worst imaginable dryness**

0 1 2 3 4 5 6 7 8 9 10

2. How severe has your **fatigue** been during the last 2 weeks?

No fatigue ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ **Worst imaginable fatigue**

0 1 2 3 4 5 6 7 8 9 10

3. How severe has your **pain** (joint or muscular pains in your arms or legs) been during the last 2 weeks?

No pain ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ **Worst imaginable pain**

0 1 2 3 4 5 6 7 8 9 10

[redacted]

16.8 Appendix 8: IDEEL

Symptom Bother

These questions ask about the symptoms you may experience due to dry eyes.

1. **OVER THE LAST TWO WEEKS**, how often did you experience dry eye symptoms?

None of the time	A little of the time	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

The following questions ask about how bothersome dry eye symptoms were to you **OVER THE LAST TWO WEEKS**. If you had the symptom, please choose **how much the symptom bothered you** (not at all, slightly, moderately, or very much). If you did not have the symptom over the last two weeks, choose the "I did not have this symptom / Not applicable" box. Please choose only one box per question.

OVER THE LAST TWO WEEKS, how much did each of the following symptoms bother you?	I did not have this symptom / Not applicable	**OVER THE LAST TWO WEEKS, I had this symptom and it bothered me:**			
		Not at all	Slightly	Moderately	Very much
2. Eyes that felt gritty or sandy	☐	☐	☐	☐	☐
3. Felt like I needed to close my eyes even though I was not tired	☐	☐	☐	☐	☐
4. Burning or stinging eyes	☐	☐	☐	☐	☐
5. Tired eyes	☐	☐	☐	☐	☐
6. Blurry vision	☐	☐	☐	☐	☐
7. Itchy eyes	☐	☐	☐	☐	☐
8. Irritated eyes	☐	☐	☐	☐	☐
9. Eyes that felt like they had been scratched by something	☐	☐	☐	☐	☐
10. Eye dryness	☐	☐	☐	☐	☐

Impact of Dry Eye Disease on Everyday Life (IDEEL) 1

[redacted]

OVER THE LAST TWO WEEKS, how much did each of the following symptoms bother you?	I did not have this symptom / Not applicable	**OVER THE LAST TWO WEEKS, I had this symptom and it bothered me:**			
		Not at all	Slightly	Moderately	Very much
11. Mucus in, around, or coming out of my eyes	☐	☐	☐	☐	☐
12. Puffy or swollen eyes	☐	☐	☐	☐	☐
13. Eye redness	☐	☐	☐	☐	☐
14. Aching or sore eyes	☐	☐	☐	☐	☐
15. Felt like something was in my eye	☐	☐	☐	☐	☐
16. Frequent and/or rapid blinking	☐	☐	☐	☐	☐
17. Difficulty blinking because of little or no moisture in my eyes	☐	☐	☐	☐	☐
18. Sensitivity to light, glare, and/or wind	☐	☐	☐	☐	☐
19. Sensitivity to re- circulated air (such as air conditioning and heat)	☐	☐	☐	☐	☐
20. Headaches associated with dry eye symptoms	☐	☐	☐	☐	☐

Thank you for finishing this questionnaire.
Please make sure that you answered every question.

[redacted]