Clinical trial results:
An open-label, non-randomized, within-patient dose-finding study followed by a randomized, subject, investigator and sponsor-blinded placebo controlled study to assess the efficacy and safety of CDZ173 (leniolisib) in patients with APDS/PASLI (Activated phosphoinositide 3-kinase delta syndrome/ p110-activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency).

Summary

EudraCT number	2014-003876-22
Trial protocol	GB CZ NL IE FR IT
Global end of trial date	16 August 2021

Results information

Result version number	v1 (current)
This version publication date	08 March 2022
First version publication date	08 March 2022

Trial information

Trial identification

Sponsor protocol code	CCDZ173X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02435173
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Study Director, Novartis Pharmaceuticals, 41 + 1 862 778 8300, Novartis.email@Novartis.com
Scientific contact	Study Director, Novartis Pharmaceuticals, 41 + 1 862 778 8300, Novartis.email@Novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 August 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 August 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belarus: 1
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 20
Worldwide total number of subjects	37
EEA total number of subjects	13

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	1
Adolescents (12-17 years)	13
Adults (18-64 years)	23
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 10 investigative sites in 9 countries.

Pre-assignment

Screening details:

The participants were screened within 50 days prior to enrollment. After screening and baseline assessments, the treatment period started on Day 1.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Part I: CDZ173

Arm description:

Participants consecutively received CDZ173 10 mg b.i.d. from Day 1 to Day 28, CDZ173 30 mg b.i.d. from Day 29 to Day 56 and CDZ173 70 mg b.i.d. from Day 57 to Day 84.

Arm type	Experimental
Investigational medicinal product name	Leniolisib
Investigational medicinal product code	CDZ173
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants consecutively received CDZ173 10 mg b.i.d. from Day 1 to Day 28, CDZ173 30 mg b.i.d. from Day 29 to Day 56 and CDZ173 70 mg b.i.d. from Day 57 to Day 84.

Arm title	Part II: CDZ173 70 mg

Arm description:

Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.

Arm type	Experimental
Investigational medicinal product name	Leniolisib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.

Arm title	Part II: Placebo

Arm description:

Participants received Placebo b.i.d. from Day 1 to Day 85.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received Placebo b.i.d. from Day 1 to Day 85.

Number of subjects in period 1	Part I: CDZ173	Part II: CDZ173 70 mg	Part II: Placebo
Started	6	21	10
Pharmacokinetics (PK) Analysis Set	6	19 [1]	0 [2]
Pharmacodynamic (PD) analysis set	6	19 [3]	8 [4]
Completed	6	21	10

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Pharmacokinetics (PK) Analysis Set and Pharmacodynamic (PD) analysis set SUBSETS

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Pharmacokinetics (PK) Analysis Set and Pharmacodynamic (PD) analysis set SUBSETS

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Pharmacokinetics (PK) Analysis Set and Pharmacodynamic (PD) analysis set SUBSETS

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Pharmacokinetics (PK) Analysis Set and Pharmacodynamic (PD) analysis set SUBSETS

Baseline characteristics

Reporting groups	
Reporting group title	Part I: CDZ173
Reporting group description:	
Participants consecutively received CDZ173 10 mg b.i.d. from Day 1 to Day 28, CDZ173 30 mg b.i.d. from Day 29 to Day 56 and CDZ173 70 mg b.i.d. from Day 57 to Day 84.	
Reporting group title	Part II: CDZ173 70 mg
Reporting group description:	
Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	
Reporting group title	Part II: Placebo
Reporting group description:	
Participants received Placebo b.i.d. from Day 1 to Day 85.	

Reporting group values	Part I: CDZ173	Part II: CDZ173 70 mg	Part II: Placebo
Number of subjects	6	21	10
Age Categorical Units: Participants			
<=18 years	2	9	5
Between 18 and 65 years	4	12	5
>=65 years	0	0	0
Age Continuous Units: Years			
arithmetic mean	22.2	22.2	26.7
standard deviation	± 5.64	± 10.00	± 13.43
Sex: Female, Male Units: Participants			
Female	2	10	6
Male	4	11	4
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	6	18	7
More than one race	0	1	1
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	37		
Age Categorical Units: Participants			
<=18 years	16		
Between 18 and 65 years	21		
>=65 years	0		

Age Continuous Units: Years arithmetic mean standard deviation	 -		
Sex: Female, Male Units: Participants			
Female	18		
Male	19		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	2		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	2		
White	31		
More than one race	2		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Part I: CDZ173

Reporting group description:

Participants consecutively received CDZ173 10 mg b.i.d. from Day 1 to Day 28, CDZ173 30 mg b.i.d. from Day 29 to Day 56 and CDZ173 70 mg b.i.d. from Day 57 to Day 84.

Reporting group title	Part II: CDZ173 70 mg

Reporting group description:

Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.

Reporting group title	Part II: Placebo

Reporting group description:

Participants received Placebo b.i.d. from Day 1 to Day 85.

Subject analysis set title	Part I: CDZ173 10 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants consecutively received CDZ173 10 mg b.i.d. from Day 1 to Day 28, CDZ173 30 mg b.i.d. from Day 29 to Day 56 and CDZ173 70 mg b.i.d. from Day 57 to Day 84.

Subject analysis set title	Part II: CDZ173
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.

Subject analysis set title	Part II: CDZ173
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.

Subject analysis set title	Part II: CDZ173
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.

Subject analysis set title	Part II: CDZ173
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.

Subject analysis set title	Part II: CDZ173
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.

Primary: Part I: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Part I: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)[1]

End point description:

Number of participants with AEs and SAEs, including significant changes from baseline in physical findings, vital signs, electrocardiograms and laboratory values qualifying and reported as AEs. The number of participants in each category (AEs and SAEs) is reported per dose level: CDZ173 10 mg from Day 1 to Day 28, CDZ173 30 mg from day 29 to day 56 and CDZ173 70 mg from day 57 to day 84.

End point type	Primary

End point timeframe:

From the start of treatment to 30 days after end of treatment, assessed up to maximum duration of 114 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this primary outcome

End point values	Part I: CDZ173 10 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Participants				
CDZ173 10 mg AEs	2			
CDZ173 10 mg SAEs	0			
CDZ173 30 mg AEs	2			
CDZ173 30 mg SAEs	0			
CDZ173 70 mg AEs	4			
CDZ173 70 mg SAEs	0			

Statistical analyses

No statistical analyses for this end point

Primary: Part I: CDZ173 dose concentration

End point title	Part I: CDZ173 dose concentration[2][3]

End point description:

Venous whole blood samples were collected for the assessment of the dose-PD and the PK/PD relationship of CDZ173 in participants with APDS/PASLI for dose selection in Part II. CDZ173 was determined by a validated Liquid chromatography - Mass spectometry (LC-MS) method; anticipated Lower Limit of Quantification (LLOQ) was 3 ng/mL. Concentrations below the LLOQ were reported as "zero" and no methods for imputation of missing data were used.

End point type	Primary

End point timeframe:

Days 1, 29 and 57 (0.25 and 3 h post morning dose) and Day 84

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this primary outcome

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this primary outcome

End point values	Part I: CDZ173			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Nanogram / millilitre				
arithmetic mean (standard deviation)				
Day 1: 0.25 h post-dose	10.10 (± 1.10)			
Day 1: 3 h post-dose	321.00 (± 115.00)			
Day 29: 0.25 h post-dose	249.00 (± 540.00)			
Day 29: 3 h post-dose	916.00 (± 185.00)			

Day 57: 0.25 h post-dose	150.00 (± 143.00)			
Day 57: 3 h post-dose	1710.00 (± 782.00)			
Day 84	998.00 (± 455.00)			

Statistical analyses

No statistical analyses for this end point

Primary: Part I: Percentage of inhibition of unstimulated and stimulated pAkt levels in B cells

End point title	Part I: Percentage of inhibition of unstimulated and stimulated pAkt levels in B cells[4][5]

End point description:

Phosphorylation of Akt in ex vivo stimulated and unstimulated B cells was quantified at baseline and at the end of the 4-week treatment period for each of the three dose levels. Determination of the percentage (%) of CD20B+ phospho-Akt positive cells after ex vivo stimulation of whole blood was performed by flow cytometry analysis. The percentage of inhibition of pAkt was defined as (-1) * percent change from baseline pAkt value. Unstimulated cells served as controls at each time point. Baseline was defined as the mean of the day -1 value and the pre-dose value on Day 1 when both were available (if one was missing, then baseline was defined as the existing value). A higher percentage of inhibition of stimulated B cells indicates improvement. No methods for imputation of missing data were used.

End point type	Primary

End point timeframe:

Baseline, days 29 and 57 (3 and 12 h post-dose) and day 84

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this secondary outcome

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this primary outcome

End point values	Part I: CDZ173			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Percentage				
arithmetic mean (standard deviation)				
CD20B Unstimulated: Day 29 - 3 h post-dose (n=6)	82.07 (± 7.25)			
CD20B Stimulated: Day 29 - 3 h post-dose (n=5)	78.00 (± 7.25)			
CD20B Unstimulated: Day 29 - 12 h post-dose (n=6)	50.58 (± 18.73)			
CD20B Stimulated: Day 29 - 12 h post-dose (n=6)	47.14 (± 7.83)			
CD20B Unstimulated: Day 57 - 3 h post-dose (n=2)	86.61 (± 5.26)			
CD20B Stimulated: Day 57 - 3 h post-dose (n=3)	60.98 (± 54.05)			
CD20B Unstimulated: Day 57 - 12 h post-dose (n=5)	53.18 (± 16.59)			

CD20B Stimulated: Day 57 - 12 h post-dose (n=3)	63.65 (± 21.03)			
CD20B Unstimulated: Day 84 (n=5)	74.35 (± 11.03)			
CD20B Stimulated: Day 84 (n=4)	78.65 (± 12.00)			

Statistical analyses

No statistical analyses for this end point

Primary: Part II: Change from baseline in the log10 transformed sum of product of diameters (SPD) in the index lesions

End point title	Part II: Change from baseline in the log10 transformed sum of product of diameters (SPD) in the index lesions[6]

End point description:

For the assessment of the impact of CDZ173 on lymphadenopathy, participants were scanned in a magnetic resonance imaging (MRI) or a computed tomography (CT) scanner as based on clinical practice and local regulation. MRI or CT imaging of the neck, chest, abdomen and pelvis was performed. Index lesions were selected from measurable nodal and extranodal lesions as per the Cheson methodology. A maximum of six of the largest dominant lesions were selected and documented at baseline and assessed again at the end of treatment. The change in lymph node size was measured using the log10 transformed sum of product of diameters (SPD), the sum of the longest lesion diameter (mm)" and "longest perpendicular diameter (mm)". A lower score indicates index lesions SPD reduction. A negative change from baseline indicates improvement.

End point type	Primary

End point timeframe:

Baseline and Day 85

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this primary outcome

End point values	Part II: Placebo	Part II: CDZ173		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8	18		
Units: Millimeter on Log10 scale				
least squares mean (standard error)	-0.06 (± 0.06)	-0.30 (± 0.04)		

Statistical analyses

Statistical analysis title	SPD in the index lesions
Comparison groups	Part II: Placebo v Part II: CDZ173
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0012
Method	ANCOVA
Parameter estimate	Adjusted means difference
Point estimate	-0.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	-0.11
Variability estimate	Standard error of the mean
Dispersion value	0.06

Primary: Part II: Change from baseline in percentage of naïve B cells out of total B cells

End point title	Part II: Change from baseline in percentage of naïve B cells out of total B cells[7]

End point description:

APDS/PASLI patients suffer from dysregulation in B cell function and differentiation with low numbers of naive B cells. Change from baseline in percentage of naïve B cells out of total B cells at the end of treatment was assessed by flow cytometry to evaluate the pharmacodynamic effect of CDZ173 on B cell immunophenotyping. A higher percentage in naïve B out of total B cells is a positive outcome. A positive change from baseline indicates improvement.

End point type	Primary

End point timeframe:

Baseline and Day 85

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary outcome

End point values	Part II: Placebo	Part II: CDZ173		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	5	8		
Units: Percentage change from baseline				
least squares mean (standard error)	-5.37 (± 3.95)	34.76 (± 3.08)		

Statistical analyses

Statistical analysis title	Naïve B cells out of total B cells
Comparison groups	Part II: Placebo v Part II: CDZ173
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Adjusted means difference
Point estimate	40.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.51
upper limit	51.75

Variability estimate	Standard error of the mean
Dispersion value	5.04

Secondary: Part I & II: Area Under the Plasma Concentration-time Curve From Time Zero to the Last Quantifiable Concentration (AUClast) for CDZ173

End point title	Part I & II: Area Under the Plasma Concentration-time Curve From Time Zero to the Last Quantifiable Concentration (AUClast) for CDZ173[8]

End point description:

Venous whole blood samples were collected for activity-based pharmacokinetics characterization. AUClast was calculated from plasma concentration-time data using non-compartmental methods. AUClast was calculated at the first day of every CDZ173 dose level (10, 30 and 70 mg) for Part I and (70 mg) for Part II. No methods for imputation of missing data were used.

End point type	Secondary

End point timeframe:

Part I: Days 1, 29 and 57 / Part II: Day 1

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary outcome

End point values	Part I: CDZ173	Part II: CDZ173		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	6	19		
Units: Hour * nanogram / millilitre				
arithmetic mean (standard deviation)				
Day 1	1760.0 (± 441.0)	10400.0 (± 2800.0)		
Day 29	4760.0 (± 816.0)	0 (± 0)		
Day 57	10800.0 (± 3310.0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part I & II: Maximum Observed Plasma Concentration (Cmax) for CDZ173

End point title	Part I & II: Maximum Observed Plasma Concentration (Cmax) for CDZ173[9]

End point description:

Venous whole blood samples were collected for activity-based pharmacokinetics characterization. Cmax was calculated from plasma concentration-time data using non-compartmental methods. Cmax was calculated at the first day of every CDZ173 dose level (10, 30 and 70 mg) for Part I and (70 mg) for Part II. No methods for imputation of missing data were used.

End point type	Secondary

End point timeframe:

Part I: Days 1, 29 and 57 / Part II: Day 1

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary outcome

End point values	Part I: CDZ173	Part II: CDZ173		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	6	19		
Units: Nanogram / millilitre				
arithmetic mean (standard deviation)				
Day 1	393.0 (± 137.0)	2150.0 (± 576.0)		
Day 29	1060.0 (± 222.0)	0 (± 0)		
Day 57	2540.0 (± 747.0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part I & II: Mental component summary (MCS) and Physical component summary (PCS) from Short Form 36 (SF-36) Survey

End point title	Part I & II: Mental component summary (MCS) and Physical component summary (PCS) from Short Form 36 (SF-36) Survey[10]

End point description:

The SF-36 is a widely used and extensively studied instrument to measure health-related quality of life (HRQoL) among healthy subjects and patients with acute and chronic conditions. It consists of eight subscales that can be scored individually: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. The subscales are aggregated to derive two overall summary scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores. PCS and MCS scores range from 0 to 100 with a higher score indicating a more favorable health state (range = 0 "worst" - 100 "best"). No methods for imputation of missing data were used.

End point type	Secondary

End point timeframe:

Part I: Baseline and Days 29, 57 and 84 / Part II: Baseline and Days 29, 57 and 85

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary outcome

End point values	Part I: CDZ173	Part II: Placebo	Part II: CDZ173	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	8	19	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Day -1: MCS	47.94 (± 8.22)	45.94 (± 8.14)	47.36 (± 7.98)	
Day -1: PCS	47.54 (± 9.24)	44.06 (± 8.59)	44.49 (± 7.08)	
Day 29: MCS	47.94 (± 8.22)	49.52 (± 6.70)	49.98 (± 8.06)	
Day 29: PCS	47.54 (± 9.24)	44.62 (± 7.57)	47.87 (± 7.66)	

Day 57: MCS	47.94 (± 8.22)	45.92 (± 7.31)	49.12 (± 8.17)	
Day 57: PCS	47.54 (± 9.24)	47.20 (± 9.75)	47.04 (± 7.30)	
Day 84 (Part I) / Day 85 (Part II): MCS	47.94 (± 8.22)	47.32 (± 8.73)	49.22 (± 8.17)	
Day 84 (Part I) / Day 85 (Part II): PCS	47.54 (± 9.24)	47.48 (± 8.48)	47.59 (± 6.22)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part I & II: Physician's Global Assessment (PGA)

End point title	Part I & II: Physician's Global Assessment (PGA)[11]

End point description:

In the physician's global assessment questionnaire the Investigator rated the disease activity of their patient using 100 mm Visual analogue Scale (VAS) ranging from "no disease activity" (0) to "maximal disease activity" (100). To enhance objectivity, the physician was not aware of the specific patient's global assessment, when performing his own assessment on that patient. No methods for imputation of missing data were used.

End point type	Secondary

End point timeframe:

Part I: Baseline and Days 29, 57 and 84 / Part II: Baseline and Days 29, 57 and 85

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary outcome

End point values	Part I: CDZ173	Part II: Placebo	Part II: CDZ173	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	8	19	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=6, 19, 8)	34.7 (± 17.07)	41.38 (± 17.78)	47.10 (± 17.65)	
Day 29 (n=6, 18, 8)	21.8 (± 9.70)	29.75 (± 9.99)	38.81 (± 23.73)	
Day 57 (n=6, 19, 8)	22.5 (± 13.55)	24.13 (± 18.34)	34.02 (± 18.89)	
Day 84 (Part I) / Day 85 (Part II) (n=6, 19, 8)	8.8 (± 4.12)	25.88 (± 16.15)	26.70 (± 22.82)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part I & II: Patient's Global Assessment (PtGA)

End point title	Part I & II: Patient's Global Assessment (PtGA)[12]

End point description:

In the patient's global assessment questionnaire patients are asked about their APDS/PASLI related well-being using 100 mm visual analogue scale (VAS) ranging from "very poor" (0) to "very good" (100). No methods for imputation of missing data were used.

End point type	Secondary

End point timeframe:

Part I: Baseline and Days 29, 57 and 84 / Part II: Baseline and Days 29, 57 and 85

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary outcome

End point values	Part I: CDZ173	Part II: Placebo	Part II: CDZ173	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	8	19	
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Baseline	62.0 (± 21.90)	62.50 (± 26.56)	54.53 (± 21.47)	
Day 29	65.0 (± 22.21)	57.75 (± 24.03)	68.37 (± 19.31)	
Day 57	67.5 (± 21.83)	69.50 (± 21.93)	64.79 (± 19.61)	
Day 84 (Part I) / Day 85 (Part II)	72.5 (± 13.37)	60.25 (± 23.66)	67.58 (± 16.57)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part I & II: High Sensivity C reactive protein (hsCRP) as biomarker for systemic inflammation

End point title	Part I & II: High Sensivity C reactive protein (hsCRP) as biomarker for systemic inflammation[13]

End point description:

High Sensitivity C reactive protein is a blood test biomarker for inflammation in the body. Sequential blood samples were collected in all participants. HsCRP was measured in serum using a latex immunochemilunminometric assay (ICMA). No methods for imputation of missing data were used.

End point type	Secondary

End point timeframe:

Part I: Baseline and Days 1, 15, 29, 57, 84 / Part II: Baseline and Days 1, 15, 29, 57, 85

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary outcome

End point values	Part I: CDZ173	Part II: Placebo	Part II: CDZ173	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	8	19	
Units: Milligram / liter				
arithmetic mean (standard deviation)				
Baseline (n=6, 4, 2)	2.49 (± 1.29)	5.70 (± 2.19)	10.58 (± 17.84)	
Day 1 (n=6, 4, 2)	2.43 (± 1.43)	7.85 (± 4.88)	8.95 (± 14.56)	

Day 15 (n=6, 18, 7)	0.93 (± 0.70)	2.06 (± 1.02)	9.19 (± 23.12)	
Day 29 (n=6, 18, 8)	0.77 (± 0.36)	2.40 (± 1.75)	5.55 (± 11.21)	
Day 57 (n=6, 18, 8)	1.20 (± 0.71)	8.90 (± 16.66)	6.57 (± 9.18)	
Day 84 (Part I) / Day 85 (Part II) (n=5, 18, 8)	2.82 (± 4.11)	2.65 (± 1.79)	7.54 (± 18.37)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part I & II: Lactate dehydrogenase (LDH) as biomarker for systemic inflammation

End point title	Part I & II: Lactate dehydrogenase (LDH) as biomarker for systemic inflammation[14]

End point description:

Lactate dehydrogenase is a blood test biomarker for inflammation in the body. Sequential blood samples were collected in all participants. LDH was measured in serum using a latex immunochemilunminometric assay (ICMA). No methods for imputation of missing data were used.

End point type	Secondary

End point timeframe:

Part I: Baseline and Days 1, 15, 29, 57, 84 / Part II: Baseline and Days 1, 15, 29, 57, 85

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary outcome

End point values	Part I: CDZ173	Part II: Placebo	Part II: CDZ173	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	6	8	19	
Units: Units / liter				
arithmetic mean (standard deviation)				
Baseline (n=6, 19, 8)	130.42 (± 18.28)	169.38 (± 41.95)	172.92 (± 72.25)	
Day 1 (n=6, 17, 7)	132.17 (± 23.10)	175.71 (± 53.72)	170.88 (± 72.28)	
Day 15 (n=6, 18, 7)	132.17 (± 11.44)	155.14 (± 48.09)	190.94 (± 71.54)	
Day 29 (n=6, 18, 8)	125.17 (± 9.85)	185.25 (± 51.62)	227.17 (± 163.41)	
Day 57 (n=6, 19, 7)	135.50 (± 17.66)	167.14 (± 40.45)	193.11 (± 64.75)	
Day 84 (Part I) / Day 85 (Part II) (n=5, 19, 8)	142.60 (± 18.53)	179.13 (± 73.96)	190.63 (± 57.62)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part II: Beta2 microglobulin as biomarker for systemic inflammation

End point title	Part II: Beta2 microglobulin as biomarker for systemic inflammation[15]

End point description:

Beta2 microglobulin is a blood test biomarker for inflammation in the body. Sequential blood samples were collected in all participants. Beta2 microglobulin was measured in serum using a latex immunochemilunminometric assay (ICMA). No methods for imputation of missing data were used.

End point type	Secondary

End point timeframe:

Baseline and Days 1, 15, 29, 57, 85

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary outcome

End point values	Part II: Placebo	Part II: CDZ173		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8	19		
Units: Milligram / liter				
arithmetic mean (standard deviation)				
Baseline (n=19, 8)	2.32 (± 0.96)	2.46 (± 0.87)		
Day 1 (n=19, 8)	2.31 (± 0.95)	2.43 (± 0.88)		
Day 15 (n=18, 7)	2.31 (± 1.09)	2.10 (± 1.03)		
Day 29 (n=18, 8)	3.21 (± 1.61)	2.02 (± 1.17)		
Day 57 (n=19, 8)	2.42 (± 1.17)	1.90 (± 0.72)		
Day 85 (n=19, 8)	2.57 (± 1.19)	2.01 (± 1.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part II: Ferritin as biomarker for systemic inflammation

End point title	Part II: Ferritin as biomarker for systemic inflammation[16]

End point description:

Ferritin is a blood test biomarker for inflammation in the body. Sequential blood samples were collected in all participants. Ferritin was measured in serum using a Electrochemiluminescence immunoassay (ECLIA). No methods for imputation of missing data were used.

End point type	Secondary

End point timeframe:

Baseline and Days 1, 15, 29, 57, 85

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary outcome

End point values	Part II: Placebo	Part II: CDZ173		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8	19		
Units: Microgram / liter				
arithmetic mean (standard deviation)				
Baseline (n=18, 8)	62.05 (± 81.65)	139.16 (± 399.73)		
Day 1 (n=18, 8)	61.34 (± 82.04)	142.67 (± 411.57)		
Day 15 (n=17, 7)	24.61 (± 17.41)	146.99 (± 494.88)		
Day 29 (n=16, 8)	48.43 (± 61.83)	187.65 (± 641.16)		
Day 57 (n=18, 8)	51.40 (± 64.95)	199.97 (± 657.31)		
Day 85 (n=18, 8)	63.16 (± 56.64)	139.42 (± 368.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part II: Fibrinogen as biomarker for systemic inflammation

End point title	Part II: Fibrinogen as biomarker for systemic inflammation[17]

End point description:

Fibrinogen is a blood test biomarker for inflammation in the body. Sequential blood samples were collected in all participants. Fibrinogen was measured in serum using an Electrochemiluminescence immunoassay (ECLIA). No methods for imputation of missing data were used.

End point type	Secondary

End point timeframe:

Baseline and Days 1, 15, 29, 57, 85

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary outcome

End point values	Part II: Placebo	Part II: CDZ173		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8	19		
Units: Gram / liter				
arithmetic mean (standard deviation)				
Baseline (n=19, 8)	2.68 (± 0.44)	2.66 (± 0.76)		
Day 1 (n=19, 8)	2.65 (± 0.42)	2.61 (± 0.81)		
Day 15 (n=17, 7)	2.67 (± 0.42)	2.65 (± 0.62)		
Day 29 (n=18, 8)	2.66 (± 0.58)	2.53 (± 0.54)		
Day 57 (n=19, 8)	2.83 (± 1.13)	3.01 (± 0.68)		
Day 85 (n=19, 8)	2.61 (± 0.57)	2.81 (± 0.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part II: Erythrocyte sedimentation rate (ESR) as biomarker for systemic inflammation

End point title	Part II: Erythrocyte sedimentation rate (ESR) as biomarker for systemic inflammation[18]

End point description:

Erythrocyte sedimentation rate (ESR) is a blood test biomarker for inflammation in the body. Sequential blood samples were collected in all participants. ESR was measured in whole blood using the Westergren method. No methods for imputation of missing data were used.

End point type	Secondary

End point timeframe:

Baseline and Days 1, 15, 29, 57, 85

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary outcome

End point values	Part II: Placebo	Part II: CDZ173		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8	19		
Units: Millimeter / hour				
arithmetic mean (standard deviation)				
Baseline (n=16, 8)	25.44 (± 24.88)	28.09 (± 19.79)		
Day 1 (n=16, 8)	25.13 (± 24.51)	26.88 (± 19.33)		
Day 15 (n=14, 7)	16.00 (± 12.21)	19.50 (± 13.52)		
Day 29 (n=15, 8)	26.00 (± 25.26)	18.33 (± 13.80)		
Day 57 (n=17, 8)	27.88 (± 23.04)	18.06 (± 15.36)		
Day 85 (n=17, 8)	19.63 (± 18.03)	16.35 (± 15.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part II: 3D volume of index lesions

End point title	Part II: 3D volume of index lesions[19]

End point description:

Participants were scanned in a magnetic resonance imaging (MRI) or a computed tomography (CT) scanner as based on clinical practice and local regulation. MRI or CT imaging of the neck, chest, abdomen and pelvis was performed. The 3D volume of index lesions was identified as per the Cheson criteria. A reduction of the 3D volume of the index lesions indicated a positive outcome.

End point type	Secondary

End point timeframe:

Baseline and Day 85

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary outcome

End point values	Part II: Placebo	Part II: CDZ173		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8	19		
Units: Millimeter^3				
arithmetic mean (standard deviation)				
Baseline	37123.69 (± 67325.94)	20142.12 (± 15617.13)		
Day 85	40169.28 (± 81844.45)	7858.08 (± 6290.98)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part II: 3D volume of the spleen

End point title	Part II: 3D volume of the spleen[20]

End point description:

Participants were scanned in a magnetic resonance imaging (MRI) or a computed tomography (CT) scanner as based on clinical practice and local regulation. MRI or CT imaging of the spleen was performed and its 3D volume was identified as per the Cheson criteria. A reduction of the spleen volume indicated a positive outcome.

End point type	Secondary

End point timeframe:

Baseline and Day 85

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary outcome

End point values	Part II: Placebo	Part II: CDZ173		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8	19		
Units: Millimeter^3				
arithmetic mean (standard deviation)				
Baseline	448456.15 (± 328641.78)	586448.74 (± 311482.61)		

Day 85	480333.09 (± 445371.99)	411130.98 (± 193977.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part I & II: Overall work impairment due to health score from Work Productivity Activity Impairment and Classroom Impairment Questionnaire (WPAI-CIQ)

End point title	Part I & II: Overall work impairment due to health score from Work Productivity Activity Impairment and Classroom Impairment Questionnaire (WPAI-CIQ)[21]

End point description:

The Work Productivity Activity Impairment (WPAI) questionnaire measures the amount of absence or presence for work attendance and daily work activity impairment attributable to APDS/PASLI. As younger participants (age 12 and above) were enrolled in the study the WPAI-CIQ was used for all participants as it also measures the amount of absence or presence for school attendance and daily classroom activity impairment. Participants answered for classroom or work-related questions depending on their situation. WPAI-CIQ consists of 10 questions that yield 4 types of scores: absenteeism, presenteeism, work/classroom productivity loss and activity impairment. The Overall work impairment due to health (%) score ranges from 0 to 100% with 100% indicating total work impairment and 0% no impairment at all. No methods for imputation of missing data were used.

End point type	Secondary

End point timeframe:

Part I: Baseline and Days 29, 57 and 84 / Part II: Baseline and Days 29, 57 and 85

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary outcome

End point values	Part I: CDZ173	Part II: Placebo	Part II: CDZ173	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	2	2	9	
Units: Percentage				
arithmetic mean (standard deviation)				
Baseline (n=2, 9, 2)	25.00 (± 35.36)	5.00 (± 7.07)	51.25 (± 37.23)	
Day 29 (n=1, 9, 2)	44.00 (± 0)	5.00 (± 7.07)	35.31 (± 23.12)	
Day 57 (n=1, 8, 2)	62.31 (± 0)	10.00 (± 14.14)	35.49 (± 24.70)	
Day 84 (Part I) / Day 85 (Part II) (n=2, 9, 2)	44.41 (± 7.90)	25.00 (± 7.07)	35.59 (± 31.85)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part I & II: Overall classroom impairment due to health score from the Work Productivity Activity Impairment and Classroom Impairment Questionnaire (WPAI-CIQ)

End point title	Part I & II: Overall classroom impairment due to health score from the Work Productivity Activity Impairment and Classroom Impairment Questionnaire (WPAI-CIQ)[22]

End point description:

The Work Productivity Activity Impairment (WPAI) questionnaire measures the amount of absence or presence for work attendance and daily work activity impairment attributable to APDS/PASLI. As younger participants (age 12 and above) were enrolled in the study the WPAI-CIQ was used for all participants as it also measures the amount of absence or presence for school attendance and daily classroom activity impairment. Participants answered for classroom or work-related questions depending on their situation. WPAI-CIQ consists of 10 questions that yield 4 types of scores: absenteeism, presenteeism, work/classroom productivity loss and activity impairment. The Overall classroom impairment due to health (%) score ranges from 0 to 100% with 100% indicating total classroom impairment and 0% no impairment at all. A higher percentage indicates a negative outcome. No methods for imputation of missing data were used.

End point type	Secondary

End point timeframe:

Part I: Baseline and Days 29, 57 and 84 / Part II: Baseline and Days 29, 57 and 85

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary outcome

End point values	Part I: CDZ173	Part II: Placebo	Part II: CDZ173	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	4	5	
Units: Percentage				
arithmetic mean (standard deviation)				
Baseline (n=3, 5, 4)	65.68 (± 33.49)	23.75 (± 30.92)	47.33 (± 44.75)	
Day 29 (n=3, 2, 4)	57.30 (± 18.09)	22.65 (± 24.37)	0.00 (± 0)	
Day 57 (n=2, 2, 4)	70.13 (± 18.68)	22.40 (± 26.16)	12.14 (± 3.03)	
Day 84 (Part I) / Day 85 (Part II) (n=3, 1, 2)	68.52 (± 18.74)	5.00 (± 7.07)	51.00 (± 0.00)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Part I and Part II: Adverse events (AEs) were reported from the start of treatment to 30 days after end of treatment, assessed up to maximum duration of 114 days for Part I and 115 days for Part II.

Adverse event reporting additional description:

Any sign or symptom that occurs during the study treatment plus 30 days post treatment. For Part I AEs are reported based on the CDZ173 dose level received when AE started. So the 30 days post treatment are only applicable for the CDZ173 70 mg arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Part I: CDZ173 10 mg

Reporting group description:

Participants received CDZ173 10 mg b.i.d. from Day 1 to Day 28.

Reporting group title	Part II: Placebo

Reporting group description:

Participants received Placebo b.i.d. from Day 1 to Day 85.

Reporting group title	Part I: Total

Reporting group description:

Participants consecutively received CDZ173 10 mg b.i.d. from Day 1 to Day 28, CDZ173 30 mg b.i.d. from Day 29 to Day 56 and CDZ173 70 mg b.i.d. from Day 57 to Day 84.

Reporting group title	Part II: CDZ173 70 mg

Reporting group description:

Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.

Reporting group title	Part I: CDZ173 30 mg

Reporting group description:

Participants received CDZ173 30 mg b.i.d. from Day 29 to Day 56.

Reporting group title	Part I: CDZ173 70 mg

Reporting group description:

Participants received CDZ173 70 mg b.i.d. from Day 57 to Day 84.

Serious adverse events	Part I: CDZ173 10 mg	Part II: Placebo	Part I: Total
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	2 / 10 (20.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Lipase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Coma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Dependence on oxygen therapy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary hypertension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Mastoiditis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Failure to thrive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part II: CDZ173 70 mg	Part I: CDZ173 30 mg	Part I: CDZ173 70 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 21 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Lipase increased			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Coma			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Lymphadenopathy			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Dependence on oxygen therapy			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary hypertension			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastoiditis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Failure to thrive			

subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part I: CDZ173 10 mg	Part II: Placebo	Part I: Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	9 / 10 (90.00%)	4 / 6 (66.67%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vasculitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 10 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Vascular device occlusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Adnexa uteri cyst			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Menstrual disorder			

subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	1 / 6 (16.67%)	1 / 10 (10.00%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Investigations			
Amylase increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 10 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 10 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Body temperature increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase			

increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 10 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Pancreatic enzymes increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Protein urine present			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Iliotibial band syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Road traffic accident			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Joint injury			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sunburn			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Congenital, familial and genetic disorders			

Methylenetetrahydrofolate reductase gene mutation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	2 / 10 (20.00%)	1 / 6 (16.67%)
occurrences (all)	0	3	1
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Taste disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
External ear pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Hypoacusis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Episcleritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Aphthous ulcer			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dental caries			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dyspepsia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	3 / 10 (30.00%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Toothache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dermatitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dermatitis atopic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Seborrhoeic dermatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Rash maculo-papular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Anuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Flank pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Clostridium difficile colitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Conjunctivitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Fungal skin infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastrointestinal infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Groin infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nasal herpes			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Oral candidiasis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Otitis externa			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Rhinitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	2 / 10 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part II: CDZ173 70 mg	Part I: CDZ173 30 mg	Part I: CDZ173 70 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 21 (85.71%)	2 / 6 (33.33%)	4 / 6 (66.67%)
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Vasculitis			

subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Fatigue			
subjects affected / exposed	2 / 21 (9.52%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Vascular device occlusion			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Adnexa uteri cyst			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Menstrual disorder			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Oropharyngeal pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Investigations			
Amylase increased			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Lipase increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Body temperature increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pancreatic enzymes increased			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Protein urine present			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Weight increased			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural			

complications			
Contusion			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Iliotibial band syndrome			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Road traffic accident			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Joint injury			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal injury			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Sunburn			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Congenital, familial and genetic disorders			
Methylenetetrahydrofolate reductase gene mutation			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 21 (23.81%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	6	1	0
Dizziness			

subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Taste disorder			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
External ear pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoacusis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Vertigo			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Episcleritis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			

Abdominal discomfort			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Aphthous ulcer			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Constipation			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dental caries			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Diarrhoea			
subjects affected / exposed	2 / 21 (9.52%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Dyspepsia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Haematochezia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Vomiting			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Dermatitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dermatitis atopic			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	2 / 21 (9.52%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Hyperhidrosis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Rash maculo-papular			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Anuria			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			

Bursitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	2 / 21 (9.52%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	2 / 21 (9.52%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Clostridium difficile colitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fungal skin infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Gastrointestinal infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Lower respiratory tract infection			

subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Groin infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nasal herpes			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Otitis externa			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	4 / 21 (19.05%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	4	1	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 21 (9.52%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Urinary tract infection			

subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2015	The purpose of this amendment is to address feedback received by the National Institute of Allergy and Infectious Diseases (NIAID) IRB, NIH, USA, the FDA and the MHRA in relation to the study protocol. Inclusion/exclusion criteria have been amended to remove inconsistencies.
01 March 2015	The purpose of this protocol amendment is to provide updated information related to safety findings observed in an ongoing 39-week toxicology study and related additional safety measures implemented in relation to the potential risk of infections and gastrointestinal infection, in particular.
01 June 2015	The purpose of this protocol amendment is to enable the use of the new 70 mg capsule of CDZ173 for the 70 mg b.i.d. dose level, rather than 7 capsules of 10 mg CDZ173 b.i.d.
01 September 2015	The purpose of this protocol amendment is to revise the requirements related to contraception in-line with the "recommendations related to contraception and pregnancy testing in clinical trials" issued by the European Heads of Medicine Agencies (HMA) clinical trial facilitation group (CTFG) in September 2014.
01 December 2015	The purpose of this protocol amendment is to revise the restrictions of concomitant medication use following the outcome of a preliminary data review of a drug-drug interaction study (CCDZ173X2102).
01 April 2016	One purpose of this amendment is to introduce a safety measure based on information emerging from another PI3Kδ inhibitor.
01 July 2017	The main purpose of this protocol amendment is to adjust the design, endpoints and biomarkers of the study Part II based on the results obtained from the study Part I.
01 February 2019	The main purpose of this amendment is to change eligibility criteria to allow for inclusion of APDS patients with more severe disease phenotype, who often do not have stable maintenance immunoglobulin replacement treatment, but receive varying doses according to their actual need. Eligibility criteria for vital signs of the pediatric patient population are slightly adapted. Furthermore, the restricted medication section is updated to allow for treatment with higher dose of corticosteroids, since patients could be in need of this rescue medication.
01 February 2020	The purpose of this amendment is to address changes to trial conduct in the case of an epidemic or pandemic that limits or prevents on-site visits (e.g. COVID-19 pandemic). The protocol is adapted to allow alternative methods of providing continuing care as well as remote collection of efficacy endpoints, where possible.
16 October 2020	The purpose of this amendment is to address questions and comments raised by the Health Authority in Germany (BfArM). The Risks and benefits section has been expanded to include a sub-section to show the specific benefit / risk profile of adolescents (12 – 15 years of age). In addition, in accordance with internal Novartis guidelines, a COVID-19 test prior to enrollment into the study has been included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported