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CFZ533

Clinical Trial Protocol CCFZ533B2201E1 / NCT04541589

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

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List of abbreviations

ACR	American College of Rheumatology
ADA	Anti-drug antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
[redacted]	[redacted]
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
[redacted]	[redacted]
CFR	Code of Federal Regulation
ClinRO	Clinician Reported Outcomes
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus (Human- Cytomegalovirus)
CNS	Central nervous system
CO	Country Organization
COA	Clinical Outcome Assessment
COVID-19	Coronavirus Disease 2019
CRF	Case Report/Record Form (paper or electronic)
CRP	C-reactive protein
CSR	Clinical study report
CTC	Common Terminology Criteria
Ctrough	Trough concentration
CV	coefficient of variation
DMARD	Disease modifying antirheumatic drug
DMC	Data Monitoring Committee
dsDNA	double-stranded deoxyribonucleic acid
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
eCRF	Electronic case report form
EDC	Electronic Data Capture
EOS	End of study
[redacted]	[redacted]
eSource	Electronic Source
ESR	Erythrocyte sedimentation rate
ESSDAI	EULAR Sjögren's syndrome disease activity index
ESSPRI	EULAR Sjögren's syndrome patient reported index
EULAR	European League Against Rheumatism
[redacted]	[redacted]

FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
HBc	HB core antigen
HBs	HB surface antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
hCG	Human chorionic gonadotropin
HDL	High density lipoprotein
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
[redacted]	[redacted]
IEC	Independent Ethics Committee
IFU	Instructions for use
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
LDH	lactate dehydrogenase
LDL	Low density lipoprotein
LFT	Liver function test
LLOQ	lower limit of quantification
LN	Lupus nephritis
LVV	Large vessel vasculitis
mAb	Monoclonal antibody
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMF	Mycophenolate Mofetil
NHP	Non-human primates
NSAID	Nonsteroidal anti-inflammatory drugs
OL	Open-label

[redacted]	[redacted]
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PFS	Prefilled syringe
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PNS	Peripheral nervous system
PoC	Proof of Concept
PRO	Patient Reported Outcomes
pSS	primary Sjögren's syndrome
PT	prothrombin time
PTLD	Post-transplantation proliferative disorder
PTT	Partial thromboplastin time
Q2W	every 2 weeks, bi-weekly
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RA	Rheumatoid arthritis
[redacted]	[redacted]
s.c.	subcutaneous
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SD	standard deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SjS	Sjögren's Syndrome
SLE	Systemic lupus erythematosus
SoC	Standard-of-care
SOP	Standard operating procedures
SSA	Sjögren's syndrome-related antigen A
[redacted]	[redacted]
SUSAR	Suspected Unexpected Serious Adverse Reaction
TD	Study Treatment Discontinuation
TDAR	T cell-dependent antibody response
TEAE	Treatment emergent adverse events
TFQ	Trial feedback questionnaire
TMDD	Target mediated drug disposition
ULN	upper limit of normal
VAS	Visual analog scale
WBC	white blood cell(s)
WHO	World Health Organization

WOCBP	Women of child-bearing potential

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or 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 participant

Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 1 (17-Feb-2021)

Amendment rationale

The main purpose of this protocol amendment is to include an additional assessment time point as part of the Interactive Response Technology (IRT) algorithm criteria for participant rollover from the TWINSS core study (CCFZ533B2201) to extension study. ESSDAI and ESSPRI scores at Week 0 may be used for the IRT algorithm in the absence of a score at Week 4 of the core study. This change will allow participants who have missed their ESSDAI (Cohort 1 and Cohort 2) and/or ESSPRI (Cohort 2) assessments at Week 4 to be considered for inclusion in the extension study if these assessments were completed at Week 0 (baseline) of the core study.

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

The following sections have been updated in the amended protocol:

- Section 3 and Section 6.1.3 updated to include the use of ESSDAI (Cohort 1 and Cohort 2) and ESSPRI (Cohort 2) scores at Week 0 for the IRT algorithm if a score is missing at Week 4 of the core study.
- Section 4.1 text updated to clarify rationale for study design.
- Section 4.6 added for Public Health Emergency mitigation procedures. Section 6.7, Section 8, Section 8.3, Section 8.4 and Section 8.4.3 have been updated accordingly.
- Section 5.2 exclusion criterion #6 added to exclude a participant rolling over from the core study to the extension study in the case of a missing ESSDAI (Cohort 1 and Cohort 2) or ESSPRI (Cohort 2) score in the core study at Weeks 0 and 4 or Weeks 40 and 48.
- Figure 6-1 IRT Algorithm for treatment reassignment updated to include the use of ESSDAI (Cohort 1 and Cohort 2) and ESSPRI (Cohort 2) scores at Week 0 if a score is missing at Week 4 of the core study.
- Section 6.3.2 updated to clarify the process for transfer of ESSDAI and ESSPRI data from the core study to the extension study IRT database.
- Section 6.4 deletion of text to clarify that blood samples for PK, immunogenicity and [redacted].
- Section 6.5.2 and Section 8 updated to clarify the treatment period and follow-up period of the extension study.

- Section 6.7.2 updated with following text for more clarity: "Prior to self-administration at home, participants should contact the investigator/site staff in the case they are experiencing any AE/SAEs or have any concerns or there have been changes to the ongoing concomitant medications."
- Section 7 updated to include information on the digital injection care management device.
- Section 8.3 Instructions were added to use paper PRO as a back-up solution in case of case of device(s) failure.
- Table 8-3 Laboratory evaluations (Section 8.4.1) updated to remove FSH listed under additional assessments as fertility will not be assessed in the extension study.
- Section 8.5.1.2 text added to clarify that the PFS Questionnaire feedback is anonymous and individual participant level responses will not be reviewed by Investigators.
- Section 10.2.2, Table 16-1 and Table 16-4 updated to reflect the correct standard units for potassium and protein-creatinine ratio parameters.
- Section 16.5 Appendix 5: Blood Logs updated to align the blood volumes as per central laboratory requirements.

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.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

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.

Protocol summary

Protocol number	CCFZ533B2201E1
Full Title	A TWINSS extension trial to evaluate the safety and tolerability of CFZ533 (iscalimab) at two dose levels administered subcutaneously in patients with Sjögren's Syndrome
Brief title	Study of safety and tolerability of CFZ533 in 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 1-year extension study is to provide additional safety and tolerability information of the two doses of CFZ533 (iscalimab 600 mg and 300 mg) administered via prefilled syringes (PFS).
Primary Objective(s)	The primary objective of this study is to evaluate the safety and tolerability of iscalimab at two dose levels (600 mg and 300 mg) in patients with Sjögren's Syndrome, who participated in the TWINSS core study, CCFZ533B2201.
Secondary Objectives	Objective 1: To assess the pharmacokinetics (PK trough levels) and dose-exposure relationship of iscalimab Objective 2: To assess immunogenicity of iscalimab
Study design	Study CCFZ533B2201E1 is a multicenter extension study. Study blinding for the extension study will be maintained until final database lock of the core study, CCFZ533B2201, upon which the participants and Investigators will be unblinded, making it an open-label study through Week 120 (end of study visit).
Study population	The study population will consist of approximately 160 male and female participants (≥18 years old at the time of consent) who completed the core study (CCFZ533B2201) and who meet the inclusion/exclusion criteria.
Key Inclusion criteria	• Participants must have participated in the TWINSS core study, CCFZ533B2201, and must have completed the entire treatment period up to Week 48 and the follow-up period up to Week 60 • In the judgement of the Investigator, participants must be expected to clinically benefit from continued iscalimab therapy
Key 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 • Use of other investigational drugs other than iscalimab during the core study • Active uncontrolled viral, bacterial or other infections requiring systemic treatment at the time of enrollment, or history of recurrent clinically significant infection or of bacterial infections with encapsulated organisms • Missing ESSDAI (Cohort 1 and Cohort 2) or ESSPRI (Cohort 2) scores in the core study at Weeks 0 and 4 or Weeks 40 and 48
Study treatment	CFZ533 (iscalimab) will be administered as two 2 mL bi-weekly subcutaneous (Q2W s.c.) injections in prefilled syringes (PFS). Participants will be re-assigned to one of the following two treatment arms: • **Arm 1** - Iscalimab 600 mg s.c. Q2W • **Arm 2** - Iscalimab 300 mg s.c. Q2W
Pharmacodynamic assessments	[redacted]
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 [redacted].
Other assessments	• [redacted]
Data analysis	Descriptive statistics will be provided for this study. 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.
Key words	Sjögren's Syndrome, autoimmune disease, ESSDAI, ESSPRI, monoclonal antibody, anti-CD40, CFZ533, iscalimab, prefilled syringe (PFS), subcutaneous injection, TWINSS extension

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 Sjögren's Syndrome (SjS) patients (Ramos-Casals et al 2005, Theander et al 2011). Sjögren's Syndrome (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) is a fully human Fc-silenced, non-depleting, Immunoglobulin G1 (IgG1) anti-CD40 monoclonal antibody (mAb) that blocks 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 2019). 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) 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); please see current Iscalimab Investigator's Brochure (IB) for details. The overall risk/benefit profile was favorable, warranting continued development in this indication.

Limited safety data are currently available for iscalimab in any indication that is under investigation. This extension study (CCFZ533B2201E1) will allow us to demonstrate the additional safety and tolerability of two doses (600 mg and 300 mg) of treatment with iscalimab in patients with Sjögren's Syndrome (SjS).

1.2 Purpose

Study CCFZ533B2201 (TWINSS) is a double-blinded Phase IIb study enrolling two distinct populations of patients with SjS and is defined as the "core study". Study CCFZ533B2201E1

is designed as a 1-year extension to the core study. The extension study will be open only to eligible participants from the TWINSS core study who, in the opinion of the Investigator, may potentially derive clinical benefit from continued administration of CFZ533 (iscalimab). The primary purpose of this 1-year extension study is to provide additional safety and tolerability information of the two doses of iscalimab (iscalimab 600 mg and 300 mg) administered via prefilled syringes (PFS). Additionally, this extension study will further explore the pharmacokinetics (PK) and efficacy of iscalimab 600 mg and 300 mg doses. Key additional safety data will be used to better understand the overall safety profile of iscalimab at two dose levels and potentially inform study design elements of subsequent clinical studies (i.e. Phase III).

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

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

[redacted]

2.1 Primary estimands

Not applicable.

2.2 Secondary estimands

Not applicable.

3 Study design

TWINSS Core Study (CCFZ533B2201) Design

TWINSS is a basket trial consisting of two distinct study parts termed Cohort 1 and Cohort 2. Cohort 1 is a randomized, double-blind, placebo-controlled, parallel group, dose-range finding study, planned to enroll approximately 160 participants. Cohort 2 is a randomized, double-blinded, placebo-controlled proof-of-concept study, planned to enroll approximately 100 participants.

During a 6-week screening period, all participants fulfilling the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2016 classification criteria will be assessed for all 12 ESSDAI domains and will be randomized to Cohort 1 (Arms A, B, C and D) or Cohort 2 (Arms E and F) accordingly (refer to CCFZ533B2201 core study protocol for further details). The study design for the TWINSS core study is provided in Section 16.11.

TWINSS Extension Study (CCFZ533B2201E1) Design

Study CCFZ533B2201E1 is a continuation of the core study and is planned as a multicenter trial. This study will offer continuation of treatment for participants who have completed the core study and are deemed by the Investigator to clinically benefit from continued iscalimab therapy.

Enrollment will be determined by the number of participants completing the core study. It is estimated that approximately 160 participants from both Cohort 1 and Cohort 2 of the core study

may choose to enter the extension study. Study blinding for the extension study will be maintained until final database lock of the core study, upon which the participants and Investigators will be unblinded, making it an open-label study through Week 120 (end of study visit). All visit numbers (in weeks) used in the extension study are relative to the baseline visit of the core study. The baseline for the extension study (Week 60E1) will be carried out on the same day as the Week 60 visit of the core study. For more details refer to Table 8-1

The extension study is a 48-week treatment study, with a safety follow-up period of 12 weeks (Figure 3-1). Participants who complete 48 weeks of treatment and the mandatory 12 weeks of follow-up in the core study are eligible to participate in the extension study. The 12 weeks of follow-up in the core study is considered mandatory to obtain PK data. The study will help to evaluate the sustainability of response (ESSDAI) after a year of treatment in the core study.

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

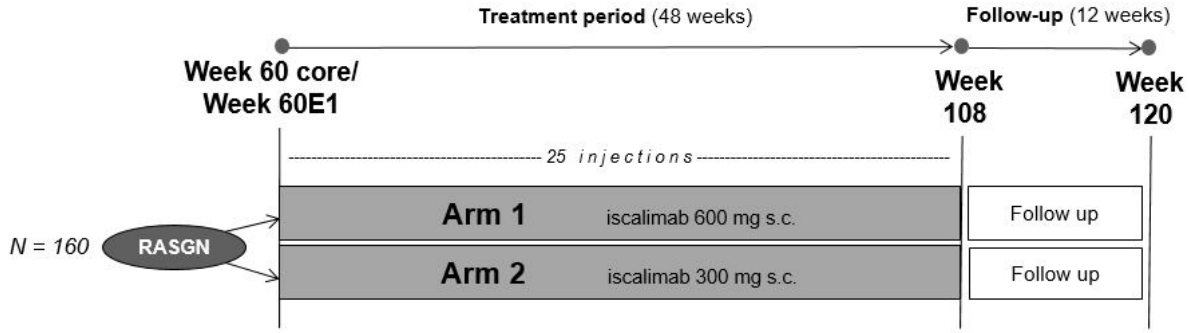
The treatment will be offered in PFS in the extension study. This is a change from the core study, which used s.c. injections prepared from vials. During the treatment period, 25 treatment administration visits are planned, including a weekly loading regimen (Week 60E1, Week 61, Week 62) at the start of the treatment period.

All participants enrolled in the extension study will receive a weekly loading regimen (Week 60E1, Week 61, Week 62) at the start of the treatment period followed by a s.c. maintenance regimen (600 or 300 mg s.c. every 2 weeks (Q2W)). One administration equals two s.c. injections. Refer to Section 4.2 for more details on dosages of the weekly loading regimen in both arms.

To maintain extension study blinding until final database lock of the core study, an Interactive Response Technology (IRT) algorithm will be used to re-assign participants to either iscalimab 600 mg (Arm 1) or 300 mg (Arm 2) s.c. Q2W in the extension study using ESSDAI (Cohort 1 and Cohort 2) and ESSPRI (Cohort 2) scores from predefined time points (Week 4 (or Week 0 if a score is missing at Week 4) and Week 48 (or Week 40 if a score is missing at Week 48)) in the TWINSS core study (refer to Section 6.1.3 for further details).

Participants will be instructed in detail how to self-administer the s.c. injection using the PFS formulation. Each injection will be administered into an appropriate injection site of the body (thighs, arms, or abdomen). For the first four visits of the study (through Week 64), all injections will be performed at the study site. If a participant had good safety and tolerability, with no indication of hypersensitivity or other acute reactions from the previous doses, starting from Week 66, the participant is allowed to self-administer the study treatment at home according to the assessment schedule (Table 8-1). The participant may continue to present at 2 week intervals to the study site for injection administrations, based on the participant's preference and the Investigator's judgment. Site staff will administer the injection to participants who are not able or unwilling to self-administer the PFS injection. The treatment period is from Week 60E1 to Week 108.

Figure 3-1 TWINSS extension study (CCFZ533B2201E1) design



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

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

4 Rationale

4.1 Rationale for study design

This 1-year extension study will provide additional safety data for two doses of iscalimab (600 mg and 300 mg). This study will also provide continued administration of iscalimab for participants that as per Investigator may potentially derive clinical benefit after completing the core study. The extension study will provide additional key safety data for the two doses of iscalimab to better understand the overall safety of iscalimab and potentially inform study design elements of subsequent clinical studies (i.e., Phase III). The study will allow for the assessment of continued evaluation of efficacy and tolerability. Furthermore, digital data collected as part of the extension study will build on existing digital data for further validation.

A follow-up period of 12 weeks (14 weeks after the last dose) is required to reach sub-pharmacological exposures after completion of dosing and was estimated taking into consideration the non-linear pharmacokinetics (target-mediated disposition) of iscalimab - see Section 4.2 below for detailed PK considerations.

The study is blinded until the final database lock of the core study to protect the integrity of the data in the ongoing core study. Participants can exit the study upon their own wish or based on advice of the Investigator at any time.

4.1.1 Rationale for choice of background therapy

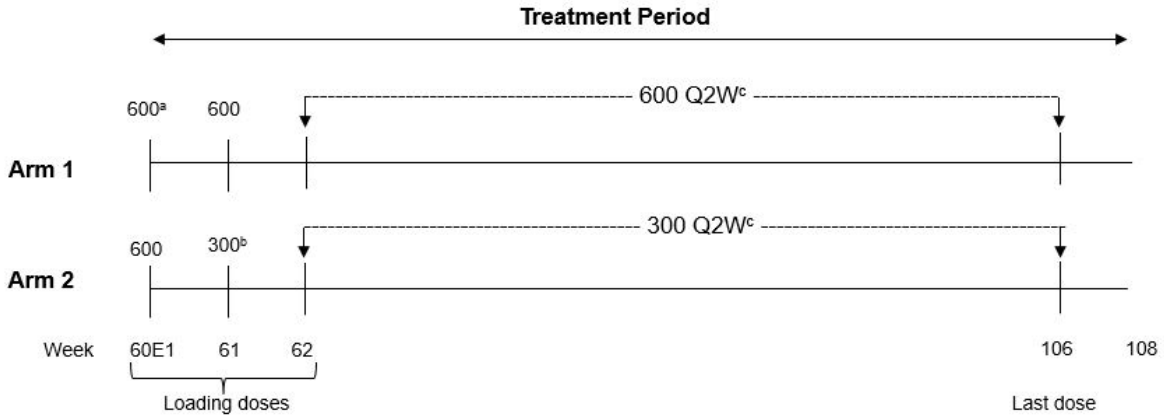
Local remedies for symptom relief and systemic background medication as per local practice is allowed, as long as participants are on stable dose (Section 6.2.1) and in accordance with the inclusion/exclusion criteria.

4.2 Rationale for dose/regimen and duration of treatment

CFZ533 (iscalimab) 600 mg or 300 mg will be administered s.c., weekly for the first 3 doses (Weeks 60E1, 61 and 62); then, from Week 64, iscalimab will be administered s.c. bi-weekly (every other week or Q2W). This is illustrated in Figure 4-1 for Arm 1 (iscalimab 600 mg maintenance regimen) and Arm 2 (iscalimab 300 mg maintenance regimen).

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

Figure 4-1 Iscalimab doses and regimen



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

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-CD154 (CD40 ligand) pathway blockade if CD40 receptors are not fully saturated.

The proposed loading regimen is aiming to rapidly achieve the CD40 receptor saturation and minimal CD40-mediated elimination, in conditions where CD40 expression might be enhanced and additionally also to rapidly establish 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. Based on these results the loading and further maintenance regimen will rapidly provide and sustain the systemic exposures above the threshold of 40 µg/mL for a broad population. This threshold was associated with complete suppression of germinal center development in cortical B cell areas of lymph nodes and T cell dependent antibody response in non-human primates (NHP).

As demonstrated in the PoC Study CCFZ533X2203 in pSS, a single s.c. dose of 600 mg iscalimab at Day 1 will deliver plasma concentrations generally above 40 µg/mL after 1 week. Subsequent weekly doses on Week 61 and 62 in Arms 1 and 2 are expected (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.

Further supportive arguments on the selected loading dosing regimen are provided in the Rationale for dose/regimen and duration of treatment of the TWINSS core study protocol (refer to Section 4 of the core study protocol).

Rationale for maintenance regimen

The maintenance regimen of 600 mg s.c. Q2W is expected to provide 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).

The maintenance regimen of 300 mg s.c. Q2W 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.

The between subject variability in exposure within the two treatment arms (to a lesser extent in the 600 mg treatment arm) is likely to depend on the biology of CD40 in target tissues (expression level, turnover) and its potential modulation during the treatment period.

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 600 mg 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 IB).

A 12-week follow-up period (14 weeks after the last dose) 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 drugs (comparator/placebo) or combination drugs

There is no placebo or active control group in this study given the purpose and main objectives are to extend treatment of participants who completed the core study. The use of two different doses of iscalimab (iscalimab 600 mg and 300 mg) will allow evaluation of both doses in terms of safety, tolerability and sustainability of clinical benefits. Placebo injection will be provided

to maintain blinding until the final database lock of the core study to protect the integrity of the data in the ongoing core study. For more details refer to Section 6.1.1.

4.4 Purpose and timing of interim analyses/design adaptations

There is no interim analysis planned for the study. The final analysis of the study will be performed at the end of the study. The end of the study is defined when all re-assigned participants have completed Week 120 or discontinued earlier. The extension study may be amended if deemed necessary based on the results of the TWINSS core study Week 24 primary analysis.

4.5 Risks and benefits

The risk to participants in this trial may be minimized by compliance with the eligibility criteria (refer to Section 5) and study procedures, as well as close clinical monitoring.

Risks:

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.

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

Table 4-1 Potential risks associated with CFZ53

Risk 1 Infections
Participants 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, participants will have adequate preformed antibody to maintain protective humoral response for extended periods of time (months). The participants will be monitored during the study for any signs and symptoms of infections including serology tests for cytomegalovirus (CMV; human-cytomegalovirus) infection.
Risk 2 Malignancy including Lymphoproliferative disorder
With immunosuppression there is a risk of developing lymphoproliferative disorders. Of note, lymphomas are also known to occur more frequently in participants 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 participants 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.
Risk 3 Thrombophilia/ 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, participants with conditions such as antiphospholipid syndrome, who are at a higher risk for thromboembolism, will be excluded unless they are receiving antithrombotic prophylaxis. CFZ533 binds to CD40 receptor and is Fc-silent mAb hence does not appear to carry the same risk of thrombosis. Both preclinical and clinical data from an extensive Phase 2 clinical program across healthy subjects and participants across different indications have not indicated a risk of thrombosis with CFZ533.

Risk 4 Immunogenicity

As with any monoclonal antibody, there is a hypothetical 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 including injection site reactions.

Risk 5 Vaccination Failure

Vaccination of participants 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. Administration of live attenuated vaccines should be avoided while receiving CFZ533 treatment and for at least 14 weeks thereafter.

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 administration of the study medication, low lymphocyte count at baseline and concomitant immunosuppressive medications like MMF and prednisolone. 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. Specific detection measures have been implemented 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 will continue to be closely monitored and mitigated in the current study.

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 participant 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 current edition of the CFZ533 IB.

Benefits:

The study design allows that all participants 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) and the potential risks and benefits from these medicines are known. Based on the preliminary safety and efficacy data from the exploratory PoC study of iscalimab in pSS, it is possible that a number of participants in one or both iscalimab dose arms experience clinically important benefit from iscalimab treatment in the current study.

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 Study Population

The study population will consist of male and female participants ≥ 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) who have completed the entire treatment period up to Week 48 and the mandatory 12 weeks follow-up period up to Week 60 of the TWINSS core study. The study population has previously been described in detail in the core study protocol (refer to Section 5 of the core study protocol). Enrollment will be determined by the number of participants completing the core study. It is estimated that approximately 160 participants may choose to enter the extension study from the core study.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Participants must have participated in the TWINSS core study, CCFZ533B2201, and must have completed the entire treatment period up to Week 48 and the follow-up period up to Week 60
2. Signed informed consent must be obtained prior to participation in the extension study (i.e. before commencement of the Week 60 assessments of the core study)
3. In the judgement of the Investigator, participants must be expected to clinically benefit from continued iscalimab therapy

5.2 Exclusion criteria

Participants 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 other than iscalimab during the core study
3. Active uncontrolled viral, bacterial or other infections requiring systemic treatment at the time of enrollment, or history of recurrent clinically significant infection or of bacterial infections with encapsulated organisms
4. 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
5. 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 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 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. Missing ESSDAI (Cohort 1 and Cohort 2) or ESSPRI (Cohort 2) scores in the core study at Weeks 0 and 4 or Weeks 40 and 48.

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) 300 mg provided in 2.0 mL PFS for s.c. injection
- Placebo provided in 2.0 mL PFS for s.c. injection required for blinding
- CFZ533 (iscalimab) 300 mg provided in 2.0 mL PFS for s.c. administration (open-label (OL) supplies)

Before enrollment in this extension study, all participants electing to continue will sign an Informed Consent form. At extension study entry, participants/caregiver will be provided with detailed instructions for self-administration of the s.c. injection (Instructions for Use (IFU)) using the PFS formulation. In cases where the participant is not comfortable or confident that he/she can successfully self-administer the full dose of PFS in a home setting, a caregiver can be trained to administer the treatment to the participant.

Each injection will be administered by the participant/caregiver into an appropriate injection site of the body. Site staff will administer the injection to participants who are not able or unwilling to self-administer the PFS injection. For the first four visits at Weeks 60E1, 61, 62 and 64, injections will be performed at site. Starting from Week 66 participants will have the choice of self-administration or injection by caregiver (once trained) at home or continuing with administration at site, based on personal preference and the Investigator's clinical judgment.

The study is blinded until the final database lock of the core study to protect the integrity of the data in the ongoing core study. Once study unblinding occurs after the final database lock of the core study, the participants will continue to receive the same dose of iscalimab (either 600 mg or 300 mg) and for those assigned to the 300 mg regimen, they will no longer receive the placebo PFS.

Note: PFS do not need to be prepared at the site. PFS will be packaged both as open-label and double-blind supplies. When the final database lock for the TWINSS core study is achieved, the extension study will become an OL study and the PFS will be provided in an OL manner with no further requirements for placebo PFS injections.

Novartis Global Clinical Supply (GCS) would provide the following IMPs in the trial. No other medication would be supplied by GCS.

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 300 mg/2 mL	Solution for injection	Subcutaneous Use	Blinded; PFS	Novartis Pharma AG
Placebo/2 mL	Solution for injection	Subcutaneous Use	Blinded; PFS	Novartis Pharma AG
CFZ533 300 mg/2 mL (OL)	Solution for injection	Subcutaneous Use	Open-label; PFS	Novartis Pharma AG

Instructions for administration of CFZ533 (iscalimab) and matching placebo are described in a separate manual.

6.1.2 Additional study treatments

No other treatment beyond investigational drug is included in this trial.

6.1.3 Treatment arms/group

No re-randomization is planned for the extension study. The treatment re-assignment for the extension study occurs at visit Week 60E1 which is the last visit of the core study (Week 60). Upon completion of the core study, Investigators will use their clinical judgment including responder definitions provided below to decide if it is beneficial for participants to continue with the extension study based upon response to therapy at the end of the treatment period of the core study.

Participants will be re-assigned to one of the following two treatment arms:

- Arm 1 - Iscalimab 600 mg s.c. Q2W
- Arm 2 - Iscalimab 300 mg s.c. Q2W

At Week 60 of the TWINSS core study, all eligible participants from the core study can opt to be enrolled in the extension study via IRT. The Week 60E1 visit will be performed on the same day once the Week 60 visit of the core study is completed by the participant. The Investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the extension study inclusion/exclusion criteria. An IRT algorithm will be programmed to assign the participant to blinded treatment in the extension study using ESSDAI (Cohort 1 and Cohort 2) and ESSPRI (Cohort 2) assessment scores from predefined time points in the TWINSS core study.

- For participants rolling over from Cohort 1 in the TWINSS core study, the change in ESSDAI score between Week 4 and Week 48 will be used to determine if the participant responded to treatment in the core study. If an ESSDAI score is missing at Week 4 and/or Week 48, then Week 0 or Week 40 scores should be respectively used for the algorithm. A decrease of 3 points or more from Week 4 (or Week 0 if the ESSDAI score is missing at Week 4) will classify the participant as a treatment responder in Cohort 1.

- For participants rolling over from Cohort 2 in the TWINSS core study, a change in both ESSDAI and ESSPRI scores between Week 4 and Week 48 will be used to determine if the participant responded to treatment in the core study. If an ESSDAI or ESSPRI score is missing at Week 4 and/or Week 48, then Week 0 or Week 40 scores should be respectively used for the algorithm. A decrease of 1 point or more in both the ESSDAI and ESSPRI scores from Week 4 (or Week 0 if the ESSDAI or ESSPRI score is missing at Week 4) will classify the participant as a treatment responder in Cohort 2.

Week 4 is being used as a baseline assessment to assess change over time, solely for the purposes of re-assigning patients to 300 mg or 600 mg, in a non-randomized manner, in this extension trial and was selected to minimize any potential placebo effect and regression to the mean observed at study treatment initiation in clinical trials.

Taking the treatment received during Treatment Period 2 of the TWINSS core study, and the responder status as the reference, the IRT algorithm will re-assign a dose level for extension study treatment. The maintenance treatment assigned for the extension study will be the same dose as in the core study or a higher dose level (Figure 6-1).

- Participants receiving iscalimab 600 mg s.c. Q2W or 300 mg s.c. Q2W in the core study and who meet the definition of a response will continue with the same dose in the extension study.
- Participants receiving iscalimab 600 mg s.c. Q2W in the core study and who do not meet the definition of a response will continue in the extension study with the same dose.
- Participants receiving iscalimab 150 mg s.c. Q2W in the core study and who meet the definition of a response will be re-assigned to 300 mg s.c. Q2W in the extension study.
- Participants receiving iscalimab 300 mg s.c. Q2W or 150 mg s.c. Q2W in the core study and who do not meet the definition of a response will be re-assigned to 600 mg s.c. Q2W in the extension study.

Figure 6-1 IRT Algorithm for treatment reassignment

TWINSS Core Study Cohort 1 - Datapoints for algorithm		TWINSS Core Study Cohort 2 - Datapoints for algorithm			
ESSDAI	Week 4 (or 0)	**ESSDAI**	Week 4 (or 0)	**ESSPRI**	Week 4 (or 0)
	Week 48 (or 40)		Week 48 (or 40)		Week 48 (or 40)
Definition of «Response»	-3 points or more change from Week 4 (or 0)	**Definition of «Response»**	-1 point or more change from Week 4 (or 0)	**AND**	-1 point or more change from Week 4 (or 0)
«Responder» if definition met	+		+		+

TWINSS Core Study		Maintenance dose levels assigned for extension study (NOTE: as reference consider the dose level in Treatment Period 2 of core study)
«Baseline»	**Response Week 48 (or 40)**	
Week 4 (or 0)	**+**	300 mg and 600 mg patients continue to extension on the same dose 150 mg → go to 300 mg
Week 4 (or 0)	**-**	600 mg → continue to extension on the same dose 300 mg → go to 600 mg 150 mg → go to 600 mg

+ = Response (definition met for purpose of IRT algorithm)
- = No response

6.1.4 Treatment duration

The planned duration of study treatment is 48 weeks. Participants may be discontinued from treatment earlier (see Section 9.1.1).

6.2 Other treatment(s)

Participants 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. Participants 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).

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. Participants 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 participant 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 re-assigning treatment for a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant 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.

Short term use of oral analgesics (NSAIDs, paracetamol) is permitted. Azathioprine (up to 150 mg/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 during the extension study and tapering is permitted at intervals not exceeding prednisone 2.5 mg/2 weeks.

Pre-emptive therapy with lamivudine or entecavir is allowed for participants with Hepatitis B surface antigen (HBsAg) seroreversion while on study treatment. Similarly, CMV antiviral medication used as pre-emptive therapy is allowed for participants 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 6-2 Prohibited medication

Medication	Prohibited in Study Period	Action to be taken
Other experimental therapies	All	Study treatment discontinuation required, participants should remain in the study and follow visit schedule
Other biologics (for treatment of autoimmune diseases e.g., SjS, SLE, RA)	All	Study treatment discontinuation required, participants should remain in study and follow visit schedule

Medication	Prohibited in Study Period	Action to be taken
DMARDs or other immune suppressive agents or changes in an existing DMARD regimen (hydroxychloroquine, methotrexate, azathioprine)	Treatment period	Study treatment discontinuation may be required on a case-by-case basis
Prednisone >10 mg (or equivalent other corticosteroid)	Treatment period	Study treatment discontinuation may be required on a case-by-case basis
Intravenous or oral cyclophosphamide; oral cyclosporine; oral MMF	All	Study treatment discontinuation required, participants should remain in the study and follow visit schedule
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).	Treatment period	Study treatment discontinuation may be required on a case-by-case basis
Live/attenuated vaccine	During treatment and for at least 14 weeks thereafter	Study treatment discontinuation required, participants should remain in the study and follow visit schedule

Wolff A, Joshi R, 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. Participants 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 6-2). When in doubt the Investigator should contact the Novartis medical monitor before treatment reassignment or allowing a new medication to be started. If any of the medications listed in Table 6-2 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. Participants must be encouraged to continue the follow-up visits even when discontinued permanently from the study treatment.

Corticosteroids may be administered to participants for SjS clinical disease flares after enrollment into this study as determined necessary by the responsible Investigator. [redacted]:

- 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.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.) that is assigned when the participant is enrolled into core study, CCFZ533B2201, and is retained for the participant throughout his/her participation in the trial. This being an extension study, the Participant No. will remain the same as that of the core study; new participant numbers will not be assigned.

The Participant No. consists of the Centre Number (Centre No.) assigned by Novartis to the investigative site with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. During the extension study, each participant will be uniquely identified by a Participant No..

6.3.2 Treatment assignment, randomization

No re-randomization will be performed in this study. At Week 60 of the core study, all eligible and consenting participants from the core study will be enrolled via Interactive Response Technology (IRT) and will be re-assigned to one of the treatment arms (refer to Section 6.1.3). An IRT algorithm will be programmed to assign the participant to blinded treatment in the extension study using ESSDAI (Cohort 1 and Cohort 2) and ESSPRI (Cohort 2) scores from predefined time points in the TWINSS core study. ESSDAI and ESSPRI scores at predefined time points will be transferred to the extension study IRT database by the electronic clinical outcome assessment (eCOA) vendor after the Investigator or his/her delegate has confirmed this transfer in the core study (for details, refer to the IRT user guide). The IRT will assign a number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

- For participants rolling over from Cohort 1 in the TWINSS core study, the change in ESSDAI score between Week 4 and Week 48 will be used to determine if the participant responded to treatment in the core study. If an ESSDAI score is missing at Week 4 and/or Week 48, then Week 0 or Week 40 scores should be respectively used for the algorithm. A decrease of 3 points or more from Week 4 (or Week 0 if the ESSDAI score is missing at Week 4) will classify the participant as a treatment responder in Cohort 1.
- For participants rolling over from Cohort 2 in the TWINSS core study, a change in both ESSDAI and ESSPRI scores between Week 4 and Week 48 will be used to determine if the participant responded to treatment in the core study. If an ESSDAI or ESSPRI score is missing at Week 4 and/or Week 48, then Week 0 or Week 40 scores should be

respectively used for the algorithm. A decrease of 1 point or more in both the ESSDAI and ESSPRI scores from Week 4 (or Week 0 if the ESSDAI or ESSPRI score is missing at Week 4) will classify the participant as a treatment responder in Cohort 2.

6.4 Treatment blinding

This will be a double-blind treatment **until the final database lock of Core study**. Participants, Investigator, site staff, and persons performing the assessments will remain blinded to the identity of the treatment until the final database lock of the core study, using the following methods:

1. Treatment assignment data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the exception of the bioanalyst
2. The identity of the treatments will be concealed by the use of investigational treatments that are all identical in packaging, schedule of administration and appearance

The re-assignment codes associated with participants from whom PK samples are taken will only be disclosed to the PK bioanalysts who will keep the PK results confidential until primary database lock of the core study (Week 24). Blood samples for PK, immunogenicity and [redacted] assessment will be collected for all participants.

Whenever needed or requested by the clinical team, before the open-label part of the extension study, the bioanalyst will share bioanalytical data in a blinded fashion with the pharmacokineticist.

Up to final database lock of core study, unblinding will only occur in the case of subject emergencies (see Section 6.6.2).

After final database lock of core study, the treatment arm for individual participant will be unblinded and the study will be conducted open-label.

Unblinding of the CTT will occur at the time of the primary database lock at Week 24 for each cohort of the core study.

Table 6-3 Blinding and unblinding plan

Role	Time or Event				
	Treatment re-assignment list generated	**Treatment allocation & dosing**	**Safety event (single participant unblinded)**	**Primary database lock at Week 24 of core study**	**Final database lock of core study**
Participants	B	B	B	B	U
Site staff	B	B	UI	B	U
PK sample analyst(s)	B	U	UI	U	U
Global Clinical Supply and Randomization Office	U	U	U	U	U

Role	Time or Event				
	Treatment re-assignment list generated	**Treatment allocation & dosing**	**Safety event (single participant unblinded)**	**Primary database lock at Week 24 of core study**	**Final database lock of core study**
Unblinded Pharmacovigilance sponsor staff	B	UI	UI	UI	U
Data Monitoring Committee (DMC)	B	U	U	U	U
CTT and other sponsor teams (trial team, project team, management & decision boards, support functions)	B	B	B	U	U

Key:

UI: Allowed to be unblinded on individual participant level

U: Unblinded

B: Remains blinded

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.

6.5.2 Dose interruptions

For participants 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 1 dose of study treatment may be missed in a 3 month 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 participant can continue or needs to be withdrawn from the treatment.

Treatment Period

- No dose interruptions are allowed prior to completion of Week 66 (Day 463): this is a critical period to ensure CD40 occupancy in target tissues

- From Week 68 (Day 477) to Week 108 (Day 757): 1 dose of study treatment may be missed in a 3 month period

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

Participants 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 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 participants 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 participants 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.

The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the Investigator and/or study personnel at each visit based on information provided by the participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

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 participant safely. Blinding codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the Investigator to select the participant’s next treatment regimen, and after discussion and agreement with the sponsor. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant 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 participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The Investigator will then receive details of the investigational drug treatment for the specified

participant 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. Participants 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
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding 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.

Investigator staff will identify the study medication kits to dispense to the participant 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 participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

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, delivery of IMP directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 3-month's supply. In this case, regular phone calls or virtual contacts (every 4 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, drug accountability, investigation of any adverse events, ensuring participants continue to benefit from treatment and discussion of the participant´s health status until the participants can resume visits at the study site.

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 IB. Clinical supplies are to be dispensed only in accordance with the protocol. The Investigator should educate the participant on how to properly store the study treatment if the participant is self-administering at home. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

The investigational drug iscalimab will be provided in PFS of 300 mg/2mL as a solution for s.c. administration. The matching placebo will be provided in PFS of 0 mg/2 mL as a solution for s.c. administration. Two injections of 2 mL each will be administered to the participant at every dosing visit, as follows:

Loading regimen:

CFZ533 (iscalimab) 600 mg or 300 mg will be administered s.c., weekly for the first 3 doses (Weeks 60E1, 61 and 62); then, from Week 64, iscalimab will be administered s.c. bi-weekly (every other week or Q2W) as described below.

Maintenance regimen:

- **Arm 1 (iscalimab 600 mg):** two 2 mL syringes, each containing 300 mg of iscalimab
- **Arm 2 (iscalimab 300 mg)**: one 2 mL syringe of placebo and one 2 mL syringe containing 300 mg of iscalimab

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 participant 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. Participants 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.

If local regulations allow, some study participants will be asked to use a Digital Injection Care Management device for disposal of used syringes after home use in a Smart Sharps bin rather than in a standard biohazard sharps bin. This is an optional pilot project that will be conducted at selected countries/sites. The digital box allows to capture the real time date and image of the disposal of the syringe. The connected device/box reminds the participant when medication is due, tracks when medication is taken and interventions as per the Novartis trial protocols. Detailed instructions on use and handling will be described in a separate manual. For the study participants using the Digital Injection Care Management device, there are no risks associated with the disposal of used syringes after home use in the Smart Sharps bin and/or return of the Smart Sharps bin with the used syringes after home use to the study site.

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.

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.

Study treatment (iscalimab 600 mg and 300 mg) will be administered s.c. by the participant, caregiver or site staff. The PFS will be provided by the site staff to the participant, who will self-administer the injections at the specified study time point. Participants will be instructed in detail how to self-administer the s.c. injection using the PFS. Site staff will administer the injection to those participants who are not able or unwilling to self-administer the PFS injection. Detailed instructions on the self-administration of the study treatment will be described in the IFU and provided to each participant. It shall be recorded on the corresponding eCRF(s) whether the participant self-administered the PFS or whether site staff or caregiver administered the PFS and whether it was administered at home or at the site.

Iscalimab 600 mg s.c. Q2W

- Iscalimab loading doses will be 600 mg s.c. (2 injections of 300 mg/2 mL) on Week 60E1 (Day 421), Week 61 (Day 428) and Week 62 (Day 435)
- From Week 62 the participant will receive 600 mg s.c. Q2W iscalimab until Week 106 (last dose)

Iscalimab 300 mg s.c. Q2W

- Iscalimab loading doses will be 600 mg s.c. (2 injections of 300 mg/2 mL) on Week 60E1 (Day 421), 300 mg s.c. (1 injection of 300mg/2 mL and 1 injection of 2 mL of the placebo) on Week 61 (Day 428) and 300 mg s.c. Week 62 (Day 435)
- From Week 62 the participant will receive 300 mg s.c. Q2W iscalimab until Week 106 (last dose)

The first study treatment administration will occur at Week 60E1 after the inclusion/exclusion criteria have been confirmed, all study scheduled assessments have been performed and the scheduled blood samples have been drawn. For the loading doses on Week 60E1 (Day 421), Week 61 (Day 428) and Week 62 (Day 435), all injections will be self-administered by the participant at the study site under the supervision of a site staff member after the study assessments for the visit have been completed. Participants will be required to attend the study site for the Week 64 visit and starting at Week 66, the participants will be allowed to self-administer the study medication at home on an alternating basis through to Week 106 or continue to present at the study site for injection administrations, based on the participant's preference and the investigator's judgment.

The trial-related safety and efficacy procedures will be conducted as indicated in Table 8-1. While at the site visits, participants will be asked to refer to the IFU and to proceed with self-injection. At study visits requiring pre-dose blood samples, the participant will self-administer study treatment only after the blood samples have been collected.

For each study visit at the site, all study assessments including completion of Patient Reported Outcomes (PROs) should be completed prior to the self-administration of the study treatment.

All dosages prescribed and dispensed to the participants and all dose changes during the study must be recorded on the Dosage Administration Record CRF. Immediately before dispensing the package to the participant, site staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that participant's unique participant number.

The investigator should promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant should be instructed to contact the Investigator if he/she is unable for any reason to take the study treatment as prescribed.

Administration

Single syringes will be packed in individual boxes. The site and participant should refer to the IFU for storage and handling instructions. Each injection should be administered into an appropriate injection site of the body (thighs, arms, or abdomen). Each new injection should be administered at the same site on opposite sides of the body or given on two different body sites. If the participant chooses the abdomen, a 2-inch area around the navel should be avoided. Investigational drug should not be injected into areas where the skin is tender, bruised, red, or hard or where participant has scars or stretch marks. Injection sites should be alternated to reduce the risk of reaction. Used safety syringes should be disposed immediately after use in a sharps container or according to the regulatory needs to the respective countries.

Home administration

Participants (or caregivers) will be allowed to self-administer the PFS at home when they are not visiting the site for any other trial-related procedures. Participants will be allowed to self-administer the PFS at home (starting at Week 66) only if they have exhibited correct use for self-administering the PFS at the site during the first 4 visits for treatment during the extension study. At such time points, if requested by the participant, a caregiver would be allowed to administer the study medication. Optional site visits have been included in the assessment table between the visits at which trial-related procedures are not to be conducted at the site. Participants will be allowed to self-administer the PFS at home or to visit the site during the optional visits to self-administer the PFS under the supervision of the site staff. If the participant is not able or not confident to self-administer the PFS, he/she should visit the site at every optional site visit (e.g., every 4 weeks) during the treatment period and the site staff will administer the PFS.

Prior to self-administration at home, participants should contact the investigator/site staff in the case they are experiencing any AE/SAEs or have any concerns or there have been changes to the ongoing concomitant medications.

7 Informed consent procedures

The following informed consents are included in this study:

1. Main study consent, which also includes a subsection that requires a separate signature for the optional consent for digital assessments and optional consent for digital injection care management device.

2. As applicable, Pregnancy Outcomes Reporting Consent for female subjects who took study treatment.

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding. If the participant 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 participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH 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 IB. This information will be included in the participant informed consent and should be discussed with the participant 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 participant.

Women of child bearing 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 after IRB/IEC approval.

Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible.

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

Visits can be performed with the following time windows:

Treatment Period

- +/- 1 calendar day: from Week 60E1 (Day 421) to Week 61 (Day 428)
- +/- 2 calendar days: from Week 62 (Day 435) to Week 66 (Day 463)
- +/- 5 calendar days: from Week 68 (Day 477) to Week 108 (Day 757)

Follow-up Period

+/- 5 calendar days from Week 112 (Day 785) to Week 120 (Day 841)

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.

Missed or rescheduled visits should not lead to automatic discontinuation. Participants 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 CRF.

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 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 on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule

Period	**Extension-Treatment**																			
Visit Name	**Wk 60E1**[1]	**Wk 61**	**Wk 62**	**Wk 64**	**Wk 66**	**Wk 68**	**Wk 70**	**Wk 72**	**Wk 74**	**Wk 76**	**Wk 78**	**Wk 80**	**Wk 82**	**Wk 84**	**Wk 86**	**Wk 88**	**Wk 90**	**Wk 92**	**Wk 94**	**Wk 96**
Days	**421**	**428**	**435**	**449**	**463**	**477**	**491**	**505**	**519**	**533**	**547**	**561**	**575**	**589**	**603**	**617**	**631**	**645**	**659**	**673**
Weeks	**60**	**61**	**62**	**64**	**66**	**68**	**70**	**72**	**74**	**76**	**78**	**80**	**82**	**84**	**86**	**88**	**90**	**92**	**94**	**96**
Optional site visit[2]					X		X		X		X		X		X		X		X	
Informed consent	X[3]																			
Inclusion / Exclusion criteria	X																			
Contact IRT	X[4]	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	X	X	X	X	X	X	X
Demography	X																			
Smoking history	X																			
Medical history/current medical conditions	X																			
Prior therapy for Sjögren's Syndrome	X																			
Adverse Events[5]	X	X	X	X	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	X	X	X	X
Physical Examination	C[6]			S[7]		S[7]		S[7]		S[7]		S[7]		S[7]		S[7]		S[7]		S[7]
Vital signs and body measurements	C[6]	X	X	X		X		X		X		X		X		X		X		X
Electrocardiogram (ECG)	X																			
[redacted]																				
Hepatitis and CMV monitoring (local)[9]	C[6]							S[7]						S[7]						S[7]

Period	**Extension-Treatment**																			
Visit Name	**Wk 60E1**[1]	**Wk 61**	**Wk 62**	**Wk 64**	**Wk 66**	**Wk 68**	**Wk 70**	**Wk 72**	**Wk 74**	**Wk 76**	**Wk 78**	**Wk 80**	**Wk 82**	**Wk 84**	**Wk 86**	**Wk 88**	**Wk 90**	**Wk 92**	**Wk 94**	**Wk 96**
Days	**421**	**428**	**435**	**449**	**463**	**477**	**491**	**505**	**519**	**533**	**547**	**561**	**575**	**589**	**603**	**617**	**631**	**645**	**659**	**673**
Weeks	**60**	**61**	**62**	**64**	**66**	**68**	**70**	**72**	**74**	**76**	**78**	**80**	**82**	**84**	**86**	**88**	**90**	**92**	**94**	**96**
Hematology	C[6]			X		X		X		X		X		X		X		X		X
Clinical Chemistry	C[6]			X		X		X		X		X		X		X		X		X
Coagulation Panel[10]	X							X						X						X
Immunology	C[6]					X				X				X				X		
Cryoglobulins[11]	C[6]							X						X						X
Pregnancy test[12]	C[6]			X		X		X		X		X		X		X		X		X
PK blood collection[13]	C[6]									X								X		
Immunogenicity[13]	C[6]									X								X		
[redacted]																				
Urinalysis dipstick	C[6]			X		X		X		X		X		X		X		X		X
[redacted]																				
Prefilled syringe questionnaire[16]																				
Trial feedback questionnaire[16]																				

Period	**Extension-Treatment**						**Post-Treatment Follow-Up**	
Visit Name	**Wk 98**	**Wk 100**	**Wk 102**	**Wk 104**	**Wk 106**	**Wk 108/TD[19]**	**Wk 112**	**Wk 120/EOS[20]**
Days	**687**	**701**	**715**	**729**	**743**	**757**	**785**	**841**
Weeks	**98**	**100**	**102**	**104**	**106**	**108**	**112**	**120**
Optional site visit[2]	X		X		X			
Informed consent								
Inclusion / Exclusion criteria								
Contact IRT		X		X				
Study drug administration	X	X	X	X	X[21]			
Demography								
Smoking history								
Medical history/current medical conditions								
Prior therapy for Sjögren's Syndrome								
Adverse Events[5]	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Physical Examination		S[7]		S[7]		S[7]	S[7]	S[7]
Vital signs and body measurements		X		X		X	X	X
Electrocardiogram (ECG)						X		
[redacted]								
Hepatitis and CMV monitoring (local)[9]						S[7]		S[7]
Hematology		X		X		X	X	X
Clinical Chemistry		X		X		X	X	X
Coagulation Panel[10]						X		
Immunology		X				X	X	X
Cryoglobulins[11]						X		X
Pregnancy test[12]		X		X		X	X	X

Period	**Extension-Treatment**						**Post-Treatment Follow-Up**	
Visit Name	**Wk 98**	**Wk 100**	**Wk 102**	**Wk 104**	**Wk 106**	**Wk 108/TD**[19]	**Wk 112**	**Wk 120/EOS**[20]
Days	**687**	**701**	**715**	**729**	**743**	**757**	**785**	**841**
Weeks	**98**	**100**	**102**	**104**	**106**	**108**	**112**	**120**
PK blood collection[13]						X		X
Immunogenicity[13]						X		X
[redacted]								
Urinalysis dipstick		X		X		X	X	X
[redacted]								
Prefilled syringe questionnaire[16]						X		
Trial feedback questionnaire[16]								X

Period	Extension-Treatment						Post-Treatment Follow-Up	
Visit Name	Wk 98	Wk 100	Wk 102	Wk 104	Wk 106	Wk 108/TD[19]	Wk 112	Wk 120/EOS[20]
Days	687	701	715	729	743	757	785	841
Weeks	98	100	102	104	106	108	112	120

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[1] Corresponds to the Week 60 visit of the core study. Assessments carried out as part of Week 60 as per core study protocol should be used for Week 60E1 of the extension study.
[2] Optional site visits - Week 66, 70, 74, 78, 82, 86, 90, 94, 98, 102, 106. Participants who are unable to self-administer the PFS injections at home will visit the site and site staff will supervise self-administration or administer the PFS injection for them. Other participants who can self-administer the PFS injection can do so at home at these optional visits.
[3] Informed consent should be obtained before commencement of the Week 60 assessments of the core study.
[4] Contact IRT for new treatment reassignment.
[5] AEs/SAEs occurring after the participant has signed the informed consent must be captured on the appropriate eCRF page.
[6] C - These assessments shall be conducted as part of the core study CCFZ533B2201 and will not be repeated in this extension study
[7] S - Assessment to be recorded in the source documentation only
[8] [redacted].
[9] Local lab testing of CMV IgG, IgM and DNA (by PCR) must be performed every 3 months until end of study. Hepatitis B monitoring applicable to HBsAg (-) patients who were HBcAb (+) and HBV DNA (-) at screening during the core study. Local lab testing of HBsAg and HBV DNA must be performed every 3 months until end of study.
[10] While on treatment, coagulation monitoring applies only to participants 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 of the TWINSS core study protocol.
[11] Analysis of cryoglobulins will be done only for participants who were positive at screening in the TWINSS core study.
[12] Urine pregnancy tests will be performed throughout the study
[13] Blood sample is collected pre-dose.
[14] [redacted]
[15] [redacted].
[16] Optional
[17] [redacted].
[18] [redacted].
[19] In case of premature discontinuation, participants will enter the follow-up after completing assessments for this visit.
[20] Mandatory to all participants, including those who have discontinued the study prematurely.
[21] Week 106 is the last dose administration visit in the Treatment Period.

8.1 Screening

Not applicable for this extension study.

8.1.1 Information to be collected on screening failures

Not applicable for this extension study.

8.2 Participant demographics/other baseline characteristics

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

Participant demographic and baseline characteristic data to be collected on all participants include: age, sex, race, ethnicity, smoking history, 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.

[redacted]

[redacted]

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, regular phone or virtual calls can occur (every 4 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 Section 10.

Table 8-2 Assessment and Specifications

Assessment	Specification
Physical examination	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 participant 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 participant has been sitting for five 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 Section 16.1.
Body measurements	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 8-1. 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 Section 16.1.

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 participant 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 hepatitis monitoring (HBsAg and HBV-DNA) applicable to HBsAg-negative, anti-HBc positive participants continuing from the TWINSS core study and CMV monitoring.

Table 8-3 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)
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, 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.
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	[redacted] Complement (C3, C4)
CMV, Hepatitis monitoring (locally, as applicable)	HBsAg, HBV-DNA, CMV serology (CMV IgG, IgM) and CMV DNA by PCR
Additional tests	Cryoglobulins (local testing), PK, PD ([redacted]) and immunogenicity (anti-CFZ533 anti-bodies) blood samplings, [redacted]
Pregnancy Test	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, and 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, participant number, date and time, and filed in the study site source documents. Any identifier details must be redacted (e.g., participant initials, date of birth). Results must be entered into the eCRF.

For any ECGs with participant 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 participant is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

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

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have local urine pregnancy tests monthly, as indicated in Table 8-1. 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 β-hCG test (serum pregnancy test). If positive, the participant 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.

If participants cannot visit the site to have pregnancy tests, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first, and only if the test result is negative are they to proceed with administration of the study treatment. 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 participants 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. An SAE report should be completed for malignancies occurring until the last visit (for participants in follow-up) or for 14 weeks after the last dose of study treatment taken (for participants in the treatment period or who completed the treatment period).

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 participant is hospitalized an SAE report must be completed and reported.

8.4.5 Appropriateness of safety measurements

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

8.5 Additional assessments

[redacted]

Trial Feedback

This trial will include an option for participants to complete an anonymized questionnaire, 'Trial Feedback Questionnaire' (TFQ) for participants 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 participants across different therapeutic areas.

The optional questionnaire will be completed at the site at Week 120, end of the study period.

TFQ questions relate to both protocol-specified and site-specific components, including study burden and interaction with site staff. Feedback is anonymous. Individual participant 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 participant'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 eCOA vendor provider database, separate from the clinical trial database.

Satisfaction with self-injection using a prefilled syringe questionnaire (PFS Questionnaire)

This trial will include an option for participants self-administering CFZ533 (iscalimab) or placebo with PFS outside of clinic to complete a study-specific questionnaire to evaluate their experience and satisfaction with using the PFS (Section 16.10). Feedback is anonymous. Individual participant level responses will not be reviewed by Investigators.

The questionnaire consists of five questions and measures the confidence, ease of use, convenience, satisfaction and the participant's willingness to self-inject. Each question has five answers from "1 = not easy/not confident/not convenient/not satisfied/definitely not" to "5 =

very easy/very confident/very convenient/very satisfied/yes definitely". The scores will be reported per question and no overall score will be calculated. Higher scores mean higher satisfaction, better experience. The questionnaire will be available in each language for each country participating in this study following a validated translation process.

The optional questionnaire will be completed at the site at Week 108, end of the treatment period.

Site and participants will receive clear instructions on the completion of the questionnaire. Site must allow participants to complete the questionnaire on their own without any assistance from the site staff.

The PFS data will be stored in the eCOA vendor database, separate from the clinical trial database.

8.5.2 Pharmacokinetics

Free CFZ533 (iscalimab) plasma concentrations will be measured in all participants.

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 Section 16.5. 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 assay. 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 participants, 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 will be described in a separate laboratory manual.

All samples will be given a unique sample number as listed in the Section 16.5. The data and details of the analytical methods will be provided in a standalone Bioanalytical Data Report.

[redacted] [redacted]

[redacted]

[redacted]

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[redacted] [redacted]

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

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

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

Study treatment must be discontinued under the following circumstances:

- Participant/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 participant
- Following emergency unblinding of the treatment arm
- Emergence of the following adverse events:
  - Persistent neutropenia Common Terminology Criteria (CTC) grade 3 or higher
  - SAEs or severe AEs of infection
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant’s overall status, prevents the participant from continuing participation in the study

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

Participants 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 participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. 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 participant's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section (Section 6.6.2).

9.1.1.1 Replacement policy

Participants who are prematurely withdrawn or discontinued from the study will not be replaced.

9.1.2 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the study anymore, and
- Does not want any further visits or assessments, and
- Does not want any further study related contacts

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

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

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 participant are not allowed unless safety findings require communicating or follow-up.

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

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.3 Lost to follow-up

For participants 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 participant, e.g., dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the time point of his/her 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 participant finishes their Study Completion visit (all visits until Week 120 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. The final analysis of the study will be performed at the end of the study (EOS). The EOS is defined when all re-assigned participants have completed Week 120 or discontinued earlier. All available data in the extension study will be included in the analysis and will be reported in a final CSR.

The investigator must provide follow-up medical care for all participants who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care may include another treatment outside of the study as deemed appropriate by the investigator.

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 Section 16.1.

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

10.1.2 Serious adverse events

An 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 an 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 an 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.

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 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 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.

10.1.5 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.

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 eCRF	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 Section 16.2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Section 16.2 should be followed up by the investigator or designated personnel at the trial site as summarized below. Detailed information is outlined in Section 16.2.

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
- 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 dipstick proteinuria ≥3+ OR Protein-creatinine ratio ≥150 mg/g or ≥15 mg/mmol
   - New dipstick hematuria ≥3+ on urine dipstick. Every renal laboratory trigger or renal event as defined in Section 16.3 should be followed-up by the investigator or designated personnel at the trial site as summarized.

10.2.3 Data Monitoring Committee

No separate data monitoring committee (DMC) will be formed for the extension study. The DMC of the core study may review the safety data of this trial at less frequent intervals (i.e., planned every 6 months) until final database lock of the core study. Specific details regarding the DMC process will be available in the core study DMC charter.

Additional meetings may be scheduled if discussion of any issue is required.

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) 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 participant 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.

Re-assignment codes and data about all study treatment(s) dispensed to the participant 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 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. Monitors are responsible to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. 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 analysis will be conducted after all participants have finished the extension 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.

12.1 Analysis sets

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

The Safety Set (SAF) includes all participants who received at least one dose of study treatment during the extension study. Participants will be analyzed according to the study treatment received, where treatment received is defined as the assigned treatment if the participant took at least one dose of that treatment or the first treatment received if the assigned treatment was never received. Only data in the extension study will be included in the analysis.

12.2 Participant demographics and other baseline characteristics

Analyses will be based on the FAS.

Demographics and baseline characteristics:

Summary statistics will be presented for continuous demographic and baseline characteristic variables from core study for each treatment group. The number and percentage of participants in each category will be presented for categorical variables for each treatment group and all participants.

Medical history:

Disease-specific medical history and any condition entered as medical history or current medical conditions at core baseline will be coded using the MedDRA dictionary. They will be summarized by system organ class and preferred term of the MedDRA dictionary.

12.3 Treatments

Analyses of treatment will be based on the SAF.

Study treatment:

The duration of exposure to study treatment will be summarized by treatment group. In addition, the number of participants with exposure of at least certain thresholds (e.g., any exposure, ≥2 weeks ≥4 weeks ≥6 weeks ≥8 weeks etc.) will be displayed.

Prior and concomitant medication:

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and the date of the last study visit will be a concomitant medication, including those which were started pre-baseline and continued into the period where study treatment is administered.

Prior and concomitant medications will be summarized in separate tables. Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will show the overall number and percentage of participants 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 participants receiving systemic therapies for pSS as prior and concomitant background medication will be presented separately by preferred term.

12.4 Analysis of the primary endpoint(s)/estimand(s)

The analysis for the primary endpoint will be performed on SAF.

12.4.1 Definition of primary endpoint(s)/estimand(s)

All safety data, including laboratory measurements, vital signs, and AEs are considered primary endpoints.

12.4.2 Statistical model, hypothesis, and method of analysis

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

Adverse events:

Treatment emergent adverse events (TEAEs) will be summarized. Only primary paths within MedDRA will be considered for AE reporting. The definition for "treatment emergent" is as follows:

- Events started on or after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term;
- AEs observed four weeks after last study-drug administration will not be considered as treatment-emergent

AEs will be summarized by presenting, for each treatment group, the number and percentage of participants having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a participant reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a participant reported more than one AE within the same primary system organ class, the participant will be counted only once with the greatest severity at the system organ class level, where applicable.

SAEs will also be summarized.

Separate summaries will be provided for deaths, SAEs, and other significant AEs leading to discontinuation.

All AEs including non-treatment emergent AEs will be listed.

Laboratory data:

The summary of laboratory evaluations will be presented for two groups of laboratory tests (hematology and serum chemistry). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test and treatment group. Change from baseline will only be summarized for participants with both baseline and post-baseline values. For each parameter, the maximum change from baseline will be analyzed analogously. Number and percentage of participants with notable abnormalities will be summarized.

Vital signs:

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for participants with both baseline and post-baseline values. Number and percentage of participants with notable abnormalities will also be summarized.

12.4.3 Handling of remaining intercurrent events of primary estimand

All the data will be included in the analysis, regardless of intercurrent events that have occurred.

12.4.4 Handling of missing values not related to intercurrent event

Not applicable.

12.4.5 Sensitivity analyses for primary endpoint/estimand

Not applicable.

12.4.6 Supplementary analysis

Not applicable.

12.4.7 Supportive analyses

Not applicable.

12.5 Analysis of secondary endpoints/estimands

12.5.1 Pharmacokinetics

Trough free iscalimab plasma concentrations will be listed by 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), steady state (ss), 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.

12.5.2 PK/PD relationships

Data from this study may be used with pharmacokinetics/pharmacodynamics (PK/PD) models developed based on the core study CCFZ533B2201. This will be reported separately, if applicable.

12.5.3 Immunogenicity

All the results for immunogenicity data (anti-iscalimab antibodies) will be listed by visit/time.

If appropriate, summary statistics and shift tables will also be presented.

[redacted]

12.7 Interim analyses

Not applicable.

12.8 Sample size calculation

It is estimated that approximately 160 participants enrolled in the core study will complete the core study and be eligible for entry into the extension study.

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 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, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. 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 monitor, 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 will be submitted for publication and 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 publication policy including authorship criteria, please refer to the publication policy training materials that were provided to you 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 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 participants 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.

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, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant 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 participant 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.

15 References

References are available upon request

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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		
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 µmol/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
Hematology variables: Differential		

Laboratory variable **Liver function and related variables**	**Standard units**	**SI units**
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)	

16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-2 Liver event and laboratory trigger definitions

LIVER LABORATORY TRIGGERS LIVER EVENTS	**Definition/ threshold** • 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN • 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.,	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	conmeds, med hx, lab) in the appropriate CRF	
> 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.,	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

Criteria	Actions required	Follow-up monitoring
	conmeds, med hx, lab) in the appropriate CRF	
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

*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.
[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.*

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-4 Specific Renal Alert Criteria and Actions and Event Follow-up

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 ≥3+ OR Protein-creatinine ratio ≥150 mg/g or ≥15 mg/mmol	Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New dipstick hematuria ≥3+ on urine dipstick	Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder
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 and interpretation

Not Applicable

16.5 Appendix 5: Blood Logs

Table 16-5 (A) - Blood Logs

Period	Visit Name	Days	Weeks	[redacted]	Hematology	Clinical Chemistry	Coagulation Panel[2]	Immunology	Cryoglobulins[3]	PK blood collection[4]			Total (mL)
					Size (mL)	Size (mL)	Size (mL)	Size (mL)	Size (mL)	Size (mL)	Sample Number	Dose reference ID	
Extension-Treatment	Wk 60E1[5]	421	60		-	-	1.8	-	-	-	-	-	9.3
	Wk 61	428	61		-	-	-	-	-	-	-	-	0
	Wk 62	435	62		-	-	-	-	-	-	-	-	0
	Wk 64	449	64		2	2.5	-	-	-	-	-	-	4.5
	Wk 66	463	66		-	-	-	-	-	-	-	-	0
	Wk 68	477	68		2	2.5	-	6	-	-	-	-	10.5
	Wk 70	491	70		-	-	-	-	-	-	-	-	0
	Wk 72	505	72		2	2.5	1.8	-	2	-	-	-	8.3
	Wk 74	519	74		-	-	-	-	-	-	-	-	0
	Wk 76	533	76		2	2.5	-	6	-	3	101	1	13.5
	Wk 78	547	78		-	-	-	-	-	-	-	-	0
	Wk 80	561	80		2	2.5	-	-	-	-	-	-	4.5
	Wk 82	575	82		-	-	-	-	-	-	-	-	0
	Wk 84	589	84		2	2.5	1.8	6	2	-	-	-	21.8
	Wk 86	603	86		-	-	-	-	-	-	-	-	0
	Wk 88	617	88		2	2.5	-	-	-	-	-	-	4.5

Period	Visit Name	Days	Weeks	[redacted]	Hematology	Clinical Chemistry	Coagulation Panel[2]	Immunology	Cryoglobulins[3]	PK blood collection[4]			Total (mL)
					Size (mL)	Size (mL)	Size (mL)	Size (mL)	Size (mL)	Size (mL)	Sample Number	Dose reference ID	
	Wk 90	631	90		-	-	-	-	-	-	-	-	0
	Wk 92	645	92		2	2.5	-	6	-	3	102	2	13.5
	Wk 94	659	94		-	-	-	-	-	-	-	-	0
	Wk 96	673	96		2	2.5	1.8	-	2	-	-	-	8.3
	Wk 98	687	98		-	-	-	-	-	-	-	-	0
	Wk 100	701	100		2	2.5	-	6	-	-	-	-	10.5
	Wk 102	715	102		-	-	-	-	-	-	-	-	0
	Wk 104	729	104		2	2.5	-	-	-	-	-	-	4.5
	Wk 106	743	106		-	-	-	-	-	-	-	-	0
	Wk 108/ TD[6]	757	108		2	2.5	1.8	6	2	3	103	3	24.8
Post-Treatment Follow-Up	Wk 112	785	112		2	2.5	-	6	-	-	-	-	10.5
	Wk 120/ EOS[7]	841	120		2	2.5	-	6	2	3	104	3	15.5
	Total 164.5 mL												

[1] [redacted]. [2] While on treatment, coagulation monitoring applies only to participants 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 of the TWINSS core study protocol. [3] Analysis of cryoglobulins will be done only for participants who were positive at screening in the TWINSS core study. [4] Blood sample is collected pre-dose. [5] Corresponds to the Week 60 visit of the core study. Assessments carried out as part of Week 60 as per core study protocol can be used for Week 60E1 of the extension study. [6] In case of premature discontinuation, participants will enter the follow up after completing assessments for this visit. [7] Mandatory to all subjects, including those who have discontinued the study prematurely.

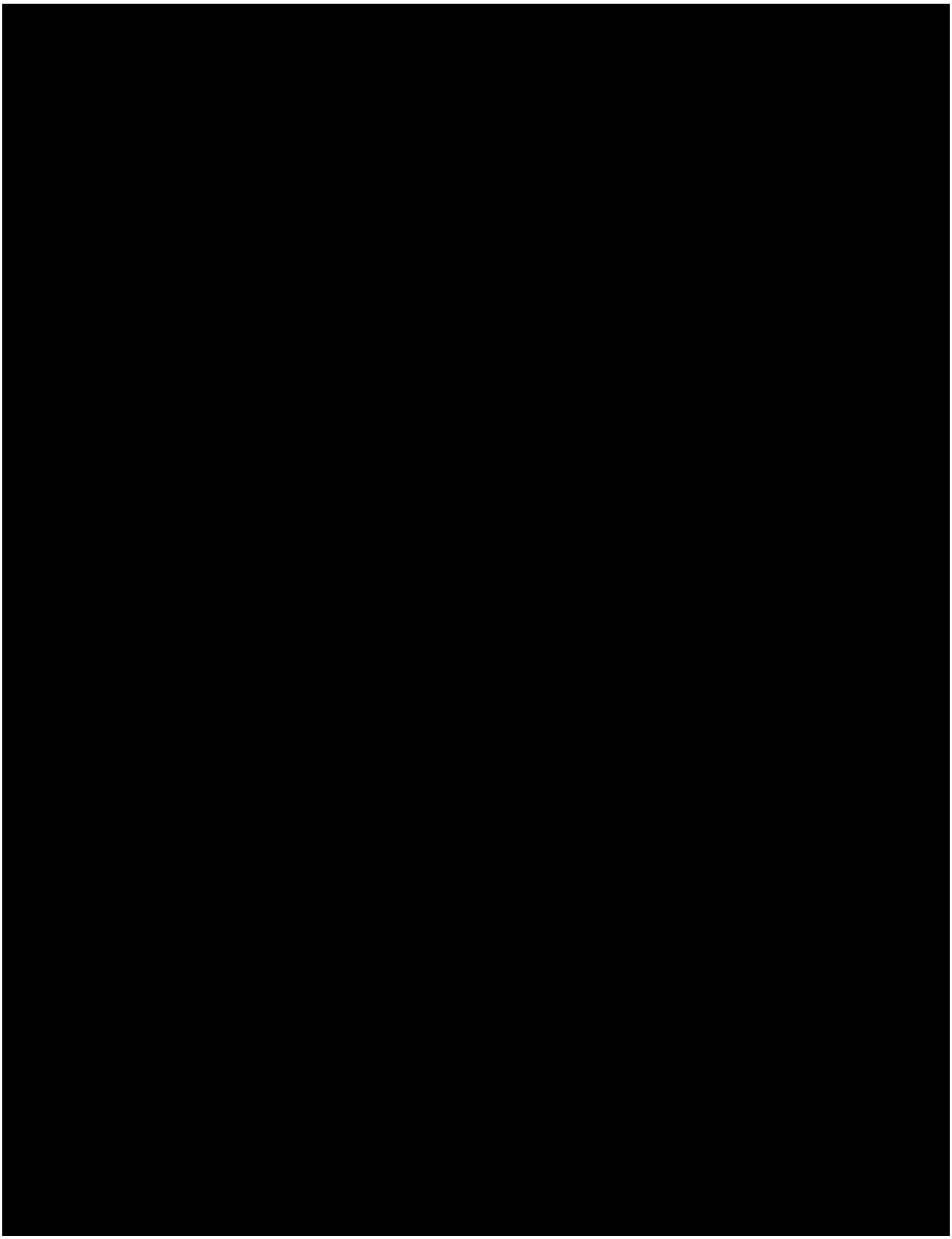
Table 16-6 (B) - Blood Logs

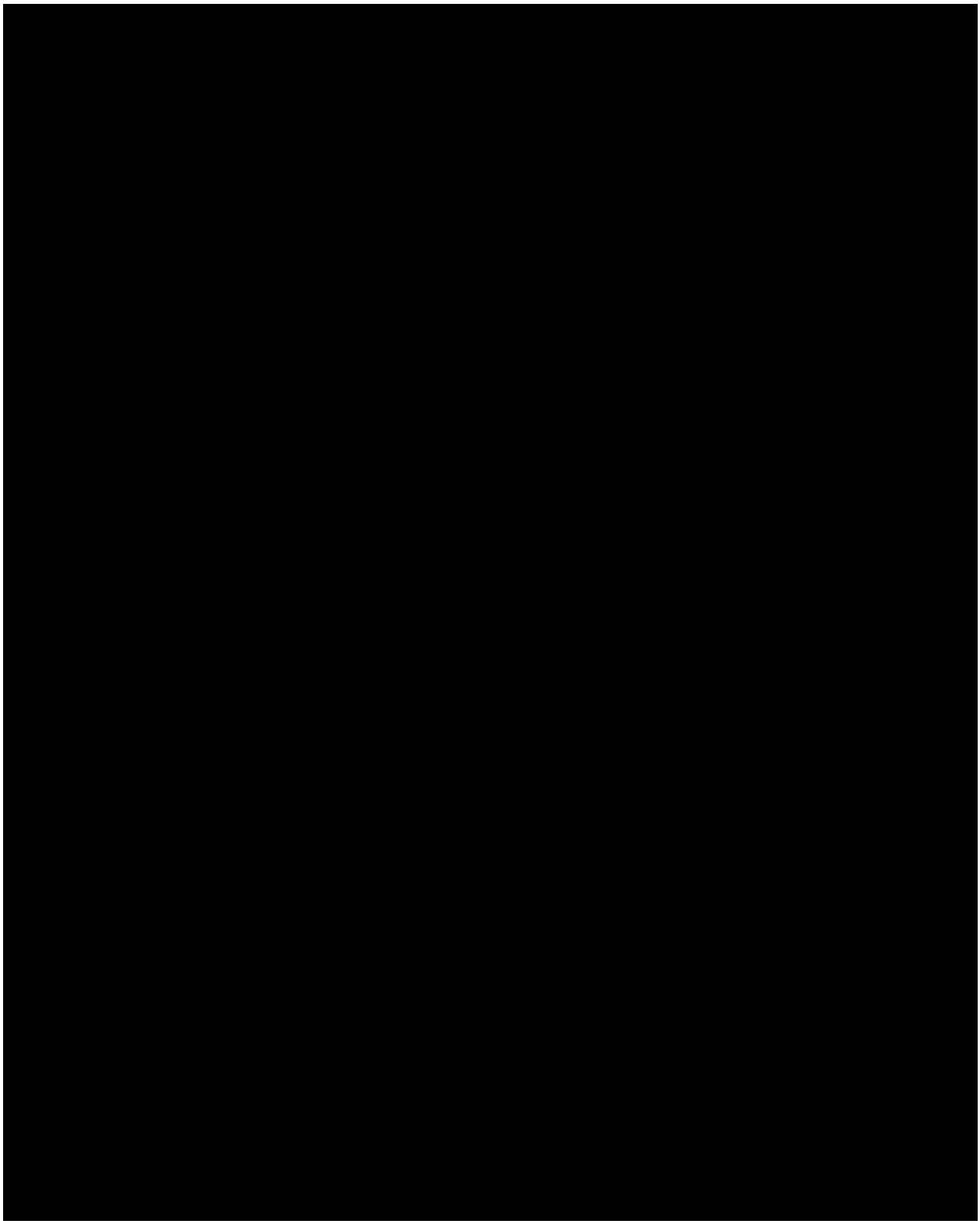
Period	Visit Name	Days	Weeks	Immunogenicity[1]		[redacted]	Total (mL)
				Size (mL)	Sample ID		
Extension-Treatment	Wk 60E1[2]	421	60	-	-		0
	Wk 61	428	61	-	-		0
	Wk 62	435	62	-	-		0
	Wk 64	449	64	-	-		0
	Wk 66	463	66	-	-		0
	Wk 68	477	68	-	-		0
	Wk 70	491	70	-	-		0
	Wk 72	505	72	-	-		0
	Wk 74	519	74	-	-		0
	Wk 76	533	76	4	201		6
	Wk 78	547	78	-	-		0
	Wk 80	561	80	-	-		0
	Wk 82	575	82	-	-		0
	Wk 84	589	84	-	-		0
	Wk 86	603	86	-	-		0
	Wk 88	617	88	-	-		0
	Wk 90	631	90	-	-		0
	Wk 92	645	92	4	202		6
	Wk 94	659	94	-	-		0
	Wk 96	673	96	-	-		0
	Wk 98	687	98	-	-		0
	Wk 100	701	100	-	-		0
	Wk 102	715	102	-	-		0

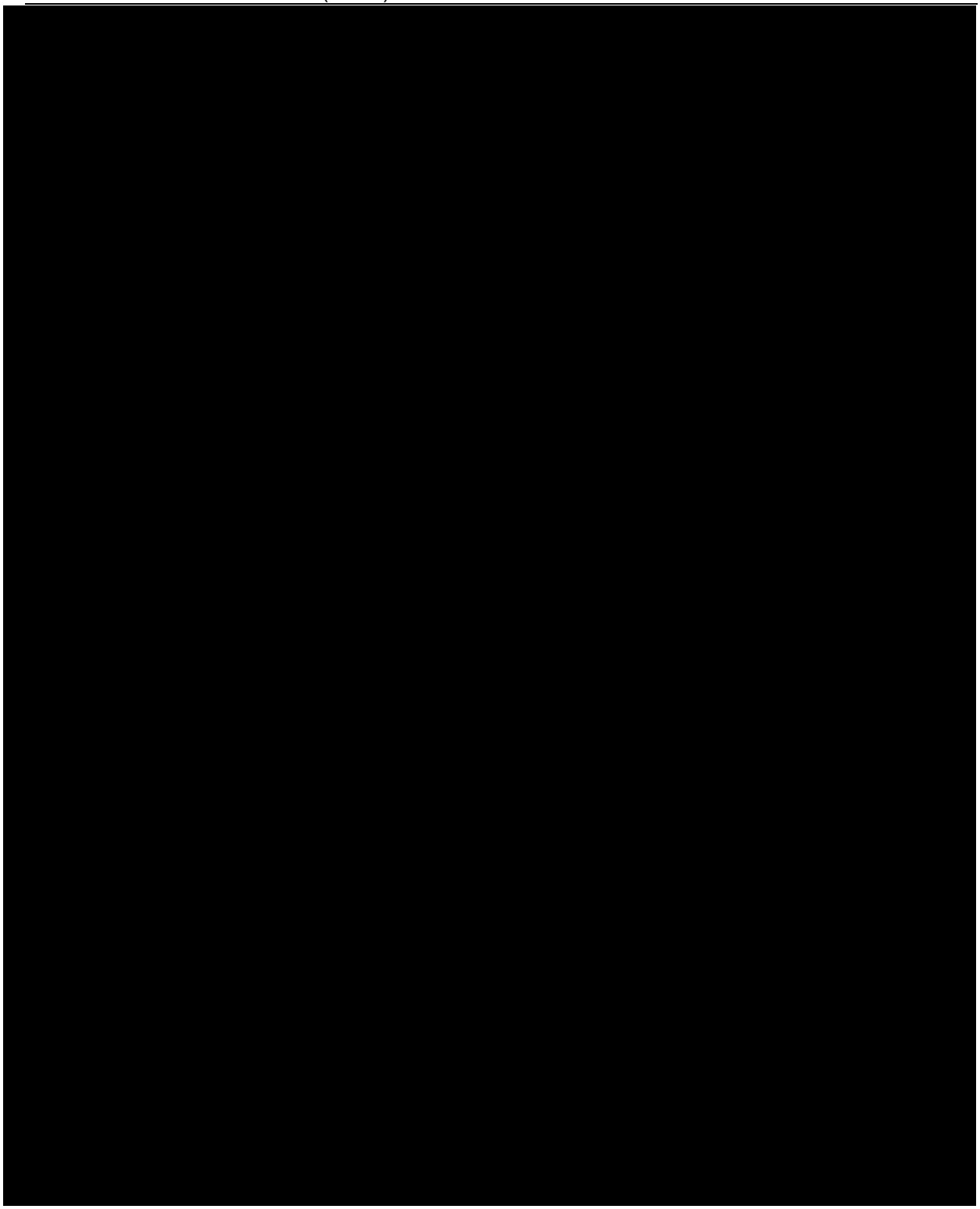
Period	**Visit Name**	**Days**	**Weeks**	**Immunogenicity[1]**		[redacted]	**Total (mL)**
				Size (mL)	**Sample ID**		
	Wk 104	**729**	**104**	**-**	**-**		**0**
	Wk 106	**743**	**106**	**-**	**-**		**0**
	Wk 108/TD[3]	**757**	**108**	**4**	**203**		**6**
Post-Treatment Follow-Up	**Wk 112**	**785**	**112**	**-**	**-**		**0**
	Wk 120/EOS[4]	**841**	**120**	**4**	**204**		**6**
	Total 24.0 mL						

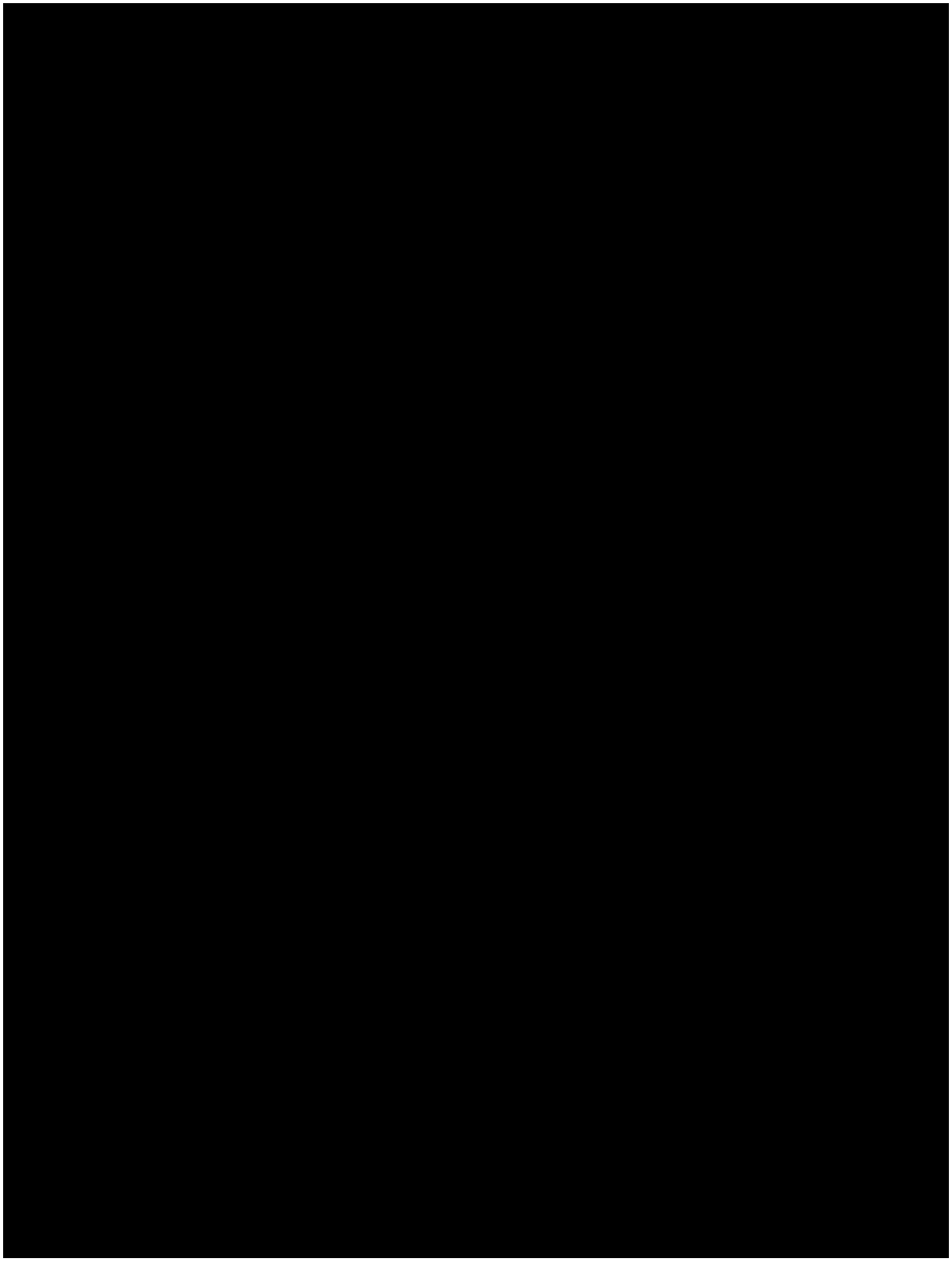
[1] Blood sample is collected pre-dose. [2] Corresponds to the Week 60 visit of the core study. Assessments carried out as part of Week 60 as per core study protocol can be used for Week 60E1 of the extension study. [3] In case of premature discontinuation, participants will enter the follow up after completing assessments for this visit.

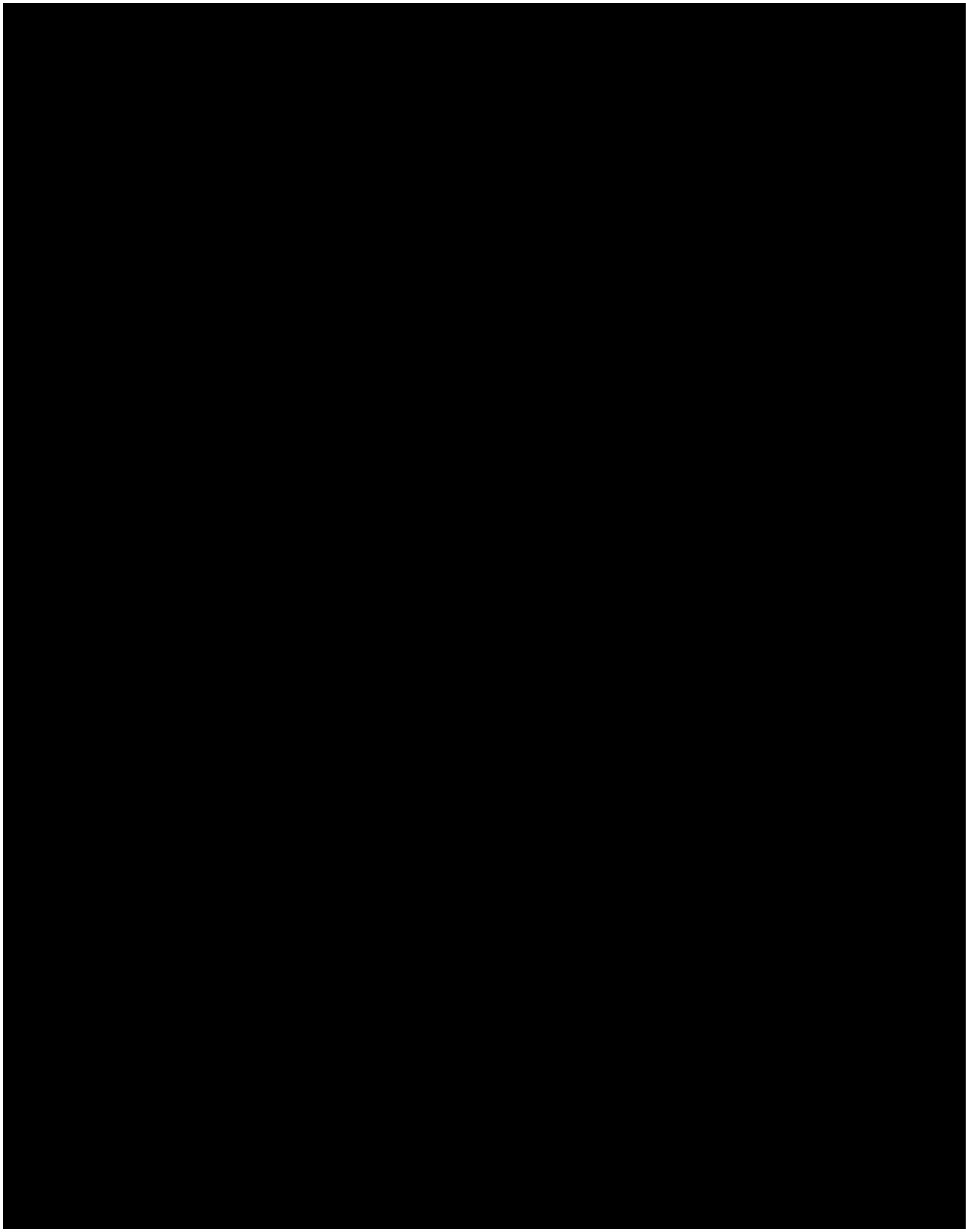
[4] Mandatory to all subjects, including those who have discontinued the study prematurely.

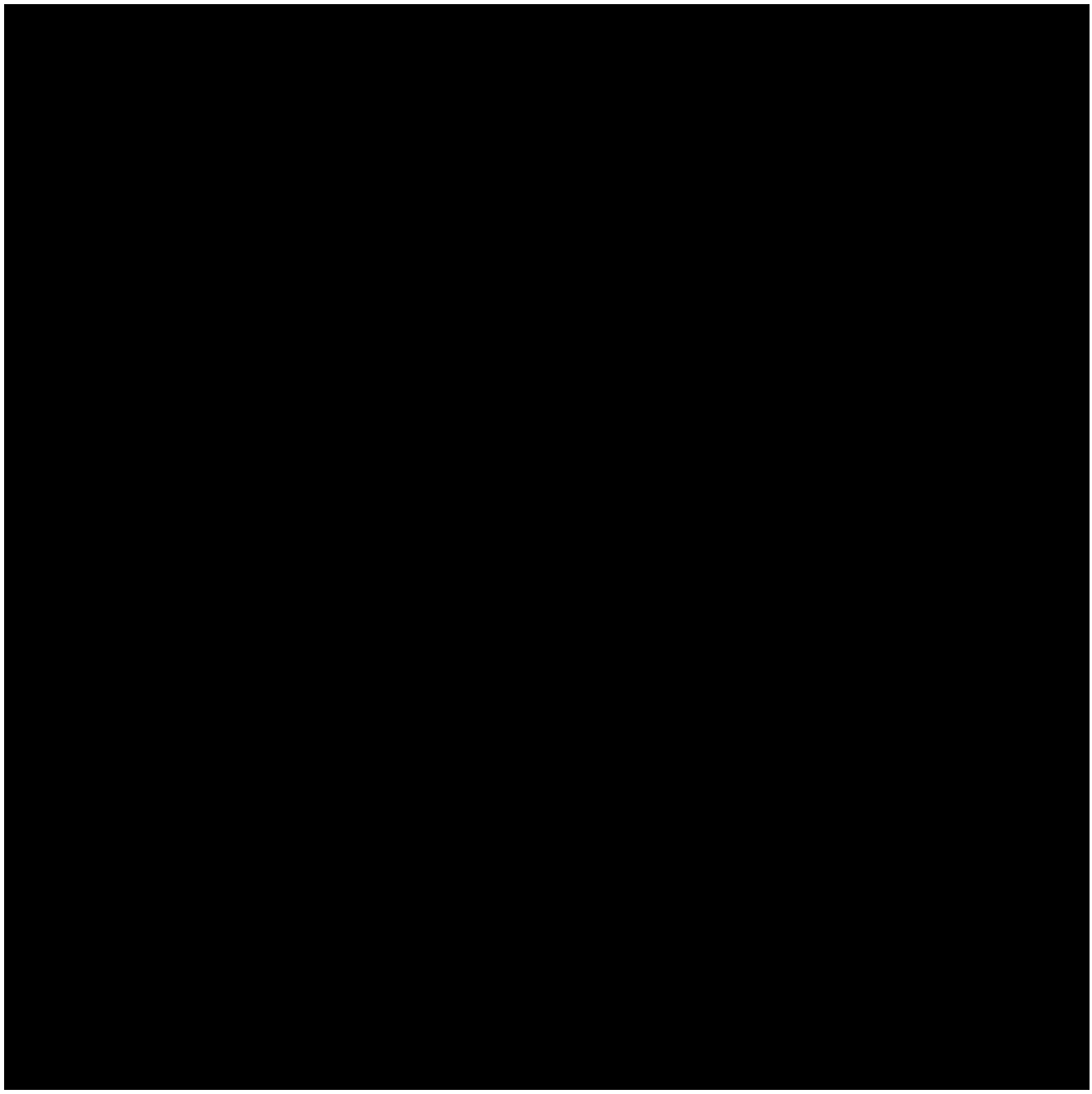


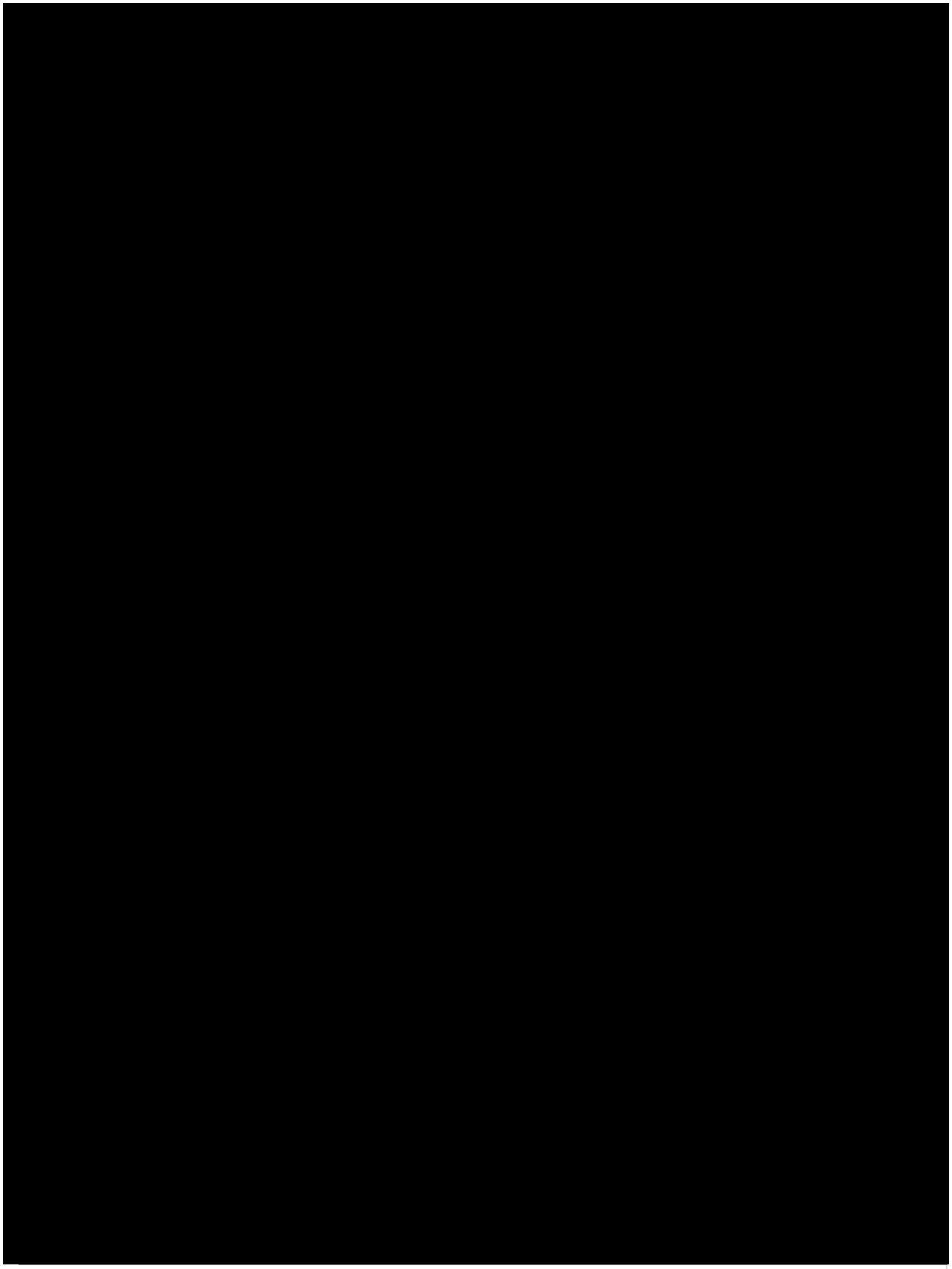


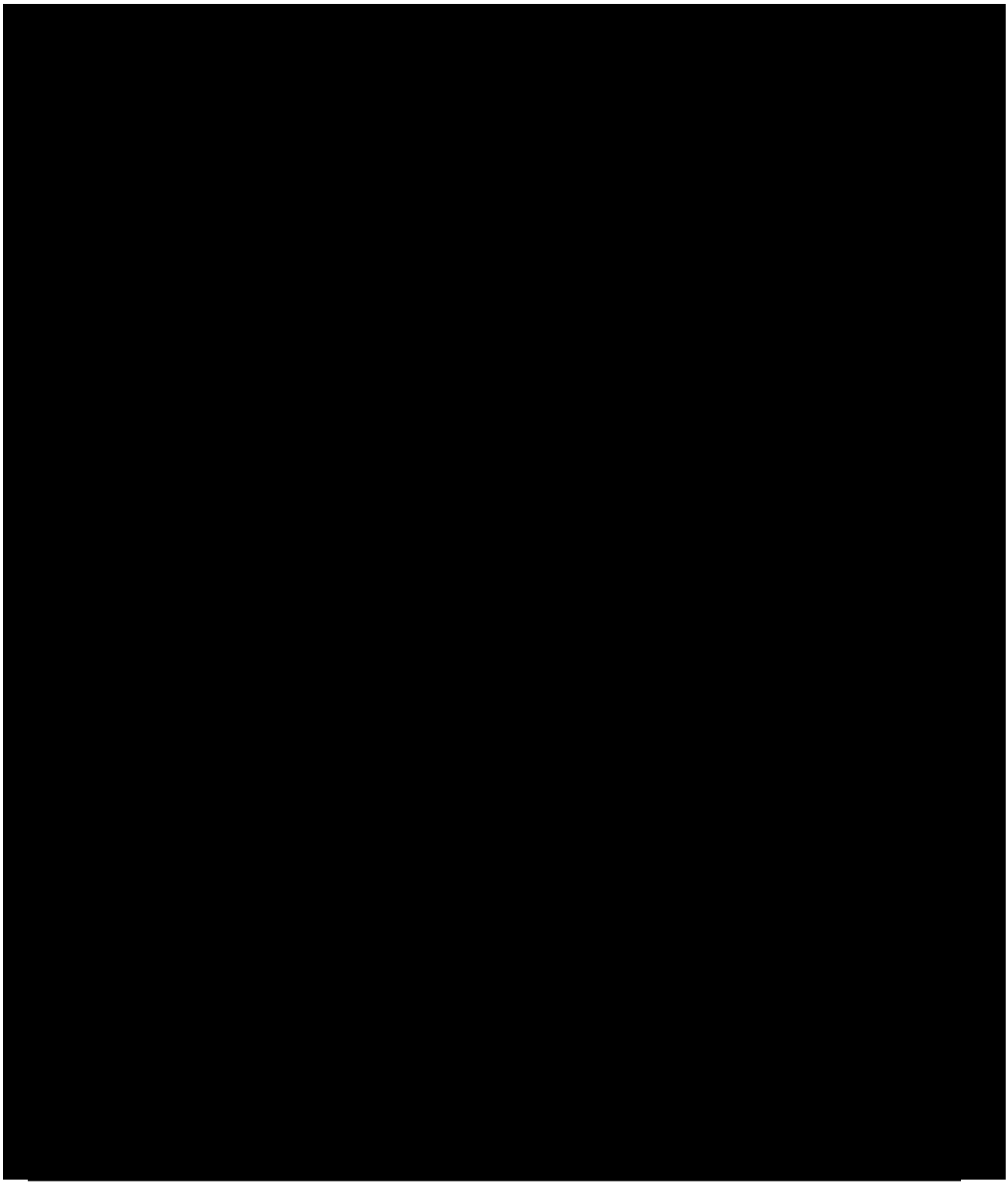


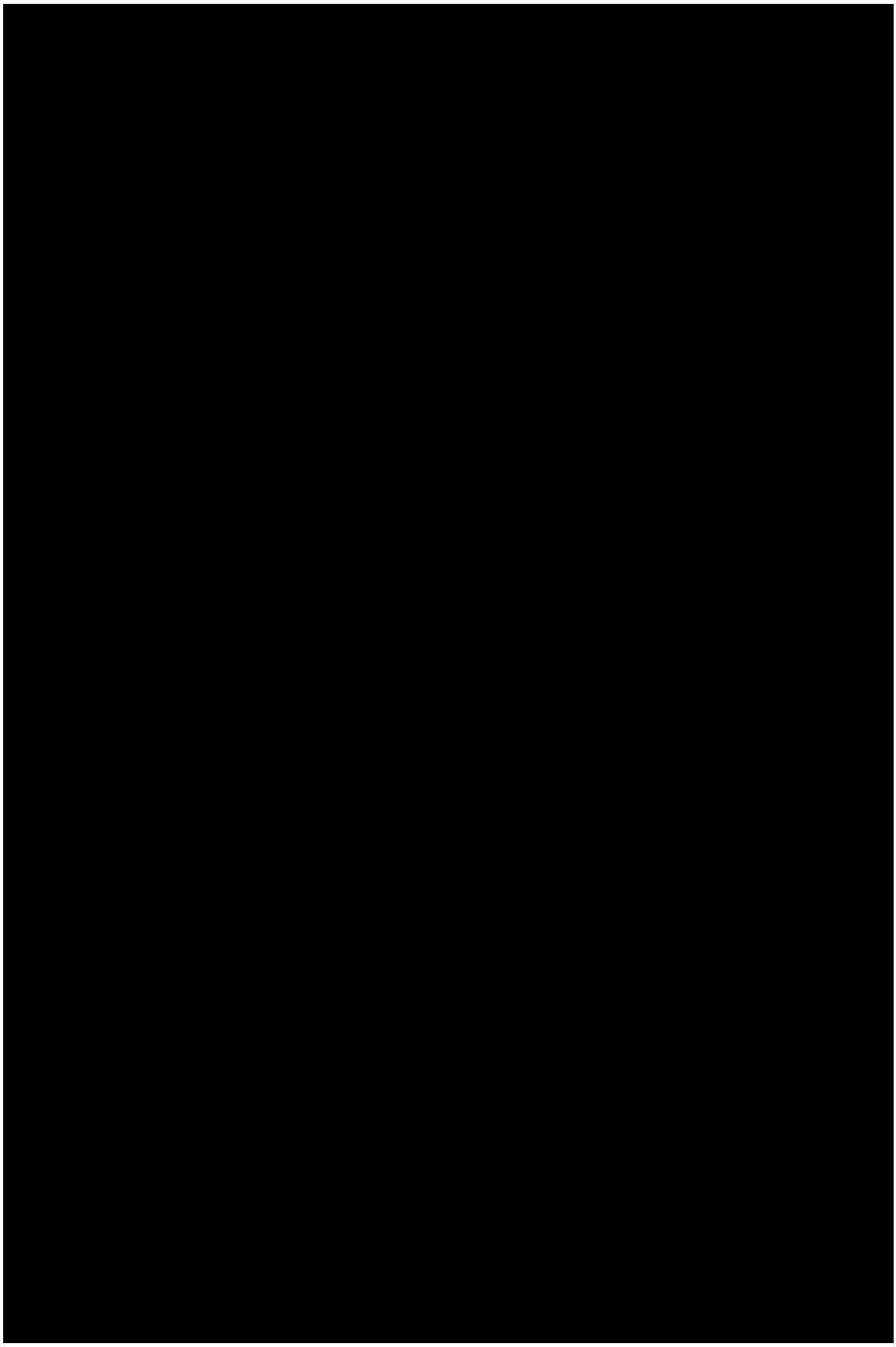












16.10 Appendix 10: Satisfaction with self-injection using a prefilled syringe questionnaire

Table 16-15 Satisfaction with self-injection using a prefilled syringe questionnaire

Satisfaction with self-injection using a pre-filled syringe

INSTRUCTIONS:
The following questions ask about your experiences and overall satisfaction with using the pre-filled syringe to give yourself an injection.

Please select only one answer for each question.

1) How confident do you feel using the pre-filled syringe to give yourself an injection?

- ☐ Very confident
- ☐ Quite confident
- ☐ Moderately confident
- ☐ A little confident
- ☐ Not confident at all

2) How easy is it to use the pre-filled syringe to give yourself an injection?

- ☐ Very easy
- ☐ Quite easy
- ☐ Moderately easy
- ☐ A little easy
- ☐ Not easy at all

3) How convenient is it to give yourself an injection to treat your Sjögren's Syndrome?

- ☐ Very convenient
- ☐ Quite convenient
- ☐ Moderately convenient
- ☐ A little convenient
- ☐ Not convenient at all

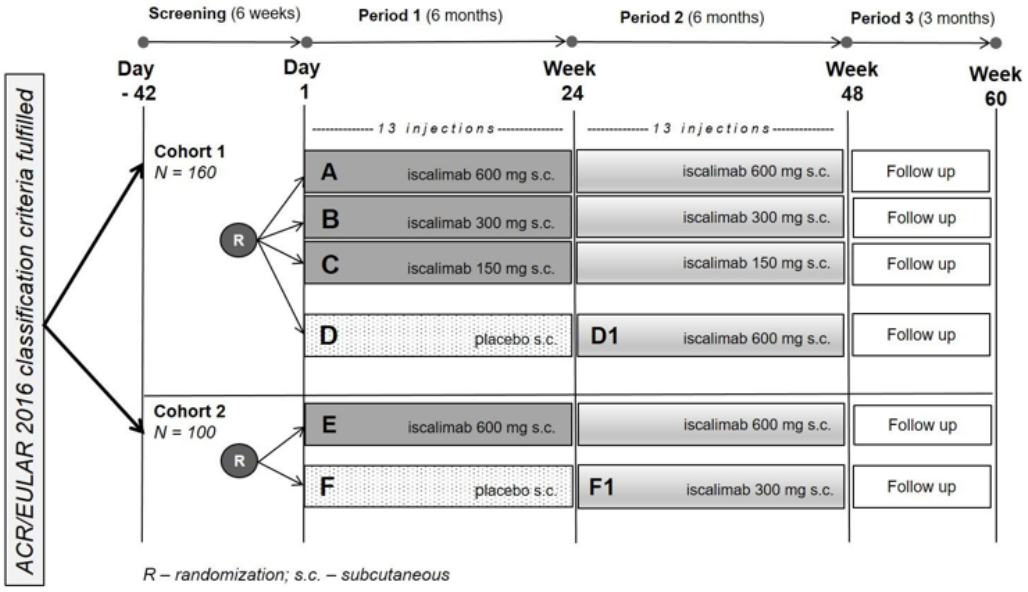
4) Overall, how satisfied are you with giving yourself an injection to treat your Sjögren's Syndrome?

- ☐ Very satisfied
- ☐ Quite satisfied
- ☐ Moderately satisfied
- ☐ A little satisfied
- ☐ Not satisfied at all

5) If you had the option, would you continue to use a treatment that you could self-inject?

- ☐ Yes, definitely
- ☐ Yes, probably
- ☐ I don't know
- ☐ Probably not
- ☐ Definitely not

16.11 Appendix 11: Study design of core study CCFZ533B2201



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)	

The core 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, 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.

Primary analysis will occur at Week 24 including all participants but the analysis for Cohort 1 and analysis for Cohort 2 may occur at different time points depending on patient recruitment and preparation timelines. While maintaining the blinding at Week 24, participants in the placebo arms D and F will be automatically switched to iscalimab (Arms D1 and F1, respectively) for treatment Period 2. All other participants (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 participants who will continue to receive only placebo.