CCDZ173X2201E1

NCT Nr. 02859727

Statistical Analysis Plan 13MAR2025

Pharming

Pharming Technologies B.V.

CDZ173 (Leniolisib)

CCDZ173X2201E1

An open-label, non randomized extension study to evaluate the long term safety, tolerability, efficacy and pharmacokinetics 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):	[redacted] Trial Statistician
Document type:	SAP Documentation
Document status:	FINAL V3.0
Release date:	13MAR2025
Number of pages:	26

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
02-NOV-2016	Prior to DB lock	Creation of initial version	N/A - First version	NA
01-FEB-2018	Prior to DB lock	Incorporate updates from protocol amendments up to V04		Throughout whole document
05-MAR-2019	Prior to DB lock	Finalization		Throughout whole document
13-MAR-2025	Prior to DB lock	To reference the latest protocol, incorporate additional information and include details of additional analyses.		Throughout whole document

Table of contents

List of tables

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 **"CCDZ173X2201E1".**

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

1.2 Study reference documentation

This SAP has been developed using Clinical Trial Protocol version v11 dated 13 December 2022.

1.3 Study objectives

1.3.1 Primary objective

- To evaluate the long term safety and tolerability of CDZ173 in patients with APDS/PASLI

1.3.2 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 gelatine capsules

1.3.3 Exploratory objectives

- To explore biomarkers that may provide additional measures of efficacy.
- To assess impact on lymphoadenopathy (non-index lesions and spleen) on patients who participated in CCDZ173X2201 study

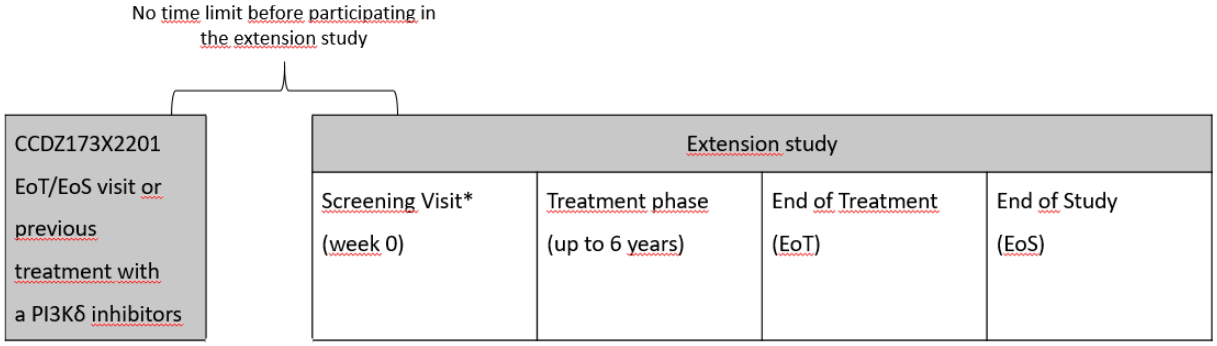
1.4 Study design and treatment

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 CDZ173X2201 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 up to 6 years for an individual patient.

Figure 1-1 Study Design



*Not to be performed if patients rolls-over directly from CCDZ173X2201 EoT or EoS visit

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.

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 a 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. 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.

2 First interpretable results (FIR)

First interpretable results (FIR) will not be provided for this trial.

3 Interim analyses

Formal 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. In this case, the analyses as described in the sections below are conducted for the relevant endpoints.

Interim analysis in the form of DMC summaries will be performed as per the details in section 3.1.

3.1 Data Monitoring Committee

The DMC will be established (according to previous Sponsor's 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.

3.1.1 DMC Requirements

Safety data including treatment exposure, demographics, adverse events and laboratory parameters (including but not limited to lab parameters outside the normal ranges; absolute and change from baseline of erythrocytes, hemoglobin, leukocytes, differential white blood cell count including neutrophil count, platelet count, AST, ALT, AP and bilirubin) systolic and diastolic blood pressure, pulse rate, PR, QRS, QT and QTcF intervals measured by ECGs.

Raw safety and efficacy data will be provided to the DMC chair in a regular and timely way.

In case an IA is performed the report will be made available to the DMC.

Summaries include (but not limited to):

- AE table by preferred term
- Treatment exposure heat maps
- Demographic table
- Individual and mean plots for:
    - Lab data

- Vital Signs (systolic/diastolic blood, pressure, pulse rate, PR, QRS, QT and QTcF)
- VAS
- Biomarkers
- Immunoglobulin data (by type and total)
- EBV/CMV data.

SDTMs required for DMC requirements:

AE, SUPPAE, BO, CO, DM, SUPPDM, DS, SUPPDS, DV, EX, SUPPEX, LB, SUPPLB, MH, QS, SC, SE, SU, SV, VS, SUPPVS, ZD

4 Statistical methods: Analysis sets

Data from the core study will be presented along with the data from this extension study.

Baseline should be taken from the core study if there is no gap longer than 6 weeks between end of core study to beginning the extension study. If there is a gap longer than 6 weeks, the baseline would then be the start of the extension.

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

All subjects that received study drug and with no protocol deviations with relevant impact on safety will be included in the safety analysis set.

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

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 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*
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set

Category Deviation code	Text description of deviation	Data exclusion
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*

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

5 Statistical methods for Pharmacokinetic (PK) parameters

5.1 Variables

PK samples will be obtained and evaluated in all patients.

Noncompartmental methods applied with a validated software program Phoenix WinNonlin (Certara, Version 8.3.5 or later) to the plasma concentrations of Leniolisib and S-Leniolisib will be used to determine the following PK parameters:

Parameter	Units[a]	Definition
$AUC_{\tau,ss}$	ng.h/mL	area under the concentration versus time curve during one dosing interval at steady state (τ = 12 hour)
$C_{max,ss}$	ng/mL	maximum observed drug concentration at steady state
$t_{max,ss}$	h	time of maximum observed drug concentration at steady state

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] The AUC will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule).

Pharmacokinetic analysis will be carried out using actual dose administered (mg) and actual postdose blood sampling times. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

Predose will be used as trough sample for each patient for derivation of pharmacokinetic parameters.

The parameters $C_{max,ss}$ and $t_{max,ss}$ will be obtained directly from the concentration-time profiles. If $C_{max,ss}$ occurs at more than 1 timepoint, $t_{max,ss}$ will be assigned to the first occurrence of $C_{max,ss}$.

Steady-state drug exposure will be summarized in terms of trough concentration (C_{trough}).

Additional PK parameters may be calculated, as appropriate. The software and version used for the final analyses will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the CSR.

5.1.1 Criteria for Calculation and Reporting of Area Under the Concentration-time Curve

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification. If there are only 3 consecutive concentrations, at least 1 should follow C_{max}.

5.1.2 Criteria for Handling Concentrations Below the Limit of Quantification or Missing Concentrations for Pharmacokinetic Analysis

Plasma concentrations below the limit of quantification (BLQ) will be assigned a value of 0 before the first measurable concentration and thereafter BLQ concentrations will be treated as missing. The following rules apply to the specific situations defined below:

- If an entire concentration-time profile is BLQ, it will be excluded from PK analysis.
- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters, unless they are considered to be a true characteristic of the profile of the drug.
- If a predose plasma concentration is missing, it will be set to 0 by default within Phoenix WinNonlin.

5.1.3 Treatment of Outliers in Pharmacokinetic Analysis

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude the value from the PK analysis. However, the exclusion of any data must have strong justification and will be documented in the CSR.

Any quantifiable predose concentration value will be considered anomalous and set to missing for the PK analysis. This will be set to 0 by default in Phoenix WinNonlin.

5.1.4 Presentation of Pharmacokinetic Data

If the actual time of sample collection deviates from the nominal time by more than ±10%, the plasma concentrations will be flagged and excluded from the summary statistics. Individual concentrations deemed to be anomalous will be flagged in the listings and excluded from the summary statistics.

For plasma concentration data, the following rules will apply:

- Values that are BLQ will be set to 0 for the calculation of summary statistics.

- Arithmetic mean or median values that are BLQ will be presented as 0.

For PK parameters, the following rule will apply:

- Geometric mean and coefficient of variation will not be calculated for t_{max}.

5.2 Descriptive analyses

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 and formulation as appropriate, including the frequency (n, %) of concentrations below the LLOQ and reported as zero. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum.

Concentrations below LLOQ will be treated as zero in summary statistics. A geometric mean will not be reported if the dataset includes zero values.

5.3 Statistical model, assumptions and hypotheses

PK parameters Cmax,ss and $AUC_{\tau,ss}$ 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 $AUC_{\tau,ss}$ 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 $AUC_{\tau,ss}$ 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.

5.4 Model checking procedures

Residual plots will be produced to assess the adequacy of the model

5.5 Graphical presentation of results

Arithmetic mean (SD) plasma concentration data will be plotted across time.

Overlaying individual plasma concentration-time profiles will be generated.

Individual plasma concentration-time profiles will be generated.

6 Statistical methods for Pharmacodynamic (PD) parameters

6.1 Secondary objectives

6.1.1 Variables

Secondary variables include: hsCRP, LDH, SF-36 and WPAI-CIQ scores, visual analogue scale scores for PGA and PtGA, and infections and other disease complications data.

6.1.1.1 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.

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

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

The following derived summary scores will be derived:

WPAI:AS

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, as follows:

Questions:

1 = currently employed
2 = hours usually work
3 = hours missed due to allergy
4 = degree allergy affected productivity while working
5 = currently student
6 = hours usually attend class
7 = hours class time missed due to allergy
8 = degree allergy affected productivity while working
9 = degree allergy affected regular activities

Scores:

Multiply scores by 100 to express in percentages.

Percent work time missed due to allergy: Q3/Q2

Percent impairment while working due to allergy: Q4/10

Percent overall work impairment due to allergy: (Q3/Q2)+[(1-(Q3/Q2))x(Q4/10)]

Percent class time missed due to allergy: Q7/Q6

Percent impairment in the classroom due to allergy: Q8/10

Percent overall classroom impairment due to allergy:
(Q7/Q6)+[(1-(Q7/Q6))x(Q8/10)]

Percent activity impairment due to allergy: Q9/10

6.1.1.3 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).

6.1.1.4 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.

6.1.1.5 Frequencies of infections

Summary statistics of frequencies of infections (AE body system of "Infections and infestations") will be provided by treatment for each year of follow-up, for groups of patients completing at least 1, 2, 3, 4, and 5 years of follow-up, see safety section below for full details of the analyses of adverse event data.

Heatmap figures will be presented for infections, pulmonary infections and all AEs with the overall time on treatment for each patient shaded in grey and the incidence of the AE highlighted in color according to severity.

Summaries of infection rates, days of infections will be presented along with a barchart of infection rates.

The number of infections and also separately for respiratory tract infections will be analyzed using counts per year per patient and analyzed using a log-linear negative binomial model including an effect for time at the start of infection (in years) and an offset for the amount of follow-up time available within each year for each patient. Data will be included for each patient up to their final partial year. A repeated statement with an exchangeable correlation structure will be used to model the intra-patient correlation. If an AE start day is missing then it will be imputed as the start of the month. If no infections are experienced in a year then the number of infections will be set to 0 for that year.

6.1.2 Descriptive analyses

Unless stated otherwise, summary statistics for PD variables will include sample size (N), mean (arithmetic and geometric as appropriate), SD, CV (arithmetic and geometric as appropriate), median, minimum and maximum. Geometric statistics will not be reported if the dataset includes zero values.

The hsCRP, LDH, SF-36 individual components and subscores, 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 treatment and visit along with changes from baseline. Similar summaries will also be presented based on the last available study visit.

The summary statistics for SF-36 will also be repeated for the following subgroups:

- Patients with norm-based or component summary scores <50 at baseline
- Patients with SF-36 Physical Component Summary norm-based scores ≤40 at baseline
- Patients with SF-36 Mental Component Summary norm-based scores ≤40 at baseline
- Patients with health domain scale or component summary norm-based scores <45 at baseline

Frequency tables with the n (%) of patients fulfilling the following responder criteria will be summarized by visit, for all patients and for the subgroup with norm-based or component summary scores <45 at baseline:

PHYSICAL FUNCTIONING SCALE: NORM-BASED	Change from baseline >=4.3 points Change from baseline >=6 points
ROLE PHYSICAL SCALE: NORM-BASED SCORE	Change from baseline >=3.4 points Change from baseline >=4 points
BODILY PAIN SCALE: NORM-BASED SCORE	Change from baseline >=4.6 points Change from baseline >=5.5 points Change from baseline >=6.2 points

GENERAL HEALTH SCALE: NORM-BASED SCORE	Change from baseline >=4 points Change from baseline >=7 points Change from baseline >=7.2 points
VITALITY SCALE: NORM-BASED SCORE	Change from baseline >=4.7 points Change from baseline >=6.2 points Change from baseline >=6.7 points
SOCIAL FUNCTIONING SCALE: NORM-BASED	Change from baseline >=4.7 points Change from baseline >=6.2 points Change from baseline >=6.9 points
ROLE EMOTIONAL SCALE: NORM-BASED SCORE	Change from baseline >=4.5 points Change from baseline >=4.6 points Change from baseline >=5 points
MENTAL HEALTH SCALE: NORM-BASED SCORE	Change from baseline >=3.7 points Change from baseline >=6.2 points Change from baseline >=6.7 points
PHYSICAL COMPONENT SUMMARY	Change from baseline >=3 points Change from baseline >=3.4 points Change from baseline >=3.8 points
MENTAL COMPONENT SUMMARY	Change from baseline >=4 points Change from baseline >=4.6 points

Frequency tables with the n (%) of patients with norm-based or component summary scores of <45 at baseline, fulfilling the following responder criteria, will be summarized by visit:

PHYSICAL FUNCTIONING SCALE: NORM-BASED	Score of ≥45 at visit
ROLE PHYSICAL SCALE: NORM-BASED SCORE	Score of ≥45 at visit
BODILY PAIN SCALE: NORM-BASED SCORE	Score of ≥45 at visit
GENERAL HEALTH SCALE: NORM-BASED SCORE	Score of ≥45 at visit
VITALITY SCALE: NORM-BASED SCORE	Score of ≥45 at visit
SOCIAL FUNCTIONING SCALE: NORM-BASED	Score of ≥45 at visit

ROLE EMOTIONAL SCALE: NORM-BASED SCORE	Score of ≥45 at visit
MENTAL HEALTH SCALE: NORM-BASED SCORE	Score of ≥45 at visit
PHYSICAL COMPONENT SUMMARY	Score of ≥45 at visit
MENTAL COMPONENT SUMMARY	Score of ≥45 at visit

6.1.2.1 Graphical presentation of results

Arithmetic mean (SE) of absolute values and change from baseline values for secondary PD variables will be plotted across time. Overlaying individual data profiles will also be plotted across time.

The following scatterplots will be presented by visit including the spearman rank correlation coefficient and corresponding p-value. The plots containing log10 transformed SPD will be repeated excluding any nodes with unknown values at any relevant timepoint:

Figure	**Analysis Set**
Scatterplot of Change from baseline in physician assessment questionnaire versus Change from Baseline in log10 transformed SPD	PD analysis set
Scatterplot of Change from baseline in patient assessment questionnaire versus Change from Baseline in log10 transformed SPD	PD analysis set
Scatterplot of Change from baseline in physician assessment questionnaire versus Change from Baseline in naive B cells	PD analysis set with less than 48% of naive B cells at baseline
Scatterplot of Change from baseline in patient assessment questionnaire versus Change from Baseline in naive B cells	PD analysis set with less than 48% of naive B cells at baseline

6.1.2.2 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.

Parameters may include 3D volume of index and measurable non-index lesions selected as per the Cheson methodology, 3D volume and bidimensional sizes of spleen and liver, where appropriate.

This assessment will be exclusively performed in patients that participated in study CCDZ173X2201 since only these patients provide baseline data. Sensitivity analyses should exclude nodes with values of “UNK” at any relevant timepoint, these sensitivity analyses will be performed for an outputs where a change from baseline and or percentage change from baseline is presented.

6.1.2.3 Descriptive analyses for exploratory imaging

Summary statistics will be provided by treatment and visit. Similar summaries will also be presented based on the last available study visit. Arithmetic mean (SE) of absolute values and change from baseline values will be plotted across time. Overlaying individual data profiles and a barchart for the count of lesions will also be plotted across time. A waterfall plot showing the percentage change from baseline for each patient will be presented by visit.

Frequency tables with the n (%) of patients fulfilling the following responder criteria will be summarized by visit:

ORGAN VOLUME (mm3)	Percent change from baseline <=-35% Reaching spleen 3D volume size of <236890 mm3
SUM OF THE LESION AREAS DERIVED	Percent change from baseline <=-25% Percent change from baseline <=-30% Percent change from baseline <=-50%

The number and percentage of patients who met the percentage change thresholds outlined in the below table will be summarized for lymph nodes (SPD) and spleen volume. Change from baseline is measured from baseline visit to study visit. Summary statistics will be provided by treatment and visit. Similar summaries will also be presented based on the last available study visit. Age-specific responder thresholds are defined for adult (>=18 years old) and pediatric (<18 years old) patients separately. Reporting will still be evaluated as one group i.e., not stratified by age, with age-appropriate thresholds used. Age-specific responder thresholds are the following:

Age	Lymph nodes (% reduction)	Spleen volume (% reduction)
Adult	30.00	27.50
Pediatric	45.00	35.00

Adult: >= 18 years of age at screening. Pediatric: < 18 years of age at screening.
Inclusion populations for these responder analyses are the following:

- Lymph nodes
  - Patients who had an enlarged lymph node at baseline (i.e. had imaging data available at baseline)
- Spleen volume
  - Patients with enlarged spleen at baseline (spleen volume >314 mL, or equivalently, 314,000mm^3)

6.1.2.4 Cellular Biomarkers: Immuno-phenotyping B cell panel

Table applicable for subjects enrolled from part 2 except first visit (301 sample number) from 2 subjects rolled-over from part 2: 1001005 and 1001006 (please see table below)

Parameter	DIVA name	Description	Population	Read out (in Wlims)
% of positive cells	B cells	% B cells out of lymphocytes	CD19+	CD19-P-%-LYM
	mature B cells	% mature B cells out of B cells	CD19+CD21+	CD21-P-%-B
	non switched memory	% non-switched memory B cells out of B cells	CD19+CD27+IgD+	CD27-P-IgD-P-%-B
	switched memory	% switched memory B cells out of B cells	CD19+CD27+IgD-	CD27-P-IgD-N-%-B
	memory B cells	% memory B cells out of B cells	CD19+CD27+CD10-	CD27-P-CD10-N-%-B
	naive B cells	% naive B cells out of B cells	CD19+CD27-CD10-	CD27-N-CD10-N-%-B
	transitional B cells	% transitional B cells out of B cells	CD19+CD27-CD10+	CD27-N-CD10-P-%-B
	plasma blasts CD38+	% plasma blasts out of B cells	CD19+CD27++/CD38++	CD27-H-CD38-H-%-B

Table applicable for all subjects enrolled from part 1 and first visit (301 sample number) from 2 subjects rolled-over from part 2: 1001005 and 1001006

Parameter	DIVA name	Description	Population	Read out (in Wlims)
% of positive cells	B cells	% B cells out of lymphocytes	CD19+	CD19-P-%-LYM
	mature B cells	% mature B cells out of B cells	CD19+CD21+	CD21-P-%-B
	non switched memory	% non-switched memory B cells out of B cells	CD19+CD27+IgD+	CD27-P-IgD-P-%-B
	switched memory	% switched memory B cells out of B cells	CD19+CD27+IgD-	CD27-P-IgD-N-%-B
	memory B cells	% memory B cells out of B cells	CD19+CD27+CD10-	CD27-P-CD10-N-%-B
	naive B cells	% naive B cells out of B cells	CD19+CD27-CD10-	CD27-N-CD10-N-%-B
	transitional B cells	% transitional B cells out of B cells	CD19+CD27-CD10+	CD27-N-CD10-P-%-B
	plasma blasts CD38+	% plasma blasts out of B cells	CD19+CD27++/CD38++	CD27-H-CD38-H-%-B

6.1.2.5 Cellular Biomarkers: Immuno-phenotyping T cell panel

Table applicable for subjects enrolled from part 2 except first visit (301 sample number) from 2 subjects rolled-over from part 2: 1001005 and 1001006 (please see table below)

Para-meter	DIVA name	Description	Population	Read out (in Wlims)
% of positive cells	T cells	%CD3+ cells out of CD45 leukocytes	CD3+	CD3-P-%-LEU
	CD4+	%CD4+ cells out of CD3+ T cells	CD4+	CD4-P-%-CD3
	CD8+	%CD8+ cells out of CD3+ T cells	CD8+	CD8-P-%-CD3
	naive CD4+	%CD4+ naive T cells out of CD4 T cells	CD4+CD45RA+CD62L+	Tnaive-%-CD4
	central memory CD4+	%CD4+ central memory T cells (T_{CM}) out of CD4 T cells	CD4+CD45RA-CD62L+	TCM-%-CD4
	effector memory CD4+	%CD4+ effector memory T cells (T_{EM}) out of CD4 T cells	CD4+CD45RA-CD62L-	TEM-%-CD4
	effector memory RA CD4+	%CD4+ effector memory RA T cells (T_{EMRA}) out of CD4 T cells	CD4+CD45RA+CD62L-	TEMRA-%-CD4
	naive CD8+	%CD8+ naive T cells out of CD8 T cells	CD8+CD45RA+CD62L+	Tnaive-%-CD8
	central memory CD8+	% CD8+ central memory T cells (T_{CM}) out of CD8T cells	CD8+CD45RA-CD62L+	TCM-%- CD8
	effector memory CD8+	% CD8+ effector memory T cells (T_{EM}) out of CD8 T cells	CD8+CD45RA-CD62L-	TEM-%- CD8
	effector memory RA CD8+	% CD8+ effector memory RA T cells (T_{EMRA})out of CD8 T cells	CD8+CD45RA+CD62L-	TEMRA-%- CD8
	CD57+ CD4+	%CD57+ out of CD4+ T cells	CD4+CD57+	CD57-P-%-CD4
	CD57+ CD8+	%CD57+ out of CD8+T cells	CD8+CD57+	CD57-P-%-CD8
	PD-1+ CD4+	%PD-1+ out of CD4+ T cells	CD4+PD-1+	PD1-P-%-CD4
	PD-1+ CD8+	%PD-1+ out of CD8+ T cells	CD8+PD-1+	PD1-P-%- CD8

Table applicable for all subjects enrolled from part 1 and first visit (301 sample number) from 2 subjects rolled-over from part 2: 1001005 and 1001006

Para-meter	DIVA name	Description	Population	Read out
% of positive cells	T cells	%CD3+ cells out of CD45 leukocytes	CD3+	CD3-P-%-LEU
	CD4+	%CD4+ cells out of CD3+ T cells	CD4+	CD4-P-%-CD3
	CD4-	%CD4- cells out of CD3+ T cells (……)	CD4-	CD4-N-%-CD3
	naive CD4+	%CD4+ naive T cells out of CD4 T cells	CD4+CD45RA+CD62L+	Tnaive-%-CD4-P
	central memory CD4+	%CD4+ central memory T cells (T_{CM}) out of CD4 T cells	CD4+CD45RA-CD62L+	TCM-%-CD4-P
	effector memory CD4+	%CD4+ effector memory T cells (T_{EM}) out of CD4 T cells	CD4+CD45RA-CD62L-	TEM-%-CD4-P
	effector memory RA CD4+	%CD4+ effector memory RA T cells (T_{EMRA}) out of CD4 T cells	CD4+CD45RA+CD62L-	TEMRA-%-CD4-P
	naive CD4-	%CD4- naive T cells out of CD4- T cells	CD4-CD45RA+CD62L+	Tnaive-%-CD4-N
	central memory CD4-	% CD4- central memory T cells (T_{CM}) out of CD4- T cells	CD4-CD45RA-CD62L+	TCM-%- CD4-N
	effector memory CD4-	% CD4- effector memory T cells (T_{EM}) out of CD4- T cells	CD4-CD45RA-CD62L-	TEM-%- CD4-N
	effector memory RA CD4-	% CD4- effector memory RA T cells (T_{EMRA})out of CD4- T cells	CD4-CD45RA+CD62L-	TEMRA-%- CD4-N
	CD57+ CD4+	%CD57+ out of CD4+ T cells	CD4+CD57+	CD57-P-%-CD4-P
	CD57+ CD4-	%CD57+ out of CD4-T cells	CD4-CD57+	CD57-P-%-CD4-N
	PD-1+ CD4+	%PD-1+ out of CD4+ T cells	CD4+PD-1+	PD1-P-%-CD4-P
	PD-1+ CD4-	%PD-1+ out of CD4- T cells	CD4-PD-1+	PD1-P-%- CD4-N

Units for Cellular biomarkers parameters in the source data will be given as IU, but this will represent % in the outputs.

6.1.2.6 Soluble Biomarkers

Soluble biomarkers may include but not limited to:

- Chemokine panels consisting of, such as
- CXCL13, MIP-3a/CCL20, MDC/CCL22, MIP-1b/CCL4, IP-10
- Cytokine panel consisting of IFN-γ, and TNF-α IgG, IgM, IgA, IgE (incl. isotypes).

6.1.2.7 Viremia markers

- CMV viremia
- EBV viremia

6.1.2.8 Descriptive analyses

All biomarker data (except for hypothesis-free platforms) will be listed by patient, treatment and visit. Summary statistics will be provided by CDZ173X2201 study treatment and visit/time. Similar summaries will also be presented based on the last available study visit. In the summary tables, the frequency (n, %) of values below the LLOQ and above the ULOQ, respectively, will be included.

For EBV and CMV surveillance due to the categorical nature of some of the results a frequency table will be used. For this data the following additional categories will be defined and a shift table presented with the frequencies and percentage of the shifts from baseline to post-baseline in each of the categories by visit

- Negative (overall): Includes categories Negative/Not Detected/Not Repeated/0/results below LLOQ
- Positive (overall): Includes all numerical reported data and categories: Positive/results above LLOQ

Frequency tables with the n (%) of patients fulfilling the following responder criteria will be summarized by visit, this will be done for all patients in the PD analysis set as well as patients with <48% percentage of naïve b cells at baseline :

Naive B cells (%)	>=25% improvement

Overlaying individual data profiles will also be plotted across time.

Handling of LLOQ and ULOQ

Biomarker data are reported as concentration results, measured using a specific assay with a working range defined by the two limits: Lower limit of quantification (LLOQ) and Upper limit of quantification (ULOQ). Values which fall below the LLOQ or above the ULOQ are reported as < LLOQ * dilution factor (dilution factor: if sample diluted and concentration measured still below LLOQ) and > ULOQ * dilution factor, respectively.

To ensure that biomarkers only have numerical values, censored values will be imputed as follows

- Values below the LLOQ are replaced by LLOQ/2.

- Values above the ULOQ are replaced by ULOQ.

Imputed values are used for summary statistics, inferential analyses and plots (with a special symbol). Values below LLOQ and values above ULOQ are shown as such in the listings. In the summary table, the frequency (n, %) of values below the LLOQ and above the ULOQ, respectively, will be included.

If the proportion of imputed data is more than 20% for any treatment group at any time point, a footnote is added to the summary statistics table stating that the proportion of values outside the limits of quantification is more than 20% for some treatment groups at some time points and that in such cases summary statistics may be heavily biased.

If the proportion of imputed data for a given biomarker, across all treatment groups and time points, is more than 50%, no summary statistics are provided and the data are only listed.

Spaghetti plots by visit of absolute and percent change from baseline will be provided.

Parameters of 'Number of events' and 'Median fluorescence intensity' in the immuno-phenotyping T cell panel are to be listed only.

7 Statistical methods for safety and tolerability data

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

7.1.1 Variables

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

7.1.2 Statistical analyses

Patient disposition and Analysis Set Assignment

Patient disposition and analysis set data will be listed. A frequency table will be provided with the number and percentage of patients completing/discontinuing each epoch of the study with

the reasons for discontinuation also summarized. The number and percentage of patients in each of the analysis sets will also be summarized along with reasons for exclusion.

Subject demographics and other baseline characteristics

All data for background, disease characteristics and demographic variables will be listed by patient. Summary statistics will be provided. The number and percentage of patients enrolled in each country and study site will be provided.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by patient. Medical history will be summarized by primary system organ class and preferred term.

Protocol deviations

Protocol deviations will be listed and summarized by protocol deviation category and protocol deviation term.

Study Treatment

Data for study drug administration will be listed by patient.

Summary statistics will be provided for the total exposure in mg and duration of exposure in weeks. The number and percentage of patients with a duration of exposure in the following categories will be presented: 1 to <2 weeks, 2 to <4 weeks, 4 to <10 weeks, 10 to <11 weeks, 11 to <12 weeks, 12 to <24 weeks, 24 to <36 weeks, 36 to <48 weeks, 48 to <60 weeks, 60 to <72 weeks, 72 to <84 weeks, 84 to <96 weeks, 96 to <108 weeks, 108 to <156 weeks, 156 to <208 weeks, 208 to <260 weeks, continue on in yearly intervals as per the data.

If diary data is not completed and a patient's dosing is as per protocol at sites for dosing, it is considered that they receive the correct daily dose on the day's diary data was not entered.

A heatmap will be provided showing the time spent on treatment for each patient.

Previous study participation details will be listed.

Prior and Concomitant therapies

Data for prior and concomitant therapies will be listed by patient and summarized by preferred term.

A barchart will be provided showing the accumulated amount of immunoglobulin replacement therapy (IRT) administered.

Immunosuppressants, antibiotics and IRT medications

Medications falling into the categories of immunosuppressants, antibiotics or IRT will be identified during data review prior to database lock. The amount consumed in grams will be derived including the following assumptions:

- For IRT use reported in mL, grams consumed will be calculated as 1g/10mL for Gamunex, 1g/10mL for Hyqvia, 1g/5mL for Cuvitru, and 1g/5mL for Hizentra.
- Frequency of PRN or unknown are assumed to be once

- For dose units of mg/kg the screening weight will be used in the derivation

Summaries by medication type, preferred term and treatment will be provided. The annualized rate for parts 1 and 2 will be derived as ((number of medicated days of therapy)/84) * 365 and summarized. For the extension data the rate of medications in yearly and six monthly intervals will be defined as the number of medicated days on therapy divided by the number of patients in the treatment arm for the follow-up category. Patients should have completed the full follow-up time in the category to be included in the analysis. Barcharts will also be used to display these rates by study for Parts 1 and 2 and by year for the extension. The time course of immunoglobin use by week will also be displayed graphically.

IRT freedom is defined as no recorded IRT use for a 3 month period, summary statistics will be presented for number of patients achieving IRT freedom, total time in patient years from the first event to the end of follow up and the mean, median and SD for time to first event.

Similar summaries will also be provided for 25% reduction and 50% reduction in IRT over a 3 month period versus baseline (the first 3 month period in the study).

The number of grams of IRT and antibiotics will be analyzed separately using counts per year per patient and analyzed using a log-linear negative binomial model including an effect for time of use (in years) and an offset for the amount of follow-up time available within each year. Data will be included for each patient up to their final partial year. A repeated statement with an exchangeable correlation structure will be used to model the intra-patient correlation. If the start day is missing then it will be imputed as the start of the month. If none of the relevant medications are experienced in a year then the count will be set to 0 for that year.

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. Overlaying profile plots will be presented.

ECG evaluations

All ECG data will be listed by patient and visit/time, abnormalities will be flagged. A separate listing will be provided with patients with ECG abnormalities. Summary statistics will be provided by visit/time. Overlaying profile plots will be presented.

Clinical laboratory evaluations

All laboratory data will be listed by patient and visit/time and if normal ranges are available abnormalities will be flagged. Separate listings will be provided presenting all parameters in a patient with any abnormal values and clinical outcomes of cytopenia. Summary statistics and boxplots will be provided by visit/time Overlaying profile plots will be presented. Frequencies of abnormalities and cytopenia will be presented.

Newly occurring liver enzyme abnormalities will be presented in a frequency table according to the following categories:

ALT > 3x ULN
ALT > 5x ULN
ALT > 8x ULN
ALT > 10x ULN
ALT > 20x ULN
ALT or AST > 3x ULN
ALT or AST > 5x ULN
ALT or AST > 8x ULN
ALT or AST > 10x ULN
ALT or AST > 20x ULN
ALT or AST > 3x ULN & TBL > 1.5x ULN
ALT or AST > 3x ULN & TBL > 2x ULN
ALT or AST > 5x ULN & TBL > 2x ULN
ALT or AST > 8x ULN & TBL > 2x ULN
ALT or AST > 10x ULN & TBL > 2x ULN
ALT or AST > 20x ULN & TBL > 2x ULN
ALP > 1.5x ULN
ALP > 2x ULN
ALP > 3x ULN
ALP > 5x ULN
TBL > 1x ULN
TBL > 1.5x ULN
TBL > 2x ULN
TBL > 3x ULN
ALT or AST > 3x ULN & TBL > 2x ULN & ALP<= 2x ULN

Adverse events

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

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term, overall and then separately by preferred term for skin and subcutaneous disorders and gastrointestinal disorder.

Additional summaries will be provided for all patients and repeated for patients with grades of 3 or above by system organ class, preferred term and treatment for all AEs, treatment related

AEs, AEs leading to discontinuation of treatment, AEs leading to study withdrawal, serious AEs. These will also be repeated by maximum toxicity.

A patient with multiple adverse events within a body system is only counted once towards the total of the body system. The overall incidence of AEs will also be split by the following age, gender, genetic categories:

Age – <18 years, >=18 years, Overall

Gender – Male, Female, Overall

Genetic diagnosis – APDS1, APDS2, Overall

The AE rate per patient year will be derived as the below and will be summarized by part:

Total number of AEs divided by the total patient follow up years

Summaries of AE rates will also be presented for treatment related AEs and serious AEs

Heatmap figures will be presented for all AEs with the overall time on treatment for each patient shaded in grey and the incidence of the AE highlighted in color according to severity.

Other data

Any other data not detailed in the sections above will be listed only.