# 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<br>Units: Participants | | | |
| <=18 years | 2 | 9 | 5 |
| Between 18 and 65 years | 4 | 12 | 5 |
| >=65 years | 0 | 0 | 0 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 22.2 | 22.2 | 26.7 |
| standard deviation | ± 5.64 | ± 10.00 | ± 13.43 |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 2 | 10 | 6 |
| Male | 4 | 11 | 4 |
| Race (NIH/OMB)<br>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<br>Units: Participants | | | |
| <=18 years | 16 | | |
| Between 18 and 65 years | 21 | | |
| >=65 years | 0 | | |

| | | | |
|---|---|---|---|
| Age Continuous<br>Units: Years<br>arithmetic mean<br>standard deviation | <br><br><br>- | | |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 18 | | |
| Male | 19 | | |
| Race (NIH/OMB)<br>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