NOVARTIS

Clinical Development

CDZ173

CCDZ173X2201 / NCT02435173

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

RAP Module 3: Detailed Statistical Methodology-Part I

Author(s):	Personal Protected Data

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1 Introduction to RAP documentation

1.1 Scope

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) of trial **"CCDZ173X2201"**. This document describes the analyses for Part I.

Module 3 (M3) provides the description of the statistical methodology used to analyze the data, **Module 7** (M7) details the presentation of the data, including shells of summary tables, figures and listings, and **Module 8 (**M8) contains programming specifications e.g. for derived variables and derived datasets, to support the creation of CSR outputs.

1.2 Changes to RAP documentation (M3)

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2 Study objectives and design

This study is designed to explore CDZ173, a selective PI3Kδ inhibitor, in patients with genetically activated PI3Kδ, i.e., patients with APDS/PASLI. The study consists of two parts. Part I is the open label part designed to establish the safety and pharmacokinetics of CDZ173 in the target population, as well as to select the optimal dose to be tested in Part II. Part II is designed to assess efficacy and safety of CDZ173 in this population.

This RAP focuses on Part I only.

2.1 Study objectives

2.1.1 Part I

2.1.1.1 Primary Objectives

- To assess the safety and tolerability of CDZ173 in patients with APDS/PASLI
- To assess the dose-PD and PK/PD relationship of CDZ173 in patients with APDS/PASLI for dose selection in Part II

2.1.1.2 Secondary Objectives

- To assess the pharmacokinetics of CDZ173 in patients with APDS/PASLI
- To assess the efficacy of CDZ173 to modify health-related quality of life in patients with APDS/PASLI
- To assess the efficacy of CDZ173 by the Physician's Global Assessment (PGA) and the Patient's Global Assessment (PtGA)
- To assess biomarkers reflecting the efficacy of CDZ173 to reduce systemic inflammatory components of the disease
- To assess the treatment benefit to individual patients

2.1.1.3 Exploratory Objectives

2.2 Study design and treatment

2.2.1 Part I

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

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

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

The first day of dosing will start on Day 1 with patients receiving 10 mg of CDZ173 b.i.d.
Commercially Confidential Information Prior to escalation of a patient to the next dose level a continuous safety review and review of PK and key PD data up to 7 days after the first dose (Day 8) must be assessed as satisfactory to proceed with next dose level.

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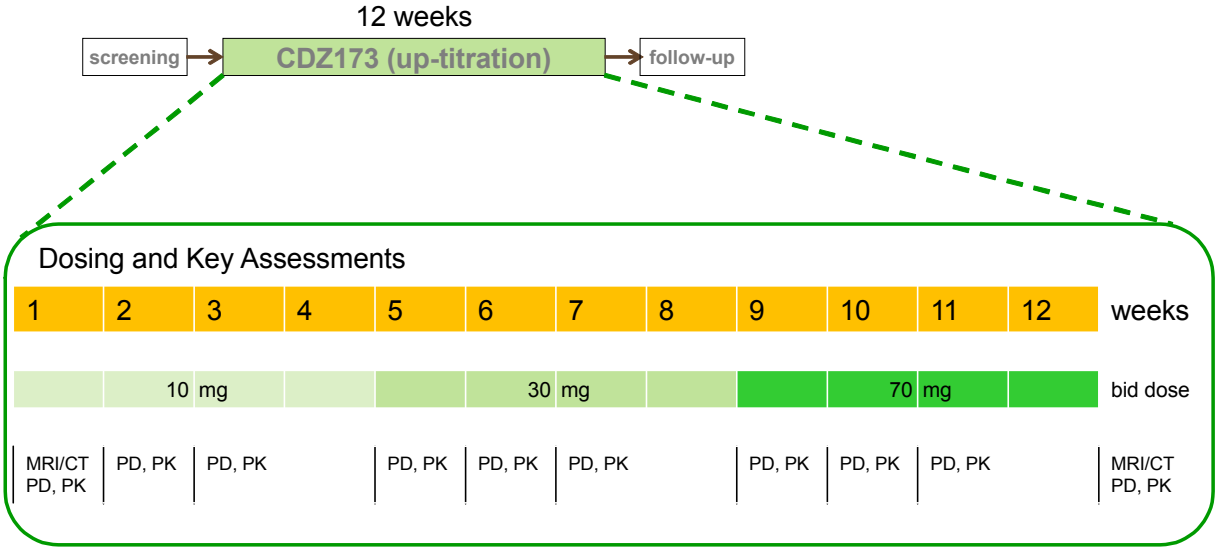
The final dose strength that patients will be receiving is 70 mg CDZ173 b.i.d CCI . Assessments done on Day 84 will include the end of treatment MRI or CT scan.

During the four weeks after the last day of dosing the patients will be followed-up for safety. On Day 112 patients will undergo the end of study visit. Patients who are withdrawn from the study prematurely will still be required to complete the follow-up period including the Study Completion Visit.

Figure 2-1 illustrates the study design for Part I.

Figure 2-1 Study Design Part I



3 First interpretable results (FIR)

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4 Interim analyses

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5 Statistical methods: 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 study drug and with no protocol deviations with relevant impact on safety.

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 experienced no protocol deviations with relevant impact on PK data.

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

Although the study includes both pediatric and adult patients, no separate analysis by age group (>18 years, ≤18 years) will be provided due to the small sample size. Listings will be provided by age group.

The analysis sets and protocol deviation codes are related as follows:

Table 5-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from all *(safety)* analysis in case of these PDs:		Exclude subject completely from all ***(safety)*** analysis sets
INCL01	*Written informed consent was not obtained before any study assessment was performed*	Yes
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis set
INCL01	*Written informed consent was not obtained before any study assessment was performed*	Yes

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
INCL01	*Written informed consent was not obtained before any study assessment was performed*	Yes
Subjects are excluded from PK and PD analysis in case of these PDs:		Exclude subject from PK and PD analysis sets
INCL01	*Written informed consent was not obtained before any study assessment was performed*	Yes

6 Statistical methods for Pharmacokinetic (PK) parameters

6.1 Pharmacokinetic parameters

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

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

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

6.2 Statistical methods for pharmacokinetic parameters

CDZ173 plasma concentration data will be listed by treatment, patient, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, Commercially Confidential Information Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented.

Commercially Confidential Information A geometric mean will not be reported if the dataset includes zero values.

Pharmacokinetic parameters will be calculated and will be listed by treatment and patient. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented.

6.3 Pharmacokinetic / pharmacodynamic interactions

Relationships between exposure (plasma concentration and PK parameters) and pAkt PD biomarkers in B and T cells (endogenous, stimulated and unstimulated), will be explored by a graphical approach and descriptive

statistics of exposure and PD or biomarker variables will be provided.

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7 Statistical methods for Pharmacodynamic (PD) parameters

7.1 Primary Objective

The primary aim of Part I, along with assessing safety and tolerability, is to determine a dose to be used in the confirmatory Part II.

7.1.1 PD Variable(s)

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The primary parameter in Part I will be % pAkt positive B cells (unstimulated and stimulated samples) and will be used as PD marker to select the dose for Part II.

In Part I, phosphorylated Akt in B cells will be quantified at baseline and at Day 1 (pre-dose, and 1h, 3h, 8h post dose), Day 8 (pre-dose) and Day 15 (pre-dose) of each of the three dose levels and at Day 28 (pre-dose) of the last dose level. The dose level (up to 70 mg b.i.d.) leading to normalization of pAkt in B cells similar to healthy volunteer levels should be carried into Part II for generation of confirmatory data. Typically, pAKT levels in endogenous B-cells of healthy volunteers are not measurable due to limitation in detecting low levels of pAkt in these cells. Therefore, an integrated pharmacology approach consisting of the concentration/dose-effect relationship in inhibition of pAkt (unstimulated and stimulated B cells), as well as an estimate of the endogenous pAkt levels in APDS patients (if measurable) will be used to inform the best estimate of the level of inhibition required for normalization. Other variables including but not necessarily limited to safety and biomarkers will be taken into account for the selection of the dose.

Average pAkt inhibition (defined as (-1)*%change from baseline) over the dosing interval of 12h will be calculated for each patient at each dose level based on the measured pre-dose and the 1h, 3h, 8h post dose samples with a trapezoidal rule as AUC over 12 hours normalized by the length of the dosing interval (12h). Baseline will be defined as the arithmetic mean of the Day -1 value and the first dose level Day 1 pre-dose value. The 12h time point will be estimated as an arithmetic mean of the Day 8 and Day 15 pre-dose values.

7.1.2 Statistical analysis of PD parameter(s)

7.1.2.1 Concentration-response (Plasma concentration vs PD parameter)

In Part I, a concentration-response model will be fitted to link systemic drug concentration and pAkt inhibition at each measured time point (the 1h, 3h, 8h post dose samples on Day 1 and pre-dose samples on Days 8 and 15 of each dose level; pre-dose samples on Day 1 of dose levels 2 and 3; and pre-dose sample on Day 28 of dose level 3). An Emax model will be considered, where the inhibition at concentration 0 is fixed at 0. The EC50, the Emax and the Hill parameter will be estimated from the data, and a random effect for EC50 and Emax will be estimated for each patient to account for the within-patient correlation between time points. Population model parameters will be converted into their dose equivalents based on desired time-averaged pathway inhibition and estimated oral drug clearance of CDZ173 in the target population.

The systemic drug concentrations used within the model will be the raw plasma concentrations measured at the same time points that the PD parameters were measured.

For the assessment of concentration-response, the following Emax model will be used:

$$Y_{ij} = \left(\frac{E_{max} \cdot C_{ij}^{h}}{EC_{50}^{h} + C_{ij}^{h}}\right) + e_{ij}$$

Y_{ij} : pAkt inhibition ((-1)*percent change from baseline) of the *i*-th patient at time point *j=1,...,18*

C_{ij} : Concentration (ng/mL) of the i-th patient at time point *j=1,....,18*

E_{max} : Maximum effect, logit transformed (between 0 and 100) = 100 / (1+exp(-Θ_1))

EC_{50}: Concentration (ng/nL) at which 50% of E_{max} is reached, log transformed exp(Θ_2)

h : Hill parameter, log transformed exp(Θ_3)

e_{ij}: residual error normally distributed

Random effects with multivariate normal distributions on transformed parameters (Θ_1,Θ_2,Θ_3) will be estimated for each patient to account for the within-subject correlation between time points using a full covariance matrix. In case of estimation issues, a diagonal covariance matrix (i.e. off-diagonal elements are zero) will be used. In case there are still estimation issues, the below steps will be successively taken until there are no estimation issues. For each step, first a full covariance matrix will be used and in case of estimation issues, a diagonal covariance matrix will be used.

1. The random effect from the Hill parameter will be removed
2. The Hill parameter will be fixed to 1
3. The random effect on E_{max} will be removed
4. The random effect on EC_{50} will be removed

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The dose D_{XX} (mg) that provides a given level (xx % of E_{max}) of time-averaged pathway inhibition over a dosing period (12h) is defined as follows:

$$D_{xx} = 10^{-3} . EC_{xx} . {}^{CL(ss)}/_{F} . 12$$

CL(ss)/F : apparent Clearance (L/h)

EC_{XX} : Concentration (ng/mL) at which XX % of Emax is reached i.e. $\left(\frac{XX}{100-XX}\right)^{1/h} \times EC_{50}$ where h is the Hill parameter and EC_{50} the concentration at which 50% of E_{max} is reached.

To estimate EC_{xx}, the value CL(ss)/F estimated from the pharmacokinetics assessment (see section 6.1) will be used.

7.1.2.2 Dose-response (Dose vs PD AUC)

The average of pAkt inhibition over the dosing interval (12h) at each dose level will also be estimated from an Emax dose-response model accounting for intra-individual correlation for the measurements at different doses.

In the E_{max} dose response model the Hill parameter is fixed to 1 and the inhibition at dose 0 is fixed to 0. The following model will be used:

$$Y_{ij} = \left(\frac{E_{max} . D_{ij}}{ED_{50} + D_{ij}}\right) + e_{ij}$$

Y_{ij} : average pAkt inhibition of the *i*-th patient on dose *j=1,2,3*

D_{ij} : Dose (mg) of the *i*-th patient on dose *j=1,2,3*

Emax : Maximum effect, logit transformed (between 0 and 100) = 100 / (1+exp(-Θ_1))

ED_{50}: Dose (mg) at which 50% of Emax is reached, log transformed exp(Θ_2)

e_{ij}: residual error normally distributed.

A random effect with normal distribution on transformed parameter Θ_2 will be estimated for each patient to account for the within-subject correlation between time points.

The dose D_{XX} (mg) that provides a given level (xx % of E_{max}) of time-averaged pathway inhibition over a dosing period (12h) is defined as

$$\left(\frac{XX}{100 - XX}\right) \times ED_{50}$$

where ED_{50} the dose at which 50% of E_{max} is reached.

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In case the above model cannot be fitted, a slope model will be fitted:

$$Y_{ij} = \beta D_{ij} + \eta_i + e_{ij}$$

Y_{ij} : average pAkt inhibition of the *i*-th patient on dose *j=1,2,3*

D_{ij} : Dose (mg) of the *i*-th patient on dose *j=1,2,3*

η_i: patient effect

e_{ij}: residual error normally distributed.

Depending on the feasibility to measure average baseline unstimulated pAkt levels, the minimum average level of inhibition needed for undetectable pAkt may be determined. If the dose achieving this level of inhibition cannot be estimated reliably from the unstimulated pAkt levels, then the stimulated pAkt levels may be used for the selection of the dose to be carried into Part II. The dose selected for Part II may be different (up to 70 mg bid) than the 3 doses studied in Part I. Other variables may also be taken into account for the selection of the dose.

7.1.3 Handling of missing values/censoring/discontinuations

In Part I, the primary analysis model will include all available data, there will be no imputation of missing data.

7.2 Analysis of secondary and exploratory variables

7.2.1 Efficacy / Pharmacodynamic

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

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

7.2.2 Efficacy: Imaging

The MRI/CT images will be analyzed by VirtualScopics as described in the imaging charter. The following quantitative and qualitative measurements are to be summarized by Covance.

- Sum of product of diameters of the index lesions and percent change in sum of product of diameters relative to baseline
- 3D volume of index lesions.
- Overall index lesion response
- Overall non-index lesion response
- Presence of newly appearing lesions,
- Liver volume
- Spleen volume
- Qualitative assessment of splenomegaly and hepatomegaly
- Overall patient response

The sum of the products of diameters (SPD) of index lesions will be log10 transformed and the change from baseline of the log transformed SPD after 12 weeks of treatment will be calculated for all patients with measureable lymph nodes at baseline. The sum of the 3D volumes of the index lesions will be log10 transformed and the change from baseline after 12 weeks of treatment will be calculated. Spaghetti plots and summary

statistics for the change from baseline of the log10 transformed SPD will be provided. Response (CR [complete response], PR [partial response], etc.) of index and non-index lesions will be analyzed qualitatively. Liver and spleen volumes will be visualized as spaghetti plots.

8 Statistical methods for safety and tolerability data

Boxplots to visualize trends in longitudinal safety data (vital signs, ECG, lab parameters) will be created.

8.1 Patient demographics and other baseline characteristics

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

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

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

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

8.3 Vital signs

All vital signs data will be listed by age group, 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.

8.4 ECG evaluations

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

8.5 Clinical laboratory evaluations

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

8.6 Adverse events

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

The number and percentage of patients with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. An adverse event starting in one ‘period’ (i.e. under one dose level in Part 1) and continuing into the next period is counted only in the onset period. A patient with multiple adverse events within a body system and treatment period is only counted once towards the total of this body system.

8.8 Pregnancy test

All pregnancy test results for women will be listed by age group, patient and visit.

9 Statistical methods for Biomarker data

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9.1 Efficacy and mechanistic markers

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CDZ173

CCDZ173X2201 – Part II / NCT02435173

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

Statistical Analysis Plan (SAP)

Author(s):	Personal Protected Data
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Release date:	05-Jan-2022
Number of pages:	23

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial "CCDZ173X2201-Part II".

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol

1.2 Study reference documentation

This Statistical Analysis Plan is based on the amended protocol v10 dated 13th-Oct-2020.

1.3 Study objectives

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

This SAP focuses on Part II only.

1.3.1 Part II

1.3.1.1 Primary Objective(s)

- To assess the clinical efficacy (lymphadenopathy and immunophenotype normalization) of CDZ173 in patients with APDS/PASLI

1.3.1.2 Secondary Objective(s)

- To assess the effect of CDZ173 on lymphadenopathy (non-index lesions and spleen)
- To assess the pharmacokinetics of CDZ173 in patients with APDS/PASLI
- To assess the efficacy of CDZ173 to modify health-related quality of life in patients with APDS/PASLI
- To assess the efficacy of CDZ173 by the Physician's Global Assessment (PGA) and the Patient's Global Assessment (PtGA)
- To assess biomarkers reflecting the efficacy of CDZ173 to reduce systemic inflammatory components of the disease
- To assess the treatment benefit to individual patients
- To assess the safety and tolerability of CDZ173 in patients with APDS/PASLI

1.3.1.3 Exploratory Objective(s)

1.3.1.4 Objective for gender split analysis

- To assess whether there is comparable efficacy and tolerability/safety of CDZ173 (70 mg b.i.d.) after 12 weeks of treatment for men and women.

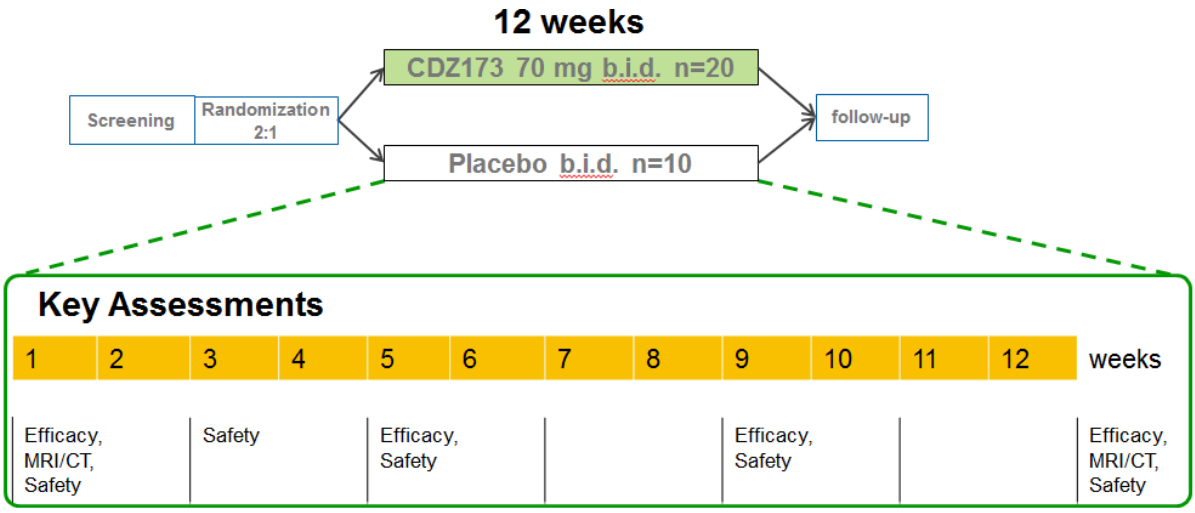
1.4 Study design and treatment

1.4.1 Part II

Part II is the randomized, subject, investigator and sponsor-blinded, placebo-controlled, fixed dose part investigating approximately 30 patients with APDS/PASLI (Figure 1-1). Since the primary endpoint (SPD) requires imaging by either MRI or CT, which results in patients being exposed to radiation, the design is planned factoring these measurements in.

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

Figure 1-1 Study Design Part II



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

Patients who are deemed eligible for enrollment into the study based on the inclusion/exclusion criteria will attend the clinic on Day -1 for baseline assessments.

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

Patients enrolled in Part I of the study will not participate in Part II, i.e. new patients will be selected.

For the patients who do not directly roll over from Part II to treatment in the extension study [CCDZ173X2201E1], the following applies:

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

Patients who discontinued study treatment prematurely will perform an early treatment discontinuation visit (named V104.1) as soon as possible after their treatment discontinuation. The assessments scheduled for this visit are the ones marked with a * in Table 8-2 of the study protocol.

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

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

2 First interpretable results (FIR)

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3 Interim analyses

Not applicable.

4 Statistical methods: Analysis sets

For all analysis sets, patients will be analyzed according to the study treatment 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 experienced no protocol deviations with relevant impact on PK data.

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

The key safety and efficacy endpoints will also be reported by age group determined at Screening visit (>=18 years old and < 18 years old).

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis set
INCL01	*Written informed consent was not obtained before any study assessment was performed*	Yes
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Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
INCL01	*Written informed consent was not obtained before any study assessment was performed*	Yes
Commercially Confidential Information		

Category Deviation code	Text description of deviation	Data exclusion
	Commercially Confidential Information	
Subjects are excluded from PK and PD analysis in case of these PDs:		Exclude subject from PK and PD analysis sets
INCL01	*Written informed consent was not obtained before any study assessment was performed*	Yes
	Commercially Confidential Information	

5 Statistical methods for Pharmacokinetic (PK) parameters

5.1 Variables

The following plasma pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): Cmax, Tmax, AUC0-8h and AUClast. Other PK parameters may be added as appropriate. After multiple doses, PK will be summarized in terms of trough concentration (Ctrough).

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

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

5.2 Descriptive analyses

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

Pharmacokinetic parameters will be calculated and will be listed by treatment and patient. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented.

Arithmetic mean (SD) profiles and geometric mean (95% CI) for plasma concentration-time data (day 1) and Ctrough versus Visit (multiple dose) data will be plotted over time.

Overlaying individual plasma concentration-time profiles (day 1) as well as for Ctrough-visit (after multiple dose) will be generated along profiles for individual subjects.

5.4 Pharmacokinetic / pharmacodynamic interactions

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

6 Statistical methods for primary efficacy parameters

6.1 Primary objective

The primary aim of Part II is to assess efficacy of CDZ173 at the selected dose (70 mg b.i.d.) after 12 weeks of treatment.

6.1.1 Estimands

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6.1.2 Variables

Index lesions will be selected from measurable nodal and extranodal lesions as per the Cheson methodology (Cheson et al 1999). A maximum of six of the largest dominant lesions should be selected and documented at baseline and assessed again at the end of treatment (i.e. the Day 85 assessment for patients who complete the 12 week treatment period or the treatment discontinuation visit for patients who discontinue treatment prematurely prior to Day 85 visit). The percentage of naïve B cells is assessed at baseline, Day 1, Day 29, Day 57 and Day 85, and at the discontinuation visit for patients who discontinue treatment prematurely prior to Day 85 visit. The co-primary variables to assess efficacy in Part II will be the change from baseline in the log10-transformed sum of the products of diameters (SPD) of the index lesions and the change from baseline in the percentage of naïve B cells out of total B cells, see Section 8.3 for details of the read-out names for all biomarkers.

6.1.3 Descriptive analyses

The SPD of index lesions will be log10 transformed and the change from baseline of the log10 transformed SPD at the end of treatment (i.e. the Day 85 assessment for patients who complete the 12 week treatment period or the treatment discontinuation visit for patients who discontinue treatment prematurely prior to Day 85 visit) will be calculated for patients with baseline and end of treatment SPD measurements. A second endpoint will be derived as the sum of the square root of the products of diameters along with the change from baseline.

The change from baseline in naïve B cells out of total B cells at Day 29, Day 57 and Day 85 and the end of treatment (i.e. the Day 85 assessment for patients who complete the 12 week treatment period or the treatment discontinuation visit for patients who discontinue treatment prematurely prior to Day 85 visit) will be calculated for patients with baseline and the corresponding time-point measurements. Baseline will be defined as the arithmetic mean of the baseline and Day 1 values when both are available, and if either baseline or the Day 1 value is missing, the existing value will be used.

Descriptive summary statistics and individual patient profiles will be provided by age group, treatment and time point.

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6.1.4 Statistical model, assumptions and hypotheses

An analysis of covariance will be performed to compare the change of the log10 transformed SPD from baseline between the two treatment groups, with treatment as a fixed effect and log10 transformed baseline SPD as a covariate. The baseline intake of glucocorticoids as well as the information about being treated with intravenous immunoglobulin G (IgG) will both be included as categorical (Yes/No) covariates. The comparison of the two treatment groups will be two-sided, with a 5% type I error. Patients with zero lesions at baseline will be excluded from the analysis.

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

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6.1.4.1 Model checking procedures

Residual plots will be inspected to assess the adequacy of the model.

6.1.4.2 Handling of missing values/censoring/discontinuations

The inferential analyses of the lymphadenopathy will include only patients with baseline and end of treatment lymphadenopathy measurements. Also patients with zero lesions at baseline will be excluded from the primary and sensitivity analysis for lymphadenopathy.

The primary analysis of the naïve B cells will include only patients who have baseline and end of treatment naïve B cells measurements and who also have a reduced percentage of naïve B cells at baseline (defined as below 48 % van Gent et al 2009).

6.1.4.3 Graphical presentation of results

Model estimated mean (SE) profiles and individual patient profiles will be provided by treatment and age group.

For the individual patient profiles using the PD analysis set all data will be displayed but the lines will be solid up to the treatment discontinuation +14 days and for subsequent time points the line will be dotted.

6.2 Secondary objectives

All subjects within the secondary efficacy analysis (efficacy parameters other than those used for primary objectives) will be included in the secondary efficacy data analysis where not otherwise specified. The rules as detailed in Section 6.1.4.2 regarding discontinuation and treatment withdrawal will also be followed for the secondary efficacy parameters.

6.2.1 Estimands

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6.2.2 Variables

Short form 36 Survey (SF-36)

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.

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

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

Patient Global assessment (PtGA) 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).

Physician's Global assessment (PGA) 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.

Imaging Data

The MRI/CT images will be analyzed by VirtualScopics as described in the imaging charter. The following quantitative and qualitative measurements will be summarized.

- Sum of product of diameters of the index lesions and percent change in sum of product of diameters relative to baseline
- 3D volume of index and measureable non-index lesions
- Presence of newly appearing lesions
- Liver volume and bi-dimensional size
- Spleen volume and bi-dimensional size
- Qualitative assessment of splenomegaly and hepatomegaly

6.2.3 Descriptive analyses

The change from baseline of SF-36 and WPAI-CIQ summary scores, and of visual analogue scale scores for PGA and PtGA, will be calculated and summary statistics will be provided by age group, treatment and visit. Mean (SD) profiles and individual profile plots will be provided by age group and treatment.

Summary statistics by age group, treatment and visit will be provided for the change from baseline in High Sensitivity C-reactive protein (hsCRP), Lactate dehydrogenase (LDH), beta2 microglobulin, ferritin, fibrinogen and erythrocyte sedimentation rate (ESR). Treatment with glucocorticoid drugs (e.g., prednisolone) can have an effect on these parameters and product, dose and timing of such treatment will be captured. Appropriate information needed for

interpretation will be added to the outputs as footnotes as required. Mean (SD) and individual profile plots will be provided by age group and treatment.

The 3D volume of index lesions will be log10 transformed and the change from baseline of the log10 transformed 3D volume at the end of treatment (i.e. the Day 85 assessment for patients who complete the 12 week treatment period or the treatment discontinuation visit for patients who discontinue treatment prematurely prior to Day 85 visit) will be calculated for patients with baseline and end of treatment measurements. Individual profile plots and summary statistics will be provided by age group and treatment.

6.2.4 Statistical model, assumptions and hypotheses

An analysis of covariance will be performed for SF-36 and WPAI-CIQ scores, and of visual analogue scale scores for PGA and PtGA, to compare the change from baseline at the end of treatment (i.e. the Day 85 assessment for patients who complete the 12 week treatment period or the treatment discontinuation visit for patients who discontinue treatment prematurely prior to Day 85 visit) between the two treatment groups, with treatment as a fixed effect and baseline as a covariate. The use of glucocorticoids and intravenous IgG at baseline will both be included as categorical (Yes/No) fixed effects. Comparison of the two treatment groups will be two-sided, with a 5% type I error.

The change from baseline will also be analyzed using a longitudinal mixed model, with treatment, time (as categorical), treatment by time, baseline and baseline by time interaction as fixed effects. The use of glucocorticoids and intravenous IgG at baseline will both be included as categorical (Yes/No) fixed effects. For patients who complete the treatment period, this repeated measures analysis will include all measurements in the treatment period (Baseline, Day 29, Day 57 and Day 85). An unstructured covariance matrix will be fitted to adjust for correlations among the measurements made on the same patient. The difference between the treatment groups in the change from baseline after 12 weeks of treatment will be assessed at two-sided 5% significance level.

An analysis of covariance will be performed for the 3D volume of index and measureable non-index lesions and 3D volume and bi-dimensional size of spleen to compare the change of the log10 transformed value from baseline between the two treatment groups, with treatment as a fixed effect and baseline as a covariate. The use of glucocorticoids and intravenous IgG at baseline will both be included as categorical (Yes/No) fixed effects. Comparison of the two treatment groups will be two-sided, with a 5% type I error.

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6.3 Exploratory objectives

6.3.1 Variables

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6.3.2 Descriptive analyses

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7 Statistical methods for safety and tolerability data

All patients within the safety analysis set will be included in the safety data analysis.

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7.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, as well as patient demographics, baseline characteristics, and treatment information.

7.1.1 Variables for gender split analysis

Variables to be used in the gender split analysis for safety and tolerability are: adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements.

7.2 Descriptive analyses

Patient demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment and patient. Summary statistics will be provided by age group and treatment and will also include PIK3CD mutation. Demographic summary will be provided by using the Safety set and all enrolled patients.

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

Treatment

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

Vital signs

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

Summary statistics will also be provided by gender, treatment group and visit/time.

ECG evaluations

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

Summary statistics will also be provided by gender, treatment group and visit/time.

Clinical laboratory evaluations

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

Summary statistics will also be provided by gender, treatment group and visit/time.

Adverse events

All information obtained on adverse events will be displayed by age group, treatment and patient. The number and percentage of patients with adverse events will be tabulated by body system and preferred term with a breakdown by age group and treatment. A patient with multiple adverse events within a body system is only counted once towards the total of this body system.

All information obtained on adverse events will also be displayed by gender, treatment and patient.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 0% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

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Pregnancy test

All pregnancy test results for pre-menopausal women who are not surgically sterile will be listed by age group, treatment, patient and visit/time.

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7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created.

8 Statistical methods for biomarker data

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9 References

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