NOVARTIS

Novartis Institutes for BioMedical Research

CDZ173

Clinical Trial Protocol CCDZ173X2201 / NCT02435173

An open-label, non-randomized, within-patient dose-finding study followed by a randomized, subject, investigator and sponsor-blinded placebo controlled study to assess the efficacy and safety of CDZ173 (Leniolisib) in patients with APDS/PASLI (Activated phosphoinositide 3-kinase delta syndrome/ p110δ-activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency)

Document type:	Amended Protocol Version
EUDRACT number:	2014-003876-22
Version number:	v10 (Clean)
Development phase:	II/III
Release date:	13-Oct-2020

Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct.

Notification of serious adverse events

Refer to Section 9.2 of the protocol for definitions and reporting requirements for Serious Adverse Events (within 24 hours after awareness of the SAE to the local Novartis Chief Medical Office and Patient Safety Department and notify the Clinical Trial Leader).

Contact information is listed in the SOM.

Table of contents

Commercially Confidential Information (CCI)

Commercially Confidential Information

List of tables

Commercially Confidential Information

Commercially Confidential Information

List of figures

Commercially Confidential Information

List of abbreviations

AE	adverse event
AIHA	Autoimmune hemolytic anemia
ALT	alanine aminotransferase
ALP	alkaline phosphatase
APC	Antigen presenting cell
APDS	Activated Phosphoinositide 3-kinase-Delta Syndrome
AST	aspartate aminotransferase
AV	Atrioventricular
BCRP	Breast cancer resistance protein
b.i.d.	bis in die (twice a day)
BMI	Body Mass Index
BSA	Body Surface Area
BUN	blood urea nitrogen
CD-ROM	compact disc – read only memory
CDS	Core Data Sheet (for marketed drugs)
CFR	Code of Federal Regulation
CIA	Collagen-induced arthritis
CK	creatinine kinase
CMO&PS	Chief Medical Office and Patient Safety
	Commercially Confidential Information
CPAP	Continuous positive airway pressure
CRF	Case Report/Record Form (paper or electronic)
CO2	carbon dioxide
COVID-19	Coronavirus disease
CRO	Contract Research Organization
CRP	C- reactive protein
CSF	Clinical Service Form
CT	Computed Tomography with X rays
CTC	Common Toxicity Criteria
CTRD	Clinical Trial Results Database
CV	coefficient of variation

CYP	Cytochrome
DDI	Drug-drug interaction
DS&E	Drug safety and Epidemiology
DSMB	Data safety monitoring board

Commercially Confidential Information

EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
DMC	Data Monitoring Committee
FIH	First in Human
FDA	Food and Drug Administration
GCP	Good Clinical Practice
γ-GT	Gamma-glutamyl transferase
h	hour

Commercially Confidential Information

HV	Healthy Volunteer
IA	Interim analysis
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITP	Idiopathic Thrombocytopenic purpura
i.v.	Intravenous
kD	kilo Dalton
LFT	Liver function testLDH lactate dehydrogenase

Commercially Confidential Information

MAD	Multiple ascending dose
MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic Resonance Imaging
mTOR	Mammalian target of rapamycin
mg	milligram(s)
ml	milliliter(s)
NCDS	Novartis Clinical Data Standards
NOAEL	No observed adverse effect level
NOVDD	Novartis Data Dictionary
NTI	Narrow therapeutic index
OC/RDC	Oracle Clinical/Remote Data Capture
OGTT	Oral glucose tolerance test
P-gp	P-glycoprotein
PA	posteroanterior
pAkt	phosphorylated Akt
PASLI	p110δ-activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency
PBPK	physiology based pharmacokinetics
PD	pharmacodynamic(s)
PDK1	Phosphoinositide-dependent protein kinase
PGA	Physician Global Assessment
PI3K	Phosphoinositide 3-kinases
PI3Kδ	Phosphoinositide 3-kinase delta
PIP3	Phosphatidylinositol-3,4,5-trisphosphate
PK	pharmacokinetic(s)
p.o.	per os (oral(ly))
pSS	primary Sjögren's syndrome
PtGA	Patient's Global Assessment
q.d.	quaque die (once a day)
RBC	red blood cell(s)
RoW	Rest of World

SAD	Single ascending dose
SAE	serious adverse event
s.c.	subcutaneous
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SD	standard deviation
SF-36	Short Form 36
SOM	Site operational manual
SPD	Sum of product of diameters
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
ULN	upper limit of normal
ULQ	upper limit of quantification
WBC	white blood cell(s)
WHO	World Health Organization
WPAI-CIQ	Work Productivity Activity Impairment and Classroom Impairment Questionnaire

Commercially Confidential Information Pharmacokinetic definitions and symbols

Pharmacokinetic definitions and symbols

Ae0-t	Amount of drug (or defined metabolite) excreted into the urine from time zero to time 't' where t is a defined time point after administration [mass units or % of dose]
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]
AUCtau	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau [mass x time / volume]
AUCtau,ss	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau at steady state [mass x time/volume]
Cav,ss	The average steady state plasma (or serum or s) concentration during multiple dosing
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]
Cmin,ss	The lowest plasma (or serum or blood) concentration observed during a dosing interval 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]
CLr	The renal clearance from plasma (or serum or blood) [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	The volume of distribution during the terminal elimination phase following intravenous administration [volume]
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]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with USA CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with "investigational new drug" or "test substance"
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data:	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.

Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Protocol synopsis

Protocol number	[CCDZ173X2201]
Title	An open-label, non-randomized, within-patient dose-finding study followed by a randomized subject, investigator and sponsor-blinded, placebo controlled study to assess the efficacy and safety of CDZ173 (Leniolisib) in patients with APDS/PASLI (Activated phosphoinositide 3-kinase delta syndrome/ p110δ-activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency)
Brief title	Study of efficacy of CDZ173 in patients with APDS/PASLI
Sponsor and Clinical Phase	Novartis Phase II/III
Intervention type	Drug
Study type	Interventional
Purpose and rationale	This study is designed to explore CDZ173, a selective PI3Kδ inhibitor, in patients with genetically activated PI3Kδ, i.e. patients with APDS/PASLI. The study consists of two parts. Part I was the open label part designed to establish the safety and pharmacokinetics of CDZ173 in the target population, as well as to select the optimal dose to be tested in Part II. Part II is designed to assess efficacy and safety of CDZ173 in this population.
Primary Objective(s)	Part I: To assess the safety and tolerability as well as the dose-PD and PK/PD relationship of CDZ173 in patients with APDS/PASLI enabling dose selection for Part II Part II: To assess the clinical efficacy of CDZ173 in patients with APDS/PASLI
Secondary Objectives	Part II: To assess the effect of CDZ173 on lymphadenopathy (non-index lesions and spleen). Part I and II: To assess the pharmacokinetics of CDZ173 in patients with APDS/PASLI Part I and II: To assess the efficacy of CDZ173 to modify health-related quality of life in patients with APDS/PASLI Part I and II: To assess the efficacy of CDZ173 by the Physician's Global Assessment and the Patient's Global Assessment Part I and II: To assess biomarkers reflecting the efficacy of CDZ173 to reduce systemic inflammatory components of the disease Commercially Confidential Information Part II: To assess the safety and tolerability of CDZ173 in patients with APDS/PASLI

Study design	Part I of the study was the non-randomized, open-label, within-patient up-titration dose-finding part in 6 patients with APDS/PASLI. Safety, tolerability, pharmacokinetics (PK) and in vivo pharmacodynamics (PD pAkt) were assessed at three different dose levels of CDZ173. The starting dose was 10 mg followed by 30 mg and 70 mg b.i.d. for 4 weeks at each dose level respectively. Part II is the randomized, subject, investigator and sponsor-blinded, placebo-controlled, fixed dose part investigating approximately 30 patients with APDS/PASLI. Efficacy with respect to reduction of lymphadenopathy measured by sum of product diameters (SPD) in the index lesions selected as per the Cheson methodology from MRI or CT imaging as well as with respect to immunophenotype as assessed by change from baseline in percentage of naïve B cells out of total B cells will be investigated. Safety, tolerability, PK, and PD of CDZ173 will also be assessed.
Population	A total of 6 patients with APDS/PASLI were enrolled in the study in Part I. In Part II of the study approximately 30 patients will be randomized. Male and female patients age 12 to 75 years of age (inclusive), who have a documented APDS/PASLI-associated genetic PI3K delta mutation.

Inclusion criteria	• Male and female patients 12 to 75 years of age (inclusive), who have a documented APDS/PASLI-associated genetic PI3K delta mutation. Patients with mutations in either PIK3CD or PIK3R1 can be included.
	• In Part I and Part II, patients must have nodal and/or extranodal lymphoproliferation, and clinical findings and manifestations compatible with APDS/PASLI such as a history of repeated oto-sino-pulmonary infections and/or organ dysfunction (e.g., lung, liver). Additionally, in part II, patients must have at least one measurable nodal lesion on a CT or MRI scan.
	• At screening, vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position after the patient has rested for at least three minutes. Sitting vital signs should be within the following ranges:
	  • Systolic blood pressure, 90-139 mm Hg
	  • Diastolic blood pressure, 50-89 mm Hg
	  • Pulse rate, 50 - 100 bpm; up to 110 bpm in adolescents

Exclusion criteria	• Previous or concurrent use of immunosuppressive medication such as:
	  • use of an mTOR inhibitor (e.g., sirolimus, rapamycin, everolimus) or a PI3Kδ inhibitor (selective or non-selective PI3K inhibitors) within 6 weeks prior to first dosing, however short-term use for up to a total of 5 days is allowed but only up to 1 month prior to enrollment in the study.
	  • B cell depleters (e.g., rituximab) within 6 months prior to first dosing of study medication; if patients have received prior treatment with a B cell depleter, absolute B lymphocyte counts in the blood must have regained normal values.
	  • Belimumab or cyclophosphamide within 6 months prior to first dosing of study medication.
	  • Cyclosporine A, mycophenolate, 6-mercaptopurine, azathioprine or methotrexate within 3 months prior to first dosing of study medication.
	  • Glucocorticoids above 25 mg prednisone or equivalent per day within 2 weeks prior to first dosing of study medication.

	• Other immunosuppressive medication where effects are expected to persist at start of dosing of study medication. Commercially Confidential Information • Administration of live vaccines (this includes any attenuated live vaccines) starting from 6 weeks before study entry, during the study and up to 7 days after the last dose of CDZ173 • Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test. Commercially Confidential Information
Investigational and reference therapy	Part 1 : CDZ173 Part 2 : CDZ173 and placebo
Efficacy/PD assessments	• pAkt inhibition in unstimulated and stimulated whole blood (only in Part I) • Reduction of lymphadenopathy based on CT or MRI • Immunophenotype as assessed by changes from baseline in percentage of naïve B cells out of total B cells • SF-36 Survey and WPAI-CIQ • Visual analogue scales for Patient and Physician Global assessment Commercially Confidential Information
Safety assessments	• Adverse events • Physical exam • Vital signs • ECG • Safety laboratory (hematology, blood chemistry, urinalysis)
Other assessments	• In Part I: Single and multiple dose PK parameters (including but not limited to Cmax and AUC) • In Part II: Single dose (Day 1) CDZ173 PK parameters (including but not limited to Cmax and AUC) and trough evaluations after multiple dose

Data analysis	The primary aim of Part I, along with assessing safety and tolerability, was to determine a dose to be used in the confirmatory Part II. The primary aim of Part II is to assess efficacy of CDZ173 at the selected dose (70 mg b.i.d.) after 12 weeks of treatment. Commercially Confidential Information In Part II, lymphadenopathy will be measured by the SPD of index lesions selected as per the Cheson methodology from MRI/CT imaging and immunodeficiency will be measured by percentage of naïve B cells out of total B cells. The co-primary endpoints are the change from baseline in the log10 transformed SPD of index lesions and the change from baseline in the percentage of naïve B cells at the end of treatment. Commercially Confidential Information
Key words	APDS/PASLI

1 Introduction

1.1 Background

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 kilo Dalton (kD) regulatory subunit (p85) and one of three different 110 kD catalytic subunits (p110α, p110β and p110δ). PI3Kδ is expressed primarily in hematopoietic cells and functionally relevant in the activation of leukocytes of the adaptive as well as the innate immune system.

Mutations in the p110δ subunit that recruit the kinase to the plasma membrane independent of exogenous activation have been recently described, hence resulting in a gain-of-function of PI3Kδ (Lucas et al 2014; Angulo et al 2013; Crank et al 2014). This rare disease has been named "Activated PI3Kδ Syndrome" (APDS) or "p110δ-activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency" (PASLI). More than 200 APDS patients have been identified (Michalovich and Nejentsev 2018).

The clinical phenotype frequently includes massive lymphoproliferation (lymphadenopathy, e.g., affecting breathing by mediastinal obstruction or leading to intestinal obstruction; splenomegaly; hepatomegaly), recurrent oto-sino-pulmonary infections leading to lung destruction, chronic viremia (e.g., Epstein-Barr Virus (EBV), Cytomegalovirus (CMV)), increased risk for autoimmune diseases (e.g., Idiopathic Thrombocytopenic Purpura (ITP) - or Autoimmune Hemolytic Anemia (AIHA) -like diseases), inability of successful vaccination (notably with carbohydrate antigens), and risk of lymphomas. Current treatment options are only symptomatic.

CDZ173 is a small molecule inhibitor of p110δ that inhibits the production of phosphatidylinositol-3,4,5-trisphosphate (PIP3).

Commercially Confidential Information

CDZ173 has also been investigated in a study (CCDZ173X2203) in patients with primary Sjögren's syndrome (pSS).

Given the specificity of CDZ173 to selectively inhibit the p110δ subunit of PI3K class IA, which harbors the gain-of-function mutation driving APDS/PASLI, we hypothesize that CDZ173 will specifically target the causative factor resulting in the pathogenesis of APDS/PASLI, and thereby provides effective treatment for this newly described disease with a significant unmet medical need.

1.1.1 Relevant data summary

The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the Investigators Brochure (IB).

1.1.1.1 Preclinical data

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

1.1.1.3 Human safety and tolerability data

Commercially Confidential Information

Furthermore, a study in primary Sjögren's Syndrome (CCDZ173X2203) enrolled 20patients, receiving 70 mg bid, and 10 patients, receiving matching placebo.

Six (6) APDS patients have completed the study Part I of the present protocol, and the results can be found in the interim analysis (IA) clinical study report and are also published (Rao et al 2017). All six patients from the Part I study are currently on treatment in the extension study (CCDZ173X2201E1) and results from a recent IA with long-term safety and efficacy data were presented at the European Society for Immunodeficiencies (ESID) conference 2018 (Rao et al 2018).

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

1.2 Data from Study Part I

Six APDS/PASLI patients completed study Part I of the present protocol (amendment #8). CDZ173 was found safe and well tolerated at all three dose levels. There were no SAEs and no premature treatment discontinuations due to AEs. In summary, 12 week treatment with CDZ173 led to significant improvements in the clinical presentation of the patients, including regression of lymph nodes and decrease in spleen size, naïve B cell numbers normalization, decrease of elevated transitional B cell numbers, reduction of senescent CD4+ and CD8+ T cells, reduction of elevated serum chemokines and suppression of the PI3K/Akt pathway activity. Mean oral plasma clearance at steady-state in the APDS patients was found to be 3.8 L/h, a value in close agreement to that seen in healthy volunteers. Also, no relevant time-dependencies or deviations from dose-proportionality were evident.

For further details of results please refer to the Clinical Study Report.

1.3 Study purpose

This study is designed to evaluate CDZ173, a selective PI3Kδ inhibitor, in patients with genetically activated PI3Kδ, i.e. patients with APDS/PASLI. The study consists of two parts. Part I of the present protocol is now complete and was the open label part designed to establish the safety and pharmacokinetics of CDZ173 in the target population, as well as to select the optimal dose to be tested in Part II. Part II is the subject, investigator and sponsor-blinded, randomized part designed to assess efficacy and safety of CDZ173 in this population.

2 Study objectives

2.1 Primary objective(s)

Objective	Endpoint
• Part I: To assess the safety and tolerability of CDZ173 in patients with APDS/PASLI	• All safety parameters (including AEs, physical exam, vital signs, ECG, safety laboratory (hematology, blood chemistry, urinalysis))
• Part I: To assess the dose-PD and PK/PD relationship of CDZ173 in patients with APDS/PASLI for dose selection in Part II	Single and multiple dose concentrations of CDZ173 and pAkt inhibition in unstimulated and stimulated whole blood
• Part II: To assess the clinical efficacy (lymphadenopathy and immunophenotype normalization) of CDZ173 in patients with APDS/PASLI	Co-primary endpoint; • Change from baseline in the log10 transformed sum of product of diameters (SPD) in the index lesions selected as per the Cheson methodology from MRI/CT imaging. • Change from baseline in percentage of naïve B cells out of total B cells

2.2 Secondary objective(s)

Objective	Endpoint
• Part II: To assess the effect of CDZ173 on lymphadenopathy (non-index lesions and spleen)	• MRI/CT imaging – e.g. 3D volume of index and measurable non-index lesions selected as per the Cheson methodology, and 3D volume and bi-dimensional size of the spleen
• Part I and II: To assess the pharmacokinetics of CDZ173 in patients with APDS/PASLI	• Single dose CDZ173 PK parameters (including but not limited to Cmax and AUC) and trough evaluations after multiple dose
• Part I and II: To assess the efficacy of CDZ173 to modify health-related quality of life in patients with APDS/PASLI	• SF-36 (Short Form 36) Survey and WPAI-CIQ (Work Productivity Activity Impairment plus Classroom Impairment Questionnaire)
• Part I and II: To assess the efficacy of CDZ173 by the Physician's Global Assessment (PGA) and the Patient's Global Assessment (PtGA)	• Visual analogue scales for PGA and PtGA (for Part II the PGA is a key secondary endpoint)
• Part I and II: To assess biomarkers reflecting the efficacy of CDZ173 to reduce systemic inflammatory components of the disease	• C reactive protein (CRP), Lactate dehydrogenase (LDH) • For Part II additional: beta2 microglobulin, ferritin, fibrinogen and erythrocyte sedimentation rate (ESR)
• Part I and II: To assess the treatment benefit to individual patients	• Narratives
• Part II: To assess the safety and tolerability of CDZ173 in patients with APDS/PASLI	• All safety parameters, including AEs, physical exam, vital signs, ECG, safety laboratory (hematology, blood chemistry, urinalysis)

2.3 Exploratory objective(s)

Commercially Confidential Information

3 Investigational plan

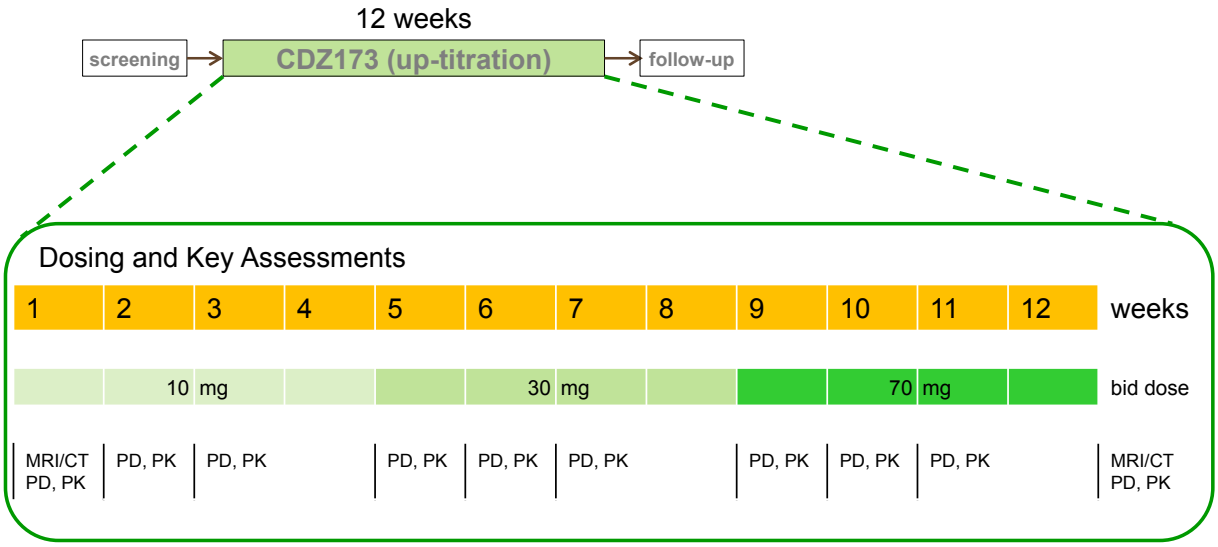
3.1 Study design

3.1.1 Part I

Part I of the study was the non-randomized, open-label, within-patient up-titration dose-finding part performed in 6 patients with APDS/PASLI. Safety, tolerability, pharmacokinetics (PK) and in vivo pharmacodynamics (PD pAkt) were assessed at three different dose levels of CDZ173. The starting dose was 10 mg followed by 30 mg and 70 mg b.i.d. for 4 weeks at each dose level respectively.

Figure 3-1 illustrates the study design of part I.

Figure 3-1 Study Design Part I



Screening Period/Baseline Visit

During the Screening Visit (Day -50 to Day -2) patients' eligibility was assessed and then reviewed during the Baseline Visit. During this phase patients were assessed for the following: Safety assessments which will include physical examinations, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), adverse event and serious adverse event monitoring and cardiac safety which were monitored by means of triplicate 12-lead electrocardiograms (ECG). Further assessments included SF-36 and WPAI questionnaires and patient global assessment.

Patients who were deemed eligible for enrollment into the study based on the inclusion/exclusion criteria attended the clinic on Day -1 for baseline assessments which include vital signs, ECG and PD blood collection.

An MRI or CT scan (for further information see Section 8.3.1.1) was performed prior to Day 1 – this could be carried out during screening or baseline periods, depending on the logistical requirements of both the site and patient.

Commercially Confidential Information

Treatment Period (Day 1 to Day 84)

The first day of dosing was started on Day 1 with patients receiving 10 mg of CDZ173 b.i.d.

Commercially Confidential Information

Prior to escalation of a patient to the next dose level a continuous safety review and review of PK and key PD data up to 7 days after the first dose (Day 8) was performed and had to be assessed as satisfactory to proceed with next dose level.

Commercially Confidential Information

The final dose strength that patients received was 70 mg CDZ173 b.i.d CCI .
Assessments done on Day 84 included the end of treatment MRI or CT scan.

Follow-Up/End of study visit

During the four weeks after the last day of dosing the patients were followed-up for safety. On Day 112 patients underwent the end of study visit.

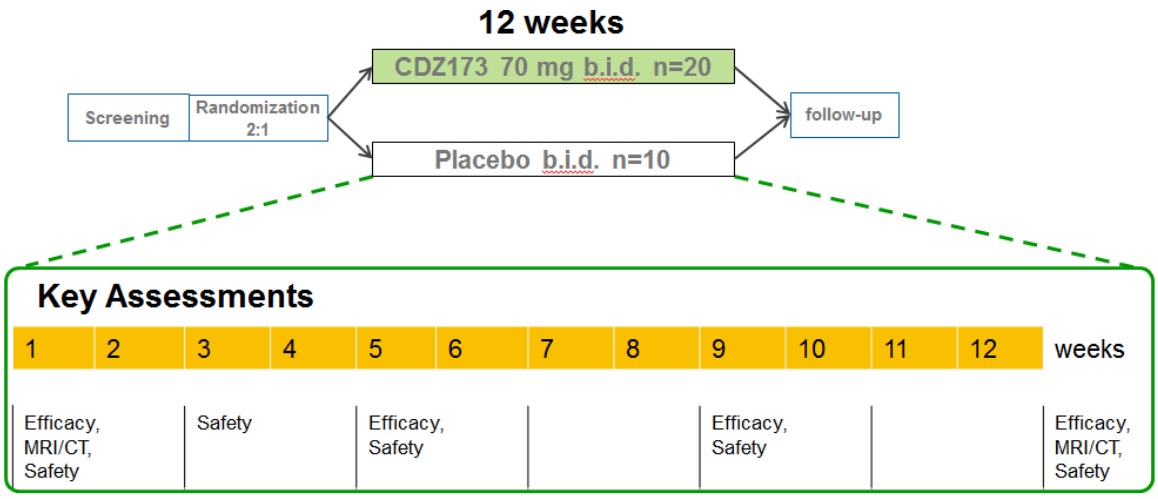
3.1.2 Part II

Part II is the randomized, subject, investigator and sponsor-blinded, placebo-controlled, fixed dose part investigating approximately 30 patients with APDS/PASLI (Figure 3-2). Efficacy with respect to reduction of lymphadenopathy measured by SPD in the index lesions selected as per the Cheson methodology from MRI or CT imaging as well as with respect to immunophenotype as assessed by change from baseline in percentage of naïve B cells out of total B cells will be investigated. For imaging, sites may choose either of the two imaging modalities (MRI or CT) as per clinical practice and local regulations (see Imaging Review Charter). Baseline and end of treatment assessments must be done using the same modality. Safety, tolerability, PK, and patient reported outcomes of CDZ173 will also be assessed.

The CDZ173 dose to be used in this part is selected based on safety, tolerability, PK and PD data from Part I. See Section 3.2 for more details.

The study design is illustrated in Figure 3-2.

Figure 3-2 Study Design Part II



Screening Period/Baseline Visit

During the Screening Visit (Day -50 to Day -2) patients' eligibility will be assessed and then reviewed during the Baseline Visit.

Commercially Confidential Information

During this phase patients will be assessed for the following: Safety assessments which will include physical examinations, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), adverse event and serious adverse event monitoring and cardiac safety which will be monitored by means of triplicate 12-lead electrocardiograms (ECG). Further assessments will include an MRI or CT scan (for further information see Section 8.3.1.1).

Patients who are deemed eligible for enrollment into the study based on the inclusion/exclusion criteria will attend the clinic on Day -1 for baseline assessments which include physical exam, vital signs, ECG, blood collection and PRO questionnaires.

Treatment Period (12 weeks)

On Day 1 patients will be randomly allocated to one of the two treatment groups in a 2:1 ratio to receive either 70 mg CDZ173 b.i.d. or matching placebo for a twelve week period in a patient, investigator and sponsor blind fashion.

Efficacy, safety and PK assessments will be performed at scheduled times. Safety assessment will include physical examination, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, urinalysis), adverse event and serious adverse event monitoring.

Commercially Confidential Information

Follow-Up/End of study visit

For the patients who do not directly roll over from Part II to treatment in the extension study (CCDZ173X2201E1) at the Part II End of treatment visit, the following applies:

During the four weeks after the last day of dosing the patients will be followed-up for safety. On Day 112 patients will undergo the end of study visit.

Premature discontinuation of study treatment

Patients who discontinue study treatment prematurely will perform an early treatment discontinuation visit (named V104.1) with the assessments marked with a * in the assessment schedule (including imaging), as soon as possible after their treatment discontinuation.

If the premature discontinuation from study treatment happens before the scheduled V104, the patients will be asked to also return at Day 85, and complete the Visit 105 (without further imaging assessments to avoid additional radiation). This will be considered their last Visit.

If on the other hand the premature discontinuation from study treatment happens at or after the scheduled V104, the patients will in addition to the early treatment discontinuation visit be asked to perform the EOS visit 4 weeks after the treatment discontinuation visit. This will be considered their last Visit.

Rationale of study design

The design of this study addresses the primary objective of decreasing lymphoproliferation and its sequelae in patients with APDS/PASLI and takes into account the rarity of this disease.

Commercially Confidential Information

After completion of Part I, the dose selection for Part II was based on the safety and tolerability profile observed during up-titration in Part I (and also in the FIH study), and on a combined assessment of all available

PK/PD and biomarker data. This included PD biomarkers immediately downstream of PI3Kδ (notably *ex vivo* stimulated and non-stimulated cellular pAkt levels) as well as biomarkers further downstream (such as cytokine serum levels) to ensure that the selected dose for Part II adequately suppresses the genetically activated pathway.

CT or MRI imaging in Part I allowed assessment of feasibility with these imaging modalities in APDS/PASLI patients and a first estimation of the effect size.

Part II aims to demonstrate evidence of efficacy and further information on safety and tolerability. Lymphoproliferation, including lymphadenopathy, hepatomegaly, splenomegaly and lymphocytic aggregates in intestinal and bronchial mucosa, is a hallmark of the disease and considered responsible for sequelae such as infections (such as pneumonia), bronchiectasis and obstructions. The second major phenotype of patients with APDS/PASLI is an immunodeficiency leading to frequent bacterial, fungal and viral infections, including opportunistic infections; these infections further contribute to the tissue destruction in the pulmonary tract. Thus, measures for lymphoproliferation and immunodeficiency have been selected as co-primary endpoints in Part II.

Commercially Confidential Information

3.2 Rationale of dose/regimen, duration of treatment

3.2.1 Part I

Commercially Confidential Information

The same maximum dose of 70 mg CDZ173 b.i.d. is proposed for both adults and adolescents (12 years of age and older).

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

3.2.2 Part II

Lymphoma showed a time to response - assessed by Cheson criteria - of 1-2 months (Gopal et al 2014, Brown et al 2014). Therefore, Novartis considers reduction of lymphadenopathy a clinically relevant endpoint in a 12-week efficacy study.

Based on the results from the Part I study, Part II will be performed with 70 mg b.i.d. CDZ173. All 6 patients enrolled in Part I completed the 12 week treatment period as planned, with no significant safety or tolerability issues. CDZ173 treatment reduced PI3Kδ-pAkt pathway activity as measured by the phosphorylation of Akt (pAkt) in B cells and results from the 3 different dose levels indicate that 70 mg b.i.d. is needed for adequate suppression of the pathway

Commercially Confidential Information

3.3 Rationale for choice of comparator

There is no approved treatment for APDS/PASLI and standard of care is primarily symptomatic treatment including intravenous (i.v.) or subcutaneous (s.c.) immunoglobulin replacement and antibiotic therapy for infections, and steroids or other immunosuppressants to control lymphoproliferation. In the absence of disease-modifying approved treatment, this study does not use an active comparator but explores CDZ173 on top of pre-established symptomatic treatment.

The conclusions from Part I for dose selection in Part II are based on objective laboratory biomarkers and no relevant subjective influence is expected; further, comparisons will be done between dose-levels (during up-titration) within subjects. Thus, no critical information would be obtained from including placebo patients and Part I was designed uncontrolled which also accounts for the rarity of patients with the studied disease.

Part II includes both objective and subjective assessments necessitating the use of placebo to introduce a subject, investigator and sponsor-blinded design. Furthermore, APDS has been described only recently and the natural history of the disease is not well-characterized. In this situation subject, investigator and sponsor-blinded, placebo-controlled design is needed to determine if potential changes from baseline are due to the effects of CDZ173 or to natural changes in disease characteristics over time. To account for the rarity of patients with the studied disease, patients will be randomized 2:1 as described in Section 3.1.2.

3.4 Purpose and timing of interim analyses/design adaptations

Commercially Confidential Information

3.5 Risks and benefits

APDS/PASLI patients have a mutation in the gene encoding the PI3Kδ, leading to a constitutive activation of the PI3Kδ – pAkt pathway, which is considered to be the etiopathology of the disease manifestations (see Section 1.1). CDZ173 inhibits the PI3Kδ – pAkt pathway (see Section 1.1.1.5), thus, CDZ173 may be effective in counter-regulating the constitutive activation of this pathway. Although, 12 weeks treatment with CDZ173 in the open-label Part I of the study led to significant improvements in the clinical presentation of the patients, it is still unknown whether this can solely be attributed to the treatment with CDZ173 and whether such beneficial effects can be confirmed in a larger group of patients in Part II of this study.

Commercially Confidential Information

Currently only a limited number of APDS/PASLI patients have been exposed to CDZ173 and this patient group could show additional adverse events and/or a different PK profile than healthy volunteers. The study design applying within-patient up-titration in Part I minimized the risk associated with unexpected adverse events in this population.

Risks and benefits evaluation for the adolescent population (12 – 15 years of age)

APDS/PASLI is a disease more common in pediatric patients than in adults. Infections and obstructions caused by the immunodeficiency and the lymphoproliferation associated with APDS/PASLI lead to permanent tissue destructions such as bronchiectasis (Lucas et al 2014; Angulo et al 2013). Thus, early treatment is predicted to be advantageous. Furthermore, senescent T cells are a hallmark of APDS/PASLI (Lucas et al 2014). The thymus, the major site of T cell production and thus the source of T cell replenishment, undergoes in childhood and notably under the influence of sex hormones during puberty, an involution characterized by a decrease in size, weight and activity (Appay et al 2010). It may be expected that an early treatment of patients with APDS/PASLI, prior to near-complete involution of the thymus, might be beneficial.

Due to the seriousness of the disease and its early onset, adolescent APDS patients already have a long history of hospital visits, including those with invasive measures (e.g. IVIG). Although the additional burden of this clinical trial is relatively modest, procedures, pain and burden will be minimized in adolescents. In particular there will be pain prevention (e.g. by local anesthesia if wished by the participant) and timing coordinated with daily activities as far as possible and defined in the protocol.

MRI or CT scans have associated risks related to the contrast media such as nausea, hypersensitivity reactions, accumulation and functional impact of contrast agents in several organs. In case of known hypersensitivity, no contrast media will be used. Burdens may include discomfort, claustrophobia, fear, pain from venipuncture and heat sensation in case of contrast agent injection and need for specialist setting. Patients will be fully informed about all details of the procedure. During the procedure patients carry an emergency button with them, allowing premature termination of the procedure at any time.

Commercially Confidential Information

4 Population

A total of 6 patients with APDS/PASLI were enrolled in the study in Part I. In Part II of the study approximately 30 patients will be randomized. Patients enrolled in Part I of the study will not participate in Part II, i.e. new patients will be recruited.

The Investigator must ensure that all patients being considered for the study meet the following eligibility criteria.

Patient selection is to be established by checking through all eligibility criteria at screening. 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 patient from enrollment into the study.

The inclusion and exclusion criteria listed in Section 4.1 and Section 4.2 are valid for the population to be included in Part I and Part II of the study, no additional differentiation should be made between patients selected for Part I or II.

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 and female patients age 12 to 75 years of age (inclusive), who have a documented APDS/PASLI-associated genetic PI3K delta mutation.

   Commercially Confidential Information
3. In Part I and II of the study patients must have nodal and/or extranodal lymphoproliferation and clinical findings and manifestations compatible with APDS/PASLI such as a history of repeated oto-sino-pulmonary infections and/or organ dysfunction (e.g., lung, liver). Additionally in Part II, patients must have at least one measurable nodal lesion on a CT or MRI scan.

   Commercially Confidential Information
4. At screening, vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position after the patient has rested for at least three minutes. Sitting vital signs should be within the following ranges:
   - Systolic blood pressure, 90-139 mm Hg
   - Diastolic blood pressure, 50-89 mm Hg
   - Pulse rate, 50 - 100 bpm; up to 110 bpm in adolescents
5. Commercially Confidential Information
6.

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. Commercially Confidential Information
2.
3. Previous or concurrent use of immunosuppressive medication such as:
   - mTOR inhibitor (e.g. sirolimus, rapamycin, everolimus) or a PI3Kδ inhibitor (selective or non-selective PI3K inhibitors) within 6 weeks prior to first dosing, however short-term use for up to a total of 5 days is allowed but only up to 1 month prior to enrollment in the study.
   - B cell depleters (e.g., rituximab) within 6 months prior to first dosing of study medication; if patients have received prior treatment with a B cell depleter, absolute B lymphocyte counts in the blood must have regained normal values.

- Belimumab or cyclophosphamide within 6 months prior to first dosing of study medication.
- Cyclosporine A, mycophenolate, 6-mercaptopurine, azathioprine or methotrexate within 3 months prior to first dosing of study medication.
- Glucocorticoids above 25 mg prednisone or equivalent per day within 2 weeks prior to first dosing of study medication.
- Other immunosuppressive medication where effects are expected to persist at start of dosing of study medication.

4. Commercially Confidential Information

5.

6.

7.

Commercially Confidential Information

8.

9.

10.

11.

12.

13. Administration of live vaccines (including any attenuated live vaccines) starting from 6 weeks before study entry, during the study and up to 7 days after the last dose of CDZ173 should be excluded.
14. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
15.

Commercially Confidential Information

Commercially Confidential Information

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:

Commercially Confidential Information

5.2 Prohibited treatment

It is recommended that a pharmacist should review a patient's concomitant medication in relation to the potential drug interactions described below.

5.2.1 Drugs that are prohibited

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.

Vaccination

Live/Attenuated Vaccination: The study drug is considered to decrease activities of cells of the immune system, thus from 6 weeks prior to start of treatment, until 7 days after end 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.

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

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 the Site Operations Manual. The subject number assigned to a patient at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see 'Subject numbering' section in the SOM.

6.1.1 Investigational treatment

The investigational drug, CDZ173 10 and 70 mg capsules and matching placebo capsules will be prepared by Novartis and supplied to the investigator site as open label patient-specific packs for Part I and blinded patient specific packs for Part II.

6.2 Treatment arms

CDZ173 capsules or matching placebo capsules will be administered orally as follows:

Part I of the study was open-label; all patients sequentially received 10 mg, 30 mg and 70 mg CDZ173 b.i.d. for 4 weeks duration.

Commercially Confidential Information

Part II

Study treatments are defined as:
a: 70 mg oral dose of CDZ173 b.i.d. for 12 weeks
b: matching placebo b.i.d. for 12 weeks

Commercially Confidential Information

6.3 Permitted dose adjustments and interruptions of study treatment

Commercially Confidential Information

6.4 Treatment assignment

Treatment numbers for Part I of the study and randomization numbers for part II of the study will be assigned in ascending, sequential order to eligible subjects (see Site Operations Manual for details). The Investigator will enter the randomization/treatment number on the CRF.

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

6.5 Treatment blinding

Part II of the study is subject, investigator and sponsor-blinded: patients, investigator staff, and sponsor persons performing the assessments, and data analysts will remain blind to the identity of study treatments. An independent data monitoring committee (DMC) will evaluate unblinded data for safety purposes (See Section 10.3)

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.

Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions: DMC members, unblinded pharmacist or authorized designee at site, unblinded monitor (where used) and the PK bioanalyst.

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

6.6 Emergency breaking of assigned treatment code

Emergency unblinding should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. A complete set of emergency code break cards will be provided to the investigator site(s) and a complete set will be available at Novartis. All code break cards must be retained until the end of the study and returned to Novartis. They must be stored in a secure place but be accessible in case of emergency. The investigator will receive a blinded code break card for each subject, with the details of drug treatment covered by a removable, scratch-off cover. In an emergency, the scratch-off cover can be removed to determine the treatment. The scratch-off covers are not to be removed for any reason other than an emergency. When the investigator removes the scratch-off cover he/she must note the date, time, and reason for removing it and retain this information with the case report form documentation. **The unblinded treatment code should not be recorded on the CRF.** The investigator must also immediately inform the Novartis local monitor that the code has been broken.

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

6.7 Treatment exposure and compliance

Sequential blood samples will be collected in all patients up to 8 hours post after the first dose administration (Day 1). Commercially Confidential Information In addition, trough samples to assess PK steady-state will be taken at weekly or two-weekly intervals in Part I and Part II of the study, respectively.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with CDZ173, as detailed in Section 8.5.

Patients will complete a patient diary to ensure compliance in taking study medication and study drug accountability will be performed by study personnel.

6.8 Recommended treatment of adverse events

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

Commercially Confidential Information

Commercially Confidential Information

6.9 Concomitant treatment

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

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

The Investigator should discontinue study treatment for a given patient if, on balance, they believe that continuation would be detrimental to the patient's well-being.

Study treatment must be discontinued under any of the following circumstances:

- Patient withdraws consent
- Pregnancy
- The patient experiences a drug-related serious adverse event
- Diarrhea of CTCAE Grade 2 or higher on 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

Commercially Confidential Information

The following deviations from the prescribed dose regimen for study treatment:

- More than 10 missed doses in Part I of the study and more than 28 missed doses of study treatment in Part II (cumulative; whether consecutive or otherwise).

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, see Section 5.2

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

Patients who discontinued study treatment prematurely will perform an early treatment discontinuation visit (named V104.1) with the assessments marked with a * in the assessment schedule (including imaging), as soon as possible after their treatment discontinuation.

If the premature discontinuation from study treatment happens before the scheduled V104, the patients will be asked to also return at Day 85, and complete the Visit 105 (without further imaging assessments to avoid additional radiation). This will be considered their last Visit.

If on the other hand the premature discontinuation from study treatment happens at or after the scheduled V104, the patients will in addition to the early treatment discontinuation visit be asked to perform the EOS visit 4 weeks after the treatment discontinuation visit. This will be considered their last Visit.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 7.3). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, and letter) should be made to contact them as specified in Section 7.2.1.

7.2 Study completion and post-study treatment

Each patient will be required to complete the study in its entirety, unless consent is withdrawn. All patients completing the study will be offered continuous treatment in the extension study CCDZ173X2201E1. Study completion is defined as when the last patient completes their End of Study visit, or in the event of an early study termination decision, the date of that decision.

Study completion is defined as when the last patient completes 12 weeks treatment and his/her End of Study visit, or the Visit 105 in the case where the patient rolls over to continuous treatment in the CCDZ173X2201E1 study.

At a minimum, patients will be contacted for safety evaluations during the 30 days followingcompletion of treatment, either via the scheduled EOS visit or via the first visits in the CCDZ173X2201E1 study in the cases where patient rolls over directly to this study for continued treatment .

If the patients directly continue treatment in the extension study (CDZ173X2201E1), the safety follow up is not needed as they will be followed up during the Visits in the extension study. Documentation of attempts to contact the patient should be recorded in the source documentation.

7.2.1 Lost to follow-up

For patients 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 patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.3 Withdrawal of consent

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

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

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

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

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

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

Commercially Confidential Information

7.4 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 patients experience a drug-related serious adverse event
- More than two patients in Part I or more than three patients in Part II 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 (e.g. in the case of pre-clinical safety findings, or issues with the study drug)

7.5 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, patients should be seen as soon as possible and treated as a prematurely withdrawn subject. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests.

The Investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

Table 8-1 Assessment schedule Part I

Patients should be seen for all visits on the designated day, with the assessments performed as per schedule, within the allowed "visit/assessment.

Study phase	SCR	BSL	Dose 1 (10 mg)				Dose 2 (30 mg)				Dose 3 (70mg)				EOS
[1] *Visit Numbers*	*1*	*2*	*101*	*102*	*103*	*199*	*201*	*202*	*203*	*299*	*301*	*302*	*303*	*304*	*499*
Days	-50 to -2	-1	1	8	15	28	29	36	43	56	57	64	71	84	112
Visit Windows		-3 days*		+/- 1 day	+/- 1 day		+/- 1 day	+/- 1 day	+/- 1 day		+/- 1 day	+/- 1 day	+/- 1 day	+3 days	+/- 2 days
Written Informed Consent	X														
Inclusion /Exclusion criteria	X	X[2]													
Relevant medical History / Current medical conditions	X	X[2]													
Demography	X														
CCI															
Physical examination	X	X					X				X			X	X
CCI	X														
CCI	X[3]	X					X				X			X	X
Vital signs and body measurements															
Body height	X														
Body weight	X	X													X
Body temperature	X	X	X	X	X		X	X	X		X	X	X	X	X
Blood pressure / Pulse rate[4]	X	X	X[5]	X	X		X[5]	X	X		X[5]	X	X	X	X
ECG evaluation (triplicates)	X	X	X[5]	X	X		X[5]	X	X		X[5]	X	X	X	X
Hematology, Blood chemistry, Urinalysis	X	X	X	X	X		X	X	X		X	X	X	X	X
CCI	X														
CCI		X	X				X				X			X	
CCI		X	X				X				X			X	
CCI									X[6]						
PK blood collection			X[7]	X	X		X[7]	X	X		X[7]	X	X	X	
PD blood collection		X	X[8]	X	X		X[8]	X	X		X[8]	X	X	X	
CCI		X	X				X				X			X	
		X	X				X				X			X	
PBMC for functional T cell assay		X												X	
CCI		X												X	
Drug administration record[9]			X	X	X	X	X	X	X	X	X	X	X	X	
MRI or CT scan	X[11]													X[12]	
SF-36/WPAI-CIQ Questionnaires		X					X				X			X	
Physican/Patients Global assessment		X					X				X			X	
Patient Narratives														X	
Phase/Study completion		X				X				X				X[14]	X
Comments	As required														
Adverse Events (comment)	As required														
Concomitant meds/Therapies	As required														

Commercially Confidential Information

Table 8-2 Assessment Schedule Part II

Epoch	Screening		Treatment					Follow-up	Notes
Visit name	SCR	BSL	Treatment				EOT	EOS	
[1] *Visit Numbers, Core Period*	*1*	*2*	*101*	*102*	*103*	*104*	*105*	*199*	[1] Visit structure given for internal programming purpose only
Days	-50 to -7	-1	1	15	29	57	85	112	
Visit windows				+/- 3 day	+/- 3 day	+/- 3 day	+/- 3 day	+/- 5 day	
Written Informed Consent	X								
Inclusion /Exclusion criteria	X	X[2]							
Relevant medical History / Current medical conditions	X	X[2]							
Demography CCI	X								
Physical examination*	X	X	X[16]	X	X	X	X	X	
	X						X		
CCI	S								
	X[4]	X			X	X	X	X	
	S								
Randomisation			X						
Vital signs and body measurements									
Body height*	X						X		
Body weight*	X	X			X	X	X	X	
Body temperature*	X	X	X	X	X	X	X	X	
Blood pressure / Pulse rate[5*]	X	X	X[6]	X	X	X	X	X	
ECG evaluation*	X	X	X[6]	X	X	X	X	X	
Hematology, Blood chemistry, Urinalysis[7*]	X	X	X	X	X	X	X	X	
CCI	S								
		X	X		X	X	X		

Commercially Confidential Information

Epoch	Screening		Treatment					Follow-up	Notes
Visit name	SCR	BSL	Treatment				EOT	EOS	
[1] *Visit Numbers, Core Period*	*1*	*2*	*101*	*102*	*103*	*104*	*105*	*199*	[1] Visit structure given for internal programming purpose only
Days	-50 to -7	-1	1	15	29	57	85	112	
Visit windows				+/- 3 day	+/- 3 day	+/- 3 day	+/- 3 day	+/- 5 day	
CCI		X	X		X	X	X		Commercially Confidential Information
		X[8]							
PK blood collection*			X[10]		X	X	X		
CCI		X	X		X	X	X		
		X	X		X	X	X		
PBMC for functional T cell assay*		X					X		
CCI		X					X		
Drug administration record[12]*			X	X	X	X	X[17]		
MRI or CT scan*	X[13]						X[13]		
SF-36/WPAI-CIQ Questionnaires*		X			X	X	X		
	X								
CCI	X					X			
		X					X		
Patient/Physician global assessment*		X			X	X	X		
Patient Narratives							X		
Study/Epoque completion information		X						X[15]	
Comments	As required								
Adverse Events (comment)	As required								
Concomitant meds/Therapies	As required								

Footnotes Assessment Schedule Part II

BSL: Baseline, SCR: Screening, EOT: End of treatment, EOS: End of Study, ICF: Informed Consent Form, S: source data only (not to be captures in the eCRF), X for any blood collection unless otherwise mentioned pre-dose is meant.

Patients can roll over for continuous treatment in the open-label CCDZ173X2201E1 extension study, after their EOT visit. For the patients who do not directly roll over to treatment in the extension study (CCDZ173X2201E1) at the EOT visit, the following applies: During the four weeks after the last day of dosing the patients will be followed-up for safety. On Day 112 patients will undergo the EOS visit.

8.1 Informed consent procedures

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

If incapable of doing so, in cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

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

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. Any changes to the proposed consent form suggested by the Investigator must be agreed to by Novartis before submission to the IRB/IEC.

Commercially Confidential Information

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 demographics/other baseline characteristics

Patient demographics: year of birth, sex, race, predominant ethnicity and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the CRF. Where possible, the diagnoses and not symptoms should be recorded.

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 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.

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.

Commercially Confidential Information

8.3 Efficacy / Pharmacodynamics

8.3.1 Efficacy

Commercially Confidential Information

8.3.1.1 Imaging with MRI/CT

For the assessment of the impact of CDZ173 on lymphadenopathy, patients will be scanned in an MRI or a CT scanner as based on clinical practice and local regulation. The same imaging modality will be used throughout the study for the same patient.

Commercially Confidential Information

Commercially Confidential Information

In Part I of the study MRI or CT imaging modalities was used in APDS/PASLI patients for a first estimation of the effect size. In Part II clinical efficacy will be assessed. The SPD approach will be used for primary endpoint while more experimental yet accurate 3D measures will be used for secondary endpoint.

For further details on image acquisition and image analysis, see site operations manual/MRI/CT subject scanning guide and imaging review charter, respectively.

8.3.1.2 High Sensitivity C-reactive protein (hsCRP), Lactate dehydrogenase (LDH), beta2 microglobulin, ferritin, fibrinogen and analysis of erythrocyte sedimentation rate

The following parameters will be measured to assess biomarkers reflecting the efficacy of CDZ173 to reduce systemic inflammatory components of APDS/PASLI: High Sensitivity C-reactive protein (hsCRP), Lactate dehydrogenase (LDH) and for Part II additional: beta2 microglobulin, ferritin, fibrinogen and analysis of erythrocyte sedimentation rate.

Commercially Confidential Information

8.3.2 Pharmacodynamic assessments

Pharmacodynamic assessments are specified below, with the methods for assessment and recording specified in the Study Operations Manual. Assessments will be performed/samples collected at the timepoint(s) defined in the Assessment schedule.

8.3.2.1 *Ex vivo* stimulated phosphorylation of Akt in B cells from whole blood

The pharmacodynamic effect of CDZ173 is assessed using *ex vivo* stimulated and unstimulated phosphorylation of Akt in B cells in the Part I of the study. Akt is a direct downstream target of activated PI3Kdelta. Determination of the percentage (%) of CD20+ phospho-Akt positive cells after *ex vivo* stimulation of whole blood is performed by flow cytometry analysis. Unstimulated cells will serve as controls. The stimulation of fresh samples and freezing of stimulated and unstimulated samples are to be performed at the clinical sites.

8.3.3 Patient-Reported Outcome

8.3.3.1 Short form 36 Survey (SF-36)

The purpose of SF-36 in this study is to assess the physical and mental functioning of patients.

The SF-36 is a widely used instrument to measure generic health status. It is a 36-item questionnaire that has proven useful in monitoring generic and specific populations, comparing the relative burden of different diseases, differentiating the health benefits produced by different treatments, and in screening individual patients.

The SF-36 measures the impact of disease on overall quality of life and consists of eight subscales (physical function, pain, general and mental health, vitality, social function, physical and emotional health) which can be aggregated to derive a physical-component summary score and a mental-component summary score

All patient-reported measures should be completed at the center by the latest 3 hours post dose. Completed questionnaires will be reviewed and examined by the Investigator. The Investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the patient.

If AEs or SAEs are confirmed then the physician must record the events as per instructions given in Section 9 of the protocol. Investigators should not encourage the patients to change the responses reported in the completed questionnaires.

8.3.3.2 Work Productivity and Activity Impairment (WPAI) plus Classroom Impairment (CIQ) Questionnaire

The WPAI in this study measures the amount of absence or presence and daily activity impairment attributable to APDS/PASLI. As younger patients (age 12 and above) may also be enrolled in the study the WPAI-CIQ version of the questionnaire will be used for all patients as it also measures the amount of absence or presence for school attendance and daily classroom activity impairment attributable to APDS/PASLI.

8.3.3.3 Patient Global assessment Questionnaire

The patient's global assessment questionnaire asks patients about their APDS related well-being using 100 mm visual analogue scale (VAS) ranging from "very poor" (0) to "very good" (100).

8.3.3.4 Physician's Global assessment Questionnaire

In the physician's global assessment questionnaire the Investigator rates the disease activity of their patient using 100 mm VAS ranging from "no disease activity" (0) to "maximal disease activity" (100).

To enhance objectivity, the physician must not be aware of the specific patient's global assessment, when performing his own assessment on that patient.

8.3.3.5 Narratives

Narratives on each individual patient will be collected in order to assess the treatment benefit. Investigators will be asked for a description of the patient's disease manifestations at the end of treatment, and to provide details on the areas where the patient improved or worsened during the treatment phase.

8.4 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment Schedule detailing when each assessment is to be performed.

During an epidemic or pandemic (e.g. COVID-19 pandemic) that limits or prevents on-site study visits regular phone or virtual calls will occur (as per the assessment schedule or more frequently if needed) for safety monitoring and discussion of the participant´s health status until the participant can again visit the site.

8.4.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed.

Information for all physical examinations must be included in the source documentation at the study site and will not be recorded the 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.

If assessment of the patient's general clinical status shows no significant change between baseline (visit 2) and the first treatment visit (visit 101), the results of the physical examination at baseline (visit 2) can be used for first treatment visit (visit 101) data entry as well, and the actual physical exam does not need to be repeated.

8.4.2 Vital signs

Vital signs will include the collection of body temperature (recorded in °C), blood pressure (BP) and pulse measurements.

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, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

If vital signs are out-of-range at screening and/or baseline, two additional readings can be obtained, so that a total of up to three consecutive assessments are made, with the patient seated quietly for approximately five minutes preceding each repeat assessment. The last reading must be within the ranges provided in the eligibility criteria in order for the subject to qualify.

8.4.3 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.

Commercially Confidential Information

8.4.5 Laboratory evaluations

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.

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count, aPTT and PT/INR will be measured.

Clinical chemistry

Sodium, potassium, creatinine, urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, GGT, AST, ALT, amylase, lipase, CK, glucose, insulin, total cholesterol and triglycerides. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

Thyroid stimulating hormone (TSH), T3 and T4 will also be measured as part of the clinical chemistry safety laboratory panel.

Urinalysis

Urine test by dipstick e.g. Combur9: 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.

8.4.6 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed in triplicate (mean value recorded in the CRF) with the patient in the supine position as indicated in the Assessment Schedule. Interpretation of the tracing must be made by a qualified physician and documented on the ECG printout. Each ECG tracing should be labeled with the

- study number
- patient initials
- patient number
- date and signature of ECG interpreter

and kept in the source documents at the study site.

Clinically significant abnormalities detected during the Screening visit exam should be recorded on the relevant Medical history CRF page, and on the Adverse Events page if detected during other visits. Clinically significant findings must be discussed with the sponsor.

The CRF will contain:

- date and time of ECGs
- statement of clinically significant findings
- PR interval, QRS duration, heart rate, RR, QT, QTcF (Fridericia QT correction formula to be used).

8.5 Pharmacokinetics

Commercially Confidential Information

Pharmacokinetic (PK) samples will be collected at the time points defined in the Assessment schedule.

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

PK samples will be obtained and evaluated in all subjects at all dose levels.

Commercially Confidential Information

Untreated samples (placebo) will not be analyzed.

Concentrations will be expressed in mass per volume units and will refer to the free base.

Commercially Confidential Information

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

The following plasma pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): Cmax, Tmax and AUClast. Other PK parameters, including but not limited to AUCinf, CL(ss)/F and Cmax may be added as appropriate.

The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of T1/2 will include at least 3 data points after Cmax. If the adjusted R^2 value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported for T1/2, AUCinf and CL/F.

In addition to non-compartmental methods, individual compartmental modelling (Phoenix WinNonlin, version 6.2 or higher) may be used to derive individual estimates of oral drug clearance (CLss/F) as well other model-derived parameters such as absorption rate constant and volume of distribution.

8.6 Other assessments

Commercially Confidential Information

Commercially Confidential Information

8.6.2 Exploratory Biomarker assessments

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

8.7 Use of residual biological samples

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

The 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 patients 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 (current)

If CTC-AE grading does not exist for an adverse event, use:

- 1=mild,
- 2=moderate,
- 3=severe
- 4=life threatening.

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 an outcome of not recovered/not resolved should be reported.
4. whether it constitutes a serious adverse event (SAE) See Section 9.2 for definition of SAE
5. action taken regarding [study/investigational] treatment(select as appropriate).

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

   - no action taken (i.e. further observation only)
   - study treatment dosage adjusted/temporarily interrupted
   - study treatment permanently discontinued due to this adverse event
   - concomitant medication given
   - non-drug therapy given
   - subject hospitalized/subject's hospitalization prolonged
6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

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

The Investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patients'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 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 subject or may require medical or surgical intervention.

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

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

9.2.2 SAE reporting

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

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

Information about all SAEs (either initial or follow up information*)* is collected and recorded on the paper Serious Adverse Event Report Form. The Investigator must assess the relationship to 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 DS&E 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.

SAEs (initial and follow-up) that are recorded electronically in the Electronic Data Capture system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Drug Safety & Epidemiology immediately after Investigator signature or 24 hours after entry, whichever occurs first. Study site personnel must also inform the Clinical Trial Leader.

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 DS&E 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.

9.3 Infection Monitoring

All infections that develop during the study will be reported as AEs. Investigators are requested to specifically enquire about signs and symptoms of infections at each visit, in particular bacterial enterocolitis. Treatment and additional evaluations will be performed at the discretion of the Investigator. WBC count (including differential count) is assessed at every visit. If the neutrophil count falls below 1000 per µL, then weekly assessments of WBC are recommended until recovery to within 80% of baseline.

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.

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. The patients must also be reminded to always carry their Patient Information Card (with site contact information and which identifies them as participants in a clinical study with an agent with potential immunosuppressive effects) and to show this to any local healthcare provider they may consult and ask that the Investigator be contacted.

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 in Table 9-2.

For the liver laboratory trigger:

- Repeating the liver function test (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.

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

Baseline serum creatinine is determined as the mean of the serum creatinine measurements at screening and pretreatment on Day 1.

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 DS&E 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.

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 above.

When two or more clinical site(s) are participating in the clinical study, 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 (eCRFs) using fully validated software that conforms to 21 CFR Part 11 requirements. Designated Investigator site staff will not be given access to the Electronic Data Capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies 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 eCRF are complete and accurate. After database lock, the Investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

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

The CRO working on behalf of Novartis review the data entered into the eCRF by investigational staff for completeness and accuracy and instructs 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 the 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).

At the conclusion of a non-IRT study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis.

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the

10.3 Data Monitoring Committee

The DMC will be established (according to Novartis Standard Operating Procedures) for part II of the study. The DMC is an unblinded independent board comprised of specialists with specific knowledge related to conducting clinical studies. Specific details on the composition and the scope of its mandate will be presented in a DMC charter document.

10.4 Adjudication Committee

Not required.

11 Data analysis

11.1 Analysis sets

For all analysis sets, patients will be analyzed according to the study treatment(s) received.

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

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

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

The PD analysis set will include all patients who received any study drug and with no protocol deviations with relevant impact on PD data.

In Part II, the key safety and efficacy endpoints will also be reported by age group (>=18 years old and < 18 years old).

11.2 Subject demographics and other baseline characteristics

In Part I

All data for background and demographic variables will be listed by patient. Summary statistics will be provided for all patients.

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

In Part II

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

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

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

Data for study drug administration (rescue medication) and concomitant therapies will be listed by patient in Part I, and by treatment and patient in Part II.

11.4 Analysis of the primary variable(s)

The primary aim of Part I, along with assessing safety and tolerability, was to determine a dose to be used in the confirmatory Part II. The primary aim of Part II is to assess efficacy of CDZ173 at the selected dose (70 mg b.i.d.) after 12 weeks of treatment.

In Part I, phosphorylated Akt from unstimulated B cells was quantified at baseline and at the end of the 4-week treatment period with each of the three dose levels. The lowest dose level (up to 70 mg b.i.d.) leading to normalization of the unstimulated pAkt in B cells to healthy volunteer levels should be carried into Part II for generation of confirmatory data, but *ex vivo* stimulated pAkt in B cells and other variables may also be taken into account for the selection of the dose.

In Part II, lymphadenopathy will be measured by the SPD of index lesions (selected as per the Cheson methodology (Cheson et al 1999) from MRI/CT imaging) and immunodeficiency will be measured by percentage of naïve B cells out of total B cells. The co-primary endpoints are the change from baseline in the log10 transformed SPD of index lesions and the change from baseline in the percentage of naïve B cells out of total B cells at the end of treatment.

11.4.1 Variable(s)

The selection of the dose from Part I to be carried into Part II was based on inhibition of unstimulated or stimulated pAkt levels in B cells and other variables, including but not necessarily limited to, safety and PK data and biomarkers. Average pAkt inhibition over the dosing interval is defined as the AUC of the inhibition from baseline over 12 hours normalized by the length of the dosing interval (12 hours). Baseline is defined as the arithmetic mean of the Day -1 sample and the Dose 1 Day 1 pre-dose sample.

In Part II, index lesions will be selected from measurable nodal and extranodal lesions as per the Cheson methodology (Cheson et al 1999, see the imaging review charter for details). A maximum of six of the largest dominant lesions should be selected and documented at baseline and assessed again at the end of treatment (i.e. the Day 85 assessment for patients who complete the 12 week treatment period or the treatment discontinuation visit for patients who discontinue treatment prematurely prior to Day 85 visit). The percentage of naïve B cells is assessed at baseline, Day 1, Day 29, Day 57 and Day 85, and at the discontinuation visit for patients who discontinue treatment prematurely prior to Day 85 visit. The co-primary variables to assess efficacy in Part II will be the change from baseline in the log10-transformed sum of the products of diameters (SPD) of the index lesions and the change from baseline in the percentage of naïve B cells out of total B cells.

In Part I, the variables to assess safety consist of AEs, physical exam, vital signs, ECGs, and safety laboratory parameters.

11.4.2 Statistical model, hypothesis, and method of analysis

In Part I, a repeated measure concentration-response model will be fitted to link systemic drug concentration and (un)stimulated pAkt inhibition at each measured time point (including the trough samples taken at later visits). An Emax model will be considered, where the inhibition at dose 0 is fixed at 0. The ED50, the Emax and the hill parameter will be estimated from the data, and a random effect for ED50 and Emax will be estimated for each patient to account for the within-subject correlation between timepoints. Population model parameters will be

converted into their dose equivalents based on desired time-averaged pathway inhibition and estimated oral drug clearance of CDZ173 in the target population.

The average unstimulated pAkt inhibition over the dosing interval (12 h) at each dose level will also be estimated from an Emax dose-response model accounting for intra-individual correlation for the measurements at different doses. The average pAkt inhibition over the dosing interval of 12 h will be calculated based on the measured pre-dose and the 1 h, 3 h, 8 h post-dose samples for each dose level with a trapezoidal rule as the AUC over 12 hours normalized by the length of the dosing interval (12 h). Baseline will be defined as the arithmetic mean of the Day -1 sample and the Dose 1 Day 1 pre-dose sample. The 12h time point will be estimated as an arithmetic mean of the Day 8 and Day 15 pre-dose.

In the Emax dose-response model, the inhibition at doses 0 will be fixed to zero. The hill parameter will be fixed to 1 and the Emax (inhibition at dose of infinity) and ED50 (dose leading to 50% inhibition of unstimulated pAkt) will be estimated from the data. A random effect for ED50 will be estimated for each patient to account for within-patient correlation.

Depending on the average baseline unstimulated pAkt levels, the average level of inhibition needed to reach healthy volunteer levels will be determined. If the dose achieving this level of inhibition cannot be estimated reliably, other parameters such as ED50, either from unstimulated or simulated cells (see below) may be used for the selection of the dose to be carried into Part II. This may be a different dose (up to 70 mg b.i.d) than the 3 doses studied in Part I. All available data will be included in the model. In case it is not possible to measure or model the unstimulated pAkt levels accurately, decision may be based on modeling of the stimulated pAkt levels. Other variables may also be taken into account for the selection of the dose.

In Part II, the SPD of index lesions will be log10 transformed and the change from baseline of the log10 transformed SPD at the end of treatment (i.e. the Day 85 assessment for patients who complete the 12 week treatment period or the treatment discontinuation visit for patients who discontinue treatment prematurely prior to Day 85 visit) will be calculated for patients with baseline and end of treatment SPD measurements. An analysis of covariance will be done to compare the change of the log10 transformed SPD from baseline with treatment as fixed and log10 transformed baseline SPD as a covariate. The baseline intake of glucocorticoids as well as the information about being treated with intravenous immunoglobulin G (IgG) will both be included as categorical (Yes/No) covariates. Comparison of the two treatment groups will be two-sided, with a 5% type I error. Patients with zero lesions at baseline will be excluded from the analysis.

The change from baseline in naïve B cells out of total B cells at the end of treatment (i.e. the Day 85 assessment for patients who complete the 12 week treatment period or the treatment discontinuation visit for patients who discontinue treatment prematurely prior to Day 85 visit) will be calculated for patients with baseline and end of treatment measurements. Baseline will be defined as the arithmetic mean of the baseline and Day 1 values. An analysis of covariance will be done to compare the change from baseline in the naïve B cells between the two treatment groups, adjusted for baseline naïve B cells count. The use of glucocorticoids and intravenous IgG at baseline will both be included as categorical (Yes/No) fixed effects. Comparison of the two treatment groups will be two-sided, with a 5% type I error. Only patients with a reduced percentage of naïve B cells at baseline (defined as below 48 % van Gent et al 2009) will be included to the analysis.

In Part I, all vital signs, ECG, and laboratory data were listed by patient and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) were flagged. Summary statistics were provided by visit/time. All information obtained on adverse events was displayed by treatment and patient. The number and percentage of subjects with adverse events were tabulated by body system and preferred term with a breakdown by treatment. An adverse event starting in one period and continuing into the next period was counted only in the onset period. A patient with multiple adverse events within a body system and treatment period was only counted once towards the total of this body system and treatment.

11.4.3 Handling of missing values/censoring/discontinuations

In Part I, the primary analysis model included all available data, which were considered valid under the missing at random (MAR) assumption.

In Part II, the primary analysis of the lymphadenopathy will include only patients with baseline and end of treatment lymphadenopathy measurements. Also patients with zero lesions at baseline will be excluded from the lymphadenopathy analysis. The primary analysis of the naïve B cells will include only patients who have baseline and end of treatment naïve B cells measurements and who also have a reduced percentage of naïve B cells at baseline (defined as below 48 % van Gent et al 2009). Data collected after the treatment discontinuation visit will not be used in the primary analysis. No methods for imputation of missing data (including those due to COVID-19) are planned.

11.4.4 Supportive analyses

Commercially Confidential Information

11.5 Analysis of secondary and exploratory variables

11.5.1 Efficacy / Pharmacodynamics

In Part I

The changes from baseline of SF-36 and WPAI-CIQ summary scores, and of visual analogue scale scores for PGA and PtGA, were calculated and summary statistics were provided by visit.

Summary statistics by treatment and visit were provided for the change from baseline in High Sensitivity C-reactive protein (hsCRP) and Lactate dehydrogenase (LDH).

The SPD of index lesions will be log10 transformed and the change from baseline of the log transformed SPD at the end of treatment were calculated for all patients. Summary statistics for the change from baseline of the log10 transformed SDP were provided.

The non-index lesions were analyzed as per the Cheson criteria (Cheson et al 1999) described in the imaging manual.

In Part II

The change from baseline of SF-36 and WPAI-CIQ scores, and of visual analogue scale scores for PGA and PtGA, will be calculated and summary statistics will be provided by treatment and visit. An analysis of covariance will be done to compare the change from baseline at the end of treatment (i.e. the Day 85 assessment for patients who complete the 12 week treatment period or the treatment discontinuation visit for patients who discontinue treatment prematurely prior to Day 85 visit) between the two treatment groups, adjusted for baseline value. Comparison of the two treatment groups will be two-sided, with a 5% type I error. The change from baseline will also be analyzed using a longitudinal mixed model, with treatment, time, treatment by time, baseline and baseline by time interaction as fixed effects. For patients who complete the treatment period, this repeated measures analysis will include all measurements in the treatment period (Baseline, Day 29, Day 57 and Day 85). For patients who discontinue treatment prematurely only data up to and including the last planned visit prior to discontinuation will be included in the analysis. Data collected at the treatment discontinuation visit and thereafter will be excluded. An unstructured covariance matrix will be fitted to adjust for correlations among the measurements made on the same patient. The difference between the treatment groups in the change from baseline after 12 weeks of treatment will be assessed at two-sided 5% significance level.

Summary statistics by visit will be provided for the change from baseline hsCRP, LDH, beta2 macroglobulin, ferritin, fibrinogen and ESR.

Summary statistics for the 3D volume of index and measureable non-index lesions and 3D volume and bi-dimensional size of spleen will be provided. An analysis of covariance will be done to compare the change of the log10 transformed value from baseline between the two treatment groups, adjusted for baseline value. Comparison of the two treatment groups will be two-sided, with a 5% type I error.

In Part I and II the non-index lesions will be analyzed as per the Cheson criteria (Cheson et al 1999) described in the imaging manual.

In Part II, summary statistics for the activity parameters (e.g. mean daily number of steps, real world gait speed, overall distance of walking) will be provided by treatment and period (one week at baseline before first treatment and one week as close as possible to Day 85 visit).

11.5.2 Safety

Vital signs

In Part II, all vital signs data will be listed by treatment, patient and visit/time, and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment group and visit/time.

ECG evaluations

In Part II, all ECG data will be listed by treatment, patient and visit/time, abnormalities will be flagged. Summary statistics will be provided by visit/time.

Clinical laboratory evaluations

In Part II, all laboratory data will be listed by treatment, patient and visit/time, and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

In Part II, all information obtained on adverse events will be displayed by treatment and patient. The number and percentage of patients 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.

11.5.3 Pharmacokinetics

CDZ173 plasma concentration data will be listed by treatment, patient, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point. Commercially Confidential Information . Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Commercially Confidential Information
A geometric mean will not be reported if the dataset includes zero values.

Pharmacokinetic parameters will be calculated as described in Section 8.5 and will be listed by treatment and subject. 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.

11.5.4 Pharmacokinetic / pharmacodynamic interactions

Relationships between exposure and selected PD or biomarker variables will be explored by a graphical approach and descriptive statistics of exposure and PD or biomarker 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 Exploratory biomarkers

Commercially Confidential Information

Commercially Confidential Information

11.6 Sample size calculation

In Part I

The sample size for Part I (6 patients) was mainly based on feasibility, while still providing adequate precision to identify an appropriate dose for Part II.

Commercially Confidential Information

In Part II

For Part II, the sample size (20 patients in active and 10 patients in placebo for a total of 30 patients) is mostly driven by the analysis of one of the two co-primary efficacy variables, the change from baseline in the log10-transformed SPD of index lesions.

Commercially Confidential Information

Assuming that 10% of patients are excluded from the analysis of the other co-primary variable, the change from baseline in the percentage of naïve B cells out of total B cells, due to no reduced percentage of naïve B cells at baseline, it is anticipated that 27 patients will provide data for the analysis. Assuming an increase of 25% points and comparable variability as in Part I for the change from baseline to 12 weeks in the percentage of naïve B cells (standard deviation of 14), with 27 patients this part of the study will have 98% power to detect a statistically significant p-value at the 5% level.

With the above assumptions, the power to achieve a statistical significance in both endpoints is at least 78%.

11.7 Power for analysis of key secondary variables

Not applicable.

11.8 Interim analyses

Commercially Confidential Information

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, patient recruitment procedures (e.g. advertisements) and any other written information to be provided to patients. 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

Angulo I, Vadas O, Garçon F, et al (2013) Phosphoinositide 3-kinase delta gene mutation predisposes to respiratory infection and airway damage. Science 342: 866-871.

Appay V, Sauce D and Prelog M (2010) The role of the thymus in immunosenescence: lessons from the study of thymectomized individuals. Aging; 2:78-81.

Bartelink IH, Rademaker CM, Schobben AF, et al (2006) Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. Clin Pharmacokinet 45:1077-97.

Brown J, Byrd JC, Coutre SE, et al (2014) Idelalisib, an Inhibitor of Phosphatidylinositol 3-Kinase p110δ, for relapsed/refractory chronic lymphocytic leukemia. Blood Journal doi:10.1182/blood-2013-11-535047 [Prepublished online March 10, 2014]. http://bloodjournal.hematologylibrary.org (accessed 21 May 2014).

Buty M, Xu Ziyue, Gao M, et al (2017) Quantitative image quality comparison of reduced- and standard-dose dual-energy multiphase chest, abdomen, and pelvis CT. Tomography 3:114-122.

Cheson BD, Horning SJ, Coiffier B, et al (1999) "Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group." J Clin Oncol 17(4): 1244.

Crank MC, Grossman JK, Moir S, et al (2014) Mutations in *PIK3CD* can cause hyper IgM syndrome (HIGM) associated with increased cancer susceptibility. J Clin Immunol 34: 272-276

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

Gopal AK, Kahl BS, de Vos S, et al (2014) PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 370:1008-1018.

Howie RCS (2011) Blood sample volumes in child health research: review of safe limits. Bulletin WHO 89: 46-53

Kandel ES and Hay N (1999) The Regulation and Activities of the Multifunctional Serine/Threonine Kinase Akt/PKB. Experimental Cell Research 253: 210–229.

Kuo W, Corput M, Perez-Rovira A, et al (2016) Multicenter chest computed tomography standardization in children and adolescents with cystic fibrosis: the way forward. Eur Respir J 47:1706-1717.

Lucas C, Kuehn HS, Zhao F, et al (2014) Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110δ result in T cell senescence and human immunodeficiency. Nat Immunol 15: 88-97.

Michalovich D and Nejentsev S (2018) Activated PI3 Kinase Delta Syndrome: From Genetics to Therapy. Front Immunol 9: 369.

Nagayama Y, Oda S, Nakaura T, et al (2018) Radiation dose reduction at pediatric CT: use of low tube voltage and iterative reconstruction. Radiographics 38:1421-1440.

Rao VK, Webster S, Dalm VASH, et al (2017) Effective “activated PI3Kd syndrome”–targeted therapy with the PI3Kd inhibitor leniolisib. Blood 130(21): 2307-2316

Rao VK, Webster S, Dalm VASH, et al (2018) Safety and efficacy of long term suppression of PI3kinase pathway by small molecule PI3Kδ inhibitor leniolisib in APDS (ActivatedPI3KδSyndrome). Poster presentation ESID, Lisbon, Portugal Oct 2018.

van Gent R, van Tilburg CM, Nibbelke EE, et al (2009) Refined characterization and reference values of the pediatric T- and B-cell compartments. Clin Immunol 133: 95–107.

Wang M, Popplewell LL, Collins RH, et al (2014) Everolimus for patients with mantle cell lymphoma refractory to or intolerant of bortezomib: multicentre, single-arm, phase 2 study. British Journal of Haematology, 165: 510–518

Wang Y, Moss J, Thisted R (1992) Predictors of body surface area. J Clin Anesth. 4:4-10

15 Appendix 1

Commercially Confidential Information

Commercially Confidential Information