CCDZ173X2201E1

NCT Nr. 02859727

Clinical Trial Protocol dated 13DEC2022

Pharming Technologies B.V.

CDZ173 (Leniolisib)

Clinical Trial Protocol CCDZ173X2201E1

An open-label, non-randomized extension study to evaluate the long term safety, tolerability, efficacy and pharmacokinetics 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:	2016-000468-41
Version number:	v11 (Clean)
Clinical Trial Phase:	II/III
Release date:	13 Dec 2022

Site Operations Manual (SOM)

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

Notification of serious adverse events and special situations

Dear Investigator,

You must report SAE and Special Situation (SS) (initial or follow-up) to Pharming as summarized below. Refer to Section 9.2 of the protocol for SAE criteria and additional requirements. See also page 2 of theSOM for further details on the method of reporting a SAE and SS.

- Complete SAE reporting form
- Submit SAE reporting form to Pharming Pharmacovigilance Department (PHV) within 24 hours after awareness of the SAE or SS to e-mail address or fax number on the SAE reporting form
- Notify the Pharming Medical Monitor
- The fax number(s) and email addresses are located in the SOM.

Table of contents

List of tables

List of figures

List of abbreviations

ACR	Albumin-creatinine ratio
AE	Adverse event
AIHA	Autoimmune hemolytic anemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APC	Antigen presenting cell
APDS	Activated phosphoinositide 3-kinase (PI3K)-delta syndrome
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Atrioventricular
BCRP	Breast cancer resistance protein
β-hCG	Beta subunit of human chorionic gonadotropin
b.i.d.	bis in die (twice a day)
BMI	Body Mass Index
BP	Blood pressure
BSA	Body surface area
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CIA	Collagen-induced arthritis
CK	Creatine kinase
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
COAR	Clinical Operations analytics and regions
COVID-19	Coronavirus disease
CPK	Creatine phosphokinase
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C- reactive protein
CSF	Clinical Service Form
CT scan	Computed Tomography with X rays
CTC	Common Toxicity Criteria

CV	Coefficient of variation
CYP	Cytochrome P450
DAR	Dose administration record
DDI	Drug-drug interaction
DMC	Data Monitoring Committee
DS&E	Drug safety and Epidemiology
DSMB	Data safety monitoring board
EBV	Epstein-Barr virus
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EE	Ethinyl estradiol
EOS	End of study
EOT	End of Treatment
ESR	Erythrocyte sedimentation rate
FCT	Film-coated tablet
FDA	Food and Drug Administration
FIH	First in Human
FMI	Final market image
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GI	Gastro Intestinal
GLP	Good Laboratory Practice
γ-GT	Gamma-glutamyl transferase
h	Hour
HGC	Hard-gelatin capsule
hsCRP	High sensitivity C-reactive protein
HV	Healthy Volunteer
IB	Investigator 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
ITP	Idiopathic Thrombocytopenic purpura
IUD	Intrauterine device
IUS	Intrauterine system
i.v.	Intravenous
kD	Kilo Dalton
LDH	Lactate dehydrogenase
LFT	Liver function test
LLOQ	Lower limit of quantification
LPLV	Last patient last visit
LVG	Levonorgestrel
MAD	Multiple ascending dose
MedDRA	Medical dictionary for regulatory activities
mg	Milligram(s)
mL	Milliliter(s)
msec	Millisecond
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerable dose
mTOR	Mammalian target of rapamycin
NCA	Non-compartmental analysis
NOAEL	No observed adverse effect level
NTI	Narrow therapeutic index
OC/RDC	Oracle Clinical/Remote Data Capture
o.d.	Once a day
OGTT	Oral glucose tolerance test
PA	Posteroanterior
P-gp	P-glycoprotein
pAkt	Phosphorylated Akt
PASLI	p110δ-activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency

PBPK	Physiology based pharmacokinetics
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PDK1	Phosphoinositide-dependent protein kinase
PGA	Physician's Global Assessment
PHV	Pharming Pharmacovigilance Department
PI	Principal Investigator
PI3K	Phosphoinositide 3-kinases
PI3Kδ	Phosphoinositide 3-kinase delta
PIP3	Phosphatidylinositol-3,4,5-trisphosphate
PK	Pharmacokinetic(s)
p.o.	Oral(ly)
popPK	Population pharmacokinetics
PRO	Patient report outcome
PT/INR	Prothrombin time/international normalized ratio
pSS	Primary Sjögren's syndrome
PtGA	Patient's Global Assessment
OATP	Organic Anion-Transporting Polypeptide
q.d.	quaque die (once a day)
QTcB	Corrected QT interval by Bazett's formula
QTcF	Corrected QT interval by Fridericia's formula
RBC	Red blood cell(s)
RoW	Rest of World
SAD	Single ascending dose
SAE	Serious adverse event
sCR	Serum creatinine
SD	Standard deviation
SF-36	Short Form 36
SOM	Site operational manual
SS	Special Situation
SVT	Supraventricular tachycardia
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA	Therapeutic area
TBL	Total bilirubin

TSH	Thyroid stimulating hormone
µL	microliter
ULN	Upper limit of normal
ULQ	Upper limit of quantification
US scan	Ultrasound scan
VAS	Visual analogue scale
WBC	White blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of consent
WoCBP	Woman of child bearing potential
WPAI-CIQ	Work Productivity Activity Impairment and Classroom Impairment Questionnaire

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 blood) 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.
MRT	Mean residence time determined as AUMCinf/AUCinf following intravenous administration [time].
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]
Vc/F	The apparent initial volume of distribution of the central compartment following extravascular administration
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]
Vss/F	The apparent volume of distribution at steady state following extravascular administration [time].

Glossary of terms

Assessment	A procedure used to generate data required by the study
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with "investigational new drug" or "test substance"
Patient	An individual with the condition of interest
Personal data	Subject information collected by the Investigator that is transferred to Pharming 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
Screen failure	A patient who is screened but is not treated or randomized 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)
Subject	A trial participant
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, samplelabels, etc.
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 patient permanently stops taking study treatment prior to the defined study treatment completion date

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 study 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

Amendment 11 (December 2022)

Amendment rationale

The purpose of this amendment is to notify all stakeholders of the results of an interim analysis of the CCDZX2210E1 and the update of the Investigators Brochure,

Changes to the protocol

Section 1.3 Clinical data has been updated with recent data.

Section 3.6 Risks and benefits updated with recent data.

Section 7.1 Study completion updated, EoT visit to be last study visit if patient transfers to compassionate use program.

Table 8.1 updated, EoT visit to be last study visit if patient transfers to compassionate use program.

IRB's/IEC's

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

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.
The changes described in this amended protocol require IRB/IEC and Health Authorityapproval according to local regulations prior to implementation.

Amendment 10 (December 2021)

Amendment rationale

The purpose of this amendment is to notify all stakeholders of a change in Sponsor for this study. After finalization of the Clinical Study Report of the randomized clinical trial, Study CCDZ173X2201, Pharming Technologies BV will take over Sponsorship of Clinical Study CCDZ173X2201E1 from Novartis. Pharming has acquired the exclusive license to leniolisib in 2019 and is currently taking over the leniolisib clinical development program CDZ173/ leniolisib. Pharming will be the supplier of CDZ173 (leniolisib) following the transition of the Sponsorship.

Changes to the protocol

Changed Sponsor name from Novartis to Pharming throughout the document.

Added IMP name 'leniolisib' as per Pharming IMP label.

List of abbreviations was updated.

Section 9.2 'Serious adverse events and special situations reporting' reporting of special situations added and updated reporting details from Novartis to Pharming PHV.

IRBs/IECs

The changes herein will not affect the Informed Consent. Patients will receive written notification of the change in Sponsor.

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

The changes described in this amended protocol require IRB/IEC and (National) Health Authorityapproval according to local regulations prior to implementation.

Amendment 9 (August 2021)

Amendment rationale

The purpose of this amendment is to update the assessment schedule to correctly reflect the extended study duration (from 5 to 6 years) by adding End of Treatment (EoT) visit (V517) that was inadvertently omitted in the Protocol version 08. Also a typographical error in the List of abbreviations, for CK (creatine kinase), was corrected.

Changes to the protocol

- List of abbreviations CK abbreviation was corrected to creatine kinase.
- Table 8-1 Assessment schedule was updated to correct the extended study duration by adding the previously omitted EoT visit – Visit 517. End of Study (EOS) visit was accordingly adjusted.

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

IRBs/IECs

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

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

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

Amendment 8 (June 2021)

Amendment rationale

The purpose of this amendment is to extend the individual treatment period to 6 years duration.

The study is an extension to the core CCDZ173X2201 study, for which recruitment has been delayed due to the global COVID-19 pandemic. Extended duration will also allow continued treatment of the patients who are benefitting from leniolisib treatment and who are approaching the end of the currently allowed 5 years treatment. The long-term safety data collected so far supports the extension to 6 years treatment duration.

Changes to the protocol

- Protocol Synopsis was updated to reflect the below changes as appropriate.
- Section 1.3.1 was updated with the current number of patients treated with CDZ173, for whom no occurrence of skin rash was reported.
- Section 3.1 was updated to reflect the extension of the treatment period to 6 years
- Figure 3-1 was updated with the extended study treatment.
- Section 3.2 and Section 3.3 were updated with the extended treatment period.
- Section 3.6 was updated with the current number of patients treated with CDZ173, with no relevant AE reported.
- Table 8-1 Assessment schedule was updated with the extended study period and accordingly with an additional study visit – Visit 516.

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

IRBs/IECs

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

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

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

Amendment 7 (October 2020)

Amendment rationale

The purpose of this amendment is to align CCDZ173X2201E1 (extension study) with changes that were made to CCDZ173X2201 (core study) to address questions and comments raised by the Health Authority in Germany (BfArM).

Changes to the protocol

Section 3.6 has been expanded to include a sub-section on the risks and benefits for the adolescent population. Also, the number of patients enrolled into this study has been updated.

Section 4.2, in the exclusion criteria vital signs and QTcF ranges have been updated to align with CCDZ173X2201 (core study)

Section 5.1 was updated to include additional information for the adolescent population

Section 11.4.3 was updated to specify that no methods for imputation of missing date (including those due to COVID-19) are planned

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

IRBs/IECs

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

The changes herein do NOT affect the trial specific model ICF.

Amendment 6 (June 2020)

Amendment rationale

The purpose of this amendment is to address changes to trial conduct in the case of an epidemic or pandemic that limits or prevents on-site visits (eg COVID-19 pandemic). The protocol is adapted to allow delivery of IMP directly to a participant's home. Alternative methods of providing continuing care may be implemented, as well as remote collection of efficacy endpoints, where possible. Informed consent discussion can be done remotely.

Changes to the protocol

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

The major changes to the protocol are as follows:

- List of abbreviations was updated.
- Section 1.1 was updated with more recent information
- Section 3.6 was updated to clarify risks related to the COVID-19 pandemic.

- Section 6.1.1 was updated to include the option of IMP home delivery, in cases when an epidemic or pandemic (e.g. COVID-19 pandemic) limits or prevents on-site study visits.
- Section 8.1 was updated to allow alternative methods of replacing study visits, such as phone calls, virtual contacts (e.g. teleconsult) or visits by site staff/home nursing service to the participant´s home in cases when an epidemic or pandemic (e.g. COVID-19 pandemic) limits or prevents on-site study visits.
- Section 8.2 was updated to allow the Investigator to conduct the informed consent discussion remotely due to limits that prevent an on-site visit during an epidemic or pandemic (e.g. COVID-19 pandemic). The potential for home nursing has been added as an option for providing continuing care during an epidemic or pandemic (e.g. COVID-19 pandemic). Requirement for an additional informed consent for such case was added.
- Section 8.5.1 Remote collection of efficacy endpoints, is allowed, where possible, if an epidemic or pandemic (e.g. COVID-19 pandemic) limits or prevents on-site study visits.
- Section 8.6 was updated to allow safety monitoring and discussion of the participant´s health status to be conducted with regular phone or virtual calls during an epidemic or pandemic (e.g. COVID-19 pandemic), until the participant can again visit the site.
- Section 8.7 was updated to allow a change in sample collection schedule if an epidemic or pandemic (e.g. COVID-19 pandemic) limits or prevents on-site study visits.
- Section 8.8 was updated to allow modification of the sample collection for other assessments in case an epidemic or pandemic (e.g. COVID-19 pandemic) limits or prevents on-site study visits, or if visits by site staff to a participant's home are not feasible.

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

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

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

Amendment 5 (March 2019)

Amendment rationale

The main purpose of this global amendment is to align this protocol with the CCDZ173X2201 study protocol in relation to: eligibility criteria; prohibited medication and the option to use a low dose CT scan in adolescents between 12-15 years of age (inclusive) in sites, where local practice and local authorities/ECs/IRBs approve such CT scans in adolescents for research purposes. Additionally, the individual treatment period is extended to 5 years duration to allow continued treatment of the patients who are benefitting from leniolisib treatment and who are approaching the end of the currently allowed 3 years treatment. The long-term safety data collected so far supports the extension to 5 years treatment duration.

The exploratory objective of the treatment effect on patients' physical activity level by tri-axial accelerometer (exploratory endpoint) was removed, based on experience from the CCDZ173X2201 study and due to operational feasibility.

Based on the feedback from Russian Health Authority, the protocol is also updated to allow for patients enrolled in Russia to keep using the hard-gelatin capsules (HGC) and thus to not participate in the cross-over assessment of the pharmacokinetics and bioavailability of the new film-coated tablets (FCT) formulation relative to the HGC.

Furthermore, changes are made in the Introduction to reflect the updates in the latest Investigator's Brochure.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red~~ for deletions and red underlined for insertions. Editorial changes have been made throughout the protocol for improved clarity.

- Front page: the INN name has been added to the protocol title.
- Glossary of terms was updated with several definitions.
- Protocol Synopsis was updated to reflect the below changes as appropriate.
- Section 1.1 was updated with new CCDZ173X2201 study information.
- Section 1.3.1 was updated with information from completed study CCDZ173X2203 and the Interim Analysis of this extension study CCDZ173X2201E1.
- Section 2.3 the exploratory objective with physical activity assessment by a tri-axial accelerometers is no longer included.
- Section 3.1 was updated to reflect the extension of the treatment period to 5 years.
- Section 3.1.1 was updated with requirement of a phone contact 2 weeks after the switch to the FCT formulation. Additionally, patients enrolled in Russia are allowed to stay on the HGC and not to take part in the pharmacokinetics and relative bioavailability assessment of the FCT formulation.

- Section 3.2 and Section 3.3 were updated with the extended treatment period.
- Section 3.6 Risks and benefits were updated with current information and with the option to use a CT scan of adolescents between 12-15 years of age (inclusive) in sites where local practice and local authorities/ECs/IRBs approve CT scans for research purposes using a low dose CT scan protocol.
- Section 4.1 Inclusion criteria were updated to align with the Protocol Amendment v08 for CCDZ173X2201 study.
- Section 4.2 Exclusion criteria were updated to align with the Protocol Amendment v08 for the CCDZ173X2201 study.
- Section 5.2.1 The Table 5-1 with prohibited medication was updated to allow the use of max 25 mg per day of prednisone or equivalent.
- Section 6.8 Clarification was added for management of Grade 2 or 3 rash.
- Table 8-1 Assessment schedule was updated with clarifications regarding the imaging procedures and regarding assessments that do not need to be repeated for patients rolling over directly at their EoT/EoS of the CCDZ173X2201 study and/or having the visit 501/502 done on the same day. Also the tri-axial accelerometer assessments have been removed and the treatment period was extended to 5 years.
- Section 8.5.1.2 was updated for clarity.
- Section 8.8 The patient's physical activity assessment by the tri-axial accelerometer has been removed.
- Section 8.8.1 was updated to allow CT scans in adolescents between 12-15 years of age (inclusive) in sites where local practice and local authorities/ECs/IRBs approve CT scans in adolescents for research purposes using a low dose CT scan protocol.
- References were updated.

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

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

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

Amendment 4 (June 2018)

Amendment rationale

The protocol was amended to incorporate health authority recommendations for: 1) the management of potentially occurring skin rashes, 2) pregnancy monitoring, and 3) additional screening assessments and eligibility criteria for patients who did not participate in the core study CCDZ173X2201.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red~~ for deletions and red underlined for insertions. Editorial changes have been made throughout the protocol for improved clarity.

- Glossary of terms was updated for Personal Data and Withdrawal of study consent.
- Protocol Synopsis Key inclusion criteria were updated to require documented APDS/PASLI-associated genetic PI3K delta mutation.
- Section 1.1 was updated with CCDZ173X2201 study information.
- Section 1.2.5 Teratogenicity and reproductive toxicity data was updated.
- Section 1.3.1 was updated with latest results from study CCDZ173X2203.
- Section 3.1.1 Text related to switch in formulation and related serial PK sampling was grouped in separate section for clarity.
- Section 3.2 Rationale for study design was updated.
- Section 3.6 Risks and benefits were updated with information from the current study.
- Section 4 Population was updated to include patients 12 to 75 years of age, to be consistent with study CCDZ173X2201.
- Section 4.1 Inclusion criteria were updated with the requirements of documented APDS/PASLI-associated genetic PI3K delta mutation which is consistent with core study CCDZ173X2201.
- Section 4.2 Exclusion criteria were updated to be consistent with core study CCDZ173X2201. Additional exclusion criteria for patients who did not participate in the CCDZ173X2201 study were added.
- Section 6.8 was updated to include instruction on handling of skin rashes.
- Section 7.2 Discontinuation of study treatment criteria were amended with Grade 4 rashes.
- Section 7.3 Withdrawal of informed consent was updated with the new required language.
- Table 8-1 Assessment schedule was updated to include screen tests for HIV, Hepatitis and tuberculosis for patients who did not participate in the core study CCDZ173X2201. Additional pregnancy self-tests were amended as well.

- Section 8.2 Informed consent procedures were updated to clarify that written assent from the patient and consent from his/her parent/guardian are required for patients of 12 – 17 years old.
- Section 8.4.1 was added to include screening tests for hepatitis and HIV.
- Section 8.4.2 was added to include screening test for tuberculosis.
- Section 8.6.7 Pregnancy test was amended to include monthly self-tests.
- Section 9.3 Infection monitoring was updated to suggest more frequent assessment of WBC if deemed necessary by the Investigator if the patient presents with any signs of an infection.
- Section 10.4 Data Monitoring Committee was updated to indicate that the data monitoring committee is independent.

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

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

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

Amendment 3 (March 2018)

Amendment rationale

The protocol was amended to introduce a film-coated tablets (FCT) formulation of CDZ173 and to allow for a single sequence cross-over assessment of the pharmacokinetics and bioavailability of this new formulation relative to the CDZ173 hard-gelatin capsules (HGC).

In addition to investigating Epstein-Barr Virus (EBV) and Cytomegalovirus (CMV) viremia, this amendment introduces measures of lytic and latent burden with these two viruses by exploratory DNA and RNA assessments. Also the viral load of EBV in saliva will be quantified.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red~~ for deletions and red underlined for insertions. Editorial changes have been made throughout the protocol for improved clarity.

- List of abbreviations were updated.
- Pharmacokinetic definitions and symbols were updated
- Synopsis was updated to reflect the changes as appropriate.
- Section 1.2.1 was updated to include CDZ173 film-coated tablet (FCT).
- Section 1.4 Study purpose was updated.
- Section 2.2 Secondary objectives were updated to include evaluation of pharmacokinetics and relative bioavailability of CDZ173 FCT relative to CDZ173 HGC.
- Section 2.3 Exploratory objectives were updated to include endpoint of EBV and CMV lytic and latent in blood, and EBV DNA in saliva.
- Section 3.1 Study design was updated to include the investigation of pharmacokinetics and bioavailability of the CDZ173 FCT relative to the CDZ173 HGC by a single sequence cross-over design.
- Section 3.2 Rationale for study design was updated.
- Section 3.6.1 Blood sample volumes was updated.
- Section 6.1.1 Investigational drug was updated to include both CDZ173 FCT and CDZ173 HGC.
- Section 6.2 Treatment assignment was updated.
- Section 6.4 was updated with instructions on taking the study treatment.
- Section 6.6 was revised for better clarity.
- Section 6.7 was updated to include assessing the relative bioavailability of the two CDZ173 formulations.

- Table 8-1 Assessment schedule was updated to include serial PK assessments, saliva EBV assessment and clarify the vital signs and body measurements. Clinical status evaluation is renamed as Patient Narratives to be consistent with that in the core study.
- Section 8.5.1.2 was updated to include assessments of latent/lytic burden for EBV and CMV, as well as the viral load of EBV in saliva
- Section 8.5.2.5 Clinical Status Evaluation was re-named as Patient Narratives, to be consistent with that in core study CCDZ173X2201.
- Section 8.6.4 was revised to enhance clarity.
- Section 8.7 pharmacokinetics assessments were updated.
- Section 8.8.1 Analysis on tri-axial accelerometer monitoring was updated.
- Section 11.5.2 Analysis of pharmacokinetics variables was updated.
- Section 11.8 Power for analysis of key secondary variables was updated.
- Section 14 References were updated.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

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

Amendment 2 (October 2017)

Amendment rationale

Two main reasons are behind this protocol amendment. One is the decision to offer treatment not only to patients who participated in study CCDZ173X2201 but also to patients who participated in other trials with other PI3Kδ inhibitors and to whom no extended treatment was offered. The second is the decision to add a visit at day 14, to ensure closer monitoring for safety. This addresses the fact that CDZ173-naïve patients could be now enrolled either from the CCDZ173X2201 study placebo arm or from trials with other PI3Kδ inhibitors.

Moreover additional changes were implemented due to:

- aligning protocol with protocol amendment version 07 of the CCDZ173X2201 study.
- aligning protocol with IB edition 7.
- re-introducing the WPAI-CIQ and the SF-36 questionnaires and the physician's global assessment scale, per Health Authority requirement.

Changes to the protocol

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

- Cover page: title changed to underline that this is a non-randomized study.
- Notification of serious adverse events: Drug Safety and Epidemiology (DS&E) is re-named as Chief Medical Office and Patient Safety (CMO & PS).
- List of abbreviations is updated.
- The synopsis was updated to reflect the changes as appropriate.
- Section 1.2.3: Updated according to new IB edition 7.
- Section 1.3.1: Updated according to new IB edition 7.
- Section 1.3.2: Language modifications to enhance clarity.
- Section 1.3.3: Updated according to new IB edition 7.
- Section 1.4: Change of study purpose to provide access to the extension study not only for patients who participated in study CCDZ173X2201 but also for patients previously treated with PI3Kδ inhibitors other than CDZ173.
- Section 2.1: Changed to recognize the new access granted to patients who were previously treated with PI3Kδ inhibitors other than CDZ173.
- Section 2.2: Changed to recognize the new access granted to patients who were previously treated with PI3Kδ inhibitors other than CDZ173.
- Section 2.3: Changed to align with protocol amendment version 07 of the CCDZ173X2201 study and to recognize the new access granted to patients who were previously treated with PI3Kδ inhibitors other than CDZ173.

- Section 3.1: Changed to recognize the new access granted to patients who were previously treated with PI3Kδ inhibitors other than CDZ173.
- Section 3.2: Changed to recognize the new access granted to patients who were previously treated with PI3Kδ inhibitors other than CDZ173 and to add a new visit at day 14.
- Section 3.3: Updated according new IB edition 7.
- Section 3.6: Updated according new IB edition 7.
- Section 3.6.1: Updated to include the blood sample volume for the amended visit and to enhance clarity in the text.
- Section 4: Changed to recognize the new access granted to patients who were previously treated with PI3Kδ inhibitors other than CDZ173.
- Section 4.1: Changed to recognize the new access granted to patients who were previously treated with PI3Kδ inhibitors other than CDZ173.
- Section 4.2: Changed to align with protocol amendment version 07 of the CCDZ173X2201 study.
- Table 8-1: Assessment schedule is updated to introduce an additional visit at day 14 for closer safety monitoring; WPAI-CIQ questionnaire is re-introduced; SF-36 questionnaire and physician's global assessment scale are amended; The time interval for using the triaxial accelerometer is shortened.
- Section 8.3: Changed to recognize the new access granted to patients who were previously treated with PI3Kδ inhibitors other than CDZ173.
- Section 8.5.2: Updated in order to reintroduce the WPAI-CIQ questionnaire; to introduce the SF-36 questionnaire and physician's global assessment scale.
- Section 8.6.4: Updated to specify that only patients who are below 18 years of age at the time of enrollment will have the Tanner Staging performed.
- Section 8.8.1: Updated to shorten the time interval for using the triaxial accelerometer to align with protocol amendment version 07 of the CCDZ173X2201 study.
- Section 8.8.1: Updated to clarify the imaging details.
- Section 8.9: Updated to specify additional research and state that the ICF for additional research is required.
- Section 11.5.1: Updated in order to reintroduce the WPAI-CIQ questionnaire and to introduce the SF-36 questionnaire and physician's global assessment scale.
- Section 11.6.1: Language modifications to enhance clarity.
- Section 14: A new reference is added.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

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

Amendment 1 (March 2017)

Amendment rationale

This protocol amendment for study CCDZ173X2201E1 is being written to introduce the following changes:

- to lower the minimum age for inclusion from 16 to 12 years of age equivalent to the core study CCDZ173X2201;
- to reflect the updates in the latest Investigator's Brochure (edition 6) and contraception requirements that have been changed to include hormonal contraceptives, based on results from a DDI study with a monophasic oral hormonal contraceptive (CCDZ173X2104);
- to adjust the design based on the results obtained from study CCDZ173X2201 Part I;
- to prolong the treatment period of patients beyond 9 months (up to 3 years) based on the successful completion of the 26 week oral (gavage) administration toxicity study in rats and the 39 week oral (gavage) administration toxicity study in monkeys (relevant reports completed).

APDS/PASLI is a disease more common in pediatric patients than in adults. In a cohort of 33 patients with APDS/PASLI at the National Institutes of Health, USA, 14 patients are adults and 19 patients are pediatric (APDS/PASLI Patients - NIH Cohort Overview). 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 onset of treatment is predicted to be advantageous. Further, 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 expectedthat an early treatment of patients with APDS/PASLI, prior to near-complete involution of the thymus, might be beneficial. The juvenile toxicity study in rats as formal requirement prior to treating younger adolescents has been completed. The juvenile toxicity study has been performed in rats as the rat is an accepted model for investigation in young animals. In addition,the rat has been shown to be a relevant species for PI3K inhibitors; the cross-reactivity has beenevaluated both *in vitro* and *in vivo*. Based on this the rat is a suitable model to investigate potential effects of PI3K inhibitors in juveniles. The findings in that study were limited to reversible, minimal effects on the testes of animals from the high dose group. These results were included in the Investigator's Brochure in December 2015. The dosage form currently used for adult study patients, i.e., capsules, is also a dosage form of choice for adolescents of 12 years of age and above (EMA "Reflection Paper: Formulations of Choice for the Paediatric

Population" 2006). In summary, the preclinical safety studies do not preclude inclusion of adolescents, and it may be expected that a long term treatment of adolescent patients might provide additional benefits compared to treating adult patients. Thus, it is proposed to extend the age range to patients with APDS/PASLI above 12 years of age equivalent to the corestudy CCDZ173X2201.

In the narratives of study CCDZ173X2201 Part I increased levels of energy and/or decreased levels of fatigue were reported for all 6 patients. In an attempt to better objectify a patient's activity this will be tracked using a tri-axial accelerometer both in study CCDZ173X2201 Part II and in this extension study. The Patient report outcome (PRO) questionnaires (SF-36 and Work Productivity Activity Impairment and Classroom Impairment Questionnaire (WPAI-CIQ)) did not provide conclusive outcomes in CCDZ173X2201 Part I and these are no longer considered adequate assessments for an open-label design study enrolling also adolescent patients at a minimum age of 12 years. Hence, these questionnaires have been removed from study CCDZ173X2201 Part II and consequently the WPAI-CIQ questionnaire has been removed also from this extension study.

The reports of the 26 week toxicity study in rats and the 39 week toxicity study in monkeys were finalized recently. Rats received oral (gavage) doses of 15, 40 and 120 mg/kg/day CDZ173.In view of treatment-related skin lesions and associated mortality among animals treated at 40 or 120 mg/kg/day, the No observed adverse effect level (NOAEL) was considered to be 15 mg/kg/day (corresponding to Cmax values of 4560 and 6760 ng/mL and AUC values of 13600 and 25900 ng*h/mL in males and females, respectively). Cynomolgus monkeys received doses of 20, 40 and 60 mg/kg/day CDZ173 orally by gavage. Mucosal erosion and ulceration of the large intestine in one male at 60 mg/kg/day and increased QT and QTcB intervals during electrocardiography evaluations at 40 and 60 mg/kg/day were considered adverse. The dose of 20 mg/kg/day was therefore identified as the NOAEL which corresponded with a mean Cmax of 6570 ng/mL and an AUC of 25900 ng*h/mL in males and a mean Cmax of 6980 ng/mL and an AUC of 14700 ng*h/mL in females during Week 39. The results of these 26 week rodent and 39 week non-rodent studies support prolonging the treatment period of patients beyond 9 months in this current study.

Changes to the protocol

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

- The synopsis was updated to reflect the changes as appropriate.
- Section 1.1: Updated with data from the studies completed and on-going till December 2016.
- Section 1.2.3: Updated with long term toxicology studies' reports.
- Section 1.2.4: Improvement of text.
- Section 1.3: Updated with the studies completed and on-going till January 2017, including CCDZ173X2201 Part I.
- Section 2.2: Deletion of WPAI-CIQ from secondary objectives.
- Section 2.3: Update of the objective on lymphoproliferation and addition of the tri-axial accelerometer monitoring according CCDZ173X2201 study Part II.

- Section 3.1: Update of the study design to extend the study up to three years of treatment.
- Section 3.2: Update of the study design to extend the study up to three years of treatment.
- Section 3.3: Addition of information regarding age reduction and update to extend the study up to three years of treatment.
- Section 3.6: Updated with the results of CCDZ173X2201 study Part I and on-going studies till December 2016.
- Section 3.6.1: Updated to extend the study up to three years of treatment.
- Section 4: Updated with the age reduction, contraception new information and rolling-over occurring also at CCDZ173X2201 End of Treatment.
- Section 5.2.1: Sirolimus added to the table.
- Section 5.2.2: Hormonal contraception has been removed from prohibited medication section based on the DDI study CCDZ173X2204 and concomitant medications that are metabolized by CYP3A is changed.
- Section 5.3: Smoking habits will be checked through the whole study in order to capture any change during the long treatment period
- Section 6.5: Addition of the possibility for dose interruption.
- Section 7.2: Improvement of the text.
- Section 8-Table 8-1: Prolongation of the study, addition of the tri-axial accelerometer for physical monitoring and Tanner staging, deletion of WPAI-CIQ questionnaire.
- Section 8.2: Reminding for re-consent in case of changes added to the text.
- Section 8.3: Improvement of the text.
- Section 8.5.1.1: Improvement of the text.
- Section 8.5.2.3: Deletion of the WPAI-CIQ questionnaire and number correction of following sections.
- Section 8.6.3: Additional height measurement during the study has been added for the adolescent patients.
- Section 8.6.4: Addition of Tanner staging for adolescent patients and number correction of following sections.
- Section 8.6.5: Addition of erythrocyte sedimentation rate and removal of hsCRP and LDH in clinical chemistry, since these are already listed in Section 8.5.1.1 describing biomarkers which may reflect the impact of CDZ173 on the inflammatory components of APDS/PASLI. Moving of PT/INR and aPTT from clinical chemistry to hematology.
- Section 8.8.1: A new section is inserted on tri-axial accelerometer monitoring. This new assessment is included in Part II with the aim to better objectify the assessment of changes in the patients' activity level. It replaces the PRO questionnaires.
- Section 9.3: Safety monitoring guidelines added for neutropenia.
- Section 10.4: Addition of a Data Monitoring Committee.
- Section 11.5.1: Analyses of WPAI-CIQ scores was removed.
- Section 11.6.1: Description of handling of biomarker values which fall below the lower limit of quantification and above upper limit of quantification is changed.

- Section 14: Three new references have been added to the List of References.
  Minor editorial changes have been made throughout the protocol for improved clarity.

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

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

Protocol synopsis

Protocol number	CCDZ173X2201E1
Title	An open-label, non-randomized extension study to evaluate the long term safety, tolerability, efficacy and pharmacokinetics 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 to evaluate long-term safety, tolerability, efficacy and pharmacokinetics of CDZ173 in patients with APDS/PASLI immunodeficiency
Sponsor and Clinical Trial Phase	Pharming Technologies BV Phase II/III
Intervention type	Drug
Study type	Interventional
Purpose and rationale	This study is an open-label, non-randomized extension to study CCDZ173X2201. It aims to provide treatment with CDZ173 to patients with APDS/PASLI who participated in study CCDZ173X2201 or who were treated previously with PI3Kδ inhibitors other than CDZ173, and to obtain long term safety, tolerability, efficacy and pharmacokinetic data of CDZ173 in this patient population.
Primary Objective(s)	• To evaluate the long term safety and tolerability of CDZ173 in patients with APDS/PASLI.
Secondary Objectives	• To evaluate the long term efficacy of CDZ173 to modify health-related quality of life in patients with APDS/PASLI. • To evaluate the long term efficacy of CDZ173 by means of biomarkers reflecting the efficacy of CDZ173 to reduce systemic inflammatory components of the disease in patients with APDS/PASLI. • To characterize the pharmacokinetics (trough concentrations) of CDZ173 in patients with APDS/PASLI. • To evaluate the pharmacokinetics and relative bioavailability of CDZ173 film-coated tablets compared to CDZ173 hard-gelatin capsules
Study design	This is a multicenter, multinational, open-label, non-randomized trial to extend active treatment with oral CDZ173 70 mg b.i.d. to those patients with APDS/PASLI who participated in study CCDZ173X2201 or who were treated previously with PI3Kδ inhibitors other than CDZ173, in order to collect long term safety, tolerability, efficacy and pharmacokinetic data. Patients can be enrolled in this extension study either directly at the EOT or EOS visit of the study CCDZ173X2201 or later in time. Patients who were treated previously with PI3Kδ inhibitors other than CDZ173 can be enrolled if they meet the eligibility criteria at the screening visit. The study consists of a screening visit (if the patient rolls-over directly from the CCDZ173X2201 EOT/EOS visit, the screening visit is coincident with the CCDZ173X2201 EOT or EOS visit), a treatment period with CDZ173 oral 70 mg b.i.d., an end of treatment visit and approximately 12 weeks of

	follow-up, including the EOS visit. Treatment with CDZ173 in study CCDZ173X2201E1 will last at maximum 6 years for an individual patient. In case a patient will roll-over directly at the CCDZ173X2201 EOT/EOS visit, the results of the physical examination, pregnancy tests, vital signs and body measurements, ECG evaluation, hematology, blood chemistry and urinalysis of the CCDZ173X2201 EOT or EOS visit will be used as the screening visit assessments for the extension study and will be reported as such in the electronic case report form (CRF) of the extension study. Patients who do not directly roll-over will need to undergo the screening visit assessments at the time of enrollment in this extension study. Moreover the screening visit and the start of treatment (Day 1) can be performed on the same day, if this is needed to enable immediate access to CDZ173 for any patient who participated in the CCDZ173X2201 study. All the inclusion and exclusion criteria should be verified within that day (including laboratory results) and if the patient is enrolled in the afternoon, only one dose will be administered. Then from the next morning the patient will start taking CDZ173 as an oral 70 mg b.i.d. regimen. All patients will receive oral 70 mg b.i.d. CDZ173 hard gelatin capsules (HGC) from Visit 502 until the Investigator site is set up to administer CDZ173 film-coated tablets (FCT). When the Investigator site is ready, at the patient'snext visit, the patient will have a last dose of CDZ173 HGC and have serial PK samples before switching to CDZ173 FCT. The day before this visit, the patient should record the time of his/her evening dose of CDZ173 HGC and provide the information to the Investigator. Next morning on the visit day, after an overnight fasting, the patient will have oral administration of CDZ173 HGC 70 mg administered at the site either under fasting condition, or half an hour after a light breakfast. The dosing time should be 12 hours from that of previous evening, or as close as possible. PK blood samples will be taken before and after dosing until 8 hours post-dose. Safety, biomarker samples and other assessments will be taken as well. The patient will be dispensed CDZ173 FCT and discharged from the site on the same day after completion of all assessments, and will start to take CDZ173 FCT from that evening until next visit. On the day before next visit, the patient will again record the time of his/her evening dose. In the morning of the visit, after an overnight fasting, the patient will be administered oral CDZ173 FCT 70 mg at the site under fasting condition, or 30 minutes after light breakfast, which should be consistent with the previous visit. The dosing time should be 12 hours from that of previous evening, or as close as possible. PK blood samples will be taken before and after dosing until 8 hours post-dose. Safety, biomarker samples and other assessments will be taken as well before the patient is discharged from the site. The patient will continue to take CDZ173 FCT 70 mg b.i.d. until the end of treatment period. Immune dysfunction and lymphoproliferation are the two hallmarks of APDS/PASLI. Measurement of systemic biomarkers (immunophenotyping and chemokines) will allow the assessment of the long-term effect of CDZ173 on the immune system; Computer Tomography or Magnetic Resonance Imaging or Ultra Sound imaging will allow a long term estimation of the effect on the size of lymph nodes and other lymphatic organs. This assessment will be performed only by patients that participated in the CCDZ173X2201 study.

Population	The study population will consist of male and female patients 12 to 75 years of age (inclusive), who participated in study CCDZ173X2201 or who were treated previously with PI3Kδ inhibitors other than CDZ173 and are deemed by the Investigator to benefit from PI3Kδ inhibitor therapy. A maximum of 42 patients are expected to be enrolled in this extension study. Patients who did not complete the planned 12 week treatment period in the CCDZ173X2201 study, can only be enrolled after the unblinding of the study CCDZ173X2201 and confirmation that the patients had deteriorated on placebo treatment. Patients who deteriorated on treatment with CDZ173 in the CCDZ173X2201 study should not be re-exposed to CDZ173.
Key Inclusion criteria	Patients must have completed the study CCDZ173X2201 EOT/EOS visit, or were treated previously with PI3Kδ inhibitors other than CDZ173. Patients who are deemed by the Investigator to benefit from PI3Kδ inhibitor therapy. Patients or their legal representatives (for patients under the age of 18 years) must be able to communicate well with the Investigator, to understand and comply with the requirements of the study. Documented APDS/PASLI-associated genetic PI3K delta mutation. Patients with mutations in either PIK3CD or PIK3R1 can be included.
Key Exclusion criteria	Patients who withdrew consent from the study CCDZ173X2201. Use of other investigational drugs, except CDZ173, within 5 half-lives of enrollment, or within 30 days, whichever is longer. Concurrent use of immunosuppressive medication Administration of any 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. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 2 days after last dose of study medication. Uncontrolled chronic or recurrent infectious disease (with the exception of those that are considered to be characteristic of APDS/PASLI).
Study treatment	CDZ173 (leniolisib)
Efficacy/PD assessments	High sensitivity C reactive protein (hsCRP), lactate dehydrogenase (LDH), frequencies of infections and other disease complications, Short Form 36 (SF-36) Survey and Work Productivity Activity Impairment plus Classroom Impairment Questionnaire (WPAI-CIQ), visual analogue scale for patient's and physician's global assessments, patient narratives by Investigator

Key safety assessments	Adverse events Physical examination Vital signs Safety laboratory (hematology, blood chemistry, urinalysis)
Other assessments	PK assessments of relative bioavailability of the two CDZ173 formulations (HGC versus FCT), steady-state trough concentration of CDZ173
Data analysis	All data for vital signs, ECG evaluations and clinical laboratory evaluations will be listed by patient and summarized by descriptive statistics. All information obtained on adverse events will be displayed by patient. The number and percentage of patients with adverse events will be tabulated by body system and preferred term. A patient with multiple adverse events within a body system is only counted once towards the total of this body system. Log-transformed PK parameters Cmax,ss and AUC0-12,ss from the serial PK sampling visits will be analyzed by a fixed effects model, with formulation and subject as fixed factors. The estimated mean and 90% confidence interval of difference between formulations will be back transformed to obtain the geometric mean ratio (FCT vs. HGC) and corresponding 90% confidence interval.
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 (Jamee, 2019).

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). CDZ173 has been investigated for safety and tolerability in a first in human study (CCDZ173X2101) and 2 drug-drug interaction (DDI) studies (CCDZ173X2102 and CCDZ173X2104). Healthy volunteers have been exposed to single ascending doses up to 400 mg and multiple doses up to 140 mg b.i.d. for two weeks. CDZ173 hasalso 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 expect 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. Part I data from the ongoing Phase 2/3 study CCDZ173X2201 in APDS/PASLI support a beneficial effect of CDZ173 in this disease.

1.2 Nonclinical data

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

1.2.1 Pharmaceutical Properties

CDZ173 phosphate shows good solubility over a broad pH range (> 10 g/L at pH 6.8)

CDZ173 is provided in two formulations: a conventional capsule of granulated phosphate salt of CDZ173 constituting the primary clinical service form (CSF), also called hard gelatin capsules (HGC), and a film-coated tablet (FCT) that is expected to become the final market image (FMI). Patients will be switched from the CSF to the FCT formulation.

1.2.2 Pharmacology

CDZ173 potently inhibits PI3Kδ with a good selectivity over other class I PI3 lipid kinases and related PI3 kinases which results in a low potential to inhibit the PI3Kα-dependent insulin pathway. CDZ173 has an excellent selectivity window to target-unrelated protein kinases, proteases, receptors and ion channels which suggests a favorable *in vitro* safety profile. On the cellular level, CDZ173 potently inhibits multiple PI3Kδ-dependent B cell activities such as proliferation, cytokine production, antigen presenting cell (APC) function and antibody production. In addition, CDZ173 affects the activation and/or function of cells of the innate (mast cells, neutrophils, basophils) and of the adaptive (T cells) immune system. *In vivo*, CDZ173 shows a PK-dependent reduction of *ex vivo* stimulated B cell activation (rat, monkey). This correlates with inhibition of antibody formation in immunized rats and efficacy in rat collagen-induced arthritis. CDZ173 was efficacious in rats in the prophylactic model of collagen-induced arthritis (CIA) at 3 mg/kg.

CDZ173 inhibits, in *in vitro* studies, wild-type PI3Kδ and PI3Kδ carrying one of the published mutations of APDS/PASLI patients, with similar potency and efficacy.

1.2.3 Toxicology

CDZ173 has been tested in rats and monkeys for up to 2 weeks at dose levels up to 300 mg/kg/day. Mortality in rats and morbidity in monkeys were seen at the highest dose (300 mg/kg/day) only, and was accompanied by severe diarrhea and body weight loss. Target organs could be identified in both species as the gastrointestinal (GI) tract (degenerative/regenerative changes, inflammation) and the hemolymphopoietic system (atrophic changes). In rats, effects (mainly at 300 mg/kg/day) in the heart (degenerative changes, necrosis), liver and kidneys (inflammation), thyroid (follicular cell hypertrophy/hyperplasia) and adrenal glands (cortical vacuolation, hypertrophy), mammary gland (activation), and female reproductive system (atrophic changes, inflammation) were recorded. Full or partial reversibility was indicated at the end of a 4-week recovery period.

In addition, in 4 and/or 13-week toxicity studies in rats and monkeys, CDZ173 was tolerated up to the highest tested doses of 120 and 80 mg/kg/day, respectively. Diarrhea and emesis in the monkey limited potentially higher dosing. No test item related mortality was evident in these studies. In rats, the lymphatic tissues, the bone marrow of the sternum and the liver could be identified as target organs mainly in the high dose (120 mg/kg/day) animals. In monkeys,

histopathological findings were restricted to inflammatory effects in the gastrointestinal tract. All effects were generally observed at high dose levels and were fully or partially reversible within a 4 week recovery period. Based on these data, the no observed adverse effect level (NOAEL) in rats and monkeys after 13 weeks of treatment could be established at 30 and 20 mg/kg/day, respectively.

In a 39-week chronic toxicity study in monkeys at doses of 20, 40 and 60 mg/kg/day, 4 unscheduled deaths occurred in study weeks 11 to 16. In these animals (three low-dose and one mid–dose animal), inflammatory effects on the GI tract accompanied by diarrhea and dehydration were considered to be the cause of the moribund condition. While diarrhea has also been observed in the vehicle control group, the incidence and clinical consequence have been greater in animals receiving CDZ173, although there was no dose-response relationship observed. Evaluation of the clinical findings and bacteriology culture results provide strong evidence of a role for Campylobacter infection in these events. In conclusion, based on the available data, mortality was a result of an underlying enteric infection (Campylobacter and possibly enteropathogenic *Escherichia coli*) that may have been exacerbated by CDZ173. It is possible that the immunomodulatory properties of CDZ173 could have contributed to the incidence and severity of the observed bacterial enterocolitis in monkeys. According to the final report mucosal erosion and ulceration of the large intestine in one male at 60 mg/kg/day and increased QT and QTcB intervals during electrocardiography evaluations at 40 and 60 mg/kg/day were considered adverse. The dose of 20 mg/kg/day was therefore identified as the NOAEL.

The NOAEL of 10 mg/kg/day in male juvenile rats in a 10-week rat juvenile study has been established based on slight delays in sexual maturation, reduced sperm counts, decreased testicular weight, alteration in testicular tubular cellularity and minimal inflammatory changes in the epididymides at 30 mg/kg/day and higher dose levels. All these changes showed a clear tendency to recover and did not influence the male fertility even at high dose levels up to 90 mg/kg/day. In chronic toxicity studies in rats, these effects have been observed at the same exposures with similar incidence and severity even after 26 weeks of treatment. There was no progression observed by increasing the treatment period. The described histological changes were restricted to studies in rats and have not been observed in any study in monkeys, even after 39 weeks.

According to the final report on the 26-week rat toxicity study treatment-related skin lesions and associated mortality among animals treated at 40 or 120 mg/kg/day were observed. Consequently, the dose of 15 mg/kg/day was identified as the NOAEL.

Additionally, slight insulin insensitivity/resistance potential was observed following an oral glucose tolerance test (OGTT) study in mice at 100 mg/kg/day. No pancreatic histological effects have been observed in the repeat dose toxicity studies at doses below the maximal tolerated dose.

There was no evidence for a genotoxic or mutagenic potential of CDZ173 *in vitro* or *in vivo*. The phototoxic effect observed *in vitro* was considered to be very weak (photo irritation factor of 5.3).

1.2.4 Non-clinical pharmacokinetics and metabolism

CDZ173 showed favorable pharmacokinetics (PK) in all animal species tested.Oral bioavailability was medium to high (59-86%) and the exposures were roughly dose-proportional, with no relevant drug accumulation upon multiple dosing. The steady state plasma volume of distribution (Vss) was low-to moderate in all species (0.6 – 3.1 L/kg). CDZ173 was not found to cross the blood brain barrier in rats. The *in vitro* binding of CDZ173 to human plasma proteins was 94.5% and similar to the other tested species (87.7 to 96.2%).

In vivo (rat), [^{14}C]CDZ173 was eliminated in nearly completely by metabolism (less than 10% intact parent). Urinary excretion of total radiolabeled dose represented only about 10% of the dose after intravenous (i.v.) and oral (p.o.) administration. Extensive oxidative metabolism was also seen in human hepatocytes *in vitro*. Human oxidative metabolism of CDZ173 was found to be predominantly mediated by cytochrome P450 (CYP) isoenzyme 3A (CYP3A). CYP1A1 also has the capacity to metabolize CDZ173, suggesting a possible role for extra-hepatic metabolism. CDZ173 has low potential for covalent binding to protein.

Based on *in vitro* results and lack of auto-induction *in vivo*, CDZ173 is not expected to affect PK of co-medications by reversible CYP inhibition or induction. CDZ173 showed time-dependent inhibition of CYP1A2 and weak inhibition potential on several hepatic and renal uptake and efflux transporters but not P-glycoprotein (P-gp, for details refer to the IB). CDZ173 was found *in vitro* to be a substrate for P-gp and breast cancer resistance protein (BCRP), see also data in humans in Section 1.3.2).

1.2.5 Teratogenicity and reproductive toxicity data

Potential effects on male fertility have been assessed by careful histopathologic examination of the testes and the accessory organs in the rodent and non-rodent 2-, 13- and 26/39-week toxicity studies. Minimal and reversible effects on the testes (lack of round spermatids in single tubuli) could be observed in rats at doses of 120 mg/kg/d. These effects were not present in monkeys.

In a juvenile toxicity study in rats, animals were treated with CDZ173 for 10 weeks at dose levels up to 90 mg/kg/d. At the end of the study, male and female fertility has been assessed. At the highest dose of 90 mg/kg/d (AUC: 90900 ng*h/mL) a slight decrease of round spermatidsand/ or spermatocytes was observed, as it has been reported from previous toxicity studies at this dose level. However, there was no impact on pregnancy parameters. Total sperm head countwas reduced, but within the historical background data, recorded for animals of this strain and age. Relationship to CDZ173 is therefore considered to be unlikely.

GLP embryo fetal development studies in rats and rabbits have been performed. In rats at doses of 120 mg/kg/d, microphthalmia/ anophthalmia was evident and considered to be related to CDZ173. In rabbit studies (dose-range finding study and main study) there was no biologically relevant increase in the incidence of embryo-fetal variations and malformations or any sign for a teratogenic effect of CDZ173 up to 30 mg/kg/d. At higher doses maternal toxicity (body weight loss) was evident and in one litter two fetuses showed microphthalmia. Considering the microphthalmia in rats, a test item relationship in rabbits cannot be excluded. Based on these data, it can be concluded that CDZ173 is teratogenic in rats at doses of 120 mg/kg/d. The NOAEL for maternal toxicity and embryo-fetal development could be established at 30 mg/kg/d.

Due to these findings women of child bearing potential (WoCBP) are required to use highly effective contraception methods.

The exposure of female partners through semen of male study participants was estimated. Assuming a semen volume of 5 mL, a worst-case scenario of a maximal semen/plasma ratio of 10, 100% bioavailability in the female partner and a volume of distribution of 23.4 L, the maximal exposure of female partners is 7.8 ng/mL. This constitutes a 990-fold safety factor compared to the Cmax at the embryofetal NOAEL in rats. The estimated volume used for these calculations was taken as the central volume (Vc/F) parameter of the current population PK model, which is in close agreement to the lower range value of Vz/F (Section 1.2.4).

Preclinical data with CDZ173 did not show mutagenic, clastogenic or aneugenic potential in the GLP *in vitro* Ames test, chromosomal aberration test in human lymphocytes or *in vivo* micronucleus test in the rat.

1.3 Clinical data

1.3.1 Human safety and tolerability data

CDZ173 has been investigated for safety, tolerability and pharmacokinetics in a first-in-human (FIH) trial (CCDZ173X2101), and in 2 DDI studies (CCDZ173X2102 and CCDZ173X2104).

Single doses of CDZ173 up to 400 mg and multiple doses up to 140 mg b.i.d. for 14 days have been administered to 168 healthy volunteers. In study CCDZ173X2203 a total of 30 patients with pSS were enrolled. These were randomized in a ratio of 2:1 with 20 patients included in the CDZ173 group and 10 patients in the placebo group.

Six (6) APDS patients have completed Part I of the CCDZ173X2201 study, and the report of these results is published (Rao et al 2017). All 6 patients entered this extension study (CCDZ173X2201E1) and results from an Interim Analysis with long-term safety and efficacy data were presented at the European Society for Immunodeficiencies (ESID)conference in 2018 (Rao et al 2018).

Thirty one (31) APDS patients have completed Part 2 of the CCDZ173X2201 study, and the report of these results is published (Rao et al 2022). 29 of the 31 patients entered this extension study (CCDZX2201E1).

The IB provides a summary of safety, tolerability and pharmacokinetic data derived from the studies in healthy volunteers and patients. Overall, these studies demonstrated a favorable safety profile of CDZ173.

In the FIH study (CCDZ173X2101) a serious adverse event (SAE) in the initial 70 mg b.i.d. cohort occurred: one subject experienced on day 3 an SAE of atrioventricular reentrant tachycardia (supraventricular tachycardia, SVT). The symptoms occurred after dosing with CDZ173 and were concurrent with the onset of a minor febrile (viral) illness. The diagnosis of atrio-ventricular re-entrant tachycardia and a concealed lateral bypass tract were confirmed on electrophysiological testing. A successful radiofrequency ablation of the bypass tract was performed and the event resolved. The lateral bypass tract identified during the electrophysiology study and now recognized as a pre-existing condition was considered to be the probable source of the subject's SVT. In accordance with the protocol's stopping rules, the cohort was discontinued on day 4 for all subjects and the Data Safety Monitoring Board (DSMB) was notified. No other abnormalities or SAEs were reported in other subjects for this cohort. A complete safety review was conducted by Novartis, the principal investigator (PI) and the DSMB for the SAE. Since the causative factor of the SAE was likely a congenital condition

and no other subjects had experienced any adverse events (AE) in this cohort, it was agreed to repeat the 70 mg twice daily (b.i.d.) cohort.

An additional extended repeat 70 mg b.i.d. dose cohort and the 140 mg b.i.d. cohort showed no increase of QTcF for subjects administered CDZ173 compared to placebo. The 90% confidence intervals around the placebo-corrected QTcF change from baseline in this cohort exclude 5 msec at nearly all time points.

In the highest dose group (140 mg b.i.d.) of this multiple dose part skin rash emerged as a limiting factor for dose escalation. Three of the 8 subjects in the 140 mg b.i.d. cohort experienced an event of rash. Two subjects reported maculo-papular rash; one was of moderate severity and necessitated discontinuation from the study, the other was of mild severity. A third subject experienced a mild follicular rash. All three events were suspected by the investigator to be related to study medication. Consequently a dose of 70 mg b.i.d. was determined as MTD for multiple dose treatment with CDZ173.

A subject in the 70 mg b.i.d. cohort had an absolute neutrophil count of 900 cells/µL on Day 15 and the repeat assessment was 1000 cells/µL (the baseline value was 1800 cells/µL). At the next assessment (3 days after stopping CDZ173 treatment) the neutrophil levels returned within the range seen at baseline (1900 cells/µL).

In the drug-drug interaction study CCDZ173X2102 one male healthy subject experienced chest discomfort of moderate intensity after a single dose of 10 mg CDZ173 and a single dose of 300 mg quinidine. He was discontinued from the study and hospitalized overnight; accordingly this event was rated as an SAE. The event was not considered related to the administration of CDZ173.

Three healthy female subjects who participated in a second drug-drug interaction study evaluating the effects of multiple oral doses of CDZ173 on the pharmacokinetics of a monophasic oral contraceptive (CCDZ173X2104) and who were dosed with 70 mg b.i.d. CDZ173 experienced neutropenia of 700 - 900 cells/µL after 1–2 weeks of dosing; this laboratory finding was not associated with clinical symptoms and resolved in all subjects after stopping CDZ173 dosing: one subject with pre-existing neutropenia at baseline (1200 cells/µL) remained with neutrophil counts between 1000–1500 cells/µL, the other two subjects normalized to levels above 1500 cells/µL within 24 h post discontinuation of treatment with CDZ173.

Two out of 30 healthy subjects reported occurrence of skin rash, starting after approximately 12 days of treatment with CDZ173. In both subjects treatment with 70 mg b.i.d. CDZ173 was completed according to protocol (until Day 17) and skin rash did not increase in intensity. Skin rashes resolved approximately 10 days after treatment completion with CDZ173.

In study CCDZ173X2203, 30 patients with pSS were investigated (20 patients received 70 mg b.i.d. CDZ173, 10 patients received placebo). Skin rashes were reported by 11 out of 20 patients (55%) dosed with 70 mg b.i.d. CDZ173 and by one patient (10%) in the placebo group. Three of the 11 patients with rash under treatment with CDZ173 discontinued treatment prematurely. One of these patients was hospitalized and accordingly this AE was reported as an SAE. Skin rash is a known AE with other PI3K inhibitors (Flinn et al 2014). In the APDS population studied to date, skin rash was reported in 5 patients. This included 2 patients with an AEs of rash and 1 patient each with rash erythematous, rash maculo-papular, rash macular, and urticaria. All of the AEs of rash were mild (Grade 1). There were no SAEs of rash and no patient discontinued the study due to rash in patients with APDS.
Six APDS/PASLI patients have completed Part I of the CCDZ173X2201 study. CDZ173 was

found safe and well tolerated at all three dose levels (10, 30 and 70 mg b.i.d.). There were no SAEs and no premature treatment discontinuations due to AEs. Twelve weeks 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 CD8+ T cells, reduction of elevated serum chemokines and suppression of the PI3K/Akt pathway activity. For further details of the results please refer to the Interim Clinical Study Report (Part I) of study CCDZ173X2201.

A total of 31 patients in study CCDZ173X2201 Part 2 were given leniolisib 70 mg (21 patients) or placebo (10 patients) twice daily for 12 weeks. No deaths were reported during the study. Five patients (16.1%) reported 11 SAEs. The incidence of SAEs was lower in the CDZ173 70 mg bid group than the placebo group. None of the SAEs were suspected related to study treatment. The results of Part 2 demonstrate clinical efficacy of CDZ173 70 mg bid over placebo in reduction of lymphoproliferation and immunophenotype normalization. The drug was safe and well tolerated in APDS patients aged <18 years and ≥18 years. For details of the results please refer to the Clinical Study Report (Part II) of study CCDZ173X2201.

An interim analysis was reported in 2022 for the CCDZ173X2201E1 (extension study)
A total of 37 patients were enrolled in the extension study. Of these, 26 patients received leniolisib in study CCDZ173X2201 and 11 patients had no prior exposure to leniolisib. A total of 36/37 patients (97.3%) were ongoing in the study as of December 13, 2021. One patient with prior exposure to leniolisib experienced an SAE of cardiac arrest that resulted in discontinuation of study treatment, withdrawal from study, and death. This event was not related to the study drug. The results of the interim analysis of the long-term extension study demonstrate leniolisib is safe and well tolerated in APDS patients as chronic long-term therapy both with and without previous leniolisib treatment with continued improvement in measures of lymphoproliferation and immunophenotype reflecting immune parameters spanning beyond 5 years indicative of continued immune system reconstitution. Infection rates decreased with continued therapy despite decreased antibiotic and Ig support requirements over time.

1.3.2 Human pharmacokinetic data

In the CCDZ173X2101 study, CDZ173 showed favorable pharmacokinetics in humans. No relevant time-dependencies or deviations from dose-proportionality in either oral AUC or Cmax were seen over the entire dose range investigated. The drug was rapidly absorbed, with Tmax being attained at approximately one hour post drug administration (fasted state).

Modest drug accumulation was observed with twice daily dosing (about 1.4 fold), corresponding to an accumulation-derived effective half-life of ~7 hours. Steady-state plasma concentrations are reached in most subjects within 2 days of starting therapy. Inter-subject variability in steady-state AUC and Cmax was low with a maximum of 46% and 27% respectively.

Oral plasma drug clearance at steady state was ~4 L/h, indicating CDZ173 is a low clearance drug. Accordingly, first pass metabolic extraction is not expected to restrict absolute oral bio-availability in a relevant way (<10% of oral dose). Renal clearance was determined to be about 0.2 L/h, approximating to less than 5% of oral dose.

Single dose oral PK of CDZ173 under fed and fasted conditions showed that a high fat meal may affect the rate (~40% decrease in Cmax) but not the extent (AUCinf) of oral absorption of CDZ173. The effect of food intake on pAkt inhibition is expected to be minor and not leading to lower average or trough inhibition.

APDS patients

Mean oral plasma clearance at steady-state in APDS patients (N=6, CCDZ173X2201 Part 1) 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.

Drug-drug interactions

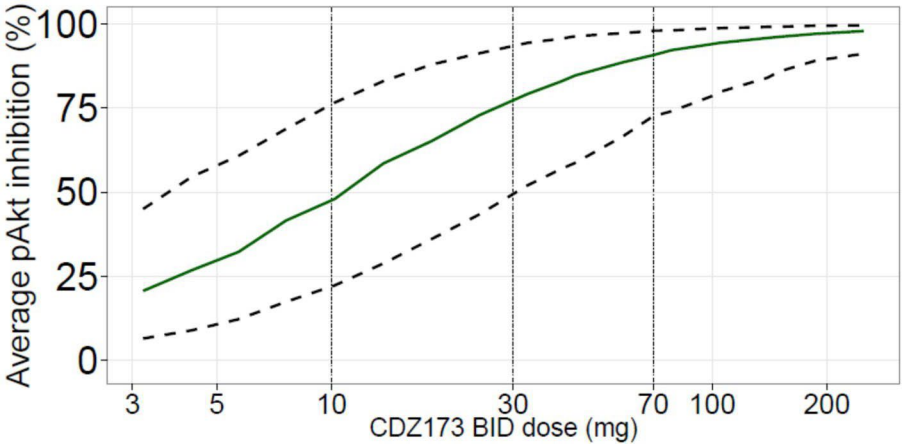
In the clinical study (CCDZ173X2102) investigating the pharmacokinetic interaction between CDZ173 and a strong dual inhibitor of CYP3A and P-gp (itraconazole) or a strong dual inhibitor of P-gp and CYP2D6 (quinidine), it was demonstrated that CDZ173 is neither a sensitive substrate of CYP3A (increase in oral exposure of CDZ173 by about 2-fold) nor a relevant *in vivo* substrate for P-gp or CYP2D6.

Another clinical DDI study assessed the pharmacokinetic effect of CDZ173 on hormonal contraceptives and indicated that CDZ173 did not affect the levonorgestrel (LVG) exposure, while a modest increase of about 1.3-fold in the ethinyl estradiol (EE) exposure was seen (CCDZ173X2104). Consequently, the efficacy of an oral contraceptive of combined EE and LVG is not expected to be compromised by concomitant use of CDZ173.

1.3.3 Human pharmacodynamic data

A population PK/PD model describing the relationship between drug exposure and inhibition of pAkt in ex-vivo stimulated B cells is being developed based on the emerging biomarker and PK data of the completed FIH study. CDZ173 potently inhibited pAkt (IC50 approx. 255 ng/mL) with a clear dose response in the dose range investigated, and the drug effect was sustained upon multiple dosing. Population median pAkt pathway inhibition was found to be about 50% at 10 mg b.i.d., and about 90% at 70 mg b.i.d. (see Figure 1-1).

Figure 1-1 Population PK-PD prediction for average pAkt inhibition (percent)

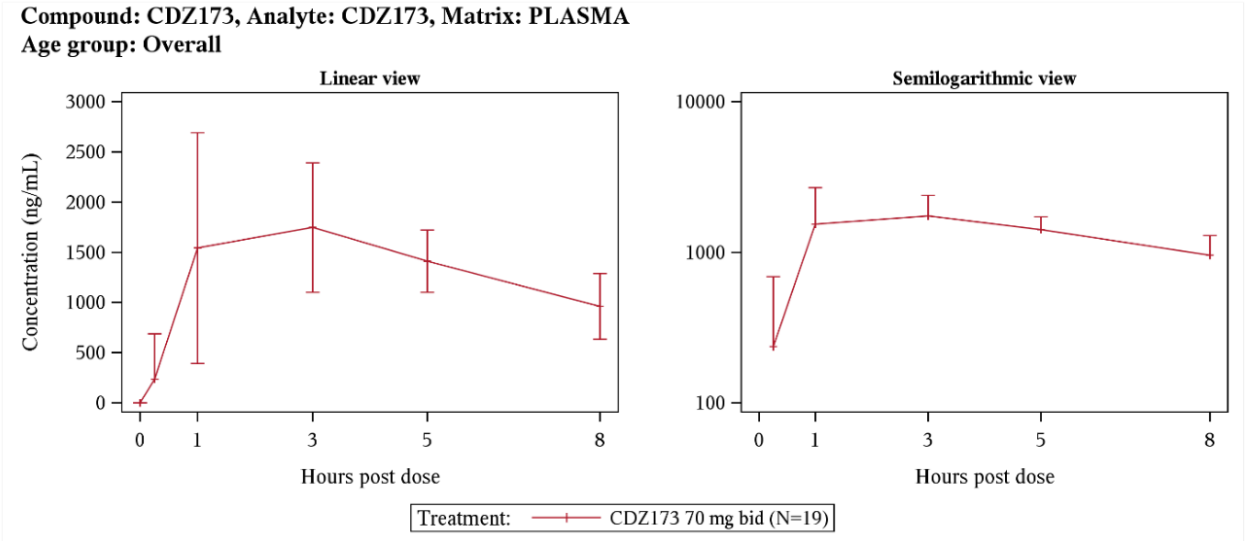


Lower and upper dashed line correspond to the predicted 10th and 90th percentile, respectively, of the population.

Six patients with APDS/PASLI were treated with CDZ173 in doses up to 70 mg b.i.d. in Part 1 of the study CCDZ173X2201. Results confirmed the *in vitro* finding that not only wild-type PI3Kδ but also the mutated PI3Kδ – that characterizes APDS/PASLI – is inhibited by CDZ173 and other finding include regression of lymph nodes and spleen size, reduction of senescent CD4+ and CD8+ T cells, reduction of elevated serum chemokines and suppression of the PI3K/Akt pathway activity.

In 2201 Part 2, systemic drug exposure was characterized by sequential sampling after the first dose administration until 8 hours post-dose and by predose sampling on Day 29, Day 57, and Day 85 after multiple dosing. Arithmetic mean (±SD) CDZ173 plasma concentration-time profiles are presented in figure x-x.

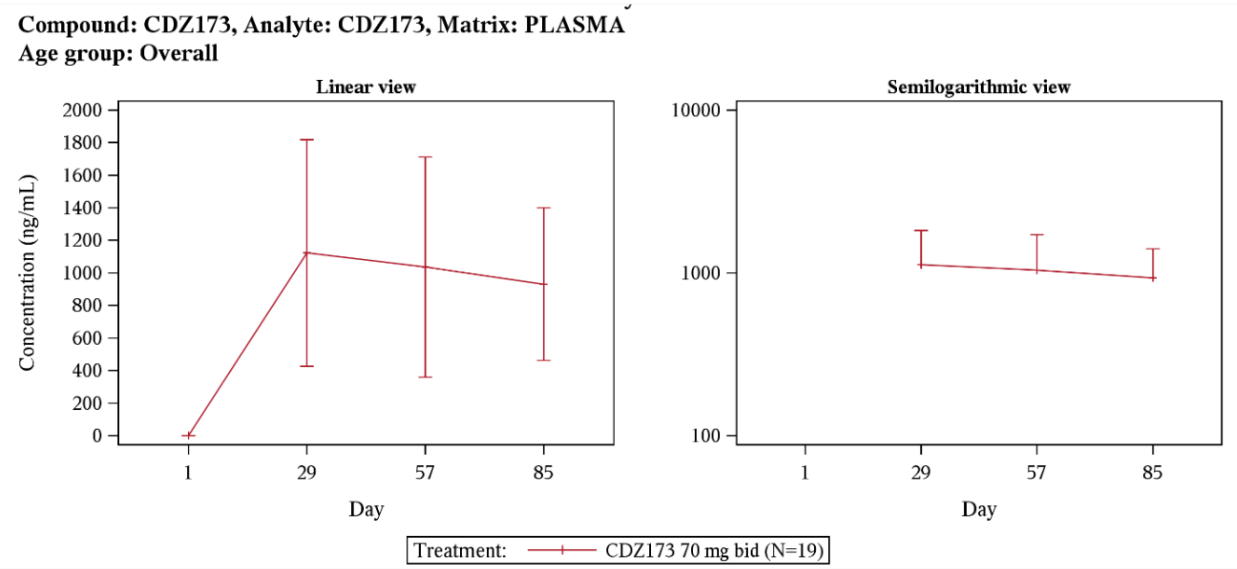
Figure 1-2: Arithmetic mean (SD) CDZ173 plasma concentration-time profiles on Day 1 - Part II (PK analysis set)



Concentrations below the LLOQ are reported as zero.
PK profile is derived from the first dose of 70mg CDZ173 on Day 1

In 2201 Part2, multiple dose PK was characterized by means of steady-state predose plasma concentrations (Ctrough) on Days 29, 57, and 85 post onset of treatment. Arithmetic mean (±SD) CDZ173 plasma concentration-time profiles are presented in figure x-y.

Figure 1-3: Arithmetic mean (SD) trough CDZ173 plasma concentration time profiles- Part II (PK analysis set)



Concentrations below the LLOQ are reported as zero

1.4 Study purpose

This study is an open-label, non-randomized extension to study CCDZ173X2201. It aims to provide treatment with CDZ173 to patients with APDS/PASLI who have participated in study CCDZ173X2201 or who were treated previously with PI3Kδ inhibitors other than CDZ173 and to obtain long term safety, tolerability, efficacy and pharmacokinetic data of CDZ173 in this patient population. Obtaining pharmacokinetic and bioavailability data of the film-coated tablets (FCT) relative to the hard-gelatin capsules (HGC) will support use and dose justification of the FCT in APDS/PASLI patients.

2 Study objectives and endpoints

2.1 Primary objective

Objective	Endpoint
• To evaluate the long term 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))

2.2 Secondary objectives

Objective	Endpoint
• To evaluate the long term 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), Visual analogue scales for Physician's Global Assessment (PGA) and Patient's Global Assessment (PtGA), patient narratives by Investigator
• To evaluate the long term efficacy of CDZ173 by means of biomarkers reflecting the efficacy of CDZ173 to reduce systemic inflammatory components of the disease in patients with APDS/PASLI	• High sensitivity C-reactive protein (CRP), lactate dehydrogenase (LDH), frequencies of infections and other disease complications
• To characterize the pharmacokinetics (trough concentrations) of CDZ173 in patients with APDS/PASLI.	• Steady-state trough concentration of CDZ173
• To evaluate the pharmacokinetics and relative bioavailability of CDZ173 film-coated tablets compared to CDZ173 hard-gelatin capsules	• PK parameters (including but not limited to AUC0-12,ss and Cmax,ss)

2.3 Exploratory objective(s)

Objective	Endpoint
• To explore biomarkers that may provide additional measures of efficacy.	May include but not limited to: • Soluble biomarkers (cytokine and chemokine panels); • EBV and CMV viremia; • EBV and CMV lytic and latent in blood; • EBV DNA in saliva; • IgM, IgG (total and subclasses), IgA; • T and B cell immunophenotyping.
• To assess impact on lymphoadenopathy (non-index lesions and spleen) on patients who participated in CCDZ173X2201 study (refer to Section 8.8.1)	• Reduction of lymphoproliferation measured using MRI/CT imaging or US – e.g. 3D volume of index and measurable non-index lesions selected as per the Cheson methodology, 3D volume and bi-dimensional sizes of spleen and liver, where appropriate.

3 Investigational plan

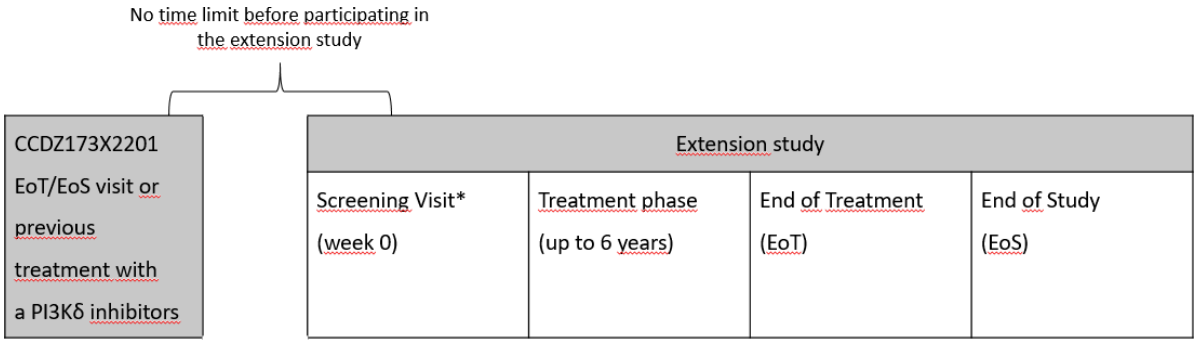
3.1 Study design

This is a multicenter, multinational open-label, non-randomized trial to extend active oral treatment with CDZ173 70 mg b.i.d. to those patients with APDS/PASLI who participated in study CCDZ173X2201 or who were previously treated with PI3Kδ inhibitors other than CDZ173, in order to collect long term safety, tolerability, efficacy and pharmacokinetic data.

The study also investigates the pharmacokinetics and relative bioavailability of the CDZ173 FCT compared to the CDZ173 HGC by a single sequence cross-over assessment.

Patients can be enrolled in this extension study either directly at the end-of-treatment (EOT) or end-of-study (EOS) visit of the study CCDZ173X2201 or later in time. Patients who were treated previously with PI3Kδ inhibitors other than CDZ173 can be enrolled if they meet the eligibility criteria at the screening visit. The study consists of a screening visit (if the patient rolls-over directly from the CCDZ173X2201 EOT/EOS visit, the screening visit is coincident with the CCDZ173X2201 EOT or EOS visit), a treatment period with CDZ173 oral 70 mg b.i.d., an end of treatment visit and approximately 12 weeks of follow-up, including the EOS visit (see Figure 3-1 and Assessment schedule for more details). Treatment with CDZ173 in study CCDZ173X2201E1 will last up to 6 years for an individual patient.

Figure 3-1 Study schema



In case a patient will roll-over directly at the CCDZ173X2201 EOT/EOS visit, the results of the physical examination, pregnancy tests, vital signs and body measurements, ECG evaluation, hematology, blood chemistry and urinalysis of the CCDZ173X2201 EOT or EOS visit will be used as the screening visit assessments for the extension study and will be reported also in the electronic case report form (e-CRF) of the extension study. Patients who do not directly roll-over will need to undergo the screening visit assessments at the time of enrollment in this extension study (see Assessment schedule, Section 8.1).

Moreover, the screening visit and the start of treatment (Day 1) can be performed on the same day, if this is needed to enable immediate access to CDZ173 for any patient who participated in the CCDZ173X2201 study. All the inclusion and exclusion criteria should be verified withinthat day (including laboratory results) and if the patient is enrolled in the afternoon, only one dose will be administered. Then from the next morning the patient will start taking CDZ173 asa 70 mg b.i.d. regimen.

Immune dysfunction and lymphoproliferation are the two hallmarks of APDS/PASLI. Measurement of systemic biomarkers (immunophenotyping and chemokines) will allow to assess the long-term effect of CDZ173 on the immune system. Performance of CT or MRI or ultrasound (US) imaging will allow a long term estimation of the effect on the size of lymph nodes and other lymphatic organs (for methodology refer to SOM and Imaging Reviewing Charter). This assessment will be performed only by patients that participated in the CCDZ173X2201 study.

Patients will be evaluated for any disease recurrence, worsening or improvement as well as for AEs, SAEs and for the criteria for discontinuation throughout the study (refer to Discontinuation of Study Treatment, Section 7.2). For this reason, patients will be encouraged to take notes on any AE and concomitant medication taken at home to be reported to the Investigator.

Safety assessments will include physical examinations, electrocardiograms (ECGs), vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), AE and SAE monitoring.

3.1.1 Treatment switch from HGC to FCT formulation and serial PK sampling

This section is not applicable for patients participating in this study in Russia; these patients will be allowed to continue on the HGC formulation without switching to the FCT formulation and thus will not take part in the pharmacokinetics and relative bioavailability assessment of the FCT formulation.

At all other sites, the treatment will be switched from the HGC formulation to FCT per the process described below:

All patients will receive oral 70 mg b.i.d. CDZ173 HGC from Visit 502 until the Investigator site is set up to administer CDZ173 FCT. When the Investigator site is ready (upon FCT supply at the site), at the patient's next visit, the patient will have a last dose of CDZ173 HGC and have serial PK samples before switching to CDZ173 FCT. The day before this visit (earliest possible visit is Visit 502.1), the patient should record the time of his/her evening dose of CDZ173 HGC and provide the information to the Investigator. Next morning on the visit day, after an overnight fasting, the patient will have oral administration of CDZ173 HGC 70 mg administered by the Investigator at the site either under fasting condition, or half an hour after a light breakfast. The dosing time should be 12 hours from that of previous evening, or as closeas possible. Patients should refrain from eating and drinking for 2 hours post dose. PK blood samples will be taken before and after dosing until 8 hours post-dose. Safety, biomarker samplesand other assessments will be taken as well. The patient will then be dispensed CDZ173 FCT and discharged from the site on the same day after completion of all assessments, provided there are no safety concerns. The patient will start to take CDZ173 FCT from that evening until nextvisit. Patients should be contacted by phone approximately 2 weeks after the start on the FCT formulation to assess for safety (any new adverse events). In case of any concerns, patients should be followed-up as deemed appropriate by the investigator; this may include an unscheduled on-site visit.

On the day before next visit, the patient will again record the time of his/her evening dose. In the morning of the visit, after an overnight fasting, the patient will be administered oral CDZ173 FCT 70 mg by the Investigator at the site under fasting condition, or 30 minutes after a light breakfast, which should be consistent with the previous visit. The dosing time should be 12 hours from that of previous evening, or as close as possible. Food and drink should not be consumed within 2 hours post dose. PK blood samples will be taken before and after dosing until 8 hours post-dose. Safety, biomarker samples and other assessments will be taken as well before the patient is discharged from the site, if no safety concerns.

The patient will continue to take CDZ173 FCT 70 mg b.i.d. until the end of treatment period.

Please refer to Assessment schedule, Section 8.1 and Site Operational Manual for detailed PK sampling and other assessments.

3.2 Rationale for study design

Currently no approved treatment exists for APDS/PASLI. Based on preclinical data (see IB for details) and early, preliminary data from the study CCDZ173X2201 Part I, CDZ173 may specifically target the causative factor of APDS/PASLI, and thereby provide effective treatment for this newly described disease with a significant unmet medical need. Thus, this extension

study will offer continuous CDZ173 therapy to patients who participated in study CCDZ173X2201 or who received previously treatment with PI3Kδ inhibitors other than CDZ173.

Moreover, this study will provide long-term safety, tolerability, efficacy and pharmacokinetic data. Efficacy endpoints may include soluble markers (such as immunoglobulin fractions, cytokines and chemokines) and lymphocyte phenotyping. Increased transitional B lymphocytes and reduced naïve B lymphocytes, as well as senescent T lymphocytes are hallmarks of APDS/PASLI (Lucas et al 2014). Many patients have a class switch defect, and the majority of patients, >80%, have low IgG2 levels and high IgM level; this is expected to contribute to the greatly increased infection risk of APDS/PASLI patients (Angulo et al 2013). Thus, these biomarkers may be supportive data for long-term efficacy of CDZ173 in APDS/PASLI. However, as these markers have so far not been validated as surrogate disease markers for efficacy in APDS, these assessments are considered exploratory. Classic albeit less specific markers of inflammation (hsCRP) and of lymphoproliferation (LDH) will also be measured.

In line with the primary purpose of the study, which is continued treatment availability for the patients that completed the study CCDZ173X2201, this extension is a single arm open-label study. This is a standard design for this type of extension studies.

Safety assessments will be performed regularly: after 14 days of treatment, every 6 weeks for the first three months, then every 3 months until week 36, after one year of treatment and then every 26 weeks until 6 years of treatment for each individual patient. This will ensure that patients who are experiencing any safety issues, considered to be due to the study drug, will exit the study; patients may also exit from the study based on the advice of the Investigator or upon patient's wish. According to the clinical data obtained thus far the Day 14 safety assessment is of specific relevance since the onset of a decrease in absolute neutrophil count was mainly seen within the first two weeks of treatment with CDZ173.

PK trough and PD assessments will be performed every 6 weeks for the first three months, then every 3 months until week 36. Based on the data generated in Part I of study CCDZ173X2201 this schedule appears to be appropriate and it restricts the volume of blood to be collected from each patient to an acceptable level.

A single sequence cross-over comparison of the pharmacokinetics and relative bioavailability of CDZ173 FCT and HGC will provide relevant data for qualification of the FCT as replacement of the HGC while minimizing impact on the overall study conduct and convenienceto study participants.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

A CDZ173 dose of 70 mg b.i.d. was well tolerated in the completed FIH study. In this study, CDZ173 demonstrated a direct pharmacokinetic (PK)/pharmacodynamic (PD) relationship (as measured by pAkt inhibition) and the population median pAkt pathway inhibition at 70 mg b.i.d. was found to be about 90% (see Figure 1-1). Seventy mg b.i.d. is also the final dose given in the preceding study CCDZ173X2201. Thus, the proposed dose for this extension study is 70 mg b.i.d.

The same maximum dose of 70 mg CDZ173 b.i.d. is proposed for both adults and adolescents (12 years of age and older). CDZ173 was found to be predominantly cleared via CYP-mediated oxidative clearance, and the relevant organ functions and metabolic clearance are expected to be mature in adolescents; for such drugs clearance is expected to be more consistent when normalized to the body surface area (BSA) than to the body weight (Bartelink et al 2006). Also the available preclinical and clinical interaction data (study CCDZ173X2102) suggests that the body weight-normalized clearance of CDZ173 is expected to be higher in adolescents relative to adults. As body weight is generally lower in adolescents, compared to adults, the proposed fixed dose regimen will institute a higher dose per kg in adolescents relative to adults, thus limiting the risk of relative under-dosing of adolescents.

Nonetheless, as age and body weight are correlated, absolute values for oral drug clearance vary likely as a function of age, hence, the population median oral drug clearance (CL/F) of CDZ173 is expected to be, on average, lower in adolescents compared to adults. In order to limit the extent of higher exposure in adolescents than in adults, a lower body weight limit of 45 kg is proposed:

- For a 45 kg adolescent with normal body habitus, the DuBois formula (Wang et al 1992) calculates the median BSA to be 1.4 m^2 (male and female), corresponding to a BSA-scaled CL/F of 3.1 L/h, which represents about 80% of the respective adult reference value (3.8 L/h, 1.75 m^2).
- Assuming similar between-subject variability in CL/F in adolescents compared to adults (geomean CV 35 %), the probability is less than 1% that any adolescent with a body weight of 45 kg will experience a drug exposure exceeding the maximum exposure observed in adults so far (59900 ng.hr/mL) at 140 mg b.i.d. At this dose, adult AUC0-12h,ss ranged 25400-59900 ng.hr/mL; in this dose cohort rashes occurred but CDZ173 was otherwise well tolerated with a promising safety profile. Also, no more than 9% of adolescents with a body weight of 45 kg are estimated to have a steady-state oral drug exposure that exceeds the adult 97.5th percentile (AUC0-12h,ss, 35500 ng.hr/mL).

Based on the direct PK/PD relationship and the short residence time (see Section 1.3.2), the same total daily dose given b.i.d. may establish more sustained pathway inhibition with less fluctuation between two consecutive doses compared to once daily (q.d.) dosing. The dosing frequency in the preceding study CCDZ173X2201 was also b.i.d. In agreement with the short half-life of CDZ173, no relevant drug accumulation was seen with b.i.d. dosing (see Section 1.3.2).

The duration of this extension study with maximum individual treatment duration of 6 years, offers to patients a longer treatment and allows for the assessment of safety, tolerability, efficacy and pharmacokinetics over a prolonged period. The available preclinical toxicology data package supports chronic treatment (see also Section 1.2.3).

While the terminal half-life of CDZ173 – approximately 10 hours – ensures a drug wash-out within a few days, the time needed for pharmacodynamic markers to start returning to (pathological) pre-treatment values is expected to be longer than the wash-out of CDZ173. Thus, a follow-up period of 12 weeks has been chosen.

3.4 Rationale for choice of comparator

Not applicable.

3.5 Purpose and timing of interim analyses/design adaptations

Interim analyses may be conducted to support decision making concerning the current clinical study, the Sponsor's clinical development projects in general or in case of any safety concerns.

3.6 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 1.3.3), thus, CDZ173 may be effective in counter-regulating the constitutive activation of this pathway. Although 12 weeks' treatment with CDZ173 in the open-label CCDZ173X2201 study Part I led to significant improvements in the clinical presentation of the patients, it is still unknown whether this can be solely attributed to the treatment with CDZ173 and whether such beneficial effects can be confirmed in a larger group of patients.

In this study, 37 APDS/PASLI patients have received treatment with 70 mgb.i.d. CDZ173 between 50 and 1664 days without relevant CDZ173-related AEs (status of March 31, 2021).

In a recently completed randomized, subject, investigator and sponsor-blinded, placebo-controlled, fixed dose part investigating in 31 adolescent and adult patients with APDS (CCDZ2201 Part 2), 21 patients received CDZ173 70 mg bid and 10 patients received placebo for 12 weeks. The primary objective was to assess the clinical efficacy (lymphadenopathy and immunophenotype normalization) of CDZ173 in patients with Activated Phosphoinositide 3-kinase-Delta Syndrome (APDS). The co-primary endpoints were improvement in lymphoproliferation as measured by 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 and improvement in immunophenotype as measured by change from baseline in percentage of naïve B cells out of total B cells. The co-primary endpoints (change from baseline in the log10 transformed SPD in index lesions and change from baseline in percentage of naïve B cells) were met. CDZ173 70 mg bid over three months was well tolerated by APDS patients. No deaths were reported during the study. Five patients (16.1%) reported 11 SAEs in the study. The incidence of SAEs was lower in the CDZ173 70 mg bid group than the placebo group. None of the SAEs were suspected related to study treatment. The majority of AEs were of Grade 1 or Grade 2 severity. Overall, 25.8% patients (23.8% in CDZ173 70 mg bid vs 30.0% in placebo) reported AEs suspected related to study treatment by the Investigator. None of the AEs led to discontinuation of study treatment. The results of this study demonstrated clinical efficacy of CDZ173 70 mg bid over placebo in reduction of lymphoproliferation and improvement in immunophenotype.

In preclinical *in vivo* studies, adverse effects have been observed after administration of high doses of CDZ173, including diarrhea and vomiting, QTc prolongation, slight insulin insensitivity and thyroid adverse effects (see IB for details). Moderate to severe diarrhea and morbidity requiring euthanasia (individual animals) have been observed in monkeys with an underlying bacterial enterocolitis (see Section 1.3.2). These effects have not been observed in healthy volunteers with single doses of CDZ173 up to and including the highest dose of 400 mg and with multiple doses up to the highest dose of 140 mg b.i.d. Multiple doses of 140 and 70 mg b.i.d. in healthy subjects caused a few events of skin rash and decreases of neutrophils (as described in Section 1.3.1). Skin rashes were also observed in patients with pSS receiving

treatment with 70 mg b.i.d. CDZ173 or placebo (data also described in Section 1.3.1).

CCDZ173X2201 Part I PK data have confirmed an oral clearance of about 4 L/h, in full agreement to the value found in healthy volunteers. At 70 mg b.i.d., median steady-state exposure (AUC0-24h,ss) will be about 35000 ng.hr/mL, which therefore remains about 1.5-fold below the NOAEL observed in the 13-week toxicity study in rats and corresponds to a similar unbound NOAEL exposure observed in the 39-week toxicity study in monkeys (the longest duration toxicity studies available to date). Based on Cmax, even larger safety margins exist (details in IB Section 4.4).

To date only a limited number of APDS/PASLI patients have been exposed to CDZ173 as described above. This sample size is not sufficiently large to exclude occurrence of adverse events in the APDS patient population which are different from those seen in healthy subjects.

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.

No risks are expected to be associated with Tanner staging or with standard physical examination. However, burden (embarrassment, discomfort, distress) is usually associated with examinations that are particularly comprehensive or intrusive such as those related to sexual development. To minimize the burden the examiner will explain every step prior to execution and will adjust the examination time to the individual.

Risks related to an infection with SARS-CoV-2 (all participants)

It is not known whether CDZ173 can have a direct impact on an infection with Coronavirus SARS-CoV-2. However, in Part I of CCDZ173X2201 study CDZ173 improved immune dysregulation in APDS patients, e.g. normalization of circulating transitional and naïve B cells and reduction of senescent T cells was observed (Rao et al 2017), which is why no additional risk is expected for APDS patients treated with CDZ173 during the COVID-19 pandemic.

The risk to subjects in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, defined stopping rules and by prohibiting concomitant medication expected to possibly lead to significant DDI.

WoCBP should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study.

No radiation dose is imparted to the patients receiving an MRI scan or an ultrasound examination. For patients receiving a CT scan, the radiation dose will be between 5 mSv to 15 mSv. This is considered to be a moderate risk level corresponding to the benefit to the patient (category III based on ICR62) and is balanced against the substantial societal benefit gained from the trial. The radiation dose from CT scans will be in accordance with local clinical practice and local regulations. Imaging is an optional procedure in this study. Adolescents between 12-15 years of age will only be assessed by MRI, or using a low dose CT scan protocol at sites where local practice and local authorities/ECs/IRBs approve such CT scans in adolescents for research purposes.

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

3.6.1 Blood sample volumes

No more than 400 mL of blood will be collected over the entire study period. Additional blood samples for monitoring safety may be required during the study. The blood loss due to sampling is not considered a risk to this patient population (both adults and adolescents) since the maximum volume collected at each visit will not exceed 65 mL, and the accumulated volume collected in 12 weeks will not exceed 200 mL.

Timings of blood sample collection are outlined in the Assessment schedule (see Section 8.1).

A summary blood log is provided in the SOM, together with instructions for all sample collection, processing, storage and shipment information.

See Section 8.9 regarding the potential use of residual samples.

4 Population

The study population will consist of male and female APDS/PASLI patients 12 to 75 years of age (inclusive), who participated in study CCDZ173X2201 or who were treated previously with PI3Kδ inhibitors other than CDZ173 and are deemed by the Investigator to benefit from PI3Kδ inhibitor therapy.

A maximum of 42 patients are expected to be enrolled in this extension study. The Investigator must ensure that all patients being considered for the study meet the following eligibility criteria.

For patients who do not roll-over directly at the EOT or EOS visit of CCDZ173X2201 study or who were treated previously with PI3Kδ inhibitors, patient selection is to be established by checking through all eligibility criteria at the Screening visit.

For patients who do roll-over directly from the CCDZ173X2201 study, patient selection is to be established by checking through all eligibility criteria at the CCDZ173X2201 EOT/EOS visit. Patients should not sign the informed consent before eligibility is confirmed at CCDZ173X2201 EOT/EOS visit. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Patients who did not complete the planned 12 week treatment period in CCDZ173X2201 study can only be enrolled after the unblinding of the study CCDZ173X2201 and confirmation that the patients had deteriorated on placebo treatment. Patients who deteriorated on treatment with CDZ173 in the CCDZ173X2201 study should be not re-exposed to CDZ173.

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

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Patients must have participated in study CCDZ173X2201 or were treated previously with PI3Kδ inhibitors other than CDZ173.
3. Patients who are deemed by the Investigator to benefit from PI3Kδ inhibitor therapy.
4. Patients or their legal representatives (for patients under the age of 18 years) must be able to communicate well with the Investigator, to understand and comply with the requirements of the study.
5. Documented APDS/PASLI-associated genetic PI3K delta mutation. Patients with mutations in either PIK3CD or PIK3R1 can be included.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are <u>not</u> eligible for inclusion in this study.

1. Patients who withdrew consent from the study CCDZ173X2201.
2. Use of other investigational drugs, except CDZ173, within 5 half-lives of enrollment, or within 30 days, whichever is longer.
3. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes.
4. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study such as:
    - History of familial long QT syndrome or known family history of Torsades de Pointes.
    - Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree atrioventricular (AV) block without a pacemaker.
    - Resting QTcF (Fridericia preferred, but Bazett acceptable) > 450 msec in male patients of the age group 16 – 75 years, > 460 msec in female patients of the age group 16 – 75 years and > 440 msec in patients of the age group 12 – 15 years, if the measurement is confirmed with an additional ECG repeated as soon as possible. Concomitant use of agents known to prolong the QT interval unless it can be permanently discontinued for the duration of the study.
5. Current use of medication known to be strong inhibitors, or moderate or strong inducers of isoenzyme CYP3A and the treatment cannot be discontinued or switched to a different medication prior to starting study treatment.

6. Current use of medications that are metabolized by isoenzyme CYP1A2 and have a narrow therapeutic index (drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g. Torsades de Pointes)).
7. 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.
8. Donation or loss of 400 mL or more of blood within 8 weeks before Day 1.
9. 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.
10. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation.
11. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 2 days after last dose of study medication. **Highly effective contraception methods include:**
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or total hysterectomy or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

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

12. Patients who were non-compliant or demonstrated a serious protocol deviation in the study CCDZ173X2201.
13. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, regardless of whether there is evidence of local recurrence or metastases.
14. Any surgical or medical condition, which may jeopardize the patient in case of participation in the study or which might significantly alter the absorption, distribution, metabolism, or excretion of drugs. Conditions due to APDS/PASLI are permitted. The Investigator should make this determination in consideration of the patient's medical history and/or clinical or laboratory evidence (e.g. assessed at the end of treatment or EOT/EOS visit of the study CCDZ173X2201):
    - Uncontrolled hypertension (≥140/90 mmHg).
    - Congestive heart failure (New York Heart Association status of class III or IV).
    - Chronic obstructive pulmonary disease (GOLD stage 3-4).
    - Inflammatory bowel disease, peptic ulcers, gastrointestinal including rectal bleeding.
    - Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection.
    - Pancreatic injury or pancreatitis.
    - Liver disease or liver injury as indicated by clinically significant abnormal liver function tests. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) greater than 2.5 times upper limit of normal (ULN).
    - History of renal injury/renal disease (e.g. renal trauma, glomerulonephritis, or one kidney only) or presence of impaired renal function as indicated by a serum creatinine level exceeding 1.5 mg/dL (133 μmol/L).
    - Evidence of urinary obstruction or difficulty in voiding at screening.
    - Uncontrolled diabetes (insulin dependent or non-insulin dependent).
15. Uncontrolled chronic or recurrent infectious disease (with the exception of those that are considered to be characteristic of APDS/PASLI)

Note: In the case where a safety laboratory assessment at screening or at the CCDZ173X2201 EOT/EOS visit is outside of the range specified above, the assessment may be repeated. Values should be within specified ranges prior to treatment.

For patients who did not participate in study CCDZ173X2201 but were treated previously with PI3Kδ inhibitors other than CDZ173, the following additional exclusion criteria apply:

16. 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 for adolescents
17. Patient must have a minimum body weight of 45 kg
18. Evidence of tuberculosis infection as defined by a positive QuantiFERON TB test (or comparable test) at screening. If presence of latent tuberculosis is established then treatment according to local country guidelines must have been completed before patients can be considered for enrollment.
19. Intentionally blank; exclusion criterion removed in this protocol amendment.
20. History of acquired immunodeficiency diseases, or a positive HIV (ELISA and Western blot) test result at screening.
21. A positive Hepatitis B surface antigen or Hepatitis C test (by PCR) result at screening.

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

5 Restrictions for Study Patients

During recruitment, screening/informed consent review, the patients must be informed and reminded of the restrictions outlined in this section.

5.1 Contraception requirements

WoCBP must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

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

For the adolescent population (12 – 15 years of age) previously or temporary abstinent adolescent males and females of child bearing potential must implement effective methods of contraception when becoming sexually active. Female adolescents of child bearing potential as well as males are only to be included in the clinical study if adequately informed about the contraceptive requirements and the need for contraception understood by the study participants and their legal representatives. Consultation, monitoring and questioning regarding potential sexual contacts at each study visit are considered a pre-requisite for adequate contraception in the adolescent population.

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 physician are encouraged to plan required vaccinations outside this window.

Immunosuppressive drugs

Immunosuppressive co-medication could increase the susceptibility to infections. Such drugs are thus prohibited during study participation (see Table 5-1).

Table 5-1 Prohibited immunosuppressive co-medication (examples)

mTOR inhibitors (e.g. sirolimus, rapamycin, everolimus)
Selective or non-selective PI3K inhibitors
B cell depleting medication (e.g. rituximab)
Belimumab
Cyclophosphamide
Cyclosporine A
Mycophenolate
6-mercaptopurine, azathioprine
Methotrexate
Systemic glucocorticoids above 25 mg prednisone or equivalent per day

Strong CYP3A inhibitors, and moderate or strong CYP3A inducers.

Concomitant use of CDZ173 with strong CYP3A inhibitors and moderate and strong inducers is prohibited. In addition, if a patient, after being enrolled, requires the concomitant use of a strong CYP3A inhibitor, then CDZ173 dosing must be interrupted. In this case, CDZ173 dosing may be interrupted for the duration of therapy and up to 1 week of an adequate washout of the inhibitor. CDZ173 dosing may then recommence following consultation with Pharming.

Please refer to Appendix 1-Table 15-1 for a list of prohibited CYP-interacting drugs. Please note that this list may not be comprehensive.

Drugs that are metabolized by CYP1A2

Time-dependent (irreversible) inhibition by CDZ173 was observed for CYP1A2. Concomitant use of CDZ173 with drugs that are primarily metabolized by isoenzyme CYP1A2**and** have a narrow therapeutic index (NTI) is prohibited. CDZ173 dosing may be interrupted (*) for clinically-required treatment with such co-medications for the duration of therapy and up to 1 week of an adequate washout of the co-medication. CDZ173 dosing may then recommence following consultation with Pharming.

(*) It is recommended to respect a CDZ173 washout of at least 3 days **prior to initiating** therapy with the NTI CYP1A2 substrate.

Please refer to Appendix 1-Table 15-1 for a list of prohibited CYP-interacting drugs. Please note that this list may not be comprehensive

5.2.2 Drug to be used with caution

Concomitant medications that are moderate inhibitors of CYP3A

Concomitant treatment of CDZ173 with moderate inhibitors of CYP3A4 is permitted, however, alternatives with less CYP3A interaction potential should be considered first. Duration of concomitant treatment with moderate inhibitors of CYP3A should be kept as short as possible. Note that co-administration of CDZ173 with strong and moderate inducers and with strong inhibitors of CYP3A is prohibited.

Drugs with a risk to induce Torsades de Pointes

If a patient requires the concomitant use of any QT prolonging medication with a risk for Torsades de Pointes, then Investigators, at their discretion, may co-administer such medications. Patients receiving such medications must however be closely monitored due to pre-clinical cardiac observations which however have not been replicated in the completed FIH trial with CDZ173. Note that some drugs with risk for Torsades de Pointes are also strong inhibitors of CYP3A (see Section 5.2.1).

Concomitant medications that are metabolized by CYP3A

CDZ173 was identified in vitro as a potential weak CYP3A inducer. Although the likelihood of an *in vivo* induction is low (as confirmed by dynamic PBPK modelling), a slight decrease in systemic exposure of concomitant medications that are sensitive substrates of CYP3A (sensitive substrates) cannot be entirely ruled out. Investigators, at their discretion, may administer concomitant medications metabolized by CYP3A but caution is advised when CDZ173 is co-administered with drugs that are sensitive substrates of CYP3A and have an NTI. Patients receiving such medications must be monitored for potentiation of toxicity/loss of efficacy due to any individual concomitant medications and may require reduction of the concomitant medication.

Concomitant medications that are substrates or inhibitors/inducers of the efflux transporters BCRP

CDZ173 was identified *in vitro* as a substrate and inhibitor for the efflux transporter BCRP. Although unlikely, an increase in systemic drug exposure and/or altered tissue uptake of oral CDZ173 when co-administered with BCRP inhibitors cannot be ruled out. Likewise, CDZ173 may increase the drug disposition of BCRP substrates. Investigators at their discretion may co-administer known BCRP inhibitors/substrates, however their duration should be kept as short as possible and patients must be closely monitored. Note that some BCRP inhibitors/substrates may also be strong or moderate inducers, or strong inhibitors of CYP3A, which are prohibited (see Appendix 1-Table 15-1).

Drugs that substrates of the hepatic uptake transporter OATP1B1/B3

CDZ173 was identified *in vitro* as a weak potential inhibitor of the uptake transporter OATP1B1/B3. *In vivo* interaction with this transporter is considered remote, however an increase in systemic exposure of OATP1B1/B3 substrates when co-administered with CDZ173 cannot be entirely ruled out. Investigators may co-administer OATP substrates at their discretion when clinically indicated, however, their duration should be kept as short as possible and/or patients must be closely monitored (see Appendix 1-Table 15-2).

Herbal medications

Interactions between herbal supplements/medications and drugs can be multiple and are in general not fully understood. Therefore, herbal supplements/medications should be avoided throughout the study and if taken it should be documented in the concomitant medication page in the CRF. Note that supplements with known CYP3A interaction potential such as St. John's Wort are prohibited as per Appendix 1-Table 15-1.

5.3 Smoking

It is recommended to reduce or completely refrain from smoking. Smoking status will be recorded in the case report form (CRF) at each visit starting from screening. CDZ173 was found to be metabolized by CYP1A1 and CYP1A2, which are inducible by polycyclic hydrocarbons which are formed and inhaled during tobacco smoking although the response varies greatly. This restriction does not apply to nicotine gum or electronic cigarettes.

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for patient numbering, prescribing/dispensing, and taking study treatment are outlined in the SOM.

6.1.1 Investigational and control drugs

The investigational drug CDZ173 (leniolisib) 70 mg will be prepared by Pharming and supplied to the Investigator site as open-label patient-specific packs.

Two formulations of CDZ173 as HGC and FCT will be supplied (except for Russia).

During an epidemic or pandemic (e.g. COVID-19 pandemic) that limits or prevents on-site study visits, delivery of IMP directly to a participant's home is generally permitted in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. Implementation will need to be discussed with Pharming. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 3-months supply. In this case, regular phone calls or virtual contacts (as per the assessment schedule or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, and discussion of the participant´s health status until the participants can again visit the site.

6.1.2 Additional study treatment

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

6.2 Treatment assignment

All patients will receive the same dose and dosing regimen of CDZ173. Patients who were rolled over from study CCDZ173X2201 will keep the patient number they were allocated in that study for the duration of this extension study. For information on patient numbering, please see 'Patient numbering' section in the SOM.

6.3 Treatment blinding

It is an open-label treatment, so no blinding is applicable.

6.4 Treating the patient

CDZ173 will be administered to the patient as oral 70 mg b.i.d. treatment.

- Patients should be instructed to take the dose of CDZ173 daily in the morning and in the evening, at approximately the same time each day. The recommendation is to take the morning dose at approximately 8 am. The evening dose should be taken approximately 12 hours after the morning dose. CDZ173 should be taken with a glass of water and consumed over as short a time as possible. Patients should be instructed to swallow the capsule or tablet as a whole and not to chew it.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.
- Missed doses should not be made up for.
- On clinic visit days, patients should NOT take their morning dose at home. Instead, the study medication will be administered by the study staff at the clinic.

See the SOM for further details.

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

6.5 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments are not permitted (see Section 7.2).

CDZ173 dosing may be interrupted for clinically required treatment with strong CYP3A inhibitors and/or narrow TI CYP1A2 substrates (see Section 5.2.1) or for tolerability or safety issues for a maximum of 28 days. If patients discontinue treatment with CDZ173 for a longer time period they are allowed to restart treatment following thorough evaluation by the Investigator. In such cases the Investigator should also discuss the case with the sponsor and should capture all relevant information in patient narratives.

6.6 Emergency breaking of assigned treatment code

Not applicable since it is an open-label study.

6.7 Treatment exposure / compliance and assessment of relative bioavailability of the two formulations

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects, as detailed in Section 8.7.

PK sampling for assessing relative bioavailability of the two CDZ173 formulations (FCT versus HGC) will be done with more time points allowing the application of non-compartmental methods to derive pharmacokinetic parameters. Eight samples will be collected on two subsequent visits when steady state is reached with either HGC or FCT treatment, as detailed in Assessment schedule.

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

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

6.8 Recommended treatment of adverse events

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

Instruction on handling of skin rashes

As outlined in the current protocol (CCDZ173X2201E1) as well as in the CDZ173 Investigator's Brochure, occurrence of skin rashes has been reported for PI3K inhibitor drugs. Treatment with CDZ173 at doses ≥ 70 mg bid caused skin rashes in a frequency < 10% in healthy subjects, while in patients with primary Sjogren's Syndrome receiving a dose of 70 mg bid skin rash was observed in a frequency of 55% (CCDZ173X2203). Yet, as of 12-Apr-2018, no skin rash has been reported in APDS patients treated with CDZ173.

The following instructions describe the recommended management of potentialCDZ173-related skin rashes in the present study.

Grade 1 skin rash (i.e. <10% body surface area (BSA) with active skin toxicity):

- Continue CDZ173 dosing at the same dose level.
- Initiate topical corticosteroids 3-4 times daily, for a maximum of 28 days.
  Preferred compounds to use are triamcinolone or betamethasone while skin toxicity is active.
- For patients with symptoms like burning, stinging and/or pruritus, add non-sedating anti-histamine.
- If active rash is not resolved within 28 days of appropriate treatment, CDZ173 should be suspended for a maximum duration of 28 days until rash/ skin toxicity is resolved.
  If longer interruption is needed, restarting CDZ173 treatment should only be initiated following thorough evaluation by the Investigator. Re-start CDZ173 at the same dose.

Grade 2 (10-30% BSA with active skin toxicity) and Grade 3 skin rash (>30% BSA with active skin toxicity):

- Suspend CDZ173 dosing until rash/skin toxicity is no longer active but fading (Grade 1), up to a maximum duration of 28 days. If CDZ173 treatment interruption is longer than 28 days, restart should only be initiated following thorough evaluation by the Investigator.
- Initiate topical corticosteroids 3-4 times daily, for a maximum of 28 days. Preferred compounds to use are triamcinolone or betamethasone while skin toxicity is active.

- In case of Grade 2, consider adding systemic corticosteroids 20-40mg/day. In case of Grade 3, add systemic corticosteroids. If rash resolves to ≤ Grade 1 within 10 days, systemic corticosteroids may be discontinued. Please note that any systemic glucocorticoids above 25 mg/day prednisone or equivalent per day will lead to patient having to discontinue CDZ173 treatment and only be followed-up for safety monitoring.
- For patients with symptoms like burning, stinging and/ or pruritus, add non-sedating anti-histamine.
- In case of first occurrence of skin rash, CDZ173 dosing can be re-started at the same dose once rash/ skin toxicity is no longer active but fading (Grade 1). In case of second occurrence, CDZ173 dosing can be re-started at the same dose once rash/ skin toxicity has resolved (this may require CDZ173 treatment interruption > 28 days, and further evaluation by the Investigator is needed).

Grade 4 skin rash (any BSA associated with extensive superinfection, with i.v. antibiotics indicated, life-threatening consequences):

- Permanently discontinue patient from CDZ173 treatment and consider dermatology consultation.
- Treatment of rash should follow instructions for Grade 3 rash above with the exception of re-challenge and with any additional measures needed.

6.9 Concomitant treatment

The Investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study.

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 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.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the Investigator should contact Pharming before treating a patient or, if the patient is already enrolled, to determine if the patient should continue participation in the study.

7 Study Completion and Discontinuation

7.1 Study completion and post-study treatment

Patients will continue in the study for 6 years. After completion of the study no further study treatment will be made available to patients unless a prolongation of this study or a compassionate use is provided.

Study completion is defined as when the last patient completes his/her End of Study visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision. In case compassionate use will be provided, the End of Treatment visit will be considered the final study visit.

7.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study treatment is stopped earlier

than the protocol planned duration. Discontinuation of study treatment can be decided by either the patient or the Investigator.

Study treatment must be discontinued under the following circumstances:

- Patient decision - patients may choose to discontinue study treatment for any reason at any time.
- The Investigator believes that continuation would negatively impact the safety of the patient or the risk/benefit ratio of trial participation.
- Any protocol deviation that results in a significant risk to the patient's safety.
- Pregnancy (see Section 8.6 (Safety) and Section 9.7 (Pregnancy reporting))
- The patient experiences a drug-related SAE.
- Diarrhea of CTC-AE Grade 2 or higher on 3 consecutive days.
- Diarrhea of CTC-AE Grade 3 or higher.
- Diarrhea or abdominal pain with accompanying fever assessed to be related to a GI infection.
- Grade 4 skin rashes as per protocol Section 6.8.
- Use of prohibited treatment as per protocol Section 5.2

If discontinuation of study treatment occurs, Investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the Dosage Administration CRF. Resuming study treatment after a full safety review of the patient needs to be agreed with the investigator and with the Sponsor.

Patients 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, Withdrawal of Informed Consent). Where possible, they should return for the assessments indicated by an asterisk (*) in the Assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the patient/pre-designated contact as specified in Section 7.4 (Lost to follow-up).

7.3 Withdrawal of informed consent

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

- Does not want to participate in the study anymore, and
- 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.

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

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

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

7.4 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.

7.5 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 Pharming:

- Two or more patients experience a drug-related SAE.
- More than three patients report CTC-AE (current version) Grade 3 or higher AEs within the same organ class that are considered to be related to study drug.
- Pharming considers that the number and/or severity of AEs justify discontinuation of thestudy.
- Pharming requests it (e.g. in the case of pre-clinical safety findings, or issues with the studydrug).

7.6 Early study termination by the sponsor

The study can be terminated by Pharming at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, patients must be seen as soon as possible and treated as a prematurely withdrawn patient. 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 patient's interests. The Investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

8.1 Assessment schedule

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

If an epidemic or pandemic (e.g. COVID-19 pandemic) limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls, virtual contacts (e.g. teleconsult) or visits by site staff/home nursing service to the participant´s home depending on local regulations and capabilities, can replace on-site study visits, for the duration of the pandemic until it is safe for the participant to visit the site again.

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

In case that a patient rolls-over directly at the End of Treatment visit of the CCDZ173X2201 study and the visits 501 & 502 are done on the same day, the extension study assessments that correspond to the CCDZ173X2201 assessments (including lab samples, PROs, vital signs, pregnancy test) will not be repeated. Please see the SOM for more guidance.

Table 8-1 Assessment schedule

Epoch	Extension-Screening	Extension-Treatment																	
Visit Name	Screening	Treatment																EoT	EOS[19]
Visit Numbers[1]	501[2]	502[3]	502.1	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	599
Study Day(s)	-7 -3 +7	1	14 -3 +3	42 -7 +7	84 -10 +10	168 -10 +10	252 -10 +10	364 -10 +10	546 ±2 weeks	728 ±2 weeks	910 ±2 weeks	1092 ±2 weeks	1274 ±2 weeks	1456 ±2 weeks	1638 ±2 weeks	1820 ±2 weeks	2002 ±2 weeks	2184 ±2 weeks	2268 ±2 weeks
Written Informed Consent[4]	X																		
Inclusion / Exclusion criteria	X																		
Medical history/current medical conditions	X																		
Demography	X																		
Physical examination*	X[5]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tanner Staging[6]	X[5]							X		X		X		X		X		X	
Pregnancy test[7]	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs and body measurements																			
Body height[8*]	X[5]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight*	X[5]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body temperature*	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure/ pulse rate[9*]	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG evaluation*	X[5]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology*	X[5]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry[10*]	X[5]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Epoch	Extension-Screening	Extension-Treatment																	
Visit Name	Screening	Treatment																EoT	EOS[19]
Visit Numbers[1]	501[2]	502[3]	502.1	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	599
Study Day(s)	-7 -3 +7	1	14 -3 +3	42 -7 +7	84 -10 +10	168 -10 +10	252 -10 +10	364 -10 +10	546 ±2 weeks	728 ±2 weeks	910 ±2 weeks	1092 ±2 weeks	1274 ±2 weeks	1456 ±2 weeks	1638 ±2 weeks	1820 ±2 weeks	2002 ±2 weeks	2184 ±2 weeks	2268 ±2 weeks
Urinalysis*	X[5]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV/Hepatitis/QuantiFeron test	X[11]																		
Trough PK blood collection[12]		X			X	X	X												
Serial PK blood collection[13]			X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]			
Phone contact to assess for safety[14]			X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]				
Soluble biomarkers		X			X	X	X												
T and B cell immunophenotyping		X			X	X	X												
Serum immunoglobulins		X			X	X	X												
EBV/CMV test[17]		X			X	X	X												
EBV test in saliva		X			X	X	X												
SF-36/WPAI-CIQ Questionnaires		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physician's/Patient's global assessment scales		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MRI or CT or US scan[15]						X[15]	X[15]												

Epoch	**Extension-Screening**	**Extension-Treatment**																	
Visit Name	**Screening**	**Treatment**																**EoT**	**EOS[19]**
Visit Numbers[1]	**501[2]**	**502[3]**	**502.1**	**503**	**504**	**505**	**506**	**507**	**508**	**509**	**510**	**511**	**512**	**513**	**514**	**515**	**516**	**517**	**599**
Study Day(s)	**-7 -3 +7**	**1**	**14 -3 +3**	**42 -7 +7**	**84 -10 +10**	**168 -10 +10**	**252 -10 +10**	**364 -10 +10**	**546 ±2 weeks**	**728 ±2 weeks**	**910 ±2 weeks**	**1092 ±2 weeks**	**1274 ±2 weeks**	**1456 ±2 weeks**	**1638 ±2 weeks**	**1820 ±2 weeks**	**2002 ±2 weeks**	**2184 ±2 weeks**	**2268 ±2 weeks**
Patient Narratives*		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration[16]		X[18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Study/epoch completion information	X																		X
Concomitant medications*			X																
Adverse events			X																
Comments			X																

Note: If several assessments are scheduled at the same time point, please see the SOM for guidance on recommended sequence of assessments

Keys

* These assessments are also to be conducted for patients who discontinue study treatment

1 Visit structure given for internal programming purpose only.

2 To be performed only if patient does not roll-over directly at CCDZ173X2201 EOT/EOS visit.

3 Visit 502 can be performed on the same day of visit 501, if all the inclusion and exclusion criteria can be verified on that day. In that case the assessments of body weight, body temperature and blood pressure/pulse rate don't have to be repeated.

4 The extension study can be described and the ICF for the extension study can be provided to the patient already during the CCDZ173X2201 study, in order to let the patient having enough time to properly think about his/her participation.

5 If patient roll-over at the CCDZ173X2201 EOT/EOS visit this assessment will correspond to the assessment performed at that visit and will not be re-done.

6 Only assessed in patients who are younger than 18 years old at the time of assessment.

7 Serum pregnancy test is required at Screening if the patient is not roll-over directly from study CCDZ173X2201EOT/EOS visit. Urine pregnancy test for all other patients and time points. Patients will carry out self-pregnancy tests between visits after Visit 504, data will be kept as source document.
8 Only assessed in patients who are younger than 18 years old at the time of assessment. Adult patients who did not participate in CCDZ173X2201 study will have one assessment at Visit 501 only.
9 Sitting blood pressure and pulse rate will be measured after 3 minutes of sitting rest.
10 Including hsCRP and LDH assessments.
11 Only assessed in patients who did not participate in CCDZ173X2201 study.
12 Not applicable for patients enrolled in Russia. Refer to SOM for timing of collections. Additional trough PK samples will not be taken if the visit has serial PK blood collection.
13 Not applicable for patients enrolled in Russia. For all other patients, serial PK blood collection will occur in any two consecutive visits from Visit 502.1 to Visit 511. The first visit has PK blood sampling before and after the final dose of HGC, and then patient should be switched to FCT. The second visit is the next study visit following the switch to FCT. Each of these two visits will have PK samples collected at pre-dose, and post dose 0.25, 0.5. 1. 2. 4. 6 and 8 hours.
14 A phone contact should be made approximately 2 weeks after the first dose of FCT to check for any potential safety issues. In case of any concerns, patients should be followed-up as deemed appropriate by the investigator; this may include an unscheduled on-site visit.
15 Optional for patient: it can be performed at Visit 505 (Day 168), or at Visit 506 (Day 252) or between these two visits. Same modality as in the CCDZ173X2201 should be used. Not to be performed by patients who did not participate in CCDZ173X2201 study.
16 Morning dose after blood sample collections. Also refer to Footnote 13 and protocol Section 3.1 for dosing details.
17 Samples for EBV/CMV test will be collected as EBV/CMV viremia (plasma) and as EBV/CMV latent (plasma).
18 If patient rolls-over directly at the CCDZ173X2201 EoT visit and visits 501 and 502 are performed on the same day (see Footnote 3 above), the extension study medication will be given as the morning dose.
19 If patient rolls-over to compassionate use the EoS visit will not take place and EoT visit will be the last study visit.

8.2 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, or parent/guardian if the patient is 12 – 17 years old, gives consent (if allowed according to local requirements) by providing written informed consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Pharming will provide to Investigators a proposed informed consent form that complies with the ICHE6 GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by Pharming before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the subject informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the patient and patients must re-consent.

Ensure patients are informed of the contraception requirements outlined in the Section 4.2 (Exclusion criteria) and in Section 5.1 (Contraception requirements).

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

During an epidemic or pandemic (e.g. COVID-19 pandemic) that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference). Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc).

In case Home Nursing is implemented during an epidemic or pandemic (e.g. COVID-19 pandemic), a separate Home Nursing consent document must be used in addition to the main ICF.

8.3 Patient screening

In case a patient will roll-over directly at the CCDZ173X2201 EOT/EOS visit, the results of the physical examination, pregnancy tests, vital signs and body measurements, ECG evaluation, hematology, blood chemistry and urinalysis of the CCDZ173X2201 EOT/EOS visit will be used as the screening visit assessments for the extension study and will be reported also in the electronic case report form (e-CRF) of the extension study.

Patients who do not directly roll-over will need to undergo the screening visit at the time of enrollment in this extension study see Assessment schedule (Section 8.1).

Patients that were treated previously with PI3Kδ inhibitors other than CDZ173 will perform the screening visit as per protocol. Information on what data should be collected for screening failures is outlined in the SOM.

8.4 Patient 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.

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

8.4.1 Hepatitis/HIV screening

All patients who did not roll-over directly from core study CCDZ173X2201 EOT/EOS will be screened for hepatitis B surface antigen (HbsAg), hepatitis C and HIV.

Screening for Hepatitis C will be based on HCV antibodies (by PCR).

Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site, e.g. Western blot.

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

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

8.4.2 Tuberculosis testing

In order to evaluate an eventual infection with tuberculosis, a QuantiFeron test (or a comparable tuberculosis blood test) will be performed at screening for patients who did not roll-over directly from core study CCDZ173X2201.

8.5 Efficacy / Pharmacodynamics

8.5.1 Efficacy

If an epidemic or pandemic (e.g. COVID-19 pandemic) limits or prevents on-site study visits, where possible efficacy endpoints could be collected remotely. For example, PRO data collection may be done by sending the patient questionnaires by post.

8.5.1.1 High Sensitivity C-reactive protein (hsCRP)/Lactate dehydrogenase (LDH)

These parameters will be measured to assess biomarkers reflecting the efficacy of CDZ173 to reduce systemic inflammatory components of APDS/PASLI.

8.5.1.2 EBV and CMV assessments

Chronic or intermittent viremia of EBV and/or CMV has been observed in APDS/PASLI patients, consistent with the described T cell defect (Lucas et al 2014). Plasma samples will be used for investigation of EBV and CMV viremia. Depending on the results, PBMC and plasma fraction will be used for investigation of latent/lytic burden of EBV and CMV. In addition the viral load of EBV in saliva will also be quantified.

8.5.1.3 Serum Immunoglobulins

Most patients with APDS/PASLI have a Hyper-IgM syndrome and/or a reduced number of class switched B memory cells (Angulo et al 2013, Lucas et al 2014, Crank et al 2014). Serum IgG (including subclasses), IgE, IgM and IgA will be quantified as measure of the B cellfunction and of class switching.

8.5.2 Patient Report Outcomes (PRO)

8.5.2.1 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.

8.5.2.2 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 below 18) 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.

8.5.2.3 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).

8.5.2.4 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.

8.5.2.5 Patient 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 during the study, and to provide details on the areas where the patient improved or worsened during the treatment phase.

8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the SOM, with the Assessment schedule (Section 8.1) 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.

8.6.1 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 AE must be appropriately recorded on the Adverse Event CRF.

8.6.2 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, 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 patient to qualify.

8.6.3 Height and weight

Height in centimeters (cm) (to be measured only at screening visit for adult patients, and to be measured at each visit for adolescent patients as per Assessment schedule) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

8.6.4 Tanner Staging

Tanner Staging will be determined for patients below 18 years of age at the time of the assessment. The assessment includes external genitals development stage I-V for males, breast development stage I-V for females and pubic hair development stage I-V for both sexes. To be performed once per year.

8.6.5 Laboratory evaluations

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

Hematology

Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differentials and platelet count, PT/INR, aPTT 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, 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.

ESR, 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.

8.6.6 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed in single 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 AEs 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).

8.6.7 Pregnancy test

All WoCBP will have pregnancy tests at visits shown in the Assessment schedule, Section 8.1. Between visits, monthly pregnancy tests are carried out by patients using the self-test kits after Visit 504. Additional pregnancy testing may be performed to meet local requirements. The test results outside of study visits will be reported to the Investigator and kept as source documentation. Results should be entered in eCRF Comments page. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative.

During an epidemic or pandemic (e.g. COVID-19 pandemic) that limits or prevents on-site study visits, relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the Site is informed of the pregnancy test results.

8.7 Pharmacokinetics

During an epidemic or pandemic (e.g. COVID-19 pandemic) that limits or prevents on-site study visits, or if visits by site staff to a participant's home are not feasible the collection of samples may be modified by Pharming and will be communicated to the Investigator.

PK samples will be collected at the time points defined in the Assessment schedule (see Section 8.1) and SOM. Follow instructions outlined in the SOM regarding samplecollection, numbering, processing and shipment. See Section 8.9 regarding the potential use of residual samples.

PK samples will be obtained and evaluated in all patients (except for patients enrolled in Russia).

CDZ173 will be determined by a validated LC-MS/MS method; the anticipated Lower Limit of Quantification (LLOQ) is approximately 3 ng/mL.

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

Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report.

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): AUC0-12,ss and Cmax,ss. Other parameters may be added. For calculation of AUC0-12,ss the pre-dose concentration will also be used as 12 h concentration.

In addition steady-state drug exposure in this extension study will be summarized in terms of trough concentration (Ctrough).

8.8 Other assessments

During an epidemic or pandemic (e.g. COVID-19 pandemic) that limits or prevents on-site study visits, or if visits by site staff to a participant's home are not feasible the collection of samples may be modified by Pharming and will be communicated to the Investigator.

8.8.1 Exploratory Biomarker assessments

Details on the assessed biomarkers are provided below. Samples will be collected at the time points defined in the Assessment schedule. Further details on sample collection, numbering, processing and shipment will be provided in the SOM.

The following biomarkers may provide additional measures of efficacy, and may include, but are not be limited to:

Soluble Biomarkers

A panel of chemokines and/or cytokines selected based on Part 1 results of CCDZ173X2201 study will be quantified in serum. Sample processing will be detailed in the SOM.

Cellular Biomarkers

To demonstrate that CDZ173 improves the disturbed immune system in a long term manner, immunophenotyping of B and T cell subsets will be explored.

Sample processing will be detailed in the SOM.

The detailed method descriptions of the assays will be included in the bioanalytical data reports.

Exploratory Imaging

Lymphoproliferation is one of the hallmarks of APDS/PASLI. As optional for a patient, MRI or CT or ultrasound may be performed for long term estimation of the CDZ173 effect on lymph nodes sizes and on extranodal lymphoproliferation. The same imaging modality as in the CCDZ173X2201 study will be used for the same patient. Adolescents between 12-15 years of age (inclusive) will be assessed by MRI, or using a low dose CT scan protocol (Buty et al 2017; Nagayama et al 2018; Kuo et al 2016) at sites where local practice and local authorities/ECs/IRBs approve such type of CT scans in adolescents for research purposes.

For further details on image acquisition and analysis, refer to SOM, MRI/CT subject scanning guide and imaging review charter.

This assessment will be exclusively performed in patients that participated in study CCDZ173X2201 since only these patients provide baseline data.

8.9 Use of residual biological samples

Any residual samples remaining after the protocol-defined analysis has been performed may be used for additional exploratory analysis. This may include, but is not limited to, using residual samples for protein binding, metabolite profiling, biomarkers of transporters or metabolic enzyme activity or other bioanalytical purposes (e.g. cross check between different sites and/or stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated. As such, the results from this exploratory analysis will not be included in the clinical study report.

Use of samples for additional, non-protocol defined endpoints would only be allowed if the subject signed the “additional (future) research” section of the Informed Consent Form.

9 Safety monitoring

9.1 Adverse events

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

In addition, all reports of Special Situations (SSs) are also consideredan AE irrespective if a clinical event has occurred. See Section 9.2 for an overview of the reporting requirements.

The occurrence of AEs must be sought by non-directive questioning of the patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits or through physical examination finding, laboratory test finding, or other assessments. Study patients will be instructed to take notes of any AE and bring those notes to the study visits.

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

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

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying AEs. Alert ranges for liver and kidney related events are included in Table 9-1 and Table 9-3, respectively. AEs must be recorded on the Adverse Events CRF under 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 AE, use:

- 1=mild,
- 2=moderate,
- 3=severe
- 4=life threatening* (see Section 9.2.1 for definition of a SAE)

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

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

2. Its relationship to the study treatment:
   - Yes or
   - No
3. Its duration (start and end dates) or if the event is ongoing an outcome of notrecovered/not resolved must be reported.
4. Whether it constitutes a SAE(see Section 9.2.1 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding investigational treatment.

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

- no action taken (e.g. further observation only)
- investigational treatment temporarily interrupted/withdrawn
- concomitant medication or non-drug therapy given
- hospitalization/prolonged hospitalization (see Section 9.2.1 for definition of SAE)

6. Its outcome (not recovered/not resolved; recovered/resolved with sequelae; fatal orunknown).

Information about common side effects already known about the investigational drug can be found in the IB. Once an AE is detected, it must 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 investigational drug, the interventions required to treat it, and the outcome.

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

9.2 Serious adverse event and special situation reporting

9.2.1 Definitions

A **Serious Adverse Event (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 followingcriteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

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

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

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 (see Annex IV, ICH-E2D Guideline).

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

All AEs (serious and non-serious) are captured on the CRF; SAEs and SSs also require individual reporting to Pharming PHV as per Section 9.2.2.

A **Special Situation (SS)** is defined as any report, whether or not associated with an AE, of:

- Use of an (investigational) medicinal product during pregnancy;
- Use of an (investigational) medicinal product during breastfeeding;
- Overdose (accidental or intentional);
- Abuse / Misuse;
- Off-label use;
- Medication error;
- Occupational exposure;
- Lack of therapeutic efficacy;
- (Suspected) transmission of an infectious agent;
- Drug-Drug or Drug-Food interactions; or
- Unexpected therapeutic benefit.

A **Suspected Unexpected Serious Adverse Reaction (SUSAR)** is defined as any adverse reaction, which is considered unexpected, serious and as having a reasonable possibility of a causal relationship with the medicinal product.

9.2.2 SAE and SS reporting

To ensure patient safety, every SAE and SS, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported by e-mail or facsimile noted below to Pharming PHV within 24 hours of learning of its occurrence using the SAE reporting form in accordance with the completion instructions. Any SAE and SS experienced after this period should only be reported to Pharming if the Investigator suspects a

causal relationship to study treatment.

Pharming PHV Department Contact Information:

- **E-mail:** safety@pharming.com
- **Fax:** +31 (0)85 0643 382

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

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

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

If the SAE and SS is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment a DS&E Department associate may urgently requirefurther information from the Investigator for (National) Health Authority reporting. Pharming may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study treatment that this SAE or SS has been reported.

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

Follow the detailed instructions outlined in the SOM regarding the submission process for reporting SAEs and SSs to Pharming. Note: SAEs and SSs must be reported to Pharming within 24 hours of theInvestigator learning of its occurrence/receiving follow-up information.

9.3 Infection monitoring

All infections that develop during the study will be reported as AEs. Investigators are requested to specifically 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 (including differential count) is to be assessed at every visit; it can be more frequently assessed if deemed necessary by the Investigator, e.g. if a patient presents with any signs of an infection. 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. This measure ensures that WBC (including differential count) is being timely checked.

9.4 Liver safety monitoring

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

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

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

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

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

For the liver laboratory trigger:

- Repeating the 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 areassociated 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
- 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 Reporting Medication errors including misuse/abuse

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

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

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

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Pharming PHV if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the AE CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Pharming PHV. As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 9-4 summarizes the reporting requirements.

Table 9-4 Summary of reporting requirements for medication errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 9.1 and Section 9.2, respectively.

9.7 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be **reported to Pharming within 24 hours** of learning of its occurrence. The pregnancy should befollowed 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 maternaland/or newborn complications.

Pregnancy must be recorded on the Pregnancy Form and reported by the Investigator to the Pharming PHV Department. Pregnancy follow-up should be recordedon the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

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.

9.8 Early phase safety monitoring

The Investigator will monitor AEs 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 Pharming representative will review the protocol and CRFs with the Investigators and their staff. During the study Pharming employs several methods of ensuring protocol and GCP complianceand 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 (GCP), the progress of enrollment, and ensure that studydrug 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. Pharming 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 CRFs using fully validated software that conforms to 21 CFR Part 11 requirements. Designated Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Pharming. The Investigator must certify that the data entered into the Electronic CRFs are complete and accurate. After database lock, the Investigator will receive copies of the patient data for archiving at the investigational site.

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

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

10.3 Database management and quality control

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

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 AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

10.4 Data Monitoring Committee

The DMC will be established (according to Pharming Standard Operating Procedures). 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.

10.5 Adjudication Committee

Not required.

11 Data analysis

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

11.1 Analysis sets

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

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

The PK analysis set will include all patients with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that 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.

11.2 Patient demographics and other baseline characteristics

All data for background and demographic variables will be listed by patient. Summary statistics will be provided for all patients in the safety analysis set.

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

11.3 Treatments

Data for study drug administration and concomitant therapies will be listed by patient.

11.4 Analysis of the primary variable(s)

The primary objective of the study is to evaluate the long term safety and tolerability of CDZ173 in APDS/PASLI patients.

11.4.1 Variable(s)

Safety and tolerability assessments include vital signs, ECG evaluations, clinical laboratory evaluations and AEs.

11.4.2 Statistical model, hypothesis, and method of analysis

All data for vital signs, ECG evaluations and clinical laboratory evaluations will be listed by patient and summarized by descriptive statistics. All information obtained on AEs will be displayed by patient. The number and percentage of patients with AEs will be tabulated by body system and preferred term. A patient with multiple AEs within a body system is only counted once towards the total of this body system.

11.4.3 Handling of missing values/censoring/discontinuations

All patients who received study drug will be included in the safety and tolerability evaluation. No methods for imputation of missing data (including those due to COVID-19) are planned.

11.4.4 Summary statistics of safety

Vital signs

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

ECG evaluations

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

Clinical laboratory evaluations

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

Adverse events

All information obtained on AEs will be displayed by patient.

The number and percentage of patients with AEs will be tabulated by body system and preferred term. A patient with multiple AEs within a body system is only counted once towards the total of this body system.

11.4.5 Sensitivity analyses

Not applicable.

11.5 Analysis of secondary variable(s)

11.5.1 Efficacy / Pharmacodynamics

The hsCRP, LDH, SF-36 and WPAI-CIQ scores, visual analogue scale scores for PGA and PtGA, will be listed by patient and visit and summary statistics will be provided by visit. Frequencies of infections and other disease complications data will be listed by patient and visit.

11.5.2 Pharmacokinetics

CDZ173 plasma concentration data will be listed by patient, and visit/sampling time point. Descriptive summary statistics will be provided by visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

PK parameters Cmax,ss and AUC0-12,ss for CDZ173 from the serial sampling visits will be the primary variables for the assessment of relative bioavailability of FCT vs HGC.

Only subjects with evaluable PK parameter data for both FCT and HGC formulations will be included in this analysis. For FCT and HGC log-transformed PK parameters Cmax,ss and AUC0-12,ss will be analyzed by a fixed effects model with formulation and subject as fixed factors.

The estimated mean and 90% confidence interval of difference in formulations between FCT vs HGC will be back transformed to obtain the geometric mean ratio and 90% confidence interval of the ratio. For each of the primary PK parameters AUC0-12,ss and Cmax,ss the 90% confidence interval for the PK parameter ratio of FCT vs HGC will be reported to represent bioavailability of FCT relative to HGC.

11.5.3 Pharmacokinetic / pharmacodynamic interactions

Not applicable.

11.5.4 Other assessments

Not applicable.

11.6 Analysis of exploratory variables

Statistical analysis for exploratory variables will be described in the SAP.

11.6.1 Exploratory biomarkers

Selected biomarker data will be listed by patient, and visit/time. Summary statistics will be provided by visit/time.

In the summary tables, the frequency (n, %) of values below the LLOQ and above the upper limit of quantification (ULOQ), respectively, will be included.

For values which fall below the lower limit of quantification (LLOQ) or above the upper limit of quantification (ULOQ), the inequality sign with the limit value should be kept in the individual listing. To avoid being treated as missing values when calculating summary statistics or analyzing, a value below the LLOQ will be replaced by LLOQ/2 and a value above ULOQ will be replaced by ULOQ.

11.7 Sample size calculation

Not applicable.

11.8 Power for analysis of key secondary variables

Relative bioavailability of FCT vs HGC formulation

For sample sizes up to the maximum planned enrollment of 42 patients tolerance limits for the 90% confidence intervals were calculated. Estimation of the confidence interval width will be measured by the ratio of the geometric means of the PK parameters AUC0-12,ss and Cmax,ss for FCT versus HGC. With complete data from 30 patients there is a 90% probability that the 90% confidence interval of PK parameter ratio is within 86% to 116% of the observed geometric mean. An intra-subject coefficient of variation of 30% was assumed in this calculation based on the results for AUC and Cmax of the study CCDZ173X2101. If the observed variability differs from the assumed 30% the calculated tolerance limits will change. Table 11-1 gives the estimated tolerance limits for the 90% confidence intervals (with 90% probability) for different CVs and different sample sizes.

Table 11-1 Estimated tolerance limits for 90 percent confidence intervals with different CVs and sample sizes

	CV (%)		
Sample Size	**20**	**30**	**40**
20	[0.88, 1.14]	[0.83, 1.21]	[0.78, 1.29]
30	[0.90, 1.11]	[0.86, 1.16]	[0.82, 1.22]
42	[0.92, 1.09]	[0.89, 1.13]	[0.85, 1.17]

11.9 Interim analyses

Interim analyses may be conducted to support decision making concerning the current clinical study, the Sponsor's clinical development projects in general or in case of any safety concerns.

12 Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principleslaid down in the Declaration of Helsinki.

12.2 Responsibilities of the Investigator and IRB/IEC

Before initiating a trial, the Investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, 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 Pharming monitors, auditors, Pharming Quality Assurance representatives, designated agents of Pharming, IRBs/IECs,and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Pharming immediately that this request has been made.

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

12.3 Publication of study protocol and results

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 patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an Investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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

13.1 Protocol Amendments

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

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

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 9 (Safety Monitoring) must be followed and the Study Lead informed.

14 References

References are 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.

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.

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.

EMA "Reflection Paper: Formulations of Choice for the Paediatric Population" (2006) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf.

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.

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 KR, Webster S, Dalm VASH, et al (2017) Effective "Activated PI3Kδ Syndrome'-targeted therapy with the PI3Kδ inhibitor leniolisib. Blood 130(21):2307-2316.

Rao K, Webster S, Šedivá A, ; Randomized, Placebo-Controlled, Phase 3 Trial of PI3Kδ Inhibitor Leniolisib for Activated PI3Kδ Syndrome. Blood; blood.2022018546. doi: https://doi.org/10.1182/blood.2022018546

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 (Activated PI3Kδ Syndrome). Poster presentation ESID, Lisbon, Portugal Oct 2018.

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

15 Appendix 1: List of prohibited CYP-interacting co-medications

Table 15-1 List of prohibited co-medications

Compound	CYP3A inhibitor[1]	CYP3A Inducer[1]	Narrow TI CYP1A2 substrates
Avasimibe		Strong	
Boceprevir	Strong		
Bosentan		Moderate	
Carbamazepine		Strong	
Clarithromycin	Strong[2]		
Conivaptan	Strong		
Efavirenz		Moderate	
Elvitegravir	Strong		
Etravirine		Moderate	
Genistein		Moderate	
Indinavir	Strong		
Itraconazole	Strong		
Ketoconazole	Strong		
Lopinavir	Strong[2]		
Mibefradil	Strong		
Mitotane		Strong	
Modafenil		Moderate	
Nafcillin		Moderate	
Nefazodone	Strong		
Nelfinavir	Strong		
Phenobarbital		Strong	
Phenytoin		Strong	
Posaconazole	Strong		
Ramelteon			yes
Rifabutin		Strong	
Rifampin		Strong	
Ritonavir	Strong[2]	Moderate	
Saquinavir	Strong[2]		
St John's Wort		Strong	
Telaprevir	Strong	Weak	
Telithromycin	Strong		
Theophylline			yes
Thioridazine		Moderate	
Tipranavir	Strong	Moderate	

Compound	CYP3A inhibitor[1]	CYP3A Inducer[1]	Narrow TI CYP1A2 substrates
Tizanidine			yes
Troleandomycin	Strong		
Voriconazole	Strong		

1. Refer to Section 5.2.1: CDZ173 dosing must be interrupted until the co-medication is considered washed out (5 terminal half-lives or at least 1 week washout for a time-dependent inhibitor or inducer). See also next footnote

2. Time-dependent inhibitor of CYP3A

Table 15-2 List of selected OATP substrates to be used with caution

Compound	OATP1B3 substrate	OATP1B1 substrate
Atorvastatin	yes	yes
Atrasentan		yes
Ezetimibe		yes
Fluvastatin		yes
Glyburide		yes
Olmesartan	yes	yes
Pitavastatin	yes	yes
Pravastatin		yes
Repaglinide		yes
Rosuvastatin	yes	yes
Simvastatin acid		yes
SN-38		yes
Telmisartan	yes	
Valsartan	yes	yes