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CFZ533

Clinical Trial Protocol CCFZ533X2203

A multi-center, randomized, double-blind, placebo-controlled, parallel group study to assess the safety, tolerability, pharmacokinetics and preliminary efficacy of CFZ533 in patients with primary Sjögren's syndrome

Personal Data

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Notification of serious adverse events

A serious adverse event (SAE) is any event which is fatal or life-threatening, which requires or prolongs hospitalization, which is significantly or permanently disabling or incapacitating, which constitutes a congenital anomaly or a birth defect, or which is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Any SAE occurring in a subject **from consent until 30 days after the last study visit** must be reported either on the paper SAE report form or via the electronic SAE form within the clinical data capture system (where available).

For SAEs reported using the **paper SAE report form**, the investigator will ensure that the form is completed and **faxed** by the **investigator to the local Novartis Chief Medical Office & Patient Safety (CMO&PS) Department within 24 hours** of learning of the occurrence of the SAE even if the SAE does not appear to be drug-related. The original SAE form, together with the fax confirmation sheet, must be kept with the case report forms at the study site.

For SAEs recorded ***electronically*** in the Novartis clinical data capture system, information should be **entered, saved and e-signed within 24 hours of awareness of the SAE**. These data will automatically be submitted to Novartis Drug Safety & Epidemiology.

More details in Section 7 of this protocol.

Personal Data

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANA	antinuclear antibody
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
b.i.d.	twice a day
BMI	Body Mass Index
BUN	blood urea nitrogen
ca.	Latin term 'circa' (signification: about)
CD-ROM	compact disc – read only memory
CFR	Code of Federal Regulation
CK	creatinine kinase
CRF	Case Report/Record Form (paper or electronic)
CO_2	carbon dioxide
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CTC	Common Toxicity Criteria
CV	coefficient of variation
DMARD	Disease-modifying anti-rheumatic drug
DMC	Data Monitoring Committee
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Intensity
EULAR	The European League Against Rheumatism
Fab	Antigen binding fragment of an antibody

Fc	Crystalizeable fragment of an antibody
FDA	Food and Drug Administration
GCP	Good Clinical Practice
γ-GT	Gamma-glutamyl transferase
h	hour
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
i.v.	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
KLH	Keyhole Limpet Hemocyanin
LFT	Liver function test
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
LLN	lower limit of normal
MedDRA	Medical dictionary for regulatory activities
MFI	Multidimensional Fatigue Inventory Questionnaire
mg	milligram(s)
ml	milliliter(s)
OC/RDC	Oracle Clinical/Remote Data Capture
o.d.	once a day
PA	posteroanterior
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
p.o.	oral(ly)
pSS	primary Sjögren's syndrome
PTT	partial thromboplastin time
q1w	(or Q1W) once every week
RBC	red blood cell(s)
REB	Research Ethics Board

RO	Receptor occupancy
SAE	serious adverse event
s.c.	subcutaneous
SF-36	Short Form (36) Health Survey
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SD	standard deviation
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TDAR	T cell dependent antibody response
ULN	upper limit of normal
ULQ	upper limit of quantification
VAS	Visual Analog Scale
WBC	white blood cell(s)
WHO	World Health Organization

Pharmacokinetic definitions and symbols

AUC0-t	The area under the plasma concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]
AUCtx-ty	The area under the plasma concentration-time curve from time 'x' to time 'y' where 'time x' and 'time y' are defined time points after administration.
Cmax	The observed maximum plasma concentration following drug administration [mass / volume]
Cmin	The observed minimum plasma concentration following drug administration
Ctrough	The observed plasma concentration that is just prior to the beginning of, or at the end of a dosing interval
Tmax	The time to reach the maximum concentration after drug administration [time]
ss (subscript)	Indicate that the parameter is defined at steady state

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product".
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.

Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment.
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject Number	A number assigned to each subject who enrolls into the study.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study.

Protocol synopsis

Protocol number	CCFZ533X2203
Title	A multi-center, randomized, double-blind, placebo-controlled, parallel group study to assess the safety, tolerability, pharmacokinetics and preliminary efficacy of CFZ533 in patients with primary Sjögren's syndrome
Brief title	Safety, pharmacokinetics and preliminary efficacy study of CFZ533 in patients with primary Sjögren's syndrome
Sponsor and Clinical Phase	Novartis Phase 2
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This study is designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary therapeutic efficacy of multiple doses of CFZ533 monoclonal antibody in patients with primary Sjögren's syndrome (pSS), which will provide data for further development of CFZ533 in the treatment of pSS.
Primary Objectives	• To assess the safety and tolerability of multiple intravenous infusions of CFZ533 in patients with primary Sjögren's syndrome as measured by adverse events (AEs). • To compare the effect of multiple intravenous infusions of CFZ533 versus placebo on the clinical disease activity of primary Sjögren's syndrome patients as measured by the change of the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) after 12 weeks treatment.
Secondary Objectives	• To assess the safety and tolerability of multiple subcutaneous doses of CFZ533 in patients with primary Sjögren's syndrome as measured by adverse events (AEs). • To compare the effect of multiple subcutaneous doses of CFZ533 versus placebo on the clinical disease activity of primary Sjögren's syndrome patients as measured by the change of the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) after 12 weeks treatment. • To assess the pharmacokinetics of multiple subcutaneous doses and multiple intravenous infusions of CFZ533 in primary Sjögren's syndrome patients. • To evaluate the effect of multiple subcutaneous doses and multiple intravenous infusions of CFZ533 versus placebo on self-reported outcomes in primary Sjögren's syndrome patients after 12 weeks treatment as measured by the EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI), the Short Form (36) Health Survey (SF-36) and the Multidimensional Fatigue Inventory (MFI) Questionnaire. • To evaluate the changes in the physician global assessment of the patient's overall disease activity as recorded by a visual analog scale (VAS) after 12 weeks treatment. • To evaluate the changes in the patients global assessment of their disease activity as recorded by a VAS after 12 weeks treatment.

Study design	Randomized, double-blind, placebo-controlled, non-confirmatory study in approximately 12 patients in Cohort 1 and 30 patients in Cohort 2, and open-label randomized study in approximately 24 patients in Cohort 3
Population	Male and female patients with primary Sjögren's syndrome, age 18 to 75 years (inclusive).

Inclusion criteria	• Diagnosis of primary Sjögren's syndrome according to revised EU/US consensus criteria (Vitali et al 2002)
	• Moderate to severe disease activity with ESSDAI score ≥ 6
	• Presence of autoantibodies at screening as determined by any of the following:
	  • Elevated serum titers of ANA (≥ 1:160) and positive rheumatoid factor (RF), or,
	  • Positive anti-SSA
	• Stimulated whole salivary flow rate > 0 mL/min for Cohort 1 and 2; and unstimulated whole salivary flow rate > 0 mL/min for Cohort 3.
	• If the patient is on oral glucocorticoid treatment at screening, the dose must NOT exceed 10 mg prednisone or equivalent per day, and must be stable for at least 2 weeks prior to randomization and for the duration of the study;
	• If the patient is on chloroquine or hydroxychloroquine at screening, the dose must be stable for at least 4 weeks prior to randomization and for the duration of the study;
	• If the patient is treated with oral or parenteral methotrexate at screening, the dose must NOT exceed 25 mg per week for at least 3 months prior to randomization and must be stable for the duration of the study.
	• If the patient is treated with oral azathioprine at screening, the dose must NOT exceed 100 mg per day for at least 3 months prior to randomization and must be stable for the duration of the study.

Exclusion criteria	• Secondary Sjögren's syndrome
	• Use other investigational drugs at the time of enrollment, or is within five half-lives of using other investigational drugs or longer if required by local regulations, at the time of enrollment
	• History of hypersensitivity to study drug or to drugs of similar chemical classes
	• Patients have received treatment with:
	  • Cyclosphosphamide within 6 months;
	  • Corticosteroid bolus i.v. dose > 1 mg/kg within 3 months
	  • Rituximab within 12 months
	  • Belimumab within 6 months;
	  • Any other biologic within 1 month or five times the half-life
	  • Any other immunosuppressives such as cyclosporine A or mycophenolate within 3 months
	• Patients where the primary cause of sicca symptoms is attributable to a medication used regularly or intermittently rather than to primary Sjögren's syndrome
	• At significant risk for thromboembolic events
	• Pancreatic injury or pancreatitis
	• History or presence of medically significant cardiac condition
	• Clinically significant systemic viral, bacterial or fungal infection within 30 days of randomization

	• Condition that would result in a significantly elevated risk for infections • History or evidence of tuberculosis • Significant surgical, medical, psychiatric or additional physical condition
Investigational and reference therapy	Cohort 1: CFZ533 Corporate Confidential Information for injection and matching placebo • CFZ533: administered subcutaneously. • Control: CFZ533 placebo Cohort 2: CFZ533 Corporate Confidential Information for injection and matching placebo • CFZ533: administered by intravenous infusion. • Control: CFZ533 placebo Cohort 3: CFZ533 Corporate Confidential Information for injection • CFZ533 s.c. once per week for 4 weeks, followed by s.c. once per week for 9 weeks • CFZ533 i.v. at Day 1, followed by s.c., starting at Day 8 once per week for 12 weeks
Efficacy and pharmacodynamic assessments	• EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) Corporate Confidential Information
Safety assessments	All Cohorts: • Physical examination • Vital signs • Laboratory evaluations: hematology, clinical chemistry, urinalysis • Electrocardiogram (ECG) • Pregnancy testing • Adverse event • Serious adverse event Corporate Confidential Information C
Other assessments	All Cohorts: • Pharmacokinetics of CFZ533 Corporate Confidential Information • EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI) • Physician's and Patient's assessment of global disease activity (VAS) Cohorts 1 and 2: • Short Form (36) Health Survey (SF-36) • Multidimensional Fatigue Inventory (MFI) Questionnaire

Data analysis	Cohorts 1 and 2: A longitudinal model describing ESSDAI change from baseline over time will be fitted for the controlled part of the study (up to Week 13) with the following covariates: baseline ESSDAI, baseline prednisone dose, treatment (placebo, CFZ533 s.c. or CFZ533 i.v), time as a continuous factor and a quadratic time effect, as well as a random intercept, a random slope and a random quadratic effect for subject. The change from baseline in ESSDAI at Week 13 will be estimated from the model for all treatments. Inference will be made in the frequentist framework. The results from the primary analysis will be assessed against the following efficacy criteria to support internal decision making: • a statistically significant reduction in ESSDAI at Week 13 in the CFZ533 group compared to placebo, at the one-sided 10% significance level, and, • an estimated mean reduction in ESSDAI in the CFZ533 group to be 5 points or greater than placebo. A positive sign of efficacy will be considered if both criteria are met. Cohort 3: Descriptive statistics and graphical displays will be used to summarize the PK concentrations in each treatment arm.
Key words	CFZ533, anti-CD40, primary Sjögren's syndrome

Assessment schedule – Cohort 1

Study phase	Screening	Baseline	Placebo-Controlled Period[1]															Open-Label Period[1]												Follow-Up Period[1]		End of Study
Visit Numbers (internal use only)	Visit 1	Visit 2	V3			V4			V5			V6			V7	V8[2]			V9			V10			V11	V12			V13[2]	V14	V777*
Week	Weeks -4 to -1		Week 1			Week 3			Week 5			Week 9			Week 11	Week 13			Week 15			Week 17			Week 19	Week 21			Week 25	Week 29	Week 33
Day	Day -28 to -2	Day -1	Day 1			Day 15			Day 29			Day 57			Day 71	Day 85			Day 99			Day 113			Day 127	Day 141			Day 169	Day 197	Day 225
Hour			Pre-dose	0	6	Pre-dose	0	6	Pre-dose	0	6	Pre-dose	0	6		Pre-dose	0	6	Pre-dose	0	6	Pre-dose	0	6		Pre-dose	0	6			
Obtain informed consent	X																															
Inclusion /Exclusion criteria	X	X																														
Relevant med history and current conditions	X	X																														
Demography	X																															
Physical examination	X	X	X		X[3]	X		X[3]	X		X[3]	X		X[3]		X		X[3]	X		X[3]	X		X[3]		X		X[3]	X		X	X
Hepatitis and HIV screen	X																															
Pregnancy test	X[4]	X[4]							X			X				X						X				X			X		X	X[4]
Purified protein derivative (PPD) skin test or Quantiferon test	X																															
Alcohol and drug screen	X	X																														X
Drug administration				X			X			X			X				X			X			X				X					
Concomitant meds/Therapies	As required																															
Adverse Events[5]		As required																														
Comments	As required																															
Vital signs and body measurements:																																
Body height	X																															
Body weight	X	X																														X
Body temperature	X	X	X		X[3]	X		X[3]	X		X[3]	X		X[3]		X		X[3]	X		X[3]	X		X[3]		X		X[3]	X		X	X
Blood pressure / Pulse rate	X	X	X		X[3]	X		X[3]	X		X[3]	X		X[3]		X		X[3]	X		X[3]	X		X[3]		X		X[3]	X		X	X
ECG evaluation	X	X				X						X				X						X				X			X		X	X
Hematology, Blood chemistry, Urinalysis	X	X				X			X			X				X			X			X				X			X		X	X
Corporate Confidential Information	X	X				X			X			X				X			X			X				X			X		X	X
Coagulation test	X	X				X			X			X				X			X			X				X			X		X	X
Corporate Confidential Information	X	X				X			X			X				X			X			X				X			X		X	X

Assessment schedule – Cohort 1 (continued)

Study phase	Screening	Baseline	Placebo-Controlled Period[1]														Open-Label Period[1]												Follow-Up Period[1]		End of Study
Visit Numbers (internal use only)	Visit 1	Visit 2	V3			V4			V5			V6			V7	V8[2]			V9			V10			V11	V12			V13[2]		V14	V777*
Week	Weeks -4 to -1		Week 1			Week 3			Week 5			Week 9			Week 11	Week 13			Week 15			Week 17			Week 19	Week 21			Week 25		Week 29	Week 33
Day	Day -28 to -2	Day -1	Day 1			Day 15			Day 29			Day 57			Day 71	Day 85			Day 99			Day 113			Day 127	Day 141			Day 169		Day 197	Day 225
Hour			Pre-dose	0	6	Pre-dose	0	6	Pre-dose	0	6	Pre-dose	0	6		Pre-dose	0	6	Pre-dose	0	6	Pre-dose	0	6		Pre-dose	0	6				
ESSDAI	X	X				X[6]			X[6]			X[6]				X[6]			X[6]			X[6]				X[6]			X		X	X
ESSPRI, MFI, SF-36		X										X[6]				X[6]						X[6]				X[6]			X		X	X
VAS Assessments by Investigator and Patient		X				X[6]			X[6]			X[6]				X[6]			X[6]			X[6]				X[6]			X		X	X
Ultrasound		X[6]														X[6]																X
Corporate Confidential Information		X														X[6]													X			X
	X															X[6]													X			X
		X														X													X			X
		X[6]														X																
		X																							X							X
		X													X										X							X
PK blood collection			X		X	X		X	X		X	X		X	X	X		X	X		X	X		X	X	X		X	X		X	X
Corporate Confidential Information			X																							X			X		X	X
Leukocyte subsets		X							X			X				X													X			
Corporate Confidential Information	X								X							X										X						X
		X				X						X				X										X						X
	X	X				X			X			X				X			X			X				X			X		X	X
			X		X	X		X	X		X	X		X	X	X		X	X		X	X		X	X	X		X	X		X	X
			X		X	X		X	X		X	X		X	X	X		X	X		X	X		X	X	X		X	X		X	X
			X		X						X			X				X						X					X		X	X
		X				X						X				X						X										
Study completion information																																X

[1] Placebo-Controlled Period includes Day 1 (Week 1) to completion of pre-dose assessments on Day 85 (Week 13). Open-Label Period includes Day 85 (dosing, Week 13) to completion of assessments on Day 169 (Week 25). Follow-Up Period includes Week 25 - Week 32.

[2] Visit 8 is the end of placebo-controlled period and the start of open-label period, Visit 13 is the end of open-label period and the start of follow-up period

[3] The post-dose 6 h assessments should include assessing injection site(s) and vitals before dismissing the subject from clinical site

[4] These should use serum pregnancy test

[5] Serious Adverse Events reporting is requird from signing the informed consent until 30 days after study completion

[6] These pre-dose assessments can be done one day before the dosing or within 6 hours post dosing

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This assessment can be performed at screening

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* Patients who discontinue the study should complete these assessments

Assessment schedule - Cohort 2

Study phase	Screening	Baseline*	Placebo-Controlled Period[1]													Open-Label Period[1]															Follow-Up Period[1]		End of Study
Visit Numbers (internal use only)	Visit 1	Visit 2	V3			V4			V5			V6			V7	V8[2]			V9			V10			V11	V12			V13[2]		V14	V777[3]
Week	Weeks -4 to -1		Week 1			Week 3			Week 5			Week 9			Week 11	Week 13			Week 15			Week 17			Week 19	Week 21			Week 25		Week 29	Week 33
Day	Day -28 to -2	Day -1	Day 1			Day 15			Day 29			Day 57			Day 71	Day 85			Day 99			Day 113			Day 127	Day 141			Day 169		Day 197	Day 225
Hour			Pre-dose	0	Post-dose 2h[4]	Pre-dose	0	Post-dose 2h[4]	Pre-dose	0	Post-dose 2h[4]	Pre-dose	0	Post-dose 2h[4]		Pre-dose	0	Post-dose 2h[4]	Pre-dose	0	Post-dose 2h[4]	Pre-dose	0	Post-dose 2h[4]		Pre-dose	0	Post-dose 2h[4]				
Obtain informed consent	X																															
Inclusion /Exclusion criteria	X	X																														
Relevant med history and current conditions	X	X																														
Demography	X																															
Physical examination	X	X	X		X[5]	X		X[5]	X		X[5]	X		X[5]		X		X[5]	X		X[5]	X		X[5]		X		X[5]	X		X	X
Hepatitis and HIV screen	X																															
Pregnancy test	X[6]	X[6]							X			X				X						X				X			X		X	X[6]
Purified protein derivative (PPD) skin test or Quantiferon test	X																															
Alcohol and drug screen	X	X																														X
Drug administration				X			X			X			X				X			X			X			X					
Concomitant meds/Therapies	As required																															
Adverse Events[7]		As required																														
Comments	As required																															
Vital signs and body measurements:																																
Body height	X																															
Body weight	X	X				X			X			X				X			X			X				X						X
Body temperature	X	X	X		X[5]	X		X[5]	X		X[5]	X		X[5]		X		X[5]	X		X[5]	X		X[5]		X		X[5]	X		X	X
Blood pressure / Pulse rate	X	X	X		X[5]	X		X[5]	X		X[5]	X		X[5]		X		X[5]	X		X[5]	X		X[5]		X		X[5]	X		X	X
ECG evaluation	X	X				X						X				X						X				X			X		X	X
Hematology, Blood chemistry, Urinalysis	X	X				X			X			X				X			X			X				X			X		X	X
Corporate Confidential Information	X	X				X			X			X				X			X			X				X			X		X	X
Coagulation test	X	X				X			X			X				X			X			X				X			X		X	X
Corporate Confidential Information	X	X				X			X			X				X			X			X				X			X		X	X

Assessment schedule Cohort 2 (continued)

Study phase	Screening	Baseline*	Placebo-Controlled Period[1]													Open-Label Period[1]														Follow-Up Period[1]		End of Study
Visit Numbers (internal use only)	Visit 1	Visit 2	V3			V4			V5			V6			V7	V8[2]			V9			V10			V11	V12			V13[2]		V14	V777[3]
Week	Weeks -4 to -1		Week 1			Week 3			Week 5			Week 9			Week 11	Week 13			Week 15			Week 17			Week 19	Week 21			Week 25		Week 29	Week 33
Day	Day -28 to -2	Day -1	Day 1			Day 15			Day 29			Day 57			Day 71	Day 85			Day 99			Day 113			Day 127	Day 141			Day 169		Day 197	Day 225
Hour			Pre-dose	0	Post-dose 2h[4]	Pre-dose	0	Post-dose 2h[4]	Pre-dose	0	Post-dose 2h[4]	Pre-dose	0	Post-dose 2h[4]		Pre-dose	0	Post-dose 2h[4]	Pre-dose	0	Post-dose 2h[4]	Pre-dose	0	Post-dose 2h[4]		Pre-dose	0	Post-dose 2h[4]				
ESSDAI	X	X				X[8]			X[8]			X[8]				X[8]			X[8]			X[8]				X[8]			X		X	X
ESSPRI, MFI, SF-36		X										X[8]				X[8]						X[8]				X[8]			X		X	X
VAS Assessments by Investigator and Patient		X				X[8]			X[8]			X[8]				X[8]			X[8]			X[8]				X[8]			X		X	X
Ultrasound		X[9]														X[8]																X
Corporate Confidential Information		X														X[8]													X			X
	X															X[8]													X			X
		X														X													X			X
		X[9]														X																
		X																														X
		X													X										X							X
PK blood collection[10] Corporate Confidential Information			X		X	X		X	X		X	X		X	X	X		X	X		X	X		X	X	X		X	X		X	X
			X																							X			X		X	X
Leukocyte subsets		X							X			X				X													X			
Corporate Confidential Information	X								X							X										X						X
		X				X						X				X										X						X
	X	X				X			X			X				X			X			X				X			X		X	X
			X		X	X		X	X		X	X		X	X	X		X	X		X	X		X	X	X		X	X		X	X
			X		X	X		X	X		X	X		X	X	X		X	X		X	X		X	X	X		X	X		X	X
			X		X						X			X				X						X				X	X		X	X
		X				X						X				X						X				X			X			
Study completion information																																X

[1] Placebo-Controlled Period includes Day 1 (Week 1) to completion of pre-dose assessments on Day 85 (Week 13). Open-Label Period includes Day 85 (dosing, Week 13) to completion of assessments on Day 169 (Week 25). Follow-Up Period includes Week 25 - Week 32.

[2] Visit 8 is the end of placebo-controlled period and the start of open-label period, Visit 13 is the end of open-label period and the start of follow-up period

[3] Patients who discontinue the study should complete these assessments

[4] This is 2 hours after the end of i.v. infusion

[5] The post-dose 2 h assessments should include assessing infusion site and vitals before dismissing the subject from clinical site

[6] These should use serum pregnancy test

[7] Serious Adverse Events reporting is required from signing the informed consent until 30 days after study completion

[8] These pre-dose assessments can be done one day before the dosing

[9] This assessment can be performed at screening

[10] PK samples should be taken from the other arm which has not been used for i.v. infusion

* Baseline safety evaluation results must be available prior to dosing and meeting eligibility criteria

Assessment schedule Cohort 3

Study phase	Screening	Baseline	Treatment Period																			Follow-up Period			End of Study[8]
Visit Numbers	V1	V2	V3			V4	V5	V6	V7		V8	V9	V10	V11		V12	V13	V14	V15		V16	V17	V18	V777
Week	w -4 to -1		w 1			w 2	w 3	w 4	w 5		w 6	w 7	w 8	w 9		w 10	w 11	w 12	w 13		w 15	w 17	w 19	w 21
Day[1]	-28 to -2	-1	1			8	15	22	29		36	43	50	57		64	71	78	85		99	113	127	141
Hour			Pre-dose	0	Post-dose 1 h				Pre-dose	0				Pre-dose	0				Pre-dose	0				
Obtain informed consent	X																							
Inclusion /Exclusion criteria	X	X																						
Med history and current conditions	X	X																						
Demography	X																							
Physical examination	X	X			X[3]				X					X					X		X	X	X	X
Hepatitis and HIV screen	X																							
Pregnancy test	X	X							X					X					X		X	X	X	X
TB (PPD) skin test/ Quantiferon test	X																							
Alcohol and drug screen	X	X																						
Concomitant meds/Therapies	As required																							
Adverse Events	As required																							
Comments	As required																							
Vital signs and body measurements:																								
Body height	X																							
Body weight	X	X																						
Body temperature	X	X	X		X[3]	X[2]	X[2]	X[2]	X		X[2]	X[2]	X[2]	X		X[2]	X[2]	X[2]	X			X		X
Blood pressure / Pulse rate	X	X	X		X[3]				X					X					X			X		X
ECG evaluation	X	X							X					X					X			X		X
Hematology, Blood chemistry, Urinalysis	X	X							X					X					X			X		X
Corporate Confidential Information	X	X							X					X					X			X		X
Coagulation test	X	X							X					X					X			X		X
Corporate Confidential Information	X	X							X					X					X					X
	X	X							X					X					X					X
ESSDAI	X	X							X					X					X					X
ESSPRI		X							X					X					X					X
VAS by Investigator		X							X					X					X					X
VAS by Patient		X							X					X					X					X
Corporate Confidential Information	X[4]								X					X					X					X
PK blood collection			X		X[7]	X[2]	X[2]	X[2]	X		X[2]	X[2]	X[2]	X		X[2]	X[2]	X[2]	X		X	X	X	X
Corporate Confidential Information			X				X[2]		X					X					X			X	X	X
	X																							X
			X				X[2]		X			X[2]		X			X[2]		X		X	X	X	X
		X	X						X					X					X			X		X
Drug administration[6]				X		X	X	X		X	X	X	X		X	X	X	X		X				
Study completion information																								X

[1] Visit windows are specified in Section 6
[2] Pre-dose
[3] Post dose assessments should include assessing injection sites, body temperature and vitals before dismissing the subject from clinical site.
[4] Unstimulated salivary flow can be assessed at screening or baseline
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[6] In treatment arm 1, subjects will receive CFZ533 s.c. at Visits 3, 4, 5, 6, and then s.c. at Visits 7, 8, 9, 10, 11, 12, 13, 14 and 15.
In treatment arm 2, subjects will receive CFZ533 i.v. at Visit 3, and then s.c. at Visits 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 15
[7] This post-dose PK sample is for treatment arm 2 first dose (i.v.) only. The sample is taken at 1 hour after the end of the i.v. infusion. No post-dose PK sample is collected after s.c. injections at Visit 3 in treatment arm 1.
[8] Patients who discontinue the study should complete these assessments

1 Introduction

1.1 Background

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease of unknown etiology. It is characterized by lymphoid infiltration and progressive destruction of exocrine glands (Youinou and Pers 2012). pSS is a common disorder, second only to rheumatoid arthritis (RA) in prevalence as a systemic autoimmune disease. The disease affects mainly women with a female/male ratio of 9:1 and can occur at any age. Although primarily organ-specific for the lacrimal, salivary and other exocrine glands, the inflammatory process can target any organ. 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.

Secretory gland failure can lead to disturbance of vision (lacrimal gland), swallowing difficulty and poor dentition (salivary gland) and sexual dysfunction (vaginal dryness). Further, many (reported as frequently as in 85% of patients) experience profound and disabling fatigue. Disease impact on quality of life (QOL) measures is substantial and comparative studies demonstrate pSS QoL scores quantitatively worse than in congestive heart failure or many cancers (Segal et al 2009; Kuenstner et al 2002; Komaroff et al 1996). Moreover, the increased B cell activity underlying pSS also results in an increased risk for malignant transformation, with lymphoma development occurring in 5% of Sjögren's syndrome patients.

Treatment for pSS patients is limited to symptomatic care for the mucosal signs and symptoms. Glucocorticoids and typical disease-modifying anti-rheumatic drugs (DMARDs) are mostly ineffective, and no pharmacologic intervention is effective against the severe, disabling fatigue. Despite a lack of convincing evidence of efficacy and based on anecdotal evidence as well as experience from similar autoimmune diseases such as systemic lupus erythematosus, antimalarials (Tishler et al 2008), methotrexate (Winzer and Aringer 2010) or azathioprine (Kaufman et al 1999) are sometimes used, in particular for the treatment of extraglandular symptoms such as renal or joint involvement.

Although small trials with the B cell depleting agent rituximab have demonstrated a degree of therapeutic efficacy, no proper, large randomized controlled trials have shown clear efficacy with regard to extra-glandular and glandular disease manifestations. A disease modifying agent that prevents secretory gland destruction and addresses extra-glandular disease manifestations would introduce a game-changing advance for the treatment of chronic pSS.

1.1.2 CD40/CD40L co-stimulation: a target for primary Sjögren's syndrome

The CD40-CD154 co-stimulation pathway has long been considered as a target for the treatment of autoimmune diseases (Toubi and Shoenfeld 2004). Humans or rodents with loss-of-function or null mutants of CD40 fail to mount T-cell dependent immune response, do not undergo affinity maturation or differentiate into memory B cells. Further, pharmacological inhibition of CD40-CD154 interactions has been demonstrated to reduce/ameliorate autoimmune disease pathology in pre-clinical and clinical studies and can prolong allograft survival in non-human primates. Using monoclonal antibodies to target CD154 has been hampered by the occurrence of thromboembolic complications (Kawai et al 2000) so an alternative approach is to target the receptor, CD40.

Several lines of evidence suggest that immune mediated pathology driven by or closely related to the CD40-CD154 pathway is essential in pSS. A hallmark of pSS is B cell hyper-reactivity such as formation of germinal center like structures (observed in 18-59% of patients), autoantibodies such as SSA, SSB or RF (Vossenkämper et al 2012). T cells predominate in pSS lesions, and are capable of provoking B cell hyperactivity and Ig secretion, and are directly involved in destruction of glands through Fas and perforin-mediated cytotoxicity (Manganelli and Fietta 2003). A portion of pSS patients have elevated serum sCD154; and T and B cell infiltrates of salivary glands show upregulation of CD40 and CD154.

Furthermore, CD40/CD154 mediated tissue inflammation may also contribute to pSS pathogenesis. Epithelial cell lines derived from pSS patients have constitutively up-regulated surface CD40 (Dimitriou et al 2002). Increased levels of micro-particles derived from platelets and also from leukocytes together with elevated sCD154 concentrations have been reported in pSS sera (Sellam et al 2009).

1.1.4 Clinical data for other anti-CD40 monoclonal antibodies

CFZ533 is closely related to another Novartis compound, lucatumumab (HCD122). Despite sharing identical CDR regions, the two antibodies can be differentiated by the engineered presence of a N297A mutation into the γ1 Fc region of CFZ533, rendering it Fc-silent. In contrast, HCD122 has an unmutated Fc region and unlike CFZ533, is able to mediate ADCC. In phase I/II studies of lucatumumab in patients (n=approx. 164) with malignancies such as chronic lymphocytic leukemia, non-Hodgkin's or Hodgkin's lymphomas and myeloma, the most common reported grade 1 and 2 events occurred during the infusion and included chills (44%), pyrexia (33%), nausea (31%) and fatigue (26%). The most commonly reported grade 3 or 4 adverse events, regardless of study drug relationship, were lipase elevations, dyspnea, and anemia. The majority of the adverse events was reversible and manageable; most were mild or moderate in severity. Elevations in lipase and amylase were observed but were primarily transient in nature and did not require medical intervention, were asymptomatic and imaging studies were negative for pancreatitis. Such elevations, which are usually rare events and not typically associated with a fully-human IgG1 monoclonal antibody in clinical trials, are likely linked to the potent ADCC activity of the compound and CD40 expression of the ductal mucosa and liver parenchyma (Vosters et al 2004). Of note, there were no thromboembolic complications in any of the Phase I/II studies with lucatumumab.

Recently published data (Goldwater et al 2013) also suggested a favorable safety and tolerability profile for the anti-human CD40 antagonist ASKP1240 monoclonal antibody in the first-in-human, phase I study which evaluated single ascending doses of intravenous ASKP1240 (0.00003 – 10 mg/kg) in healthy volunteers. There was no evidence of cytokine release syndrome or thromboembolic events. The antagonism of the CD40/CD154 interaction with ASKP1240 was overall safe and well tolerated at the doses tested.

1.2 Study purpose

This study is designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary therapeutic efficacy of multiple doses of CFZ533 monoclonal antibody in patients with primary Sjögren's syndrome (pSS). The study outcome will provide data for further development of CFZ533 in treatment of pSS.

2 Study objectives

2.1 Primary objectives

- To assess the safety and tolerability of multiple intravenous infusions of CFZ533 in patients with primary Sjögren's syndrome as measured by adverse events (AEs).
- To compare the effect of multiple intravenous infusions of CFZ533 versus placebo on the clinical disease activity of primary Sjögren's syndrome patients as measured by the change of the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) after 12 weeks treatment.

2.2 Secondary objectives

- To assess the safety and tolerability of multiple subcutaneous doses of CFZ533 in patients with primary Sjögren's syndrome as measured by adverse events (AEs).
- To compare the effect of multiple subcutaneous doses of CFZ533 versus placebo on the clinical disease activity of primary Sjögren's syndrome patients as measured by the change of the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) after 12 weeks treatment.
- To assess the pharmacokinetics of multiple subcutaneous doses and multiple intravenous infusions of CFZ533 in primary Sjögren's syndrome patients.
- To evaluate the effect of multiple subcutaneous doses and multiple intravenous infusions of CFZ533 versus placebo on self-reported outcomes in primary Sjögren's syndrome patients after 12 weeks treatment as measured by the EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI), the Short Form (36) Health Survey (SF-36) and the Multidimensional Fatigue Inventory (MFI) Questionnaire.
- To evaluate the changes in the physician global assessment of the patient's overall disease activity as recorded by a visual analog scale (VAS) after 12 weeks treatment.
- To evaluate the changes in the patients global assessment of their disease activity as recorded by a VAS after 12 weeks treatment.

3 Investigational plan

3.1 Study design

This is a double-blind followed by open-label, randomized, placebo-controlled, parallel-group, non-confirmatory study to assess the safety, tolerability, pharmacokinetics, and preliminary clinical efficacy of multiple doses of CFZ533 in the following Cohorts 1 and 2:

- Cohort 1: CFZ533 administered subcutaneously in patients with pSS, in a double-blind and placebo-controlled fashion, followed by open-label treatment;
- Cohort 2: CFZ533 administered by intravenous infusion in patients with pSS, in a double-blind and placebo-controlled fashion, followed by open label treatment.

These cohorts will be followed by an open label, randomized, parallel group, non-confirmatory part of Cohort 3:

- Cohort 3:

  In treatment arm 1, CFZ533 will be given at s.c. weekly on 4 occasions (loading regimen), followed by s.c. weekly on 9 occasions (maintenance regimen starting on study Day 29).

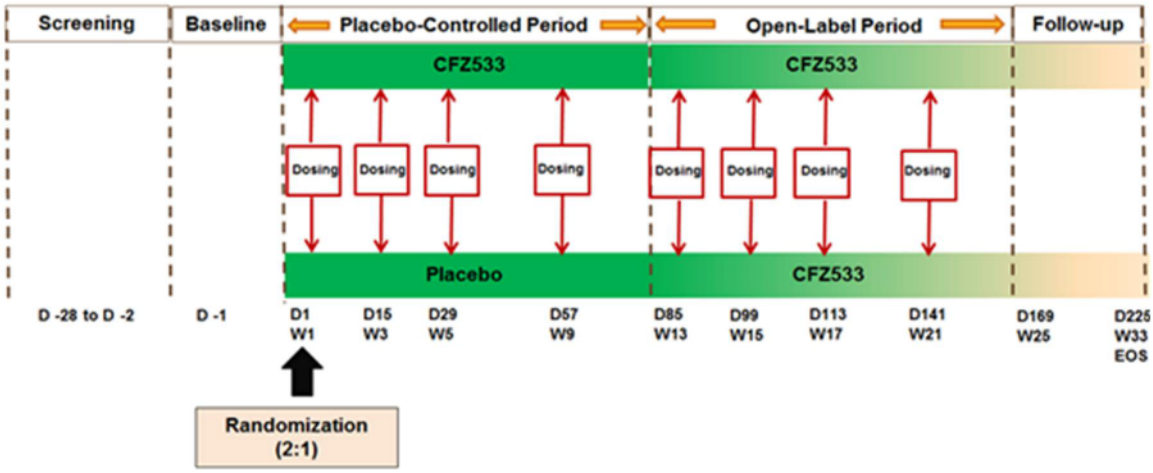
  In treatment arm 2, the loading regimen will be a single i.v. dose of CFZ533 (on study Day 1), this will be followed by s.c. weekly on 12 occasions (maintenance regimen starting on study Day 8).

The study will randomize approximately 68 patients with primary Sjögren's syndrome. In Cohorts 1 and 2, the randomization will be stratified by baseline intake of oral corticosteroids (yes/no). There will be no stratification in Cohort 3.

The study comprises three periods for Cohort 1 and Cohort 2:

1) placebo-controlled period (from Day 1, Week 1 to completion of pre-dose assessments on Day 85, Week 13), during which 4 doses of CFZ533 or placebo will be administered on top of the standard of care therapy, (e.g., low dose corticosteroid) that is necessary to treat pSS;
2) open-label period (from dosing on Day 85, Week 13 to completion of assessments on Day 169, Week 25), when all patients will receive 4 doses of open-label CFZ533 treatment, and
3) follow-up period (Weeks 25 – 32), when patients will be followed up without study medication.

Figure 3-1 Study Design Cohort 1 and Cohort 2



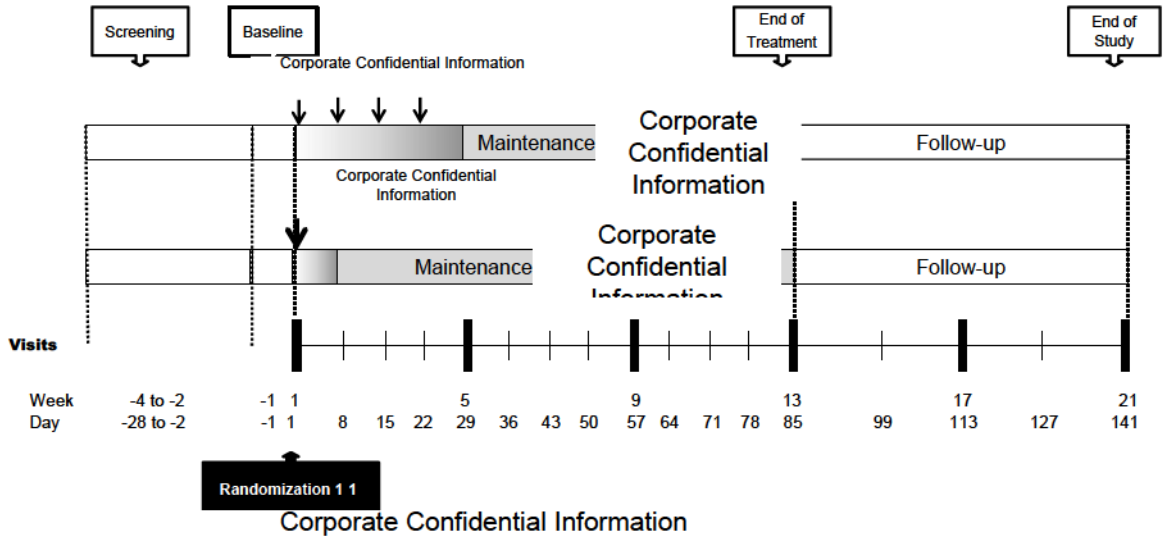
Cohort 3 comprises two periods:

1. open-label treatment period (from dosing on Day 1, Week 1 to last dose and completion of assessments on Day 85, Week 13),
2. follow-up period (from Week 13 after completion of last dose to Day 141, Week 21), when patients will be followed up for 8 weeks without study medication.

In the open-label treatment period, treatment arm 1 dosing starts with CFZ533 s.c. q1w for 4 weeks; in treatment arm 2, dosing starts with CFZ533 i.v. on Day 1.

Following that, dosing continues with CFZ533 s.c. q1w for 4 weeks (treatment arm 1) and 9 weeks (treatment arm 2), respectively.

Figure 3-2 Study Design Cohort 3



Cohort 1

This cohort will randomize approximately 12 patients. For each patient, there will be a screening period from Day -28 to Day -2. Patients who meet the eligibility criteria at screening will be admitted to baseline evaluations. Baseline evaluations may be started from Day -6 to allow completion of assessments on Day -1 prior to the treatment on Day 1. All baseline safety evaluation results must be available prior to dosing and meeting eligibility criteria. Eligible patients will enter the placebo-controlled period on Day 1 (Week 1) and will be randomized at a 2:1 ratio to receive treatment with either CFZ533 or placebo. On Day 1, a dose of CFZ533 or placebo will be administered by subcutaneous injection (s.c.), followed by PK, pharmacodynamics (PD) and safety assessments for up to 6 hours. Patients will be discharged from the site on the same day after completion of all assessments provided there are no safety concerns.

Patients will return to the study center to receive three s.c. doses of either CFZ533 or placebo (same as they have received on Day 1) on Day 15 (Week 3), Day 29 (Week 5) and Day 57 (Week 9) respectively. Safety and efficacy assessments will be conducted in these visits,
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On Day 85 (Week 13), after safety and other assessments that are assessments for the end of placebo-controlled period, all patients will enter the open-label period and receive an open-label s.c. dose of CFZ533. This is followed by three open-label s.c. doses of CFZ533 on Day 99 (Week 15), Day 113 (Week 17) and Day 141 (Week 21) respectively. Safety and efficacy assessments will be conducted in these visits, PK and biomarker samples will be collected. The blind of the controlled period will be maintained for the investigator and the patient until the end of the study.

On Day 169 (Week 25), patients will have assessments for the end of open-label period and enter follow-up period with no study medication administered. Patients will return to the study center for safety monitoring during this period.

The end of study visit will occur on Day 225 (Week 33), which will include study completion evaluations followed by discharge from the study.

Cohort 2

Approximately 12 subjects would have been enrolled in Cohort 1, Cohort 2 will begin enrollment to randomize approximately 30 patients to have approximately 24 patients completing 12 weeks treatment. The study design for Cohort 2 is identical as Cohort 1 with the exception of the dosing regimen to include multiple intravenous dosing of CFZ533 followed by PK, pharmacodynamics (PD) and safety assessments for up to 2 hours after the end of the infusion. Additionally, body weight will be measured at every dosing visit to calculate the drug dosage according to the subject's actual weight (in Cohort 1, subject's baseline weight was used throughout study).

Cohort 3

All new patients enrolled after Protocol Amendment 6 will be allocated to Cohort 3. Cohort 3 will randomize approximately 24 patients to have approximately 20 patients (10 in treatment arm 1, 10 in treatment arm 2) completing a 12-week treatment.

Patients can remain on their standard of care therapies provided that the treatments are maintained at a constant level during the study.

Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, urinalysis, pregnancy test, blood coagulation), adverse event and serious adverse event monitoring.

All s.c. injections and i.v. infusions will take place in a monitored facility. Patients will be monitored closely for at least 6 hour after s.c. injection in Cohort 1, 2 hours after completion of i.v. infusion in Cohort 2. In Cohort 3, the patients will be monitored for at least 1 hour after the completion of i.v. infusion and 30 minutes after s.c. injection, or longer at the discretion of the Investigator for vital signs, and signs or symptoms of adverse events including development of an injection reaction. Treatment of injection site reaction and allergic reactions is described under Section 5.5.6. Pharmacokinetic, pharmacodynamic, and safety assessments will be made for up to 6 hours after s.c. injection in Cohort 1, 2 hours after the completion of i.v. infusion in Cohort 2, or 1 hour after the completion of the i.v. infusion and 30 minutes after the s.c. injection in Cohort 3. Subjects will be discharged after these assessments, at the discretion of the Investigator, following satisfactory review of safety data.

PK assessment will include measurements of free CFZ533 in plasma.

3.2 Rationale for study design

This study will be conducted in patients with active pSS for which no existing treatment has been proven effective against the underlying disease. Corporate Confidential Information

Cohorts 1 and 2

Two different doses Corporate Confidential Information of CFZ533 will be assessed in two separate cohorts.

A randomized, placebo-controlled, double-blind approach is used to eliminate potential bias in reporting safety and clinical efficacy data in this first, exploratory study in pSS patients. Patients will be randomized to CFZ533 or placebo in a 2:1 ratio in order to minimize exposure to placebo and to gather more data on CFZ533. Stratified randomization is done in order to limit imbalances between active and placebo arms in baseline intake of oral corticosteroids.

The open-label period will administer CFZ533 to all patients including those who were administered placebo in the placebo-controlled period. This would provide potential treatment benefit to these patients, and collect further safety and efficacy data for CFZ533 in pSS patients.

After the open-label period, patients will enter a follow up period for which a duration of 8 weeks (12 weeks after the last dosing with CFZ533) was chosen to allow sufficient time for monitoring safety and exploring duration of response.

In addition to safety, efficacy estimated by the EULAR Sjogren's Syndrome Disease Activity Index (ESSDAI) is chosen as a key endpoint of the study. The ESSDAI has been shown to be responsive in a retrospective analysis of a randomized controlled trial on rituximab, and was suggested to be a sensitive tool to assess efficacy of rituximab treatment (Moerman et al 2014). The authors reported a significant lower ESSDAI in the rituximab group compared to the placebo group at week 12 and week 24, demonstrating some effectiveness in reducing disease activity in this small study.

Cohort 3

Because of the key objective of this cohort, no placebo control is required, and open-label treatment is justified. In Cohort 3, two treatment arms are implemented to assess whether two loading regimens (multiple s.c. doses in treatment arm 1, or single i.v. administration in treatment arm 2), followed by a maintenance regimen (multiple s.c. doses, both arms), are set to 12 weeks (Day 1 to Day 85) to establish steady state conditions for CFZ533 concen trations in plasma at a level similar to trough concentrations observed in Cohort 2 Corporate Confidential Information

The follow-up period is set to 8 weeks (Day 85 to Day 141),

(i) to follow the elimination of CFZ533 under conditions where the target is fully saturated (slow elimination), and under incomplete CD40 saturation (rapid elimination), and

(ii) to characterize the capacity of the target mediated elimination pathway for CFZ533 after 12-week treatment.

3.3 Rationale for dose/regimen, duration of treatment

No previous experience with an anti-CD40 blocking agent exists in human primary Sjögren's syndrome. Corporate Confidential Information

Cohort 1 (subcutaneous

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The 2-week dosing interval at the start is meant to ensure full CD40 saturation on peripheral B cells as well as complete suppression of CD40-CD154 interaction in tissues after subcutaneous administration. By the end of the 12-week treatment period, clinically meaningful changes in the primary endpoint and in other key efficacy and biomarker readouts are expected to occur. Based on published results with a single cycle of rituximab, significant clinical responses in pSS patients can be detected as early as at week 5, with maximum effect shown at week 12 (Meijer et al 2010). During the additional 12-week open label extension period, further data regarding longer term efficacy and safety of CFZ533 will be collected.

Cohort 2 (intravenous -

The i.v. regimen is introduced to offer higher plasma exposures throughout the treatment period, in order to ensure complete and sustained CD40 pathway blockade in target tissues, in conditions where higher CD40 expression is likely. This regimen is supported by Corporate Confidential Information

recently published data from ASKP1240.

Data from ASKP1240, a monoclonal antibody blocking CD40: A recent analysis of disclosed PK/efficacy data from Astellas' anti-CD40 antibody ASKP1240 in solid organ transplantation (Harland et al 2015) demonstrated that efficient target mediated antibody clearance in tissue, could result in loss of CD40 blockade and likely loss of efficacy, as a consequence of a significant increase of target expression in target tissues. The proposed intravenous regimen is aiming to saturate, throughout the entire treatment period, CD40 elimination pathways, in conditions where higher CD40 expression is likely.

Cohort 3

Based on results from Cohorts 1 and 2 Corporate Confidential Information an efficient dosing regimen in patients with pSS may require a loading regimen (i.v. or s.c.), providing early full CD40 saturation and minimal target mediated disposition followed by a s.c. maintenance regimen.

In Cohort 3, the dose/regimen in treatment arm 1 and in treatment arm 2 were set to assess whether a loading regimen (i.v. or s.c.), followed by a s.c. maintenance regimen is able to deliver steady state plasma concentrations similar to the i.v. regimen tested in Cohort 2, and has the ability to overcome target mediated disposition of CFZ533 via the s.c. route.

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3.4 Rationale for choice of comparator

In study Cohorts 1 and 2, the placebo to CFZ533 will be used as comparator to provide objective evidence of potential AEs and other safety data, as well as clinical efficacy and PD data generated from patients exposed to the experimental therapy. Since there is no established, clinically effective disease modifying treatment for patients with pSS, potential treatment with placebo (on top of standard of care therapy, if necessary) is justified.

3.6 Risks and benefits

3.6.1 Potential benefit

To date, no evidence-based, systemic therapy has been available for pSS patients. Based on the established role of both B cells and T cells in pSS pathogenesis, CFZ533, via the inhibition of T cell dependent B cell functions, autoantibody production, ectopic germinal center formation along with a concurrent blockade of the parenchymal CD40 mediated signaling in salivary glands, has a potential therapeutic benefit.

If CFZ533 has clinical efficacy, all patients participating in the present trial can experience this benefit as placebo patients in Cohorts 1 and 2 will be switched to CFZ533 after 12 weeks (in the open-label period). However, CFZ533 has never been used in patients with pSS, so at this stage, no statement can be made of its efficacy in treating this disease.

3.6.2 Potential risks associated with exposure to CFZ533 and their mitigation

Currently, limited data exists regarding the use of agents that block the CD40/CD154 pathway.

The current IB (Section 6, Investigator Guidance) also provides detailed instructions regarding the risks and their mitigation.

Acute hypersensitivity

Hypersensitivity or infusion reactions can manifest with itching, flushing, headache, nausea/vomiting, hypotension, urticaria, bronchospasm, or angioedema. Corporate Confidential Information

Infections

Subjects treated with CFZ533 may be at an increased risk of infection. CD40 ligation is linked to the functional activity of antigen presentation, as well as T-cell priming, B-cell differentiation, antibody production and immune memory. Administration of CFZ533 is expected to result in general immunosuppression with a decreased capacity to mount a response to novel immunogens, including those of bacterial, viral, fungal and parasitic origin when full receptor occupancy has been achieved.

Although the ability to mount a primary immune response will be affected by CFZ533, the memory B-cell repertoire and immune recall response should remain intact and protective. In addition, subjects will have adequate preformed antibody to maintain protective humoral response for extended periods of time (months).

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Subjects enrolled in the current study will be monitored regularly and carefully for signs and symptoms which might indicate a severe infection. Subjects will be informed to contact the study physician if they present with signs and symptoms of an infection such as fever, nausea, myalgia, headache, arthralgia, chills, diarrhea, stiff neck, and malaise for further assessment and treatment if necessary.

Vaccination

Vaccination of subjects during treatment with CFZ533 and prior to clearance of the antibody is likely to result in therapeutic failure (i.e., non-protective antibody titers) due to the pharmacologic activity of the antibody. For subjects participating in this study, all vaccinations should be up to date based on local guidelines. Administration of live attenuated agents will be prohibited receiving CFZ533 treatment in the current study.

Immunogenicity

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Extrapolation of immunogenicity risks from healthy subjects to pSS patients is unknown and blood samples will be collected during this trial to assess this.

Thrombosis

There is a minimal risk for thromboembolic complications when targeting this co-stimulatory pathway with this anti-CD40 mAb. Corporate Confidential Information

Although the risk is hypothetical, hematologic and coagulation parameters will be regularly monitored in the current study. Furthermore, patients with conditions such as anti-phospholipid syndrome where the risk is already high will be excluded.

Systemic inflammation and potential kidney injury

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Although not expected in this clinical study, the investigator will monitor for signs, symptoms and laboratory results consistent with clinically significant inflammation as well as for changes in renal function and signs of acute kidney injury as per local practice.

Lymphadenopathy

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The investigator will pay special attention to lymph nodes in patients during physical assessments including unusual lymphadenopathy in the absence of infection.
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Lymphoproliferative disorders

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The clinician should monitor hematology regularly for changes consistent with a lymphoproliferative disorder.

4 Population

The study population will be comprised of male and female subjects with active primary Sjögren's syndrome.

A total of approximately 12 subjects for Cohort 1, 30 subjects for Cohort 2, and 24 subjects for Cohort 3 are planned to be randomized to participate in the study. Approximately 10 subjects are expected to complete the placebo-controlled period in Cohort 1, approximately 24 subjects are expected to complete the placebo-controlled period in Cohort 2, and approximately 20 subjects are expected to complete the treatment period in Cohort 3.

The investigator must ensure that all subjects being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible subjects.

Subject selection is to be established by checking through all inclusion/exclusion criteria at screening and baseline. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a subject from enrollment into the study.

4.1 Inclusion criteria

Subjects eligible for inclusion in this study have to fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed;
2. Male and female patients 18 to 75 years of age included;
3. Subjects must have a body weight of 50 – 150 kg (inclusive);
4. Diagnosis of primary Sjögren's syndrome according to revised EU/US consensus criteria (Vitali et al 2002);
5. Moderate to severe disease activity as determined by ESSDAI score ≥6;

4.2 Exclusion criteria

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

1. Secondary Sjögren's syndrome. Patients with laboratory or clinical signs of another connective tissue disease (e.g., systemic lupus erythematous) may be eligible at the investigators discretion;
2. Use other investigational drugs at the time of enrollment, or is within five half-lives of using other investigational drugs or longer if required by local regulations, at the time of enrollment;
3. History of hypersensitivity to study drug or to drugs of similar chemical classes;

4. Patients having received the following treatments (within given timeframe before randomization):
   - Oral or i.v. cyclosphosphamide treatment within 6 months;
   - i.v. corticosteroid bolus with dose > 1 mg/kg within 3 months;
   - Rituximab within 12 months. For patient who received rituximab earlier, B cell count should be within normal range;
   - Belimumab within 6 month;
   - Any other biologic within 1 month or five times the half-life, whichever is longer;
   - Any other immunosuppressives (despite methotrexate, glucocorticoids, and hydroxychloroquine on stable doses as described in the inclusion criteria 8, 9, 10, 11) such as cyclosporine A or mycophenolate within 3 months;

11. Signs or symptoms of a clinically significant systemic viral, bacterial or fungal infection within 30 days of randomization;
12. Any condition, that would result in a significantly elevated risk for infections, as judged by the investigator, e.g.,:
    - Vaccinations as required based on local guidelines are not up to date;
    - Any form of clinically relevant immunodeficiency.

20. 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 hCG laboratory test
21. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during the study and for 12 weeks after the last study treatment. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). 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) or tubal ligation at least six weeks before taking study treatment, confirmed by medical documentation. 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, with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.

- Combination of any two of the following (a+b or a+c, or b+c):
  a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/vaginal suppository
- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

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 is she considered not of child bearing potential.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

The investigational drug, CFZ533 and matching placebo will be prepared by Novartis and supplied to the Investigator site as open-label bulk medication.

Cohorts 1 and 2

The dosage form of the supplied drug is lyophilisate in vial and needs to be reconstituted with water for injection (USP or equivalent), provided by the investigator's site. The placebo control selected for this study is a mixture of inactive excipients, matching the composition of the CFZ533 Corporate Confidential Information for injection.

Table 5-1 Study drug CFZ533 (lyophilisate)

Name	CFZ533
Formulation	Lyophilisate in vial (powder for solution for injection)
Appearance before reconstitution	White lyophilized cake
Appearance after reconstitution	Opalescent to clear, colorless solution
Unit dose	Corporate Confidential Information
Packaging	6 mL Type I glass vials

*The vials contain a 20% overfill to allow a complete withdrawal of the labeled amount of CFZ533

After reconstitution of the lyophilized powder with 1.0 mL water for injection, the resulting solution contains CFZ533 and the excipients L-Histidine, Sucrose and Polysorbate 20, pH 6.0 ± 0.5.

Cohort 3

The dosage form of the supplied drug is a 'ready to use' aqueous buffered sterile solution also referred to as CFZ533 Concentrate for infusion/solution for injection (liquid in vial). This presentation has the same composition as the reconstituted powder. The same overfill of 20% is included to allow complete removal of the intended dose. There is no placebo for this cohort.

Table 5-2 Study drug CFZ533 (liquid in vial)

Name	CFZ533
Formulation	Solution for infusion/solution for injection
Appearance	Opalescent to clear, colorless solution
Unit dose	Corporate Confidential Information

*The vials contain a 20% overfill to allow a complete withdrawal of the labeled amount of CFZ533

Clinical supplies are to be dispensed only in accordance with the specified study procedures.

An unblinded pharmacist or authorized designee is required to prepare the study drug. Instructions for storage and handling of CFZ533 vials, and preparation of CFZ533 and placebo (in Cohorts 1 and 2) injection are described in the Pharmacy Manual, provided as a separate document.

Of note, CFZ533 vials require storage between 2-8°C.

5.1.2 Additional study treatment

No additional treatment beyond investigational treatment is requested for this trial.

5.2 Treatment arms

The study will have three cohorts.

In the placebo-controlled period of Cohorts 1 and 2, all subjects will be randomized in a 2:1 ratio to one of the following two treatment arms, defined as:

Cohort 1

- CFZ533 active: multiple doses of CFZ533 s.c. injection
- CFZ533 placebo: multiple doses of placebo s.c. injection

  In the open-label period, all subjects will receive CFZ533 active treatment of multiple s.c. dosing .

Cohort 2

- CFZ533 active: multiple doses of CFZ533 i.v. infusion
- CFZ533 placebo: multiple doses of placebo i.v. infusion

  In the open-label period, all subjects will receive CFZ533 active treatment of multiple i.v. dosing

Cohort 3

In the open-label Cohort 3, the subjects will be randomized in a 1:1 ratio to one of the following two treatment arms:

- Treatment arm 1: CFZ533 will be given weekly on 4 occasions (Days 1, 8, 15 and 22; loading regimen), followed by s.c. weekly on 9 occasions (maintenance regimen starting on study Day 29, last dose on Day 85).
- Treatment arm 2: CFZ533 i.v. on Day 1, followed by c. weekly on 12 occasions (maintenance regimen starting on study Day 8, last dose on Day 85).

The Corporate Confidential Information s.c doses will consist of 4 injections or 2 injections of 1 mL CFZ533 respectively.

5.3 Treatment assignment

Randomization numbers will be assigned in ascending, sequential order to eligible subjects (see Section 5.5.1 for details). The investigator will enter the randomization number on the eCRF.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A randomization list for each cohort will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization scheme for subjects will be reviewed and approved by a member of the Novartis IIS Randomization Group.

Randomization procedure for central management of randomization numbers:

When an eligible patient at a participating study site is ready to be randomized into the study, the steps below will be followed:

- The site designee will complete a Randomization Request form and email to the Novartis designee.
- On receiving the Randomization Request form, the Novartis designee will write the next available randomization number within the randomization list for the corresponding part of the study on the form and email back.
- On receiving the allocated randomization number, the unblinded pharmacist or authorized designee will use the information on the completed form to ensure that the patient receives the correct study medication, according to the provided randomization list.

After inclusion of each new patient, the site designee will countersign the Randomization Request form, and email it back to the Novartis designee to document the correct assignment of the patient's randomization number and the date the patient received their first dose of study medication.

5.4 Treatment blinding

Cohorts 1 and 2 are double-blind: subjects, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of study treatments according to the specifications provided in Appendix 6. Randomization data are kept strictly confidential until the time of unblinding for the respective person(s). Further information regarding blinding (and unblinding) is presented in Appendix 6.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

An unblinded pharmacist at the investigator site will prepare the study treatment for injection from the bulk open-labeled supplies.

The blind of the controlled period of the study will be maintained in the open-label period for the investigator and the patient until the end of the study.

The PK/PD bioanalysts will be unblinded during the clinical study, but will not provide individual PK/PD data prior to database lock, to maintain the study blind.

The necessary safety review may lead to the Novartis study team being inadvertently unblinded; however, this information will not be communicated to the investigator.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.11) and at the time of the interim analysis and at the conclusion of the study.

Cohort 3 will be open-label. However, subjects and investigator staff remain blinded to the study treatment allocation (dosing arm) until first dosing. Further information regarding blinding (and unblinding) is presented in Appendix 6.

5.5 Treating the subject

5.5.1 Subject numbering

Screening number

Each subject screened is assigned a unique screening number. The screening number is a combination of the center number that is provided by Novartis, and a three digit number starting with 001 for each subject which is assigned by the Investigator. Therefore, if the center number is 1 (any leading 0's in the center number are dropped) the screening numbers will be assigned such as 1001, 1002, 1003 in ascending order. If the center number is 2 (or 0002), the screening numbers will be 2001, 2002, 2003 in an ascending order.

Randomization number

If the subject is deemed eligible for the study and will commence dosing, a randomization number will be assigned. Once assigned to a subject, a randomization number will not be reused.

The randomization number becomes the definitive subject number as soon as a subject receives the first dose of the respective study treatment.

There should be a source document maintained at the site which links the screening number to the randomization number (once assigned). This source document should be provided to all appropriate parties (i.e., Central Laboratory) as soon as this is available.

Cohort 1

Subjects will be assigned randomization numbers 5101-5130 in the first stratum (baseline intake of oral corticosteroids = yes) and randomization numbers 5201-5230 in the second stratum (baseline intake of oral corticosteroids = no).

Replacement subjects will be assigned randomization numbers 6101-6130 in the first stratum and 6201-6230 in the second stratum. If a subject requires a replacement, the replacement subject will be assigned a randomization number corresponding to the original subject (e.g., Subject 6103 would replace Subject 5103). Replacements are envisaged only for subjects dropping out for reasons other than safety without at least one post-baseline ESSDAI result.

Cohort 2

Subjects will be assigned randomization numbers 5601-5630 in the first stratum (baseline intake of oral corticosteroids = yes) and randomization numbers 5701-5730 in the second stratum (baseline intake of oral corticosteroids = no).

Replacement subjects will be assigned randomization numbers 6601-6630 in the first stratum and 6701-6730 in the second stratum. If a subject requires a replacement, the replacement subject will be assigned a randomization number corresponding to the original subject (e.g., Subject 6603 would replace Subject 5603). Replacements are envisaged only for subjects dropping out for reasons other than safety without at least one post-baseline ESSDAI result.

Cohort 3

Subjects will be assigned randomization numbers 5801-5840.

5.5.2 Dispensing the study treatment

The investigational drug, CFZ533 lyophilisate in vials and matching placebo (Cohorts 1 and 2), or CFZ533 liquid in vials in Cohort 3 Corporate Confidential Information will be prepared by Novartis and supplied to the investigator site as open labeled bulk medication.

For preparation of the study medication, a copy of the randomization schedule will be sent to the unblinded pharmacist at the Investigator's site or to the dispensing contractor.

Appropriate documentation of the subject specific dispensing process must be maintained.

Bulk medication labels will be in the local language, will comply with the legal requirements of each country, and will include storage conditions for the drug but no information about the subject.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

Investigational treatment must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated staff have access. Upon receipt, the study drugs should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance. Storage conditions must be adequately monitored and appropriate temperature/humidity logs maintained as Source data.

The Investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Drug accountability will be noted by the Monitor during site visits and/or at the completion of the trial.

All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by Novartis, the Investigator must not destroy any drug labels, or any partly used or unused drug supply.

At the conclusion of the study, and, if allowed during the course of the study (e.g., an un-blinded monitor), the Investigator will provide a copy of the drug accountability ledger to the Monitor.

Only after receiving a written authorization by Novartis, the Investigator/designee will send all the unused and partly used drug supplies as well as the empty containers to the address provided at the time of authorization for destruction or have the unused and partly used drug supplies as well as the empty containers destroyed by the site's pharmacist, providing a drug destruction certificate.

5.5.3.2 Handling of other study treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

CFZ533, or matching placebo (Cohorts 1 and 2 only), will be administered as an s.c. injection in Cohort 1, i.v. infusion in Cohort 2, or i.v. infusion and s.c. injection in Cohort 3 by the study center personnel following the instructions and using the material as described and specified in the Pharmacy Manual.

- In Cohort 1, the subjects will be weighed at the baseline visit and this weight value will be used for study medication preparation and the calculation of the dose.
- In Cohort 2, the dose for administration to subjects will be calculated from the individual subjects' body weight obtained at the most recent pre-dose visit.

- In Cohort 3, the i.v. dose (Day 1) for administration to subjects randomized to treatment arm 2 will be calculated from the individual subject's body weight obtained at Baseline visit. All s.c. doses in this cohort are administered as flat doses (not adjusted to body weight)

A physician shall be available, e.g., by pager, DECT etc. at all other times throughout the study.

All dosages prescribed and dispensed to the subject and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments and/or interruptions are not permitted in this study; in case of an AE or for any reason (e.g., non-compliance, operational hurdle) resulting in a deviation from the required dosing scheme, consultation and agreement with Novartis will be necessary to decide whether the subject can continue or needs to be withdrawn from the study. Any change in dosing must be recorded on the Dosage Administration Record eCRF.

In case of notable adverse events, SAEs including loss of efficacy and/or associated PK/PD data collected during the study, changes to a different dosing scheme level may be considered and implemented via a protocol amendment.

Upon review data at interim analysis, dose adjustment for study drug may occur. This will be implemented via a protocol amendment. Details are provided in Section 9.8.

5.5.6 Recommended treatment of adverse events

Parenteral administration of monoclonal antibodies can be associated with acute, severe reactions (occurring within the first few hours post dose) secondary to hypersensitivity, immunogenicity, or ADCC-mediated cell depletion. Although such events are more likely to occur during intravenous administration (infusion reaction), they cannot be fully excluded when the antibody is administered as a subcutaneous injection.

Injection site reactions can also be noted during or after subcutaneous administration and are usually less severe than infusion reactions, however, may still require medical attention and treatment.

In this study, CFZ533 will be administered as intravenous infusion and subcutaneous injection.

Patients will be monitored at the site for at least 6 hours post dose or longer in Cohort 1, at least 2 hours post dose or longer in Cohort 2, and at least 1 hour after i.v. infusion and 30 minutes after s.c. injections in Cohort 3 at the discretion of the Investigator to ensure adequate safety monitoring. In case of any signs of an acute reaction, clinical treatment will be provided as determined by the treating physician on a case-by-case basis and depending on the severity, using symptomatic treatment, anti-histamines, NSAIDs, acetaminophen, intravenous fluids, corticosteroids, or adrenaline.

For the management of allergic reaction, anaphylaxis and cytokine release, it is recommended to follow the guidelines by the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE/v4.03, Reference http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

When using CFZ533 in a subcutaneous dosing form, plasmapheresis will likely be of limited benefit to decrease the systemic concentration of CFZ533.

Use of rescue medication must be recorded on the Concomitant medications / Significant non-drug therapies eCRF after start of study drug.

5.5.7 Rescue medication

There is no established, approved immunosuppressive treatment for pSS. Patients may receive NSAIDs, paracetamol or symptomatic care at the discretion of the treating physician as outlined in Section 5.5.8. Rescue medicine is to be provided by the study center or personal physician. Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies eCRF after start of study drug.

5.5.8 Concomitant treatment

Use of artificial tears and artificial saliva/salivary stimulants (e.g., cevimeline, pilocarpine) by the patient during participation in the protocol is permitted at the discretion of the treating physician. Amount and frequency of use should be recorded at each visit. For assessments in Cohorts 1 and 2, the salivary stimulants should be stopped within 12 hours prior to, or during assessment of clinical disease outcome measurements. Artificial tears and artificial saliva are to be provided by the study center or personal physician if needed, and should not be used 4 hours prior to, or during assessment of clinical disease outcome measurements.

Currently, concomitant use of corticosteroids is allowed at a dose of max 10 mg per day (prednisone or equivalent) and no immunosuppressives such as cyclosporine, cyclophosphamide, or mycophenolate are allowed. Stable dose of methotrexate (up to 25 mg per week), azathioprine (up to 100 mg per day) and/or antimalarials are permitted. Any other drug with a potential immunosuppressive effect that is not specifically mentioned in the Inclusion/Exclusion criteria, should be discussed with the Sponsor on a case by case basis. If, based on the patient condition (such as severe extraglandular manifestation, or major disease worsening) a corticosteroid dose above 10 mg (prednisone or equivalent) per day or an immunosuppressive medication is necessary, the patient may have to be withdrawn from the study. This will be decided on the basis of a case by case evaluation by both the investigator and Sponsor.

The investigator should instruct the subject to notify the study site about any new medications he/she takes after the start of the study drug.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/ Significant non-drug therapies section of the eCRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

5.5.9 Prohibited treatment

Use of the treatments displayed in the table below are NOT allowed after the start of study drug until at least four weeks after the last administration of study drug.

Table 5-3 Prohibited treatment

Medication	Action to be taken
Other experimental therapies	Withdrawal may be required on a case-by-case basis
Other biologics	Withdrawal may be required on a case-by-case basis
Immune suppressive agents	Withdrawal may be required on a case-by-case basis
Any medication that, as judged by the Investigator, is the primary cause of dry mouth in the patients	Withdrawal may be required on a case-by-case basis
Live vaccination	Withdrawal immediately

5.5.10 Discontinuation of study treatment

Study "Stopping rules"

The following stopping rules, based on potential toxicities, will serve as the basis for placing the study on hold. Although the stopping criteria do not incorporate an absolute requirement for causality, the potential relationship between an adverse event and CFZ533 will be evaluated carefully on a case-by-case basis between the Sponsor and the Investigator. Following a review of the adverse event(s), a decision to permanently discontinue enrollment or re-initiate dosing will be made jointly by the Investigator and Sponsor.

As a guidance, dose limiting toxicities (DLTs) will be assessed according to the standardized toxicity grading scale, the NCI Common Toxicity Criteria for Adverse Events (NCI-CTCAE/v4.03, Reference http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

- Any study treatment related death,

1. Two (2) or more subjects presenting with a serious adverse event that is related to the study treatment,
2. One (1) subject presenting with study treatment related cytokine release syndrome,
3. One (1) subject presenting with a study treatment related thromboembolic event that is at least of moderate severity,
4. More than one (1) allergic reaction of Grade 3 severity of the NCI-CTCAE/v4.03 Criteria within the first 5 treated subjects or an incidence of >20% thereafter,
5. Any treatment-related, Grade 3 or higher event of the NCI-CTCAE/v4.03 Criteria considered drug related by the Investigator with the following exceptions:
    1. Events not requiring treatment, and diagnostic procedures involving elective or non-urgent hospital admission,
    2. Disease Specific Events that are due to the patients underlying pSS diagnosis,
    3. AEs/SAEs unrelated to the experimental compound as determined by the Investigator or Novartis

6. Two (2) or more subjects presenting with:
    4. Progressive renal insufficiency or acute kidney injury defined as a Grade 2 increase in serum creatinine (1.5 X ULN) in the setting of euvolemia at any time during the study,
    5. Emergent hypogammaglobulinemia defined as a reduction in total serum IgG or IgM concentration by 50% or more from baseline,
    6. Severe systemic infection or opportunistic infection that requires treatment, e.g., sepsis, urosepsis, mycoses, pneumonia.
7. Clinically significant (according to the Investigator) and study drug-related, persisting changes from baseline in vital signs, electrocardiograms, or relevant, persistent changes in laboratory parameters, which are not consistent with existing co-morbidities, in more than one (1) subject within the first 5 treated subjects or an incidence of >20% thereafter.
8. Other clinically significant changes or effects in the opinion of the Investigator or Sponsor that are deemed unsafe to continue dosing.

In addition, all blinded safety data, including disease specific events, will be evaluated by the Sponsor and Investigator continuously and at scheduled meetings. The study may be put on hold pending further data analysis, and the decision to adjust the dose or modify the medication if the following criteria occur:

- The principal investigator or the Sponsor considers that the number and/or severity of AEs justify discontinuation of the study.
- Other clinically significant changes or effects in the opinion of the Investigator or Sponsor that are deemed unsafe to continue dosing.

Individual subject withdrawal

Subjects may voluntarily discontinue the study for any reason at any time.

The Investigator should discontinue study treatment for a given subject if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

Study treatment **must** be discontinued under the following circumstances:

- Subject withdraws consent,
- Pregnancy,
- CTCAE Grade 3-4 allergic reaction,
- Major worsening of primary Sjögren's syndrome as judged by the Investigator (e.g., severe CNS or renal complications, or increase from baseline in ESSDAI of at least 7 points after more than 8 weeks of treatment (as a guidance),
- Acute, severe infection as judged by the investigator,
- Significant changes in standard coagulation test, such as prothrombin time (PT) or activated partial thromboplastin time (aPTT), suggesting an increased risk for hypercoagulability or any sign or symptom of a thromboembolic event.

Discontinuation of study treatment will be at the discretion of the Investigator, under the following circumstances:

- Any other protocol deviation that results in a significant risk to the subject's safety

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

Subjects who discontinue study treatment should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 5.5.11). They should return for the assessments indicated by an asterisk (*) in the assessment table. If they fail to return for these assessments for unknown reasons, every effort should be made to contact them as specified in Section 5.5.12.

5.5.11 Withdrawal of consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a subject 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 and does not allow analysis of already obtained biologic material.

If a subject withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

5.5.12 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show “due diligence” by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc. A subject should not be considered lost to follow-up until his/her scheduled end of study visit would have occurred.

Subjects dropping out for reasons other than safety without at least one post-baseline ESSDAI result will be replaced by an equal number of newly enrolled subjects.

5.5.13 Emergency breaking of assigned treatment

Cohorts 1 and 2:

Emergency unblinding in Cohorts 1 and 2 should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. A complete set of emergency code break cards will be provided to the investigator site(s) and a complete set will be available at Novartis. All code break cards must be retained until the end of the study and returned to Novartis. They must be stored in a secure place but be accessible in case of emergency. The investigator will receive a blinded code break card for each subject, with the details of drug treatment covered by a removable, scratch-off cover. In an emergency, the scratch-off cover can be removed to determine the treatment. The scratch-off covers are not to be removed for any reason other than an emergency. When the investigator removes the scratch-off cover he/she must note the

date, time, and reason for removing it and retain this information with the case report form documentation. **The unblinded treatment code should not be recorded on the eCRF.** The investigator must also immediately inform the Novartis local monitor that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the code break cards in case of emergency. If appropriate, the investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable.

An assessment will be done by the appropriate site personnel and the Sponsor after an emergency unblinding to assess whether or not study drug should be discontinued for a given subject and, if applicable, whether the subject can continue into the next trial phase (e.g., an unblinded extension).

Cohort 3 will be open-label.

5.5.14 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. The study will complete when the last subject completes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator.

After study participation, the patients will continue to be treated by his/her general practitioner according to the local standard clinical management related to the underlying disease.

The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.5.15 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the subject should 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 will be responsible for informing IRBs/IECs of the early termination of the trial.

6 Visit assessments

The full Assessment schedule is presented at the end of the synoptic section, above.

Subjects should be seen for all visits on the designated day with an allowed "visit window" as shown below:

1. Baseline visit assessments (V2, Day -1, Week -1) can be started from Day -6.
2. Visit V3 (Day 1, Week 1) should occur within 7 days after the Baseline visit (V2, Day -1, Week -1)
3. Subsequent visits starting from V4 up to V12 in Cohorts 1 and 2, or from V4 up to V15 in Cohort 3, inclusive: ±3 day
4. Visits V13 , V14 and V777 in Cohorts 1 and 2, or V16, V17, V18 and V777: ±7 days

Every effort should be made to take the pharmacokinetic samples at the protocol specified time. When assessments are scheduled to be performed at the same time-point, these will be taken after the pharmacokinetic sample and other blood samples.

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.

At a minimum, subjects will be contacted for safety evaluations during the 30 days following the last study visit or following the last administration of study treatment if there are post-treatment follow-up visits (whichever is later), including a final contact at the 30-day point. Documentation of attempts to contact the subject should be recorded in the source documentation.

6.1 Dietary, fluid and other restrictions

Subjects should maintain their usual diet and life habits during the entire study.

6.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data to be collected on all subjects include: date of birth, age, sex, race, predominant ethnicity.

Relevant medical history/current medical conditions data includes data until signature of informed consent. Where possible, diagnoses and not symptoms will be recorded.

The date of original diagnosis of primary Sjögren's syndrome should be recorded.

Hepatitis screen, HIV screen

All subjects will be screened for Hepatitis B surface antigen (HBsAg). Screening for Hepatitis C will be based on HCV antibodies.

Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site, e.g., Western blot. Appropriate subject counseling will be made available by the Investigator in the event of a positive finding. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator.

Results will be available as source data and will not be recorded within the eCRF.

Alcohol test, Drug screen

Subjects will be tested for substances of abuse (e.g., alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates).

Results will be available as source data and will not be recorded within the eCRF.

6.3 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with CFZ533, as detailed in Section 6.6.

6.4 Efficacy / Pharmacodynamic assessments

Exploratory clinical efficacy measurements will include components of the ESSDAI and of the ESSPRI and other patient-based assessments, Corporate Confidential Information

6.4.1 ESSDAI

The ESSDAI (Appendix 4) is an established disease outcome measure for Sjögren's syndrome.

The instrument contains 12 organ-specific domains contributing to disease activity. For each domain, features of disease activity are scored in 3 or 4 levels according to their severity. These scores are then summed across the 12 domains in a weighted manner to provide the total score.

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6.4.2 ESSPRI

The ESSPRI (Appendix 5) is an established disease outcome measure for Sjögren's syndrome that will be applied to the study patients.

6.4.3 SF-36 – Cohorts 1 and 2 only

The Short Form (36) Health Survey (SF-36) is a survey evaluating individual patients' health status which also monitors and compares patients' disease burden.

The SF-36 consists of eight scaled scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health), which are the weighted sums of the questions in their section.

6.4.4 MFI – Cohorts 1 and 2 only

The Multidimensional Fatigue Inventory (MFI) is a 20-item self-report instrument designed to measure fatigue covering the following dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity.

6.5 Safety

6.5.1 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.

Information for all physical examinations must be included in the source documentation at the study site and will not be recorded the eCRF. Significant findings that are present prior to informed consent are included in the Relevant Medical History eCRF. Significant findings observed after informed consent signature which meet the definition of an Adverse Event must be appropriately recorded on the Adverse Event eCRF.

6.5.2 Vital signs

Vital signs include blood pressure (BP) and pulse measurements. After the subject has been sitting for at least 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured using a validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

If heart-rate or blood pressure is out-of-range at screening or baseline, the Investigator may obtain two additional readings**,** so that a total of up to three consecutive assessments are made, with the subject seated quietly for approximately five minutes preceding each repeat assessment. ***At least the last reading must be within the ranges provided above in order for the subject to qualify.***

6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

6.5.4 Laboratory evaluations

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a **protocol-specified range** at screening or baseline, the assessment may be repeated once prior to randomization. If the repeat value remains outside of protocol-specified ranges, the subject is excluded from the study.

In the case where a laboratory range is **not specified by the protocol**, but is outside the reference range for the laboratory at screening or baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization.

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

Clinically 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 adverse event 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.

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (e.g., neutrophils, basophils, eosinophils, monocytes, lymphocytes) and platelet count will be measured.

6.5.4.2 Clinical chemistry

Albumin, alkaline phosphatase, total bilirubin, bicarbonate/CO_2, calcium, cholesterol, chloride, creatinine, CK, γ-GT, glucose, LDH, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, urea/BUN and uric acid.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

6.5.4.3 Urinalysis

A midstream urine sample (approximately 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

A semi-quantitative "dipstick" evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood.

If the dipstick result is positive for protein, nitrite, leucocytes or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts.

6.5.4.4 Coagulation test

Prothrombin time (PT), activated partial thromboplastin time (aPTT) will be measured. Additional parameters, e.g., INR, may be assessed at Investigator's discretion.

6.5.4.5 C-Reactive Protein (CRP)

C-reactive protein (CRP) will be assessed.

6.5.4.6 Auto-antibodies

ANA, Rheumatoid factor (RF), anti-SSA, anti-SSB, and anti-dsDNA antibodies will be assessed.

6.5.4.7 Serum IgG and IgM

Serum total immunoglobulin G (IgG) and M (IgM) will be assessed in the study.

6.5.6 Electrocardiogram (ECG)

The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12 lead ECGs are collected. The original ECGs, appropriately signed, should be collected and archived at the study site.

Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, be appropriately signed and dated to confirm review and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant ECG findings prior to dosing with investigational treatment must be discussed with the Sponsor.

Clinically significant abnormalities should be recorded on the relevant section of the medical history/Current medical conditions/AE eCRF page as appropriate.

The eCRF will contain:

- date and time of ECG
- heart rate
- PR interval
- QT uncorrected
- QTcF
- QRS duration.

6.5.7 Pregnancy

Pregnancy tests are required of all female subjects regardless of reported reproductive / menopausal status.

Serum pregnancy tests will be performed at screening, baseline and at the end of the study. At all other times urine pregnancy tests may be used.

If a urine pregnancy test is performed and is found to be positive, this will require immediate performing a serum β-hCG. If positive, the Sponsor and Investigator will decide if discontinuation from the trial is required or whether study assessments can continue without compromising the patient's safety.

When performed at screening and at baseline, the result of this test must be received before the subject may be dosed.

6.5.8 Other safety assessments

6.5.8.1 PPD skin test or QuantiFeron test

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

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

Precautions against tuberculosis should be handled according to the best medical practice consistent to the local standards in each country with prior consultation with Novartis. Patients requiring administration of antibiotics against latent tuberculosis should complete their treatment and should be considered cured prior to being re-considered for entry into this study (consultation with Novartis must occur before allowing the patient to enter the study).

Based on the study site's normal practice, QuantiFeron test may replace PPD skin test at screening. A positive QuantiFeron test at screening will exclude the subjects from the participation in the study.

T-SPOT or other types ELISPOT assays based on interferon-gamma release may also be used for tuberculosis diagnosis as per local practice.

Results will be available as source data and will not be recorded within the eCRF.

6.5.8.2 Infections

All occurrences of infections must be carefully monitored by the investigator. Significant findings, which meet the definition of infection, must be recorded in the Adverse Event eCRF.

6.6 Pharmacokinetic assessments

See Sample log tables Appendix 1.

6.6.1 PK Blood collection and processing

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. In Cohort 2 (i.v. regimen) and Cohort 3,treatment arm 2 (i.v. dose on Day 1), the PK, PD and IG samples should be taken from a different arm than the one used for i.v. infusion.

All samples will be given a unique sample number and a collection number (as listed in the blood log Appendix 1). The actual sample collection date and time will be entered on the PK blood collection page of the eCRF. Sampling problems will be commented in the eCRFs.

The details of sample processing, handling, storage, and shipment will be described in a separate laboratory manual.

6.6.2 Pharmacokinetic analytical method

The analytical method to assess free CFZ533 concentrations (target based ELISA assay) will be described in a separate laboratory manual.

6.6.3 Pharmacokinetic parameters

For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.

If data permit, the following pharmacokinetic parameters (non-exhaustive list) of CFZ533 will be determined using the actual recorded sampling times and non-compartmental method(s) with WinNonlin Pro (Version 5.2 or higher): Cmax's, Cmin's, Ctrough's, Tmax, and AUCs from the plasma concentration-time data.

Concentrations below the LLOQ will be treated as zero for PK parameter calculations. The linear trapezoidal rule will be used for AUC calculation.

6.7 Other assessments

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7 Safety monitoring

7.1 Adverse events

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

For all subjects who have signed informed consent and are entered into the study will have all adverse events **occurring after informed consent is signed** recorded on the Adverse Event eCRF.

Pre-existing medical conditions/diseases (i.e., Medical History(ies)) are considered AEs if they worsen after providing written informed consent. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, or are considered clinically significant, or they require therapy.

The occurrence of adverse events should 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, laboratory test, or other assessments.

Clinically significant abnormal laboratory values or test results should 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 to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver related events are included in Appendix 3. Adverse events must be recorded on the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

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 (no/yes), or indistinguishable
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported
4. whether it constitutes a serious adverse event (SAE)
5. action taken regarding study treatment
6. its duration (e.g., start and end date)
7. whether it constitutes a serious adverse event (SAE)
8. action taken regarding study treatment
9. whether other medication or therapies have been taken (concomitant medication/non-drug therapy)

10. its outcome.

An SAE is defined as any AE which meets any one of the following criteria:

- is fatal or life-threatening
- 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 form
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

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

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e., further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event eCRF.

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

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the informed consent and should be discussed with the subject during the study as needed.

7.2 Serious adverse event reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow up information) is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to study treatment complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

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 investigational treatment a Drug Safety and Epidemiology 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 investigational 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.

7.3 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Liver events are divided into two categories:

- Liver events of special interest (AESI) which consist of elevated liver function tests LFTs.

- Medically significant liver events which are considered as serious adverse events (SAEs) and which consist of marked elevations of LFTs.

Please refer to Table 15-1-Appendix 3 for complete definitions of liver events.

Any liver event which meets the criteria for a "**medically significant**" event should follow the **standard procedures for SAE reporting** as described in Section 7.2.

Every liver event as defined in Table 15-1-Appendix 3 should be followed up by the investigator or designated personnel at the trial site, as summarized below and detailed in Table 15-2-Appendix 3.

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the subject 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 should be recorded as appropriate in the eCRF.

7.4 Pregnancy reporting

To ensure subject safety, each pregnancy occurring while the subject is on study treatment 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 on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome.

Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.5 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigators. Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical sites are participating in the clinical study, the Sponsor will advise the Investigators at all sites in writing (e-mail) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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 form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety 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.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to Novartis or the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the subject data for archiving at the investigational site.

All data captured for this study will have an external originating source (either written or electronic), the eCRF is not considered as source.

In general the eCRF is not used as source. If the eCRF will be used as source (i.e., no prior written or electronic record of data), then the protocol must clearly identify these data.

8.3 Database management and quality control

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

Novartis staff (or CRO working on behalf of Novartis) review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff who will make the correction to the database.

Concomitant medications entered into the database will be coded using the 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. At the conclusion of a non-IRT study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis. The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis.

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8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

9.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment received.

The full analysis set will include all subjects that received any study drug.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with available PK data and no protocol deviations with relevant impact on PK data.

The PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data.

9.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and subject.

9.4 Analysis of the primary variable(s)

The primary aims of this study are to assess the safety of multiple intravenous infusion of CFZ533 in patients with pSS, and to investigate the effect of multiple intravenous infusion of CFZ533 based on ESSDAI at Week 13. Statistical analysis model will include data on the ESSDAI from all time points up to Week 13 and will provide the comparison at Week 13.

Summaries of safety and tolerability data will be provided as detailed in Section 9.5.2.

9.4.1 Variable(s)

The primary efficacy variable is the ESSDAI change from baseline.

9.4.2 Statistical model, hypothesis, and method of analysis

It is assumed that the ESSDAI will follow an approximate normal distribution. If this assumption appears to not be met, alternative statistical methods may be applied. These will be described full in the Reporting and Analysis Plan (RAP).

The analysis of the data for primary variable will be conducted combining data from both Cohorts 1 and 2. As a result, the three treatments under consideration would be Placebo (pooled), CFZ533 s.c. and CFZ533 i.v. A longitudinal model describing ESSDAI change from baseline over time will be fitted for the controlled part of the

study (up to Week 13) with the following covariates: baseline ESSDAI, baseline prednisone dose, treatment (three as mentioned above), time as a continuous factor and a quadratic time effect, as well as a random intercept, a random slope and a random quadratic effect for subject. An unstructured covariance matrix for the random effects will be fitted along with an independent error matrix. The change from baseline in ESSDAI at Week 13 (end of placebo-controlled period) will be estimated from the model for all treatments and the difference between treatments to placebo will be presented along with 80% confidence intervals. Inference will be done in the frequentist framework.

The results from the primary analysis will be assessed against the following efficacy criteria to support internal decision making (inference is done in the frequentist framework):

- a statistically significant reduction in ESSDAI at Week 13 in the CFZ533 i.v. group compared to placebo, at the one-sided 10% significance level, and
- an estimated mean reduction in ESSDAI in the CFZ533 i.v. group to be 5 points or greater than placebo.

The decrease of 5 points was chosen because it is in the range of what was observed at week 12 in a small open-label study with rituximab (Meiners et al 2012). A positive sign of efficacy will be considered if both criteria are met.

ESSDAI data after Week 12 will be summarized using descriptive statistics and displayed graphically. ESSDAI data from cohort 3 will also be summarized using descriptive statistics. More details will be described in the RAP.

9.4.3 Handling of missing values/censoring/discontinuations

All subjects with a baseline ESSDAI and at least one post-baseline ESSDAI will be included in the primary analysis. The planned mixed effects model assumes that missing values are missing at random. The guidelines for subject discontinuation given in Section 5.5.10 should ensure that the missingness mechanism is as close as possible to missing at random.

9.4.4 Supportive analyses

Other models than the one specified in Section 9.4.2 may be considered: time would be modeled as categorical variable if the time course doesn't appear to be quadratic.

Simpler covariances than the unstructured one may also be considered if needed.

9.5.2 Safety

Vital signs

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

Infections

The frequency of infections will be tabulated and compared between treatment groups with Fisher's exact test.

9.5.3 Pharmacokinetics

Plasma CFZ533 concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics. A geometric mean will not be reported if the dataset includes zero values.

Pharmacokinetic parameters will be calculated as described in Section 6.6.3 and will be listed by treatment and subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented.

A dose-independent, model-based analysis considering both i.v. and s.c. PK data may be performed as appropriate and will be reported in a separate, standalone modeling and simulation report. During modeling of PK data, the broad principles outlined in the FDA Guidance for Industry: Population Pharmacokinetics, will be followed.

9.5.4 Pharmacokinetic / pharmacodynamic interactions

PK/PD analysis Corporate Confidential Information will be explored graphically. Modeling of s.c. and i.v. PK/PD data using a population approach may be performed as appropriate and will be reported in a separate, standalone report.

These data will be summarized by cohort, treatment and subject. Descriptive statistics will also be provided such as mean, median, standard deviation, minimum and maximum, by time point, treatment and cohort.

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9.6 Sample size calculation

Cohorts 1 and 2

With 24 patients in the analysis of the primary efficacy variable (16 in the CFZ533 group and 8 in the placebo group), the study would have around 1% chance of having a false-positive result, i.e., of meeting both the efficacy criteria when the true difference between CFZ533 and placebo is zero. Additionally the chances of meeting both the efficacy criteria remain below 10% for true differences between CFZ533 and placebo of less than 2 points.

The study would have approximately 83% chance of meeting both the efficacy criteria, when the true difference between CFZ533 and placebo is 7 points.

In case the true difference between CFZ533 and placebo is only 5 points, the study would have approximately 51% chance of meeting both the efficacy criteria. These calculations assume that the primary efficacy variable, ESSDAI, follows a normal distribution with a standard deviation of 5. This estimate of the standard deviation is based on a study of rituximab in patients with primary Sjögren's syndrome (Meiners et al 2012) in which the observed standard deviation ranged from 5 at baseline to 3-7 post baseline.

With 24 patients (16 in the CFZ533 group and 8 in the placebo group), the study would have around 38% power (resp. 70% power) to detect an increase of 30% (resp. 42%) in the infection rate in the CFZ533 group, assuming a background rate of 5% on placebo.

The probabilities to observe a certain number of adverse events in each treatment arm, with this sample size, given assumed event rates, are given in Table 9-1 below:

Table 9-1 Probability of observing a certain number of adverse events in the study given assumed underlying rates

Underlying true adverse event rate (in both treatment arms)	Probability to observe at least 4/16 patients with AEs on active arm	Probability to observe at least 2/8 patients with AEs on placebo	Probability to observe at least 8/16 patients with AEs on active arm	Probability to observe at least 4/8 patients with AEs on placebo
20%	0.402	0.497	0.007	0.056
35%	0.866	0.831	0.159	0.294
50%	0.989	0.965	0.598	0.637

The estimated difference in AE rates along with 90% confidence intervals, given a certain number of observed adverse events in each treatment arm, are given in Table 9-2 below:

Table 9-2 Estimated difference in AE rates when observing a certain number of adverse events in the study

Number of patients with AE observed on active arm (out of 16)	Number of patients with AE observed on placebo (out of 8)	Estimated difference in AE rates along with the 90% confidence interval
4	2	0 (-0.308, 0.308)
8	2	0.25 (-0.075, 0.575)
12	2	0.5 (0.192, 0.808)

Calculations have been made with R 2.8.1 and NQuery 7.0.

Cohort 3

With data from 10 patients in a treatment arm, the 90% confidence interval of PK concentrations at a given time-point is expected to be within 86% to 116% of the observed geometric mean with 90% coverage probability. A coefficient of variation of 20% was assumed in this calculation. With coefficients of variation of 30%, 40% and 50%, the 90% confidence intervals are expected to be within 80% to 149%, 75% to 133% and 70% to 142% of the observed geometric mean, respectively.

To allow for a drop-out rate of 15%, approximately 24 patients will be recruited into this cohort.

Sample size calculations were performed using NQuery 7.0 based on log-transformed PK concentrations.

9.7 Power for analysis of key secondary variables

Cohorts 1 and 2

With 24 patients (16 in the CFZ533 group and 8 in the placebo group), the study would have approximately 83% chance of detecting a decrease of 2 points in the ESSPRI, assuming a normal distribution with a standard deviation of 2 for the variable. The standard deviation is based on Meiners et al (2012), in which the observed standard deviation ranged from 2.2 at baseline to 1.9-2.2 to post baseline.

Calculations have been made with NQuery 7.0.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented 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 Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent. If incapable of doing so, after such consent has been provided by a legally acceptable representative of the subject. In cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

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

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential should be informed that taking the study drug 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 requirement for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered in the study.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

10.3 Responsibilities of the investigator and IRB/IEC

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

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If the 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/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. **Only amendments that are required for subject safety may be implemented prior to IRB/IEC/REB approval.** Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the Health Authorities (where required) and the IRB/IEC/REB at the study site should be informed within 10 working days or less, if required by local regulation.

12 References

Available upon request

De Vita S, Lorenzon G, Rossi G, et al (1992) Salivary gland echography in primary and secondary Sjögren's syndrome. Clin Exp Rheumatol; 10:351–6.

Dimitriou ID, Kapsogeorgou EK, Moutsopoulos HM, et al (2002) CD40 on salivary gland epithelial cells: high constitutive expression by cultured cells from Sjögren's syndrome patients indicating their intrinsic activation. Clin Exp Immunol; 127(2):386-92.

Goldwater R, Keirns J, Blahunka P, et al (2013) A Phase 1, randomized ascending single-dose study of antagonist anti-human CD40 ASKP1240 in healthy subjects. Am J Transplant; 13:1040-6.

Harland R, Klintmalm G, Yang H, et al. (2015) ASKP1240 in De Novo Kidney Transplant Recipients. Am J Transplant;15(S3):Abstract # 3012.

Kaufman I, Schwartz D, Caspi D, et al (1999) Sjögren's syndrome - not just Sicca: renal involvement in Sjögren's syndrome. Ann Rheum Dis.58:253-6.

Kawai T, Andrews D, Colvin RB, et al (2000) Thromboembolic complications after treatment with monoclonal antibody against CD40 ligand. Nat Med; 6:114.

Komaroff AL, Fagioli LR, Doolittle TH, et al (1996) Health status in patients with chronic fatigue syndrome and in general population and disease comparison groups. Am J Med; 101:281-90.

Kuenstner S, Langelotz C, Budach V, et al (2002) The comparability of quality of life scores. A multititrait multimethod analysis of the EORTC QLQ-C30, SF-36 and FLIC questionnaires. Eur J Cancer; 38:339-48.

Manganelli P, Fietta P (2003) Apoptosis and Sjögren syndrome. Semin Arthritis Rheum. 33(1):49-65.

Meijer JM, Meiners PM, Vissink A, et al (2010) Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum; 62:960-8.

Meiners PM, Arends S, Brouwer E, et al (2012) Responsiveness of disease activity indices ESSPRI and ESSDAI in patients with primary Sjögren's syndrome treated with rituximab. Ann Rheum Dis; 71:1297-302.

Moerman RV, Arends S, Meiners PM, et al (2014) EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) is sensitive to show efficacy of rituximab treatment in a randomised controlled trial. Ann Rheum Dis; 73:472-4.

Pijpe J, Kalk WW, Bootsma H, et al (2007) Progression of salivary gland dysfunction in patients with Sjögren's syndrome. Ann Rheum Dis; 66:107-12.

Segal B, Bowman SJ, Fox PC, et al (2009) Primary Sjögren's Syndrome: health experiences and predictors of health quality among patients in the United States. Health Qual Life Outcomes; May 27; 7:46.

Sellam J, Proulle V, Jüngel A, et al (2009) Increased levels of circulating microparticles in primary Sjögren's syndrome, systemic lupus erythematosus and rheumatoid arthritis and relation with disease activity. Arthritis Res Ther; 11:R156.

Seror R, Ravaud P, Bowman SJ, et al (2011) Corrections to Seror R et al 69(6):1103. Ann Rheum Dis 70:880 doi:10.1136/ard.2009.110619corr1.

Tishler M, Yaron I, Shirazi I, et al (2008) Hydroxychloroquine treatment for primary Sjögren's syndrome: its effect on salivary and serum inflammatory markers. Scand J Rheumatol. 37:213-8.

Toubi E, Shoenfeld Y (2004) The role of CD40-CD154 interactions in autoimmunity and the benefit of disrupting this pathway. Autoimmunity; 37:457-64.

Vitali C, Bombardieri S, Jonsson R, et al (2002) Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis; 61:554-558.

Vossenkämper A, Lutalo PM, Spencer J (2012) Translational Mini-Review Series on B cell subsets in disease. Transitional B cells in systemic lupus erythematosus and Sjögren's syndrome: clinical implications and effects of B cell-targeted therapies. Clin Exp Immunol; 167:7-14.

Vosters O, Beuneu C, Nagy N, et al (2004) CD40 expression on human pancreatic duct cells: role in nuclear factor-kappa B activation and production of pro-inflammatory cytokines. Diabetologia; 47:660-8.

Winzer M, Aringer M. (2010) Use of methotrexate in patients with systemic lupus erythematosus and primary Sjögren's syndrome. Clin Exp Rheumatol. 28 (5 Suppl 61):S156-9.

Youinou P, Pers JO (2012) Latest update on the primary Sjögren's syndrome. Presse Med; 41 (9 pt 2):e437-439.

14 Appendix 2: Sample labeling and shipping information

Sample labeling and shipping instructions will be provided in a separate laboratory manual.

15 Appendix 3: Liver event definitions and follow-up requirements

Table 15-1 Liver Event Definitions

	Definition/ threshold
Adverse event of special interest	
Laboratory values	ALT or AST > 3 x ULN
	ALP > 2 x ULN
	TBL > 1.5 x ULN
Medically significant event (SAE)	
Laboratory values	ALT or AST > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction])
	ALP > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction])
	TBL > 3 x ULN
	Potential Hy's Law cases (defined as ALT/AST > 3 x ULN and TBL > 2 x ULN [mainly conjugated fraction] without notable increase in ALP to > 2 x ULN)
Adverse events	Any clinical event of jaundice (or equivalent term)
	ALT or AST > 3 x ULN accompanied by general malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any event that links to a preferred term (PT) in the MedDRA dictionary falling under the SMQ sub-module "Drug-related hepatic disorders – severe events only"* or any "Hy's law case" PT

*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.

Table 15-2 Liver Event Follow Up Requirements

Criteria	Event type	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	Medically significant	Discontinue the study drug immediately Hospitalize, if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST			
> 8 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists for *more than 2 weeks*, discontinue the study drug Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 x ULN accompanied by symptoms[b]	Medically significant	Discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Investigator & Novartis Repeat LFT once or twice in the week If elevation persists, establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 3 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
ALP (isolated)			
> 5 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, report to Novartis as an SAE Establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

Criteria	Event type	Actions required	Follow-up monitoring
> 2 to ≤5 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Investigator & Novartis Repeat LFT once or twice in the weekIf elevation persists, establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 2 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
TBL (isolated)			
> 3 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 3 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Novartis Repeat LFT once or twice in the weekIf elevation persists, establish causality	investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 1.5 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
Preferred terms			
Jaundice	Medically significant	Discontinue the study drug immediately Hospitalize the patient Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
"Drug-related hepatic disorders - severe events only" SMQ AE	Medically significant	Discontinue the study drug hospitalization if clinically appropriate Report to Novartis as an SAE Establish causality	Investigator discretion

[a] Elevated ALT/AST > 3 x ULN and TBL > 2 x ULN but with no notable increase in ALP to > 2 x ULN

[b] General malaise, fatigue, abdominal pain, nausea, or vomiting, rash with eosinophilia

[c] Resolution is defined as an outcome of one of the following: return to baseline values, stable values at three subsequent monitoring visits at least 2 weeks apart, remain at elevated level after a maximum of 6 months, liver transplantation, and death.

16 Appendix 4: ESSDAI

Table 16-1 The EULAR Sjögren's syndrome disease activity index (ESSDAI): domain and item definitions and weights

Domain [weight]	Activity level	Description
Constitutional [3]	No = 0	Absence of the following symptoms
Exclusion of fever of infectious origin and voluntary weight loss	Low = 1	Mild or intermittent fever (37.5–8.5°C)/night sweats and/or involuntary weight loss of 5-10% of body weight
	Moderate = 2	Severe fever (>38.5°C)/night sweats and/or involuntary weight loss of >10% of body weight
Lymphadenopathy [4]	No = 0	Absence of the following features
Exclusion of infection	Low = 1	Lymphadenopathy ≥1 cm in any nodal region or ≥2 cm in inguinal region
	Moderate = 2	Lymphadenopathy ≥2 cm in any nodal region or ≥3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging)
	High = 3	Current malignant B-cell proliferative disorder
Glandular [2]	No = 0	Absence of glandular swelling
Exclusion of stone or infection	Low =1	Small glandular swelling with enlarged parotid (≤3 cm), or limited submandibular or lachrymal swelling
	Moderate = 2	Major glandular swelling with enlarged parotid (>3 cm), or important submandibular or lachrymal swelling
Articular [2]	No = 0	Absence of currently active articular involvement
Exclusion of osteoarthritis	Low = 1	Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min)
	Moderate = 2	1–5 (of 28 total count) synovitis
	High = 3	≥6 (of 28 total count) synovitis

Domain [weight]	Activity level	Description
Cutaneous [3]	No = 0	Absence of currently active cutaneous involvement
Rate as 'no activity' stable long-lasting features related to damage	Low = 1	Erythema multiforma
	Moderate = 2	Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus
	High = 3	Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis
Pulmonary* [5]	No = 0	Absence of currently active pulmonary involvement
Rate as 'no activity' stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use, etc)	Low = 1	Persistent cough or bronchial involvement with no radiographic abnormalities on radiography or radiological or HRCT evidence of interstitial lung disease with no breathlessness and normal lung function test
	Moderate = 2	Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NYHA II) or abnormal lung function tests restricted to 70%>DL_{CO}≥40% or 80%>FVC≥60%
	High = 3	Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NHYA III, IV) or with abnormal lung function tests DL_{CO}<40% or FVC<60%
Renal [5]	No = 0	Absence of currently active renal involvement with proteinuria <0.5 g/day, no haematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage
Rate as 'no activity' stable long-lasting features related to damage and renal involvement not related to the disease.	Low = 1	Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/day) and without haematuria or renal failure (GFR ≥60 ml/min)
If biopsy has been performed, please rate activity based on histological features first	Moderate = 2	Moderately active renal involvement, such as tubular acidosis with renal failure (GFR <60 ml/min) or glomerular involvement with proteinuria between 1 and 1.5 g/day and without haematuria or renal failure (GFR ≥60 ml/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate
	High = 3	Highly active renal involvement, such as glomerular involvement with proteinuria >1.5 g/day or haematuria or renal failure (GFR <60 ml/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinaemia-related renal involvement

Domain [weight]	Activity level	Description
Muscular* [6]	No = 0	Absence of currently active muscular involvement
Exclusion of weakness due to corticosteroids	Low = 1	Mild active myositis shown by abnormal EMG or biopsy with no weakness and creatine kinase (N<CK≤2N)
	Moderate = 2	Moderately active myositis confirmed by abnormal EMG or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N<CK≤4N)
	High = 3	Highly active myositis shown by abnormal EMG or biopsy with weakness (deficit ≤3/5) or elevated creatine kinase (>4N)
PNS* [5]	No = 0	Absence of currently active PNS involvement
Rate as 'no activity' stable long-lasting features related to damage or PNS involvement not related to the disease	Low = 1	Mild active peripheral nervous system involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia
	Moderate = 2	Moderately active peripheral nervous system involvement shown by NCS, such as axonal sensorimotor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinamic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (maximal motor deficit of 4/5 or mild ataxia) Or cranial nerve involvement of peripheral origin (except trigeminal (V) neuralgia)
	High = 3	Highly active PNS involvement shown by NCS, such as axonal sensorimotor neuropathy with motor deficit ≤3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex, etc.), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment: motor deficit ≤3/5 or severe ataxia
CNS* [5]	No = 0	Absence of currently active CNS involvement
Rate as 'no activity' stable long-lasting features related to damage or CNS involvement not related to the disease	Moderate = 2**	Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or confirmed cognitive impairment
	High = 3	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischaemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit

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

CIDP, chronic inflammatory demyelinating polyneuropathy; CK, creatine kinase; CNS, central nervous system; DL_{CO}, diffusing CO capacity; EMG, electromyogram; EULAR, European League Against Rheumatism; FVC, forced vital capacity; GFR, glomerular filtration rate; Hb, haemoglobin; HRCT, high-resolution computed tomography; IgG, immunoglobulin G; NCS, nerve conduction studies; NHYA, New York Heart Association classification; Plt, platelet; PNS, peripheral nervous system.

*Clinical investigator subjective scoring based on availability of concurrent clinical data.

**Seror et al 2011

***CH100 may be used instead of CH50

17 Appendix 5: ESSPRI

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

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

Please take care to answer the questions. The questions marked'*' are optional (questions 4-21).

Example:

No pain ☐ ☐ ☐ ☐ ☐ ☐ ☒ ☐ ☐ ☐ ☐ Maximal imaginable pain

0 1 2 3 4 5 6 7 8 9 10

EVALUATION SCALES

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

   No dryness ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Maximal imaginable dryness

   0 1 2 3 4 5 6 7 8 9 10

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

   No fatigue ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Maximal imaginable fatigue

   0 1 2 3 4 5 6 7 8 9 10

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

   No pain ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Maximal imaginable pain

   0 1 2 3 4 5 6 7 8 9 10

4. *How severe has your **mental fatigue** (not thinking clearly, finding it hard to concentrate, forgetting things, or making mistakes) been during the last 2 weeks?

   No pain ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Maximal imaginable mental fatigue

   0 1 2 3 4 5 6 7 8 9 10

5. *How severe has your **ocular** (eye) **dryness** been during the last 2 weeks?

   No dryness ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Maximal imaginable dryness

   0 1 2 3 4 5 6 7 8 9 10

6. *How severe has your **oral** (mouth) **dryness** been during the last 2 weeks?

   No dryness ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Maximal imaginable dryness

   0 1 2 3 4 5 6 7 8 9 10

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

   No dryness ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Maximal imaginable dryness

   0 1 2 3 4 5 6 7 8 9 10

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

No dryness ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Maximal imaginable dryness
0 1 2 3 4 5 6 7 8 9 10

9. *How severe has your **tracheal** (breathing tubes) **dryness** been during the last 2 weeks?

No dryness ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Maximal imaginable dryness
0 1 2 3 4 5 6 7 8 9 10

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

No dryness ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Maximal imaginable dryness
0 1 2 3 4 5 6 7 8 9 10

If not relevant tick this box ☐

Preliminary Explanation:
You have just evaluated the severity of your symptoms. However, in your everyday life some may be more important to you than others. You are now going to evaluate their importance, try to reflect this distinction in your answers.

11. *Among the following symptoms, please identify the one you consider the **most** in need for improvement (**tick only one box**)

Dryness ☐ **Fatigue** ☐ **Pain** ☐ **Mental Fatigue** ☐

12. *Among the following symptoms, please rank them by priority order: - from **1**: the **most** in need of improvement → to **4**: the **least** in need of improvement.

Dryness	**Fatigue**	**Pain**	**Mental Fatigue**
/___/	/___/	/___/	/___/

13. *Among the following dryness symptoms, please identify the one you consider the **most** in need for improvement (**tick only one box**)

Ocular ☐ **Oral** ☐ **Skin** ☐ **Nasal** ☐ **Tracheal** ☐ **Vaginal** ☐

14. *Among the following dryness symptoms, please rank them by priority order: - from **1**: the **most** in need of improvement → to **6**: the **least** in need of improvement.

Ocular	**Oral**	**Skin**	**Nasal**	**Tracheal**	**Vaginal**
/___/	/___/	/___/	/___/	/___/	/___/

15. *How important is it to you to get rid of your dryness?

Not important at all ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Extremely important
0 1 2 3 4 5 6 7 8 9 10

16. *How important is it to you to get rid of your fatigue?

Not important at all ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ Extremely important
0 1 2 3 4 5 6 7 8 9 10

17. *How important is it to you to get rid of your pain?

Not important at all ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Extremely important

18. *How important is it to you to get rid of your mental fatigue?

Not important at all ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Extremely important

19. *Considering now your symptoms related to your Sjögren's syndrome (e.g., dryness, your fatigue, pain and your mental fatigue), as well as their consequences on your professional or personal life, how severe was your Sjögren's syndrome during the last 2 weeks?

Inactive disease ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Very active disease

20. *How long has it taken you to complete this questionnaire?

_____minutes

21. *How easy or difficult have you found it to complete this questionnaire?

Very easy ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Very difficult

Comments

18 Appendix 6: Blinding and unblinding

Randomization data are kept strictly confidential, and are accessible only to authorized personnel, until unblinding of the trial as described in the table below.

Table 18-1 Blinding levels Cohorts 1 and 2

Role	Time or Event						
	1	2	3	4	5	6	7
Drug Supply	UI	UI	UI	UI	UI	UI	UI
Randomization Office	UI	UI	UI	UI	UI	UI	UI
Investigational site unblinded pharmacist	UI	UI	UI	UI	UI	UI	UI
Subject	B	B	B	UI	B	B	UI
Treating Physician	B	B	B	UI	B	B	UI
Primary Investigator	B	B	B	UI	B	B	UI
Unblinded Physician for safety monitoring[1]	B	B	UI	UI	UI	UI	UI
Study Monitor	B	B	B	UI	B	B	UI
Clinical Trial Leader	B	B	B	UI	UI	UG	UI
Data Manager	B	B	B	UI	B	B	UI
PK Bioanalytics	B	UI	UI	UI	UI	UI	UI
PK Expert	B	B	B	UI	UI	UG	UI
Statistician	B	B	B	UI	UI	UI	UI
Translational Medicine Expert	B	B	B	UI	UI	UG	UI
Modeler	B	B	B	UI	UI	UI	UI
Programmer	B	B	B	UI	UI	UI	UI
Novartis decision teams	B	B	B	UI	UG	UG	UI

[1]Note that although the unblinded physician for safety monitoring is permitted to be unblinded, (s)he will not be provided with the randomization list until the interim analysis, in order to prevent accidental unblinding of other investigational site staff.

UG Allowed to be unblinded on treatment group level
UI Allowed to be unblinded on individual patient level
B Remains blinded
1 Generation of randomization list, QC and lock randomization list
2 Patient allocation to treatment
3 Treatment administration
4 Safety emergency event (unblinding of a single subject)
5 Interim analysis (all patients included in the analysis have completed the study)
6 Interim analysis (some patients included in the analysis have not yet completed the study)
7 Database lock

Table 18-2 Blinding levels Cohort 3

Role	Time or Event						
	1	2	3	4	5	6	7
Drug Supply	UI	UI	UI	UI	UI	UI	UI
Randomization Office	UI	UI	UI	UI	UI	UI	UI
Investigational site unblinded pharmacist	UI	UI	UI	UI	UI	UI	UI
Subject	B	B	UI	UI	UI	UI	UI
Treating Physician	B	B	UI	UI	UI	UI	UI
Primary Investigator	B	B	UI	UI	UI	UI	UI
Unblinded Physician for safety monitoring[1]	B	B	UI	UI	UI	UI	UI
Study Monitor	B	B	UI	UI	UI	UI	UI
Clinical Trial Leader	B	B	UI	UI	UI	UI	UI
Data Manager	B	B	UI	UI	UI	UI	UI
PK Bioanalytics	B	UI	UI	UI	UI	UI	UI
PK Expert	B	B	UI	UI	UI	UI	UI
Statistician	B	B	UI	UI	UI	UI	UI
Translational Medicine Expert	B	B	UI	UI	UI	UI	UI
Modeler	B	B	UI	UI	UI	UI	UI
Programmer	B	B	UI	UI	UI	UI	UI
Novartis decision teams	B	B	UI	UI	UI	UI	UI

[1]Note that although the unblinded physician for safety monitoring is permitted to be unblinded, (s)he will not be provided with the randomization list until the interim analysis, in order to prevent accidental unblinding of other investigational site staff.

UG Allowed to be unblinded on treatment group level
UI Allowed to be unblinded on individual patient level
B Remains blinded
1 Generation of randomization list, QC and lock randomization list
2 Patient allocation to treatment
3 Treatment administration
4 Safety emergency event (unblinding of a single subject)
5 Interim analysis (all patients included in the analysis have completed the study)
6 Interim analysis (some patients included in the analysis have not yet completed the study)
7 Database lock