NOVARTIS

Novartis Institutes for BioMedical Research

CDZ173

Clinical Trial Protocol CCDZ173X2203

A randomized, double-blind, placebo-controlled, parallel group study to assess the safety, tolerability, pharmacokinetics and preliminary efficacy of CDZ173 in patients with primary Sjögren's syndrome

Authors: Personal Data

Document type: Amended Protocol version

EUDRACT number: 2014-004616-12

Version number: v01 (Clean)

Development phase: II

Release date: 15-Sep-2016

Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not form part of the Clinical Study Report.

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to Section 9.2 of the protocol for SAE criteria and additional requirements. See also Site Operations Manual for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Drug Safety and Epidemiology (DS&E) within 24 hours after awareness of the SAE
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the Site Operations Manual.

Table of contents

Site Operations Manual (SOM) 2
Notification of serious adverse events 2
Table of contents 3
List of tables 7
List of figures 7
List of abbreviations 8
Pharmacokinetic definitions and symbols 11

Protocol synopsis 14
1 Introduction 17
1.1 Background 17
1.1.1 Phosphoinositide 3-kinases 18
1.1.2 Phosphoinositide 3-kinase delta 18
1.1.3 Relevant data summary 18
1.2 Study purpose 23
2 Study objectives 24
2.1 Primary objective(s) 24
2.2 Secondary objective(s) 24
2.3 Exploratory objective(s) 24
3 Investigational plan 26
3.1 Study design 26
3.2 Rationale of study design 28
3.3 Rationale of dose/regimen, duration of treatment 29
3.4 Rationale for choice of comparator 29
3.5 Purpose and timing of interim analyses/design adaptations 30
3.6 Risks and benefits 30
4 Population 31
4.1 Inclusion criteria 31
4.2 Exclusion criteria 32
5 Restrictions for study subjects 35
5.1 Contraception requirements 35
5.2 Prohibited treatment 35
5.2.1 Other investigational therapies 35
5.2.2 Vaccination 35

5.2.5 Corticosteroids 36
5.3 Drugs to be used with caution 37

5.4 Dietary restrictions and smoking 38
5.4.1 Dietary restrictions 38
5.4.2 Smoking 38
6 Treatment 39
6.1 Study treatment 39
6.1.1 Investigational treatment 39
6.2 Treatment arms 39
6.3 Permitted dose adjustments and interruptions of study treatment 39
6.4 Treatment assignment and randomization 40
6.5 Treatment blinding 40
6.6 Emergency breaking of assigned treatment code 41
6.7 Treatment exposure and compliance 41
6.8 Recommended treatment of adverse events 41
6.9 Rescue medication 42
6.10 Concomitant treatment 42
7 Discontinuation and study completion 42
7.1 Discontinuation of study treatment 42
7.2 Study completion and post-study treatment 43
7.3 Lost to follow-up 43
7.4 Withdrawal of informed consent 44
7.5 Replacement of early withdraws or discontinuations 44
7.6 Study Stopping rules 44
7.7 Early study termination by the sponsor 44
8 Procedures and assessments 45
8.1 Informed consent procedures 48

8.2 Subject screening 48
8.3 Subject demographics/other baseline characteristics 48
8.3.1 Hepatitis/HIV screening 49
8.3.2 Tuberculosis testing 49
8.3.3 Alcohol test, Drug screen 49
8.4 Efficacy 49
8.4.1 ESSPRI 50
8.4.2 ESSDAI 50
8.4.3 SF-36 50
8.4.4 MFI 50
8.4.5 Global assessments (VAS) of disease activity 50
8.4.6 Patient-Reported Outcome 51

Corporate Confidential Information

8.5 Safety 52
8.5.1 Physical examination 52
8.5.2 Vital signs 52
8.5.3 Height and weight 52
8.5.4 Laboratory evaluations 52
8.5.5 Pregnancy and assessments of fertility 54
8.5.6 Other safety evaluations 54
8.6 Pharmacokinetics 54
8.7 Other assessments 55

Corporate Confidential Information

9 Safety monitoring 58
9.1 Adverse events 58
9.2 Serious adverse event reporting 59
9.2.1 Definition of SAE 59
9.2.2 SAE reporting 60
9.3 Infection Monitoring 61
9.4 Liver safety monitoring 62
9.5 Renal safety monitoring 65
9.6 Pregnancy reporting 66
9.7 Early phase safety monitoring 67
10 Data review and database management 67

10.1 Site monitoring 67
10.2 Data collection 67
10.3 Database management and quality control 68
10.4 Data Monitoring Committee 69
10.5 Adjudication Committee 69
11 Data analysis 69
11.1 Analysis sets 69
11.2 Subject demographics and other baseline characteristics 69
11.3 Treatments 70
11.4 Analysis of the primary variable(s) 70
11.4.1 Variable(s) 70
11.4.2 Statistical model, hypothesis, and method of analysis 70
11.4.3 Handling of missing values/censoring/discontinuations 70
11.4.4 Supportive analyses 71
11.5 Analysis of secondary and exploratory variables 71
11.5.1 Efficacy / Pharmacodynamics 71
11.5.2 Safety 71
11.5.3 Pharmacokinetics 72
11.5.4 Pharmacokinetic / pharmacodynamic interactions 72
11.5.5 Other assessments 73
11.6 Sample size calculation 74
11.7 Interim analyses 74
12 Ethical considerations 75
12.1 Regulatory and ethical compliance 75
12.2 Responsibilities of the investigator and IRB/IEC 75
12.3 Publication of study protocol and results 75
13 Protocol adherence 75
13.1 Protocol Amendments 76
14 References 77

17 Appendix 3: Blinding and Unblinding 82
18 Appendix 4: Sample Log Table 83
19 Appendix 5: Sample labeling and shipping information 84
20 Appendix 6: ESSDAI 85
21 Appendix 7: ESSPRI 86

22 Appendix 8: SF-36 87
23 Appendix 9: MFI 88

List of tables

Table 8-1 Assessment schedule 45
Table 9-1 Liver Event and Laboratory Trigger Definitions 63
Table 9-2 Follow Up Requirements for Liver Events and Laboratory Triggers ... 64
Table 9-3 Specific Renal Alert Criteria and Actions 66

List of figures

Figure 3-1 Study design 28

List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANA	Anti-nuclear Antibody
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
b.i.d.	twice a day
BM	Biomarker
BMI	Body Mass Index
BUN	blood urea nitrogen
CD-ROM	compact disc – read only memory
CFR	Code of Federal Regulation
CK	creatinine kinase
CRF	Case Report/Record Form (paper or electronic)
CRP	C-reactive protein
CO_2	carbon dioxide
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
CTRD	Clinical Trial Results Database
CV	coefficient of variation

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 index
EULAR	European league against rheumatism
DMARDs	Disease-modifying anti-rheumatic drugs

DMC	Data Monitoring Committee
DSMB	Data safety monitoring board
FIH	First in Human
FDA	Food and Drug Administration
GCP	Good Clinical Practice
γ-GT	Gamma-glutamyl transferase
h	hour
HV	Healthy Volunteer
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL	Interleukin
i.v.	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
LFT	Liver function test
LDH	lactate dehydrogenase
LLQ	lower limit of quantification
LLN	lower limit of normal
MAD	Multiple ascending dose
MedDRA	Medical dictionary for regulatory activities
MFI	Multidimensional fatigue inventory questionnaire
mg	milligram(s)
ml	milliliter(s)
NCDS	Novartis Clinical Data Standards
NTI	narrow therapeutic index
OC/RDC	Oracle Clinical/Remote Data Capture
o.d.	once a day
PA	posteroanterior

PD	pharmacodynamic(s)

PGA	Physician global assessment
PI3Kδ	Phosphoinositide 3-kinases delta
PK	pharmacokinetic(s)
p.o.	oral(ly)
PoC	Proof of concept
pSS	primary Sjögren's syndrome
RAP	Reporting and analysis plan
RBC	red blood cell(s)
REB	Research Ethics Board
RF	Rheumatoid factor
SAD	Single ascending dose
SAE	serious adverse event
s.c.	subcutaneous
SF-36	Short form 36
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SD	standard deviation
SOM	site operations manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
ULN	upper limit of normal
ULQ	upper limit of quantification
VAS	Visual analog scale
WBC	white blood cell(s)
WHO	World Health Organization
WoCBP	Women of child bearing potential

Pharmacokinetic definitions and symbols

AUC0-t	The area under the plasma (or serum or blood) concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]
AUCinf	The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume]
AUClast	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
Cmax,ss	The observed maximum plasma (or serum or blood) concentration following drug administration at steady state [mass / volume]
CL	The systemic (or total body) clearance from plasma (or serum or blood) following intravenous administration [volume / time]
CL/F	The apparent systemic (or total body) clearance from plasma (or serum or blood) following extravascular administration [volume / time]
F	Bioavailability of a compound. Fabs is the absolute bioavailability, i.e. the fraction (or percentage) of the administered extravascular dose systemically available. Frel is the relative bioavailability, i.e. the bioavailability relative to a reference.
Racc	The accumulation ratio
T1/2	The terminal elimination half-life [time]
T1/2,acc	The effective half-life based on drug accumulation at steady state [time]
Tmax	The time to reach the maximum concentration after drug administration [time]
Vz/F	The apparent volume of distribution during the terminal elimination phase following extravascular administration [volume]
Vss	The volume of distribution at steady state following intravenous administration [volume]

Corporate Confidential Information

Corporate Confidential Information

Protocol synopsis

Protocol number	CCDZ173X2203
Title	A randomized, double-blind, placebo-controlled, parallel group study to assess the safety, tolerability, pharmacokinetics and preliminary efficacy of CDZ173 in patients with primary Sjögren's syndrome
Brief title	Safety, tolerability, pharmacokinetics and preliminary efficacy study of CDZ173 in patients with primary Sjögren's syndrome
Sponsor and Clinical Phase	Novartis Phase 2
Intervention type	Drug
Study type	Interventional
Purpose and rationale	This study is designed to evaluate the safety, tolerability, pharmacokinetics and preliminary therapeutic efficacy of oral administrations of CDZ173, a selective PI3K delta inhibitor, for 12 weeks, in patients with primary Sjögren's syndrome. Data from this study will provide the basis for further development of the compound for the treatment of primary Sjögren's syndrome.
Primary Objective(s)	• To assess the safety and tolerability of CDZ173 in patients with primary Sjögren's syndrome. • To compare the effect of CDZ173 versus placebo on the patient-reported outcomes of primary Sjögren's syndrome patients after 12 weeks of treatment
Secondary Objectives	• To assess the pharmacokinetics of CDZ173 in primary Sjögren's syndrome patients • To evaluate the effect of CDZ173 versus placebo on clinical disease outcomes in primary Sjögren's syndrome patients after 12 weeks of treatment • To evaluate the changes in the physician global assessment of the patient's overall disease activity after 12 weeks of treatment. • To evaluate the changes in the patients global assessment of their disease activity after 12 weeks of treatment
Study design	This is a randomized, double-blind, placebo-controlled, parallel group, non-confirmatory study.
Population	Male or female patients with primary Sjögren's syndrome, aged 18 to 75 years. It is planned to enroll approximately 27 patients.
Key Inclusion criteria	• Diagnosis of primary Sjögren's syndrome according to revised EU/US consensus criteria • Moderate to severe disease activity by ESSDAI score ≥ 6 at screening visit; • ESSPRI at screening visit ≥ 5

Key Exclusion criteria	• Secondary Sjögren's syndrome (presence of another connective tissue disease) • Patients having received the following treatments related to randomization time-point: - Oral or i.v. cyclophosphamide within 6 months; - i.v. corticosteroid bolus with dose > 1 mg/kg within 3 months; - Rituximab and other B cell depleting agents within 12 months; for patients who received such drug, their B cell count should be within normal range - Belimumab within 6 months; - Any other biologic within 1 month or five times the half-life; - Any other immunosuppressives such as systemic cyclosporine A or Mycophenolate within 3 months; • History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients; • History of malignancy of any organ system except localized basal cell carcinoma of the skin; • History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection; • History of immunodeficiency diseases; • Any live vaccines (this includes any attenuated live vaccines) starting from 6 weeks prior to randomization. • Female participants need to agree to use highly effective contraception (according to ICH M3)
Investigational and reference therapy	CDZ173 70 mg b.i.d.; matching placebo
Efficacy assessments	• EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI) • EULAR Sjögren's syndrome disease activity index (ESSDAI) • Short Form (36) Health Survey (SF-36) • Multidimensional Fatigue Inventory (MFI) Questionnaire • Physician's and Patient's assessment of global disease activity (Visual Analog Scale, VAS) Corporate Confidential Information
Key safety assessments	• Physical examination • Vital signs • Safety Laboratory(Hematology, Biochemistry, Urinalysis) • Electrocardiogram (ECG) • Adverse Events
Corporate Confidential Information	Corporate Confidential Information

Data analysis	The primary efficacy analysis will be based on a longitudinal mixed model of ESSPRI as a function of baseline ESSPRI, baseline intake of steroids (yes/no, which is a stratification factor for the randomization), treatment, time as a continuous variable (linear and quadratic terms), interaction between treatment and time, as well as a random intercept, random slope and random quadratic effects by subject to account for within-subject correlations. The difference between active treatment and placebo in change from baseline visit in ESSPRI after 12 weeks treatment will be estimated from the model and presented with 80% confidence intervals. Simpler models will also be considered in case the pre-specified model does not fit the data well. The following criteria will be considered indicative of treatment efficacy: - Statistically significant decrease in ESSPRI after 12 weeks on treatment compared to placebo (at one-sided 10% level) - Estimated mean reduction in ESSPRI after 12 weeks treatment of 1 point or more than on placebo The decrease of 1 point is considered clinically relevant as 0.67 – 1 points have been published to be the minimal clinically important improvement. In the absence of a standard of care with demonstrated long-term efficacy, no confirmation is available that a decrease of 1 point will translate into a long-term benefit.
Key words	CDZ173, PI3K pathway, primary Sjögren's syndrome

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). Current hypotheses of the underlying cause of pSS describe a viral triggering infection of the exocrine epithelial cells, resulting in release of autoantigens (Nocturne and Mariette 2013). Plasmacytoid dendritic cells are activated, resulting in release of type 1 interferons and upregulation of toll-like receptors and other innate immune responses leading to B cell activation. Plasmacytoid dendritic cells also release IL-12, leading to T cell activation and generation of Th1- and Th17-mediated inflammation and tissue destruction. Together, the activated B cells and T cells form ectopic lymphoid structures ranging from loose aggregates of lymphocytes to germinal center-like structures wherein plasmablasts and plasma cells generate autoantibodies (e.g., ANA, anti-SSA, anti-SSB, rheumatoid factor) and leading to immune complex formation.

Primary Sjögren's syndrome 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). Most patients (reported as frequently as in 85% of patients) experience profound and disabling fatigue, described as an ever-present, fluctuating, and uncontrollable lack of energy (Mengshoel et al 2014). 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 ineffective, and no pharmacologic intervention is effective against the severe, disabling fatigue. Although small trials with the B cell depleting agent rituximab have demonstrated a degree of therapeutic efficacy in approximately 50% of pSS patients, no proper, large randomized controlled trials have shown clear efficacy in pSS. Thus, a disease modifying agent that prevents secretory gland destruction and addresses extra-glandular disease manifestations would introduce a significant advance for the treatment of pSS.

1.1.1 Phosphoinositide 3-kinases

Phosphoinositide 3-kinases (PI3K) are lipid kinases that are crucial for intracellular signal transduction. Activated through tyrosine kinase coupled receptors and recruited to the plasma membrane, their principal function is the generation of phosphatidylinositol-3,4,5-trisphosphate (PIP3). PIP3 serves as an important cellular second messenger specifically activating Akt (via Phosphoinositide-dependent protein kinase [PDK1]) and regulating a multitude of cellular processes (Kandel and Hay 1999). PI3K are classified according to their structural and functional properties into three classes (IA & B, II and III). All class IA PI3K are heterodimeric molecules composed of an 85 kD regulatory subunit (p85) and one of three different 110 kD catalytic subunits (p110α, p110β and p110δ).

1.1.2 Phosphoinositide 3-kinase delta

PI3Kδ is primarily expressed in hematopoietic cells and is functionally relevant in the adaptive (particularly B cells) and the innate immune system. Specifically, PI3Kδ has been shown to contribute to key elements of autoimmune pathophysiology such as B lymphocyte activation, cytokine secretion, antigen presentation and autoantibody production. Blockade of PI3Kδ impedes B cell activation and lymphocyte germinal center formation as well as immune cell trafficking, therefore supporting the rationale that PI3Kδ–targeted therapy has a strong potential in treating autoimmune diseases, notably also pSS. In addition, specifically targeting PI3Kδ should help to avoid potential side effects associated with ubiquitously expressed PI3Kα and β isoforms (Hirsch et al 2000; Li et al 2000; Sasaki et al 2000; Patrucco et al 2004; Clayton et al 2002; Jou et al 2002).

CDZ173 is an oral, low molecular weight compound that selectively inhibits the lipid kinase PI3Kδ and may therefore be a valid treatment option in pSS.

1.1.3 Relevant data summary

Corporate Confidential Information

1.1.3.1 Preclinical data

Corporate Confidential Information

Corporate Confidential Information

Corporate Confidential Information

Corporate Confidential Information

1.1.3.2 Teratogenicity and reproductive toxicity data

Corporate Confidential Information

Corporate Confidential Information

1.1.3.3 Human safety and tolerability data

Corporate Confidential Information

Corporate Confidential Information

1.1.3.4 Human pharmacokinetic data

Corporate Confidential Information

1.1.3.5 Human pharmacodynamic data

Corporate Confidential Information

Corporate Confidential Information

Corporate Confidential Information

1.2 Study purpose

This study is designed as a proof of concept study of CDZ173 in primary Sjögren's syndrome. The purpose of the present study is to evaluate the safety, tolerability, pharmacokinetics and

preliminary therapeutic efficacy of CDZ173 in patients with pSS. The study outcome will provide data for the further development of CDZ173 in the treatment of pSS.

2 Study objectives

2.1 Primary objective(s)

Objective	Endpoint
• To assess the safety and tolerability of CDZ173 in patients with primary Sjögren's syndrome	• AEs, vital signs, ECGs, safety laboratory parameters (hematology, biochemistry, urinalysis)
• To compare the effect of CDZ173 versus placebo on the patient reported outcome of primary Sjögren's syndrome patients after 12 weeks of treatment (study week 13)	• Change in EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI)

2.2 Secondary objective(s)

Objective	Endpoint
• To assess the pharmacokinetics of CDZ173 in primary Sjögren's syndrome patients	• Single dose (Day 1) CDZ173 PK parameters (including but not limited to Cmax and AUC), and trough evaluation after multiple doses (Days 8, 15, 29, 57 and 85)
• To evaluate the effect of CDZ173 versus placebo on outcomes in primary Sjögren's syndrome patients after 12 weeks of treatment (study week 13)	• EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), 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 after 12 weeks of treatment (study week 13)	• Physician's visual analog scale (VAS)
• To evaluate the changes in the patients global assessment of their disease activity after 12 weeks treatment (study week 13)	• Patient's visual analog scale (VAS)

2.3 Exploratory objective(s)

Corporate Confidential Information

Corporate Confidential Information

Corporate Confidential Information

Corporate Confidential Information

3 Investigational plan

3.1 Study design

This is a double-blind, randomized, placebo-controlled, parallel design, non-confirmatory study to assess the safety, tolerability, pharmacokinetics and preliminary clinical efficacy of multiple oral doses of CDZ173 (70 mg b.i.d.) in patients with pSS.

The study will consist of a 4-week screening period, a baseline period prior to randomization, a 12-week treatment period and a 4-week follow-up period (no study drug or study visits) before the End of Study visit. The total duration for each patient in the study will be approximately 21 weeks.

Approximately 27 patients will be randomized (2:1) to a 12 week treatment receiving either CDZ173 or placebo. Randomization will be stratified according to baseline glucocorticoid intake (yes/no).

For the entire duration of the treatment period (12 weeks), patients will receive a *b.i.d.* dosing regimen to be administered at approximately 12 h intervals.

Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, biochemistry and urinalysis) as well as adverse event and serious adverse event monitoring.

Corporate Confidential Information

Other assessments to be completed are outlined in the Assessment schedule.

Screening and Baseline

For each patient there will be a screening period of up to 28 days (Day -28 to Day -2). The screening visit (V1) may be split over 2 days if it is in the best interest of the patient or for logistical reasons.

Subjects who meet the eligibility criteria at screening visit (V1) will be admitted to baseline evaluations. The baseline visit (V2) will occur at Day -1, but may be extended up to Day 1 to enable all assessments to be completed prior to study drug administration on Day 1 (V3).

Assessments to be completed at Screening and Baseline are outlined in the Assessment schedule.

Randomization and 12 week treatment period

Eligible patients (according to Inclusion and Exclusion criteria in Section 4), will be randomized (via IRT) to receive either CDZ173 or placebo as twice daily (*b.i.d.*) oral doses for 12 weeks. Study treatment will be initiated on Day 1 (Visit V3).

During Day 1 (V3), patients will undergo various pre-dose procedures (including PK and PD and biomarker baseline samples collection) prior to receiving the study drug. Patients will remain at the site for approximately 8 hours post dose for various safety, PK and PD and biomarker assessments at timepoints as outlined in the Assessment schedule.

Patients will then be able to return home to continue their daily treatment regimen (self-administration).

Patients will return to the study site at approximately weekly intervals for the first three weeks (V4, Week 2 and V5, Week 3), then fortnightly for V6 (Week 5) followed by approximately monthly visits for V7 (Week 9) and V8 (Week 13). At each study visit, patients will undergo assessments with various scales/questionnaires, as well as safety, PK and PD and biomarker sampling as indicated in the Assessment schedule and described in Section 8. Patients will be asked to take their morning dose of study drug at the site on these visit days.

All study visits during the treatment period will be ambulatory. However, for logistical reasons, it may be necessary for patients to come to the site the evening before their scheduled assessment visits, or to remain at the site following the visit (e.g. transport restrictions, long travel times from home to site). In these instances, the patients may stay overnight at the site, but this would not be considered as an SAE.

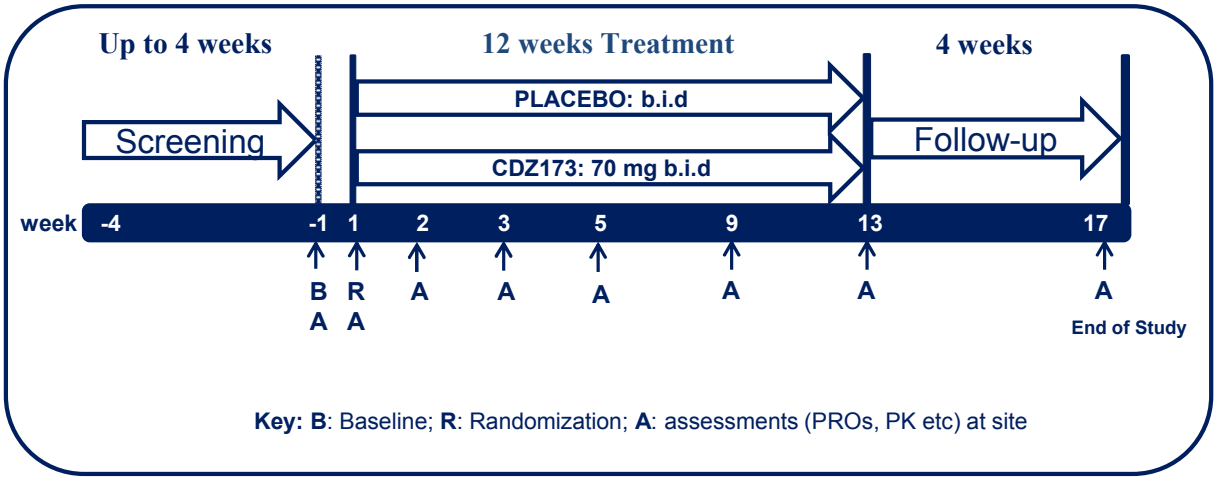
The ambulatory visits may be conducted within an allowed time window as indicated in the Assessment schedule.

Patients will be provided with a patient diary to record study drug self-administration, Adverse Events and concomitant medication use during the treatment period. The Investigator/site staff may contact the patients during the study to ensure compliance/monitor safety by telephone or other means, if it is deemed appropriate.

Follow up and end of study visit (EoS)

After the last day of dosing, patients will enter a 4-week follow-up period without study drug treatment. Patients will then be asked to return to the site at Week 17 for the End-of-Study visit. At this visit, patients will undergo final assessments as indicated in the Assessment schedule. Upon completion of this visit, patients will be discharged from the study.

Figure 3-1 Study design



3.2 Rationale of study design

CDZ173 is an oral, low molecular weight compound that selectively inhibits the lipid kinase PI3Kδ, an important mediator of immune cell activation and germinal center formation. The essential role of PI3Kδ in the adaptive as well as the innate immune system strongly supports the rationale for the PI3Kδ targeted intervention in autoimmune diseases. The interference with germinal center formation further supports expected efficacy in patients with pSS where ectopic germinal centers in salivary glands are considered pathogenically important. This study will be conducted in patients with active pSS, where no established clinically effective disease modifying treatment has been proven effective against the underlying disease.

A randomized, placebo-controlled, double-blind approach is used to eliminate potential bias in reporting safety and clinical efficacy data. Patients will be randomized to CDZ173 or placebo in a 2:1 ratio in order to minimize exposure to placebo and to gather more data on CDZ173. Stratified randomization is done in order to limit imbalances between active and placebo arms in baseline intake of oral corticosteroids.

After the double-blind period, the patients will enter a follow-up period; for which a duration of 4 weeks was chosen to allow sufficient time for safety monitoring.

In addition to safety, efficacy estimated by the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) is chosen as a key endpoint of the study (Seror et al 2011). A decrease of 1.7 points was observed at week 16 in a small open-label study with rituximab (Meiners et al 2012). In a publication the group of Seror reported 0.67 – 1 ESSPRI points to be the minimal clinically important improvement (Seror et al 2016). In addition to the ESSPRI, efficacy estimated by the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) is chosen as a second disease specific endpoint of the study. The ESSDAI assesses organ involvement in patients with pSS and has been shown to be sensitive to suggest efficacy of rituximab treatment in a randomized controlled trial (Moerman et al 2014). Further efficacy assessments include diseases-independent outcome variables (SF-36, MFI, patients' and

physicians' global assessments) Corporate Confidential Information

3.3 Rationale of dose/regimen, duration of treatment

CDZ173 will be administered orally for 12 weeks at a dose of 70 mg b.i.d. and be compared to placebo, also dosed b.i.d. Corporate Confidential Information

Corporate Confidential Information

3.4 Rationale for choice of comparator

Placebo to CDZ173 will be used as a 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 experimental therapy. Since there is no established clinically effective disease modifying treatment for patients with pSS, and considering the relatively limited duration of the trial, use of placebo is considered justified.

3.5 Purpose and timing of interim analyses/design adaptations

Corporate Confidential Information

3.6 Risks and benefits

The PI3K pathway has been identified as a key pathway in inflammation and autoimmunity in preclinical models. Its inhibition by CDZ173 is therefore expected to result in a clinical benefit in patients with active primary Sjögren's syndrome (pSS).

Corporate Confidential Information

Corporate Confidential Information

The risk to patients in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, defined stopping rules and by prohibiting concomitant medication that possibly may lead to significant drug-drug interactions.

A maximum of 420 mL of blood is planned to be collected over a period of about 21 weeks, from each subject as part of the study. Additional samples for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

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.

There may be unknown risks of CDZ173 which may be serious and unforeseen.

4 Population

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

Approximately 27 patients will be randomized to participate in the study.

The investigator must ensure that all patients 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 patients.

Patient selection is to be established by checking through all eligibility 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

Patients 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 or female patient, aged 18 to 75 years, inclusive;
3. Diagnosis of primary Sjögren's syndrome according to revised EU/US consensus criteria (Vitali et al 2002). In the event of new criteria being released, the 2002 criteria version will remain as the reference for diagnostic inclusion criteria;
4. Moderate to severe disease activity as determined by ESSDAI score ≥ 6 at screening visit;
5. ESSPRI at screening visit ≥ 5;

Corporate Confidential Information

8. Patient must be able to communicate well with the investigator, to understand and comply with the requirements of the study.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Secondary Sjögren's syndrome. Patients with laboratory or clinical signs of another connective tissue disease (e.g. systemic lupus erythematous) but not fulfilling the diagnostic criteria for that disease, may be eligible at the Investigators discretion;
2. Use of other investigational drugs at the time of enrollment, or is within 5 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 in the specified timeframe) prior to randomization:
   - Oral or i.v. cyclophosphamide treatment within 6 months of randomization;
   - i.v. corticosteroid bolus with a dose > 1 mg/kg within 3 months of randomization;
   - Rituximab or other B cell depleting drug within 12 months of randomization. For patients who received such drug, their B cell count should be within normal range;
   - Belimumab within 6 months of randomization;
   - Any other biologic within 1 month of randomization or five-times the half-life, whichever is longer;
   - Any other immunosuppressive such as systemic cyclosporine A or mycophenolate within 3 months of randomization;
   - 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 on 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;
5. Require regular or intermittent use of medications that, as judged by the Investigator, can cause dry mouth in the patient, (such as antidepressants, anticholinergics, anti-Parkinson agents, and diuretics);

7. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study. The investigator should make this determination in consideration of the subject's medical history and/or clinical or laboratory evidence of any of the following:
   - Uncontrolled hypertension (≥ 160/95 mmHg)
   - Uncontrolled diabetes (insulin dependent or non-insulin dependent)
   - Congestive heart failure (New York Heart Association status of class III or IV)
   - Severe chronic obstructive pulmonary disease (GOLD stage 3-4)
   - Inflammatory bowel disease, peptic ulcers, gastrointestinal including rectal bleeding
   - Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection
   - Pancreatic injury or pancreatitis
   - Liver disease or liver injury as indicated by abnormal liver function tests such as AST (SGOT), ALT (SGPT), alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria: ALT must NOT exceed 1.5 times upper limit of normal (ULN)
   - History of renal injury/renal disease (e.g. renal trauma, glomerulonephritis, or one kidney only) or presence of impaired renal function as indicated by a serum creatinine level exceeding 1.5 mg/dL (133 μmol/L)
   - Evidence of urinary obstruction or difficulty in voiding at screening
8. Clinically significant abnormal hematology laboratory values at screening:
   - Total white blood cell count (WBC) outside the range of 2.0-15.0 x 10^9/L
   - Platelets <100 x 109/L
   - Hemoglobin <9.0 g/dL
   - Lymphocyte count < 0.8 x 109/L
   - Neutrophil count <1.5 x 10^9/L

11. 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 serum test
12. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study medication and for 2 days after stopping study treatment. Highly effective contraception methods (according to ICH M3) 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), total hysterectomy or tubal ligation at least six weeks before taking study treatment. 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 month prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient;
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
    - In case of use of oral contraception women should have been stabile 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) or tubal ligation at least six weeks before screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment she is considered of not being of child bearing potential
13. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
14. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by a positive QuantiFERON TB-Gold test at Screening. If presence of latent tuberculosis is established then treatment according to local country guidelines must have been completed before patient can be considered for enrollment
15. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result at Screening
16. A positive Hepatitis B surface antigen or Hepatitis C test result at Screening
17. Donation or loss of 400 mL or more of blood within 8 weeks before randomization

18. History or evidence of ongoing alcohol or drug abuse, within the last 12 months before randomization
19. Any live vaccines (this includes any attenuated live vaccines) starting from 6 weeks before study entry, during the study and up to 7 day after the last dose of CDZ173 should be excluded

Note: In the case where a safety laboratory assessment at screening is outside of the range specified above, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the subject is excluded from the study.

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 Restrictions for study subjects

During recruitment, screening/informed consent review, and baseline visit, the subjects must be informed and reminded of the following restrictions:

5.1 Contraception requirements

Please refer to exclusion criteria (Section 4.2) for details of contraception requirements for the study.

5.2 Prohibited treatment

5.2.1 Other investigational therapies

Other investigational therapies must not be used while the patient is on the study. If such agents are required for a patient then the patient must be permanently discontinued from the treatment portion of the study.

5.2.2 Vaccination

Live/Attenuated Vaccination: The study drug is considered to decrease activities of cells of the immune system, thus from 6 weeks prior to randomization, until 7 days after cessation of study treatment, live vaccines (incl. attenuated viruses) are not permitted.

Dead vaccines: Due to the decreased activities of the immune cells, use of dead vaccines is expected to be less effective or ineffective. Patients should be advised that their vaccination may be ineffective if administered within the timeframe specified above. However, patients will not be discouraged from receiving dead vaccines, including the seasonal influenza vaccination.

Patients and physicians are encouraged to plan required vaccinations outside this window.

Corporate Confidential Information

Corporate Confidential Information

5.2.5 Corticosteroids

Corporate Confidential Information

If a systemic corticosteroid dose corresponding to a daily prednisone equivalent > 10 mg is deemed required for longer than 5 days, then the patient will be discontinued from study treatment but will continue in the study.

Systemic dosing of corticosteroids corresponding to a daily prednisolone ≤10 mg is known to be a weak inducer only and is therefore allowed. Patients taking oral systemic corticosteroids have to be on a stable dose of ≤10 mg/d prednisone or equivalent for at least 2 weeks before randomization, and are allowed to continue on a stable dose. Topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases or allergic rhinitis), or eye drops are also allowed.

5.3 Drugs to be used with caution

Corporate Confidential Information

Corporate Confidential Information

5.4 Dietary restrictions and smoking

5.4.1 Dietary restrictions

- Patients should be instructed to take the dose of CDZ173 daily in the morning and in the evening, at approximately the same time each day, except on the days blood collection is scheduled at the clinic, at which time the patients should take their doses at the clinic.
- The morning dose of CDZ173 should be taken at approximately the same time each day when most convenient for the patient. Patients may take CDZ173 irrespective of food intake.
- The evening dose should be taken approximately 12 hours after the morning dose. Patients may take CDZ173 irrespective of food intake.
- CDZ173 should be taken with a glass of water and consumed over as short a time as possible. Patients should be instructed to swallow the capsules whole and not to chew them
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.
- Missed doses should not be made up.

5.4.2 Smoking

It is recommended to reduce or completely refrain from smoking. Smoking status at screening will be recorded in the CRF. Corporate Confidential Information

This restriction does not apply to nicotine gum or electronic cigarettes.

6 Treatment

6.1 Study treatment

Details on the storage and management of study medication, randomization and instructions for prescribing and taking study treatment are outlined in Section 3 of the Site Operations Manual.

6.1.1 Investigational treatment

The investigational drug, CDZ173 (70 mg and matching placebo capsules) will be prepared and supplied by Novartis. Study drug will be provided in blinded packaging in a way that the patient can take the medication home for dosing. Resupply of medication may be required during the study due to shelf-life. Study treatment assignment will be done by an IRT system.

The Investigator, the patient, and the clinical trial team of the Sponsor directly involved in the study will be blinded.

6.2 Treatment arms

Patients will be randomized to CDZ173 or placebo in a 2:1 ratio in order to minimize exposure to placebo and to gather more data on CDZ173. Stratified randomization is done by baseline intake of oral corticosteroids in order to limit imbalances between active and placebo arms.

Study treatments are defined as:

- CDZ173 70 mg as oral capsules , b.i.d. for 12 weeks (84 days)
- CDZ173 matched placebo, oral capsules, b.i.d. for 12 weeks (84 days)

6.3 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments and/or interruptions are not permitted, except in the following case below.

Corporate Confidential Information

However, if study drug dosing was for any reason interrupted for cumulatively more than 28 doses (i.e., 14 days, whether consecutive or not), then the patient will be discontinued from study treatment but will continue in the study. These changes must be recorded on the Dosage Administration Record CRF.

6.4 Treatment assignment and randomization

At Baseline/Randomization visit, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients/subjects and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Randomization will be stratified by use of corticosteroids (yes/no). The randomization scheme for patients will be reviewed and approved by a member of the Randomization Office.

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of patients.

The investigator will enter the screening number and medication number in the eCRF.

6.5 Treatment blinding

This is a double blind study: subjects, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of study treatments.

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, and odor.

The Interim Analysis Team, which can be unblinded to the results at this point, may communicate interim analysis results (e.g. evaluation of efficacy and safety criteria, evaluation of PoC criteria or information needed for planning/modifying another study) to relevant Novartis teams for information, consulting and/or decision purposes. The Interim Analysis Team is defined in the SOM, and includes at a minimum the Trial Statistician, Trial Programmer and the Trial Medical Expert.

Unblinding will only occur in the case of patient emergencies (see Section 6.6), at the time of the interim analysis and at the conclusion of the study.

6.6 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and an email with an onscreen display of the medication confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team 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 IRT 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.

6.7 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with CDZ173, as detailed in Section 8.6.

Subjects will provide pre- and post-dose blood samples up to 7 hours after the first dose administration (Day 1, Visit 3), pre-and post-dose blood samples up to 3 hours post dose on Day 8 (Visit 4), and pre-dose blood samples on Day 15, Day 29, Day 57 and Day 85 (Visit 5, Visit 6, Visit 7 and Visit 8), as reported in the Assessment schedule.

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

Compliance will be assessed by the Investigator and/or study personnel at each visit using pill counts and information provided by the subject. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.8 Recommended treatment of adverse events

No medications are currently recommended to manage adverse events associated with CDZ173. AEs should be treated according to established medical practice, and the judgement of the investigator.

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.9 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 6.10. 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 in the eCRF after start of study drug.

6.10 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. The salivary stimulants should be stopped within 48 hours prior to, and during assessment of clinical disease outcome measurements. Artificial tears and artificial saliva are to be provided by the study center or personal physician.

Concomitant use of corticosteroids is allowed at a dose of max 10 mg per day (prednisone or equivalent) and no immunosuppressives such as systemic cyclosporine, cyclophosphamide, mycophenolate or azathioprine are allowed. Stable dose of methotrexate (up to 25 mg per week) 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.

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 CRF.

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.

7 Discontinuation and study completion

7.1 Discontinuation of study treatment

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

The investigator must 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

- The subject experiences a drug-related serious adverse event
- Absolute QTcF (or QTcB) >500 msec, as confirmed by repeat ECG measurements performed as soon as possible
- Diarrhea of CTCAE grade ≥ 2 on more than 3 consecutive days
- Diarrhea of CTCAE Grade 3 or higher
- Diarrhea or abdominal pain with accompanying fever assessed to be related to a gastrointestinal infection
- Increase of methotrexate dose and/or corticosteroid dose and/or chloroquine during 12 weeks of dosing (see Section 6.10).

The patient will be discontinued from study treatment and will continue in the study if deviating from the prescribed dose regimen for study treatment:

- More than 28 missed doses of study treatment cumulatively (i.e., 14 days, whether consecutive or not)

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

- Any protocol deviation or adverse event that results in a significant risk to the patient's safety
- Use of prohibited treatment other than described under Concomitant Treatment, please see also Section 5.2

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. They should return for all assessments as presented in the Assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email and letter) should be made to contact them.

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

The 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.

7.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator 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 formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.4 Withdrawal of informed 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/or** does not want any further visits or assessments **and/or** does not want any further study related contact **and/or** 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.

7.5 Replacement of early withdraws or discontinuations

The sponsor may replace patients who withdrew or discontinued from study treatment before study week 13.

7.6 Study Stopping rules

The **study** will be put on temporary hold and safety data will be reviewed if any of the following criteria are met, and no further enrollment will take place pending a full safety review conducted by the sponsor:

- Two or more subjects experience a drug-related serious adverse event
- Three or more subjects report CTCAE (current version) Grade 3 or higher adverse events within the same organ class that are considered to be related to study drug
- The sponsor considers that the number and/or severity of adverse events justify discontinuation of the study
- The sponsor requests it

7.7 Early study termination by the sponsor

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

8 Procedures and assessments

Table 8-1 Assessment schedule

Subjects should be seen for all visits on the designated day, with the assessments performed as per schedule, within the allowed "visit/assessment window" specified in below table.

Study Period	**Screening**	**Baseline**	**Treatment Period (Placebo- Controlled)**						**End of Study**
Visit Numbers/ NCDS	***V1/ V1***	***V2/ V2***	***V3/ V101***	***V4/ V102***	***V5/V103***	***V6/ V104***	***V7/ V105***	***V8/ V106***	***V199***
Week	Wk -4 to -1	Week -1	Week 1	Week 2	Week 3	Week 5	Week 9	Week 13	Week17
Day	Day -28 to -2	Day -1	Day 1	Day 8	Day 15	Day 29	Day 57	Day 85 [9]	Day 113
Visit window (day)				+/- 1d	+/- 2d	+/- 2d	+/- 3d	+/-3d	+/- 4d
Obtain informed consent	X								
Inclusion / Exclusion criteria	X	X							
Relevant medical history and current medical conditions	X	X							
Demography (including smoking status)	X								
Physical examination[11]	X	X		X	X	X	X	X	X
Hepatitis and HIV screen[10]	X								
Pregnancy test	X	Predose[3]				Predose[2]	Predose[2]	Predose[2]	X
Tuberculosis Quantiferon test [10]	X								
Alcohol and drug screen[10]	X								
Perform IRT call	X	X							
Randomization (via IRT)		X							
Vital signs and body measurements									
Body height	X								
Body weight	X	X[3]				X	X	X	X
Body temperature	X	Predose[3]		Predose	Predose	Predose	Predose	Predose	X

Study Period	**Screening**	**Baseline**	**Treatment Period (Placebo- Controlled)**						**End of Study**
Visit Numbers/ NCDS	***V1/ V1***	***V2/ V2***	***V3/ V101***	***V4/ V102***	***V5/V103***	***V6/ V104***	***V7/ V105***	***V8/ V106***	***V199***
Week	Wk -4 to -1	Week -1	Week 1	Week 2	Week 3	Week 5	Week 9	Week 13	Week17
Day	Day -28 to -2	Day -1	Day 1	Day 8	Day 15	Day 29	Day 57	Day 85 [9]	Day 113
Visit window (day)				+/- 1d	+/- 2d	+/- 2d	+/- 3d	+/-3d	+/- 4d
Blood pressure / Pulse rate	X		Predose 1,3,5 h	Predose 1,3 h	Predose	Predose	Predose	Predose	X
ECG evaluation (triplicate)	X		Predose 1,3,5 h	Predose 1,3 h	Predose	Predose	Predose	Predose	X
Hematology, Blood chemistry, Urinalysis	X	Predose[3]		Predose	Predose	Predose	Predose	Predose	X
hsCRP	X	Predose[3]		Predose	Predose	Predose	Predose	Predose	X
Corporate Confidential Information	X	Predose[3]		Predose	Predose	Predose	Predose	Predose	X
Corporate Confidential Information	X	Predose[3]		Predose	Predose	Predose	Predose	Predose	X[5]
Corporate Confidential Information	X	Predose[3]				Predose	Predose	Predose	X
ESSDAI	X	X[4]				X	X	X	X
ESSPRI	X	X[4]				X	X	X	X
Patient Questionnaires, MFI, SF-36	X	X[4]				X	X	X	X
Visual Assessment Scale (VAS) (Investigator & Patient)		X[4]				X	X	X	X
Corporate Confidential Information		Predose[3]						Predose	X
Corporate Confidential Information	X	Predose[3]						Predose	X
Corporate Confidential Information		X[1]	Predose[1]					Predose[1]	X[5;1]
PK blood collection			Predose 0.5,1,3,5,7h	Predose 1,3 h	Predose	Predose	Predose	Predose	
Corporate Confidential Information		X[12]	Predose 1,3,5 h	Predose 1,3 h	Predose	Predose	Predose	Predose	X[5]
Corporate Confidential Information		X	Predose	Predose	Predose	Predose	Predose	Predose	X[5]
Corporate Confidential Information	X	Predose[3]		Predose	Predose	Predose	Predose	Predose	X
Corporate Coı		X	Predose			Predose	Predose	Predose	X[5]

Study Period	**Screening**	**Baseline**	**Treatment Period (Placebo- Controlled)**						**End of Study**
Visit Numbers/ NCDS	***V1/ V1***	***V2/ V2***	***V3/ V101***	***V4/ V102***	***V5/V103***	***V6/ V104***	***V7/ V105***	***V8/ V106***	***V199***
Week	Wk -4 to -1	Week -1	Week 1	Week 2	Week 3	Week 5	Week 9	Week 13	Week17
Day	Day -28 to -2	Day -1	Day 1	Day 8	Day 15	Day 29	Day 57	Day 85 [9]	Day 113
Visit window (day)				+/- 1d	+/- 2d	+/- 2d	+/- 3d	+/-3d	+/- 4d
Corporate Confidential Information		X	Predose	Predose	Predose	Predose	Predose	Predose	X[5]
Corporate Confidential Information		Predose[3]		Predose	Predose	Predose	Predose	Predose	X[5]
Corporate Confidential Information			X						
Corporate Confidential Information		Predose[3]						X	
Drug dispensation [7]			←	—	—	—	→		
Drug administration **b.i.d.** [9]			←	—	—	—	—	→	
Concomitant Medications / Therapies	←	—	—	—	—	—	—	—	→
Adverse Events[6]	←	—	—	—	—	—	—	—	→
Patient Diary			←	—	—	—	—	→	
Study completion information									X

Footnotes

1 Corporate Confidential Information

2 Urine

3 Sample may be collected at any time either on Day -1 (Baseline, V2) or on Day 1 (V3) prior to morning study drug administration

4 Scales may be completed at any time either on Day -1 (Baseline, V2) or on Day 1 (V3) up to 3h post dose

5 Only in case of premature termination, otherwise not collected

6 Serious Adverse Event reporting required from signing informed consent until 30 days after the last dose of study treatment

7 Dispensation of study drug is planned at visits V3, V5, and V6 but may be adapted as required; IRT system needs to be contacted

8 Corporate Confidential Information

9 Last CDZ173 dose in study will be given at site in the morning of V8 visit after all blood samples have been taken

10 Results corresponding to these assessments will be available as source data only

11 Information will be available as source data only; significant findings are to be documented in the CRF

8.1 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.

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.

The date of signing of informed consent (and withdrawal, if later withdrawn) should be documented in the CRF.

Novartis will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. Novartis will review the Investigators proposed informed consent form to ensure it complies with the ICHE6 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.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

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.

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

8.2 Subject screening

In general it is permissible to re-screen a patient if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

Information on what data should be collected for screening failures is outlined in the Site Operations Manual.

8.3 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects.

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

Medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) prior to the start of the study will also be recorded.

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

8.3.1 Hepatitis/HIV screening

All patients 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, e.g. Western Blot.

Appropriate counseling will be made available by the Investigator in the event of a positive finding. Notification of state and federal authorities, as required by local law, will be the responsibility of the Investigator.

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

8.3.2 Tuberculosis testing

In order to evaluate a possible infection or latent infection with tuberculosis, a Quantiferon Gold® test will be performed and read at screening.

A positive QuantiFeron test at screening will exclude the subjects from the participation in the study. Results will be available as source data and will not be recorded within the (e)CRF.

8.3.3 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 (e)CRF.

8.4 Efficacy

In addition to assessments for safety, PK and PD, exploratory clinical efficacy measurements will include components of the ESSDAI and of the ESSPRI and other patient-based assessments, along with imaging, histopathology and functional assessments of the exocrine glands.

8.4.1 ESSPRI

The ESSPRI (Appendix 7) is an established disease outcome measure for Sjögren's syndrome. It consists of a questionnaire developed to assess the patients' symptoms in primary Sjögren's syndrome and covers the three key subjective areas of discomfort, i.e., dryness, pain and fatigue (Seror et al 2011). The full questionnaire has 21 questions. Subsequently, it was noted that the first three questions, Likert scales ranging from 0 – 10, capture the essence of the ESSPRI. This abbreviated version was used to define the "minimal clinically important improvement" (0.67 – 1) and the "patient-acceptable symptom state" (<5) (Seror et al 2016).

Study subjects in the present study will be asked to complete the full ESSPRI questionnaire. However the mean of the first three questions is used for the primary analysis and for the assessment of eligibility.

8.4.2 ESSDAI

The ESSDAI (Appendix 6) 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.

For assessments not listed in the protocol as mandatory tests but which may be needed to estimate ESSDAI, including radiography, high resolution computer tomography (HRCT), lung function test (DLCO, FVC), estimated glomerular filtration rate (eGFR), electromyography (EMG), muscle (or any other) biopsy, it is at the investigator's discretion to have these assessed based on the signs and symptoms of the patient so to provide correct ESSDAI readout.

8.4.3 SF-36

The Short Form Health Survey (SF-36) is a survey evaluating individual patients' health status which also monitors and compares patients' disease burden (Appendix 8).

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.

8.4.4 MFI

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 (Appendix 9).

8.4.5 Global assessments (VAS) of disease activity

8.4.5.1 Physician's global assessment

The physician's global assessment of disease activity will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question "Considering

all the ways the disease affects your patient, draw a line on the scale for how well his or her condition is today".

The investigator will then measure the distance in mm from the left edge of the scale and the value will be entered on the eCRF.

8.4.5.2 Patient's global assessment

The patient's global assessment of disease activity will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question on how well the patient is doing with the disease considering all aspects affected by the disease.

The investigator will then measure the distance in mm from the left edge of the scale and the value will be entered on the eCRF.

8.4.6 Patient-Reported Outcome

Refer to Section 8.4.1, Section 8.4.2, Section 8.4.3 and Section 8.4.4 for patient-reported Outcome.

The patients will be asked to complete a paper copy of the questionnaires or VAS scale in their local language. The printed copy will serve as source data and the patients' responses will be transcribed into the eCRF.

Completed questionnaires and VAS scale will be reviewed and examined by the Investigator before the clinical examination for responses which may indicate potential AEs or SAEs. The Investigator should review not only the responses to the VAS scale, but also for any unsolicited comments written by the patient.

If the occurrence of AEs or SAEs is confirmed, the Investigator should record the events as per instructions given in Section 9 Investigators should not encourage the patients to change the responses reported on the VAS scale.

8.5 Safety

8.5.1 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 in the CRF. Significant findings that are present prior to informed consent are included in the Relevant Medical History CRF. Significant findings observed after informed consent signature which meet the definition of an Adverse Event must be appropriately recorded on the Adverse Event CRF.

8.5.2 Vital signs

Vital signs include blood pressure (BP), pulse measurements, and body temperature.

After the patient has been sitting for 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured using an automated validated device.

The body temperature will be measured as indicated in the Assessment schedule according to local regulations. The measurement will be conducted at the same anatomical location throughout the study participation.

8.5.3 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.

Body mass index (BMI) will be calculated using the following formula:

- BMI = Body weight (kg) / [Height (m)]^2.

8.5.4 Laboratory evaluations

A central laboratory will be used in this study. Central laboratory information, including collection, shipment of samples and reporting of results, may be found in the laboratory manual.

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

In the case of a laboratory range is **not specified by the protocol**, but the laboratory is outside the reference range at screening and/or baseline visit, 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 patient 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.

8.5.4.1 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.

8.5.4.2 Clinical chemistry

Albumin, alkaline phosphatase, total bilirubin, bicarbonate/CO2, calcium, cholesterol, chloride, creatinine, CK, hsCRP, gamma-GT, glucose, LDH, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, TSH, T3, T4, urea/BUN and uric acid will be measured.

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

8.5.4.3 Urinalysis

Dipstick urine tests will be performed measuring leucocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood/ hemoglobin.

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

8.5.4.8 Electrocardiogram (ECG)

ECGs are assessed to ensure patient safety. Details of all procedures relating to ECG collection and reporting will be described in the SOM. The following measurements will be reported:

- PR interval, QRS duration, heart rate, RR, QT, QTc

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

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

8.5.5 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have regular pregnancy tests during the study.

Serum pregnancy tests will be performed at screening, baseline and at the End of 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 interruption of the study drug, until a serum β-hCG is performed, and found to be negative. If positive, the patient must be discontinued from the study medication.

When performed at screening and at baseline, the result must be received before the patient may be dosed.

8.5.6 Other safety evaluations

8.5.6.1 Infections

All occurrences of infections must be carefully monitored by the investigator (see also Section 9.3).

8.6 Pharmacokinetics

PK samples will be collected at the timepoints defined in the Assessment schedule.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

Further details on sample collection, numbering, processing and shipment can be found in the Site Operations Manual.

Pharmacokinetic (PK) samples will be obtained and evaluated in all patients.

Corporate Confidential Information

PK samples remaining after completion of the determination of parent may be used for exploratory assessment of metabolites or other bioanalytical purposes (e.g. cross check between different sites, stability assessment). Corporate Confidential Information

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

Corporate Confidential Information

PK parameters will be calculated as per Novartis Guidance on Standardization of Pharmacokinetic Parameters. Corporate Confidential Information

8.7 Other assessments

Corporate Confidential Information

Corporate Confidential Information

Corporate Confidential Information

Corporate Confidential Information

9 Safety monitoring

9.1 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 patient or clinical investigation patient *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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

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

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

Clinically significant abnormal laboratory values or test results 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 patient and identifying adverse events. Alert ranges for liver related events are included in Section 9.4.

Adverse events must be recorded on the Adverse Events CRF for patients that pass screening and enter into the study. The adverse events should be reported according to the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. the Common Toxicity Criteria (CTC) AE grade (version 4.03)
   If CTC-AE grading does not exist for an adverse event, use:
   1=mild,

2=moderate,

3=severe

4=life threatening* (see Section 9.2 for definition of a serious adverse event (SAE))

*Note: There may be cases where a CTCAE with a grade of 4 (life-threatening) may not necessarily be an SAE (e.g. certain laboratory abnormalities in the absence of meeting other seriousness criteria).

CTC-AE grade 5 (death) is not used, but is collected in other CRFs (e.g. Study Completion, Death/Survival).

2. its relationship to the study treatment (no/yes).
3. its duration (start and end dates) or if the event is ongoing at the end of study.
4. whether it constitutes a serious adverse event (SAE) See Section 9.2 for definition of SAE
5. action taken regarding investigational treatment.

   All adverse events must be treated appropriately. Treatment may include one or more of the following:

   - no action taken (e.g. further observation only)
   - investigational treatment dosage increased/reduced
   - investigational treatment interrupted/withdrawn
   - concomitant medication or non-drug therapy given
   - hospitalization/prolonged hospitalization (see Section 9.2 for definition of SAE)
6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

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

The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

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

- 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 the start of study drug
  - 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 patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

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

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

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

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

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to DS&E as per Section 9.2.2.

9.2.2 SAE reporting

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

Note: SAEs reported by subjects deemed to be screen failures must be reported to Novartis as outlined here with appropriate information also captured in the CRFs as specified in the Site Operations Manual.

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 each specific component of study treatment (if study treatment consists of several drugs) 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, notifying the Clinical Trial Leader. Contact information is listed in the Site Operations Manual.

The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the source 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.

Follow the detailed instructions outlined in the Site Operations Manual regarding the submission process for reporting SAEs to Novartis.

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

9.3 Infection Monitoring

All infections that develop during the study will be reported as AEs. Investigators are requested to specifically ask about infections at each visit, in particular bacterial enterocolitis. Treatment and additional evaluations will be performed at the discretion of the investigator. The investigator should consider early treatment with specific antimicrobial therapy on the basis of clinical diagnosis or suspicion thereof in consultation with infectious disease experts, as appropriate.

WBC will be assessed at every visit. If the neutrophil count falls below 1000 per µl, then weekly assessments of WBC are recommended.

The investigator should remind the patient of the risk of infections and to instruct them to promptly report any symptoms of infections to the investigator.

9.4 Liver safety monitoring

To ensure patient 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.

The following two categories of abnormalities / adverse events have to be considered during the course of the study:

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

Please refer to Table 9-1 and Table 9-2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event should be followed up by the investigator or designated personal at the trial site, as summarized below and detailed in Table 9-2.

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation.

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

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

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug (refer to Section 7.1, if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g. disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and

the procedures performed should be recorded as appropriate in the CRF, including the liver event overview CRF pages.

Table 9-1 Liver Event and Laboratory Trigger Definitions

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

Table 9-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for *more than 2 weeks*, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

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

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

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

[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

9.5 Renal safety monitoring

Renal events are defined as one of the following:

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

The following two categories of abnormalities/adverse events have to be considered during the course of the study:

- Serum creatinine triggers that will require follow up and repeat assessments of the abnormal laboratory parameter
- Urine dipstick triggers that will require follow up and repeat assessments of the abnormal laboratory parameter

Table 9-3 Specific Renal Alert Criteria and Actions

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

9.6 Pregnancy reporting

To ensure patient safety, each pregnancy in a patient on study drug 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. The study drug must be discontinued, though the patient may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments. Pregnancy must be recorded on a Pharmacovigilance 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 Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on an SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

9.7 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 Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented in Section 7.

The Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of patient records, the accuracy of entries on the CRFs, 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 monitor during these visits.

The investigator must maintain source documents for each patient 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 CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility 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 CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

10.2 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 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 copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and assessment schedule and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

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

10.3 Database management and quality control

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, or CRO working on behalf of Novartis, 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.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data in reference to dispensing of study drug(s) to the subject and all IRT recorded dosage changes will be tracked using Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

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

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. Any changes to the database after that time can only be made by joint written agreement between the COAR Analytics NIBR Franchise Head and the relevant NIBR TA Head.

porate Confidential Information

10.4 Data Monitoring Committee

Not required.

10.5 Adjudication Committee

Not required.

11 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

11.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) 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 at least one valid (i.e. not flagged for exclusion) PK concentration measurement, who received study drug and no protocol deviations with relevant impact on PK data.

The PD analysis set will include all subjects that received study drug and had no protocol deviations with relevant impact on PD data.

11.2 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.

11.3 Treatments

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

Summaries and listings of cumulative exposure to study drug (cumulative dose received over the treatment period) will be provided.

11.4 Analysis of the primary variable(s)

The primary aims of this study are to assess safety in patients with pSS and to investigate the effect of CDZ173 on efficacy (as measured by the ESSPRI) at study week 13. The statistical analysis model will include ESSPRI data from all time points up to study week 13 and summaries of safety and tolerability will be provided.

11.4.1 Variable(s)

The primary efficacy variable is the ESSPRI change from baseline.

11.4.2 Statistical model, hypothesis, and method of analysis

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

The primary efficacy analysis will be based on a longitudinal mixed model of ESSPRI as a function of baseline ESSPRI, baseline intake of steroids (yes/no, which is a stratification factor for the randomization), treatment, time as a continuous variable (linear and quadratic terms), interaction between treatment and time, as well as a random intercept, random slope and random quadratic effects by subject to account for within-subject correlations. An unstructured covariance matrix for the random effects will be fitted along with an independent error matrix. The difference between active treatment and placebo in change from baseline in ESSPRI at study week 13 will be estimated from the model and presented with 80% confidence intervals. Simpler models will also be considered in case the pre-specified model does not fit the data well.

The following criteria will be considered indicative of treatment efficacy:

- Statistically significant decrease in ESSPRI at week 13 visit on treatment compared to placebo (at one-sided 10% level)
- Estimated mean reduction in ESSPRI at week 13 visit of 1 point or more than on placebo (see Section 3.2)

11.4.3 Handling of missing values/censoring/discontinuations

All subjects with a baseline ESSPRI and at least one post-baseline ESSPRI will be included in the primary analysis. The primary analysis method provides unbiased estimates of the treatment effect under the assumption that data are missing at random (MAR). Guidelines for subject discontinuation should ensure that this assumption is reasonable. If a substantial proportion (e.g. more than 15%) of subjects discontinue before week 13 visit, alternative methods to account for missing data may be considered.

11.4.4 Supportive analyses

Simpler models may be considered, including simpler covariance structures. If the time course doesn't appear to be quadratic, time may be modeled as a categorical variable.

11.5 Analysis of secondary and exploratory variables

11.5.1 Efficacy / Pharmacodynamics

Corporate Confidential Information

11.5.2 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, abnormalities will be flagged. Summary statistics will be provided by treatment and visit.

A longitudinal PK-QT model using all available data will be used to see if there is any concentration-dependent increase in QT. This model may include data from other studies exploring CDZ173 and may be reported in a separate report. The model will include a random subject effect to account for the within-patient correlations. In case the direct PK-QT model doesn't fit the data appropriately, alternative models taking into account potential hysteresis will be used.

Clinical laboratory evaluations

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

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.

11.5.3 Pharmacokinetics

The pharmacokinetics of CDZ173 will be evaluated in patients in the PK analysis set.

CDZ173 plasma 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. An exception to this is Tmax where median, minimum and maximum will be presented. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values. Pharmacokinetic parameters will be calculated by non-compartmental methods as described in Section 8.6 and will be listed by treatment and subject.

Corporate Confidential Information

11.5.4 Pharmacokinetic / pharmacodynamic interactions

Relationships between exposure and selected PD variables will be explored by a graphical approach and descriptive statistics of exposure and PD variables will be provided. Additional analysis such as exposure-response models will be performed, if warranted.

11.5.5 Other assessments

11.5.5.1 Imaging biomarkers

Corporate Confidential Information

tial Information

11.6 Sample size calculation

A total of approximately 27 patients will be recruited into the study. Patients will be randomized in a 2:1 ratio to either CDZ173 (n=18) or placebo (n=9) treatment groups. This number is based firstly on the assumed treatment effect in the primary endpoint ESSPRI and secondly on an assumed drop-out rate of 10% (i.e. 3 patients).

With 24 patients for the analysis of the primary efficacy variable (16 in the CDZ173 treated group and 8 in the placebo group), the study would have around 10% chance of having a false-positive result, i.e. of meeting both efficacy criteria when the true difference between CDZ173 and placebo is zero ESSPRI points.

The power of the study is 86% (when the true difference between CDZ173 and placebo is 2 points in ESSPRI).

The criteria for success are assumed to be the efficacy criteria defined in Section 11.4.2.

These calculations assume that the change from baseline in ESSPRI is approximately normally distributed with a standard deviation of 2. This estimate of the standard deviation is based on a study of rituximab in patients with pSS (Meiners et al 2012).

The calculated numbers come from simulations done in R version 3.2.2.

11.7 Interim analyses

12 Ethical considerations

12.1 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.

12.2 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 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.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 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.

13 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 must 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.

13.1 Protocol Amendments

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

Only amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented, provided the Health Authorities and the reviewing IRB/IEC are subsequently notified by protocol amendment.

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, the CTL should be informed and (serious) adverse event reporting requirements (Section 9) followed as appropriate.

14 References

Available upon request.

Clayton E, Bardi G, Bell SE, et al (2002) A crucial role for the p110delta subunit of phosphatidylinositol 3-kinase in B cell development and activation. J Exp Med. 196(6):753-63.

Flinn IW, Kahl BS, Leonard JP et al (2014) Idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase-, as therapy for previously treated indolent non-Hodgkin lymphoma, Blood; 123(22), 3406-13.

Hirsch E, Katanaev VL, Garlanda C, et al (2000) Central role for G protein-coupled phosphoinositide 3-kinase gamma in inflammation. Science. 287(5455):1049-53.

Jou ST, Carpino N, Takahashi Y, et al (2002) Essential, nonredundant role for the phosphoinositide 3-kinase p110delta in signaling by the B-cell receptor complex. Mol Cell Biol. (24):8580-91.

Kandel ES, Hay N (1999) The regulation and activities of the multifunctional serine/threonine kinase Akt/PKB. Exp. Cell Res.; 253 (1): 210-229.

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.

Li Z, Jiang H, Xie W, et al (2000) Roles of PLC-beta2 and -beta3 and PI3Kgamma in chemoattractant-mediated signal transduction. Science; 287(5455):1046-9.

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.

Mengshoel AM, Norheim KB, Omdal R (2014) Primary Sjögren's Syndrome: Fatigue Is an Ever-Present, Fluctuating, and Uncontrollable Lack of Energy. Arthritis Care Res; 66: 1227-1232.

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.

Nocturne G and Mariette X. Nat Rev Rheumatol 2013; 9:544-556.

Patrucco E, Notte A, Barberis L, et al (2004) PI3Kgamma modulates the cardiac response to chronic pressure overload by distinct kinase-dependent and -independent effects. Cell; 118:375-87.

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.

Sasaki T, Irie-Sasaki J, Jones RG, et al (2000) Function of PI3Kgamma in thymocyte development, T cell activation, and neutrophil migration. Science; 287(5455):1040-6.

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.

Seror R, Ravaud P, Mariette X, et al (2011). EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI): development of a consensus patient index for primary Sjogren's syndrome. Ann Rheum Dis; 70:968-72.

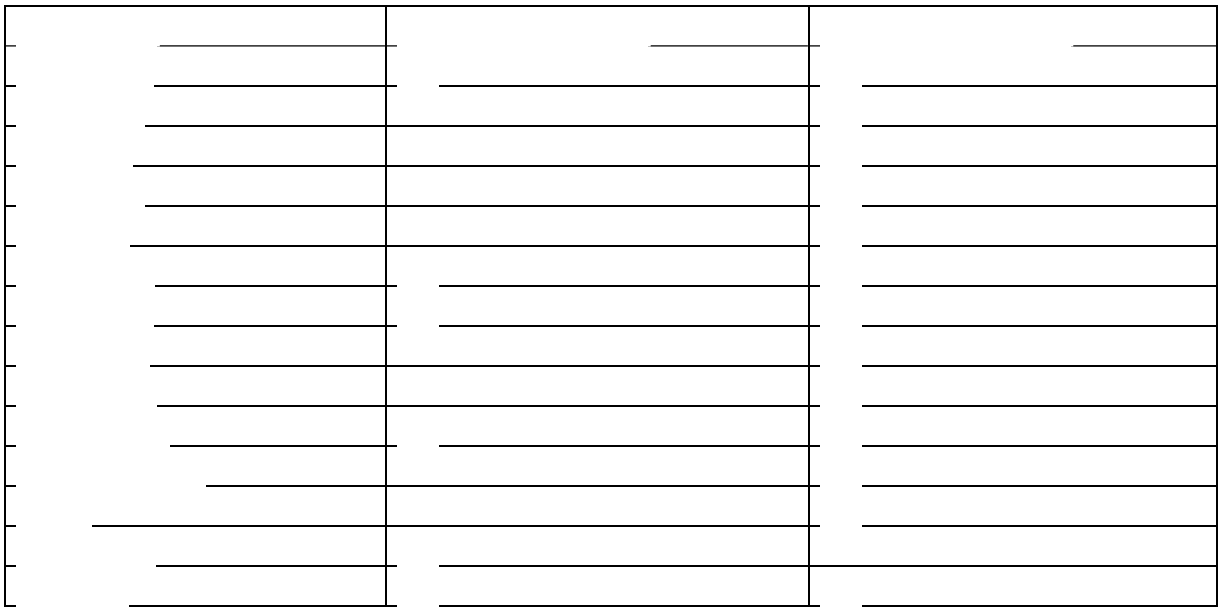
Seror R, Bootsma H, Saraux A, et al (2016) Defining disease activity states and clinically meaningful improvement in primary Sjögren's syndrome with EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI). Ann Rheum Dis; 75:382-389.

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.

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

Corporate Confidential Information

Corporate Confidential Information



17 Appendix 3: Blinding and Unblinding

Please refer to Site Operations Manual.

18 Appendix 4: Sample Log Table

Please refer to Site Operations Manual.

19 Appendix 5: Sample labeling and shipping information

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

20 Appendix 6: ESSDAI

Will be provided as a separate document.

21 Appendix 7: ESSPRI

Will be provided as a separate document.

22 Appendix 8: SF-36

Will be provided as a separate document.

23 Appendix 9: MFI

Will be provided as a separate document.