NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Not Applicable

Trial Indication(s)

APDS/PASLI (Activated phosphoinositide 3-kinase delta syndrome/ p110δ-activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency)

Protocol Number

CCDZ173X2201

Protocol Title

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/ p110δ-activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency)

Clinical Trial Phase

Phase 2/Phase 3

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: August 2015 (Actual)
Primary Completion Date: August 2021 (Actual)

Study Completion Date: August 2021 (Actual)

Reason for Termination

Not applicable

Study Design/Methodology

Part I of the study was a non-randomized, open-label, within-patient up-titration dose-finding part in 6 participants with APDS/PASLI. Part II was a randomized, subject, investigator and sponsor-blinded, placebo-controlled, fixed dose part investigating 31 participants with APDS/PASLI.

Centers

10 centers in 9 countries: United States(1), Czech Republic(1), Netherlands(1), Russia(1), Ireland(1), Italy(2), United Kingdom(1), Belarus(1), Germany(1)

Objectives:

Primary:

- Part I: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)
- Part I: CDZ173 dose concentration
- Part I: Percentage of inhibition of unstimulated and stimulated pAkt levels in B cells
- Part II: Change from baseline in the log10 transformed sum of product of diameters (SPD) in the index lesions
- Part II: Change from baseline in percentage of naïve B cells out of total B cells

Secondary:

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

- Part I & II: Maximum Observed Plasma Concentration (Cmax) for CDZ173
- Part I & II: Mental component summary (MCS) and Physical component summary (PCS) from Short Form 36 (SF-36) Survey
- Part I & II: Overall work impairment due to health score from Work Productivity Activity Impairment and Classroom Impairment Questionnaire (WPAI-CIQ)
- Part I & II: Overall classroom impairment due to health score from the Work Productivity Activity Impairment and Classroom Impairment Questionnaire (WPAI-CIQ)
- Part I & II: Physician's Global Assessment (PGA)
- Part I & II: Patient's Global Assessment (PtGA)
- Part I & II: High Sensivity C reactive protein (hsCRP) as biomarker for systemic inflammation
- Part I & II: Lactate dehydrogenase (LDH) as biomarker for systemic inflammation
- Part II: Beta2 microglobulin as biomarker for systemic inflammation
- Part II: Ferritin as biomarker for systemic inflammation
- Part II: Fibrinogen as biomarker for systemic inflammation
- Part II: Erythrocyte sedimentation rate (ESR) as biomarker for systemic inflammation
- Part II: 3D volume of index lesions
- Part II: 3D volume of the spleen

Test Product (s), Dose(s), and Mode(s) of Administration

Oral Capsules of CDZ173 for 10 mg, 30 mg or 70 mg b.i.d.

Statistical Methods

All data for background and demographic variables were listed by treatment. The changes from baseline of High Sensitivity C-reactive protein (hsCRP), Lactate dehydrogenase (LDH), the sum of product of diameters of index lesions and spleen size were calculated and summary statistics were provided by visit. The changes from baseline for the biomarker data were calculated and summary statistics were provided by visit/time point. The changes from baseline of SF-36 and WPAI-CIQ scores, and of Visual analogue scale scores for PGA and PtGA, were calculated and summary statistics were provided by visit. The CDZ173 plasma concentration data were listed by age group, patient, and visit/sampling time point. Descriptive summary statistics were provided by visit/sampling time point. Concentrations below LLOQ were reported as zero. The safety parameters were listed by treatment. The number and percentage of patients with AEs were tabulated by body

system and preferred term with a breakdown by treatment. Descriptive summary statistics were provided by treatment and visit/sampling time point.

Part I: Percentage of pAkt positive B cells was quantified at baseline and at Day 1 (pre-dose, and 1h, 3h, 8h post dose), Day 8 (pre-dose) and Day 15 (pre-dose) of each of the three dose levels and at Day 28 (pre-dose) of the last dose level.

Part II: Descriptive summary statistics and individual patient profiles were provided for log10 transformed SPD and the change from baseline of the log10 transformed SPD at the end of treatment and change from baseline in naïve B cells out of total B cells at Day 29, Day 57 and Day 85 and the end of treatment.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:
- Male and female patients 12 to 75 years of age (inclusive), who had a documented APDS/PASLI-associated genetic PI3K delta mutation.
- In Part I and Part II, patients must had nodal and/or extranodal lymphoproliferation, and clinical findings and manifestations compatible with APDS/PASLI such as a history of repeated oto-sino-pulmonary infections and/or organ dysfunction (e.g., lung, liver). Additionally, in part II, patients must had at least one measurable nodal lesion on a CT or MRI scan.
- At screening, vital signs (systolic and diastolic blood pressure and pulse rate) were assessed in the sitting position after the patient rested for at least three minutes.

Key Exclusion Criteria:
- Previous or concurrent use of immunosuppressive medication.
- Current use of medication known to be strong inhibitor or moderate or strong inducers of isoenzyme CYP3A, if treatment cannot be discontinued or switched to a different medication prior to starting study treatment.
- Current use of medications that are metabolized by isoenzyme CYP1A2 and have a narrow therapeutic index (drugs whose exposureresponse indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes)).
- Administration of live vaccines (this includes any attenuated live vaccines) starting from 6 weeks before study entry, during the study and up to 7 days after the last dose of CDZ173.
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until

the termination of gestation, confirmed by a positive hCG laboratory test.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study medication and for 2 days after stopping study treatment.

Participant Flow Table

Overall Study

	Part I: CDZ173	Part II: CDZ173 70 mg	Part II: Placebo	Total
Arm/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.	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	Participants received Placebo b.i.d. from Day 1 to Day 85.	
Started	6	21	10	37
Pharmacokinetics (PK) Analysis Set	6	19	0	25
Pharmacodynamic (PD) analysis set	6	19	8	33
Completed	6	21	10	37
Not Completed	0	0	0	0

Baseline Characteristics

	Part I: CDZ173	Part II: CDZ173 70 mg	Part II: Placebo	Total
Arm/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.	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	Participants received Placebo b.i.d. from Day 1 to Day 85.	
Number of Participants [units: participants]	6	21	10	37
Age Continuous (units: Years) Mean ± Standard Deviation				
	22.2±5.64	22.2±10.00	26.7±13.43	23.43±10.44
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)				
Female	2	10	6	18
Male	4	11	4	19
Race (NIH/OMB) (units: Participants) Count of Participants (Not Applicable)				

American Indian or Alaska Native	0	0	0	0
Asian	0	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	0	1	1	2
White	6	18	7	31
More than one race	0	1	1	2
Unknown or Not Reported	0	0	0	0
Age Categorical (units: Participants) Count of Participants (Not Applicable)				
<=18 years	2	9	5	16
Between 18 and 65 years	4	12	5	21
>=65 years	0	0	0	0

Primary Outcome Result(s)

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

(Time Frame: From the start of treatment to 30 days after end of treatment, assessed up to maximum duration of 114 days)

	Part I: CDZ173 10 mg
Arm/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.
Number of Participants Analyzed [units: participants]	6
Part I: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) (units: Participants) Count of Participants (Not Applicable)	
CDZ173 10 mg AEs	2 (33.33%)
CDZ173 10 mg SAEs	0 (%)
CDZ173 30 mg AEs	2 (33.33%)
CDZ173 30 mg SAEs	0 (%)
CDZ173 70 mg AEs	4 (66.67%)
CDZ173 70 mg SAEs	0 (%)

Part I: CDZ173 dose concentration

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

	Part I: CDZ173
Arm/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.
Number of Participants Analyzed [units: participants]	6
Part I: CDZ173 dose concentration (units: Nanogram / millilitre) 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

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

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

	Part I: CDZ173
Arm/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.
Number of Participants Analyzed [units: participants]	6
Part I: Percentage of inhibition of unstimulated and stimulated pAkt levels in B cells (units: Percentage) 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

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

(Time Frame: Baseline and Day 85)

	Part II: CDZ173	**Part II: Placebo**
Arm/Group Description	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	Participants received Placebo b.i.d. from Day 1 to Day 85.
Number of Participants Analyzed [units: participants]	18	8
Part II: Change from baseline in the log10 transformed sum of product of diameters (SPD) in the index lesions (units: Millimeter on Log10 scale)		

Least Squares Mean ± Standard Error		
	-0.30 ± 0.04	-0.06 ± 0.06

Statistical Analysis

Groups	Part II: CDZ173, Part II: Placebo	
P Value	0.0012	
Method	ANCOVA	Treatment as a fixed effect and log10 transformed baseline SPD as a covariate.
Other Adjusted means difference	-0.24	
Standard Error of the mean	0.06	
95 % Confidence Interval 2-Sided	-0.37 to -0.11	

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

(Time Frame: Baseline and Day 85)

	Part II: CDZ173	**Part II: Placebo**
Arm/Group Description	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	Participants received Placebo b.i.d. from Day 1 to Day 85.
Number of Participants Analyzed [units: participants]	8	5

Part II: Change from baseline in percentage of naïve B cells out of total B cells (units: Percentage change from baseline) Least Squares Mean ± Standard Error	34.76 ± 3.08	-5.37 ± 3.95

Statistical Analysis

Groups	Part II: CDZ173, Part II: Placebo	
P Value	<0.0001	
Method	ANCOVA	Treatment as a fixed effect and baseline as a covariate.
Other Adjusted means difference	40.13	
Standard Error of the mean	5.04	
95 % Confidence Interval 2-Sided	28.51 to 51.75	

Secondary Outcome Result(s)

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

(Time Frame: Part I: Days 1, 29 and 57 / Part II: Day 1)

	Part I: CDZ173	**Part II: CDZ173**

Arm/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.	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.
Number of Participants Analyzed [units: participants]	6	19
Part I & II: Area Under the Plasma Concentration-time Curve From Time Zero to the Last Quantifiable Concentration (AUClast) for CDZ173 (units: Hour * nanogram / millilitre) Mean ± Standard Deviation		
Day 1	1760.0 ± 441.0	10400.0 ± 2800.0
Day 29	4760.0 ± 816.0	
Day 57	10800.0 ± 3310.0	

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

(Time Frame: Part I: Days 1, 29 and 57 / Part II: Day 1)

	Part I: CDZ173	**Part II: CDZ173**
Arm/Group Description	Participants consecutively received	Participants received CDZ173 70

	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.	mg b.i.d. from Day 1 to Day 85.
Number of Participants Analyzed [units: participants]	6	19
Part I & II: Maximum Observed Plasma Concentration (Cmax) for CDZ173 (units: Nanogram / millilitre) Mean ± Standard Deviation		
Day 1	393.0 ± 137.0	2150.0 ± 576.0
Day 29	1060.0 ± 222.0	
Day 57	2540.0 ± 747.0	

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

(Time Frame: Part I: Baseline and Days 29, 57 and 84 / Part II: Baseline and Days 29, 57 and 85)

	Part I: CDZ173	**Part II: CDZ173**	**Part II: Placebo**
Arm/Group Description	Participants consecutively received CDZ173 10 mg b.i.d. from Day 1 to Day 28, CDZ173	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	Participants received Placebo b.i.d. from Day 1 to Day 85.

	30 mg b.i.d. from Day 29 to Day 56 and CDZ173 70 mg b.i.d. from Day 57 to Day 84.		
Number of Participants Analyzed [units: participants]	6	19	8
Part I & II: Mental component summary (MCS) and Physical component summary (PCS) from Short Form 36 (SF-36) Survey (units: Score on a scale) Mean ± Standard Deviation			
Day -1: Mental Component Summary	47.94 ± 8.22	47.36 ± 7.98	45.94 ± 8.14
Day -1: Physical Component Summary	47.54 ± 9.24	44.49 ± 7.08	44.06 ± 8.59
Day 29: Mental Component Summary	47.94 ± 8.22	49.98 ± 8.06	49.52 ± 6.70
Day 29: Physical Component Summary	47.54 ± 9.24	47.87 ± 7.66	44.62 ± 7.57
Day 57: Mental Component Summary	47.94 ± 8.22	49.12 ± 8.17	45.92 ± 7.31
Day 57: Physical Component Summary	47.54 ± 9.24	47.04 ± 7.30	47.20 ± 9.75
Day 84 (Part I) / Day 85 (Part II): Mental Component Summary	47.94 ± 8.22	49.22 ± 8.17	47.32 ± 8.73
Day 84 (Part I) / Day 85 (Part II): Physical Component Summary	47.54 ± 9.24	47.59 ± 6.22	47.48 ± 8.48

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

(Time Frame: Part I: Baseline and Days 29, 57 and 84 / Part II: Baseline and Days 29, 57 and 85)

	Part I: CDZ173	Part II: CDZ173	Part II: Placebo
Arm/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.	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	Participants received Placebo b.i.d. from Day 1 to Day 85.
Number of Participants Analyzed [units: participants]	2	9	2
Part I & II: Overall work impairment due to health score from Work Productivity Activity Impairment and Classroom Impairment Questionnaire (WPAI-CIQ) (units: Percentage) Mean ± Standard Deviation			
Baseline (n=2, 9, 2)	25.00 ± 35.36	51.25 ± 37.23	5.00 ± 7.07
Day 29 (n=1, 9, 2)	44.00 ± 0	35.31 ± 23.12	5.00 ± 7.07
Day 57 (n=1, 8, 2)	62.31 ± 0	35.49 ± 24.70	10.00 ± 14.14
Day 84 (Part I) / Day 85 (Part II) (n=2, 9, 2)	44.41 ± 7.90	35.59 ± 31.85	25.00 ± 7.07

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

(Time Frame: Part I: Baseline and Days 29, 57 and 84 / Part II: Baseline and Days 29, 57 and 85)

	Part I: CDZ173	Part II: CDZ173	Part II: Placebo
Arm/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.	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	Participants received Placebo b.i.d. from Day 1 to Day 85.
Number of Participants Analyzed [units: participants]	3	5	4
Part I & II: Overall classroom impairment due to health score from the Work Productivity Activity Impairment and Classroom Impairment Questionnaire (WPAI-CIQ) (units: Percentage) Mean ± Standard Deviation			
Baseline (n=3, 5, 4)	65.68 ± 33.49	47.33 ± 44.75	23.75 ± 30.92
Day 29 (n=3, 2, 4)	57.30 ± 18.09	0.00 ± 0	22.65 ± 24.37
Day 57 (n=2, 2, 4)	70.13 ± 18.68	12.14 ± 3.03	22.40 ± 26.16
Day 84 (Part I) / Day 85 (Part II) (n=3, 1, 2)	68.52 ± 18.74	51.00 ± 0.00	5.00 ± 7.07

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

(Time Frame: Part I: Baseline and Days 29, 57 and 84 / Part II: Baseline and Days 29, 57 and 85)

	Part I: CDZ173	Part II: CDZ173	Part II: Placebo
Arm/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.	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	Participants received Placebo b.i.d. from Day 1 to Day 85.
Number of Participants Analyzed [units: participants]	6	19	8
Part I & II: Physician's Global Assessment (PGA) (units: Score on a scale) Mean ± Standard Deviation			
Baseline (n=6, 19, 8)	34.7 ± 17.07	47.10 ± 17.65	41.38 ± 17.78
Day 29 (n=6, 18, 8)	21.8 ± 9.70	38.81 ± 23.73	29.75 ± 9.99
Day 57 (n=6, 19, 8)	22.5 ± 13.55	34.02 ± 18.89	24.13 ± 18.34
Day 84 (Part I) / Day 85 (Part II) (n=6, 19, 8)	8.8 ± 4.12	26.70 ± 22.82	25.88 ± 16.15

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

(Time Frame: Part I: Baseline and Days 29, 57 and 84 / Part II: Baseline and Days 29, 57 and 85)

	Part I: CDZ173	Part II: CDZ173	Part II: Placebo
Arm/Group Description	Participants consecutively received	Participants received CDZ173 70	Participants received Placebo b.i.d.

	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.	mg b.i.d. from Day 1 to Day 85.	from Day 1 to Day 85.
Number of Participants Analyzed [units: participants]	6	19	8
Part I & II: Patient's Global Assessment (PtGA) (units: Score on a Scale) Mean ± Standard Deviation			
Baseline	62.0 ± 21.90	54.53 ± 21.47	62.50 ± 26.56
Day 29	65.0 ± 22.21	68.37 ± 19.31	57.75 ± 24.03
Day 57	67.5 ± 21.83	64.79 ± 19.61	69.50 ± 21.93
Day 84 (Part I) / Day 85 (Part II)	72.5 ± 13.37	67.58 ± 16.57	60.25 ± 23.66

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

(Time Frame: Part I: Baseline and Days 1, 15, 29, 57, 84 / Part II: Baseline and Days 1, 15, 29, 57, 85)

	Part I: CDZ173	**Part II: CDZ173**	**Part II: Placebo**
Arm/Group Description	Participants consecutively received CDZ173 10 mg b.i.d. from Day 1 to Day 28, CDZ173 30 mg b.i.d.	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	Participants received Placebo b.i.d. from Day 1 to Day 85.

	from Day 29 to Day 56 and CDZ173 70 mg b.i.d. from Day 57 to Day 84.		
Number of Participants Analyzed [units: participants]	6	19	8
Part I & II: High Sensivity C reactive protein (hsCRP) as biomarker for systemic inflammation (units: Milligram / liter) Mean ± Standard Deviation			
Baseline (n=6, 4, 2)	2.49 ± 1.29	10.58 ± 17.84	5.70 ± 2.19
Day 1 (n=6, 4, 2)	2.43 ± 1.43	8.95 ± 14.56	7.85 ± 4.88
Day 15 (n=6, 18, 7)	0.93 ± 0.70	9.19 ± 23.12	2.06 ± 1.02
Day 29 (n=6, 18, 8)	0.77 ± 0.36	5.55 ± 11.21	2.40 ± 1.75
Day 57 (n=6, 18, 8)	1.20 ± 0.71	6.57 ± 9.18	8.90 ± 16.66
Day 84 (Part I) / Day 85 (Part II) (n=5, 18, 8)	2.82 ± 4.11	7.54 ± 18.37	2.65 ± 1.79

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

(Time Frame: Part I: Baseline and Days 1, 15, 29, 57, 84 / Part II: Baseline and Days 1, 15, 29, 57, 85)

	Part I: CDZ173	**Part II: CDZ173**	**Part II: Placebo**
Arm/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	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	Participants received Placebo b.i.d. from Day 1 to Day 85.

	to Day 56 and CDZ173 70 mg b.i.d. from Day 57 to Day 84.		
Number of Participants Analyzed [units: participants]	6	19	8
Part I & II: Lactate dehydrogenase (LDH) as biomarker for systemic inflammation (units: Units / liter) Mean ± Standard Deviation			
Baseline (n=6, 19, 8)	130.42 ± 18.28	172.92 ± 72.25	169.38 ± 41.95
Day 1 (n=6, 17, 7)	132.17 ± 23.10	170.88 ± 72.28	175.71 ± 53.72
Day 15 (n=6, 18, 7)	132.17 ± 11.44	190.94 ± 71.54	155.14 ± 48.09
Day 29 (n=6, 18, 8)	125.17 ± 9.85	227.17 ± 163.41	185.25 ± 51.62
Day 57 (n=6, 19, 7)	135.50 ± 17.66	193.11 ± 64.75	167.14 ± 40.45
Day 84 (Part I) / Day 85 (Part II) (n=5, 19, 8)	142.60 ± 18.53	190.63 ± 57.62	179.13 ± 73.96

Part II: Beta2 microglobulin as biomarker for systemic inflammation

(Time Frame: Baseline and Days 1, 15, 29, 57, 85)

	Part II: CDZ173	**Part II: Placebo**
Arm/Group Description	Participants received CDZ173 70 mg b.i.d. from	Participants received Placebo b.i.d. from Day 1 to Day 85.

	Day 1 to Day 85.	
Number of Participants Analyzed [units: participants]	19	8
Part II: Beta2 microglobulin as biomarker for systemic inflammation (units: Milligram / liter) Mean ± Standard Deviation		
Baseline (n=19, 8)	2.46 ± 0.87	2.32 ± 0.96
Day 1 (n=19, 8)	2.43 ± 0.88	2.31 ± 0.95
Day 15 (n=18, 7)	2.10 ± 1.03	2.31 ± 1.09
Day 29 (n=18, 8)	2.02 ± 1.17	3.21 ± 1.61
Day 57 (n=19, 8)	1.90 ± 0.72	2.42 ± 1.17
Day 85 (n=19, 8)	2.01 ± 1.04	2.57 ± 1.19

Part II: Ferritin as biomarker for systemic inflammation

(Time Frame: Baseline and Days 1, 15, 29, 57, 85)

	Part II: CDZ173	**Part II: Placebo**
Arm/Group Description	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	Participants received Placebo b.i.d. from Day 1 to Day 85.
Number of Participants Analyzed [units: participants]	19	8
Part II: Ferritin as biomarker for systemic inflammation (units: Microgram / liter) Mean ± Standard Deviation		

Baseline (n=18, 8)	139.16 ± 399.73	62.05 ± 81.65
Day 1 (n=18, 8)	142.67 ± 411.57	61.34 ± 82.04
Day 15 (n=17, 7)	146.99 ± 494.88	24.61 ± 17.41
Day 29 (n=16, 8)	187.65 ± 641.16	48.43 ± 61.83
Day 57 (n=18, 8)	199.97 ± 657.31	51.40 ± 64.95
Day 85 (n=18, 8)	139.42 ± 368.68	63.16 ± 56.64

Part II: Fibrinogen as biomarker for systemic inflammation

(Time Frame: Baseline and Days 1, 15, 29, 57, 85)

	Part II: CDZ173	**Part II: Placebo**
Arm/Group Description	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	Participants received Placebo b.i.d. from Day 1 to Day 85.
Number of Participants Analyzed [units: participants]	19	8
Part II: Fibrinogen as biomarker for systemic inflammation (units: Gram / liter) Mean ± Standard Deviation		
Baseline (n=19, 8)	2.66 ± 0.76	2.68 ± 0.44
Day 1 (n=19, 8)	2.61 ± 0.81	2.65 ± 0.42

Day 15 (n=17, 7)	2.65 ± 0.62	2.67 ± 0.42
Day 29 (n=18, 8)	2.53 ± 0.54	2.66 ± 0.58
Day 57 (n=19, 8)	3.01 ± 0.68	2.83 ± 1.13
Day 85 (n=19, 8)	2.81 ± 0.57	2.61 ± 0.57

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

(Time Frame: Baseline and Days 1, 15, 29, 57, 85)

	Part II: CDZ173	**Part II: Placebo**
Arm/Group Description	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	Participants received Placebo b.i.d. from Day 1 to Day 85.
Number of Participants Analyzed [units: participants]	19	8
Part II: Erythrocyte sedimentation rate (ESR) as biomarker for systemic inflammation (units: Millimeter / hour) Mean ± Standard Deviation		
Baseline (n=16, 8)	28.09 ± 19.79	25.44 ± 24.88
Day 1 (n=16, 8)	26.88 ± 19.33	25.13 ± 24.51
Day 15 (n=14, 7)	19.50 ± 13.52	16.00 ± 12.21
Day 29 (n=15, 8)	18.33 ± 13.80	26.00 ± 25.26
Day 57 (n=17, 8)	18.06 ± 15.36	27.88 ± 23.04
Day 85 (n=17, 8)	16.35 ± 15.99	19.63 ± 18.03

Part II: 3D volume of index lesions

(Time Frame: Baseline and Day 85)

	Part II: CDZ173	Part II: Placebo
Arm/Group Description	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	Participants received Placebo b.i.d. from Day 1 to Day 85.
Number of Participants Analyzed [units: participants]	19	8
Part II: 3D volume of index lesions (units: Millimeter^3) Mean ± Standard Deviation		
Baseline	20142.12 ± 15617.13	37123.69 ± 67325.94
Day 85	7858.08 ± 6290.98	40169.28 ± 81844.45

Part II: 3D volume of the spleen

(Time Frame: Baseline and Day 85)

	Part II: CDZ173	Part II: Placebo
Arm/Group Description	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	Participants received Placebo b.i.d. from Day 1 to Day 85.
Number of Participants Analyzed [units: participants]	19	8

Part II: 3D volume of the spleen (units: Millimeter^3) Mean ± Standard Deviation		
Baseline	586448.74 ± 311482.61	448456.15 ± 328641.78
Day 85	411130.98 ± 193977.46	480333.09 ± 445371.99

Safety Results

All-Cause Mortality

	Part I: CDZ173 10 mg N = 6	**Part I: CDZ173 30 mg N = 6**	**Part I: CDZ173 70 mg N = 6**	**Part I: Total N = 6**	**Part II: CDZ173 70 mg N = 21**	**Part II: Placebo N = 10**
Arm/Group Description	Participants received CDZ173 10 mg b.i.d. from Day 1 to Day 28.	Participants received CDZ173 30 mg b.i.d. from Day 29 to Day 56.	Participants received CDZ173 70 mg b.i.d. from Day 57 to Day 84.	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.	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	Participants received Placebo b.i.d. from Day 1 to Day 85.
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	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. For the subset of participants in Part II that rolled over to the extension study (CCDZ173X2201E1) directly after the last treatment dose in Part II, AEs were reported from the start of treatment to end of treatment, assessed up to maximum duration of 85 days.
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.
Source Vocabulary for Table Default	MedDRA (24.0)
Assessment Type for Table Default	Systematic Assessment

	Part I: CDZ173 10 mg N = 6	**Part I: CDZ173 30 mg N = 6**	**Part I: CDZ173 70 mg N = 6**	**Part I: Total N = 6**	**Part II: CDZ173 70 mg N = 21**	**Part II: Placebo N = 10**
Arm/Group Description	Participants received CDZ173 10 mg b.i.d. from Day 1 to Day 28.	Participants received CDZ173 30 mg b.i.d. from Day 29 to Day 56.	Participants received CDZ173 70 mg b.i.d. from Day 57 to Day 84.	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.	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	Participants received Placebo b.i.d. from Day 1 to Day 85.
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (14.29%)	2 (20.00%)
Blood and lymphatic system disorders						

Lymphadenopathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Infections and infestations						
Infective exacerbation of bronchiectasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Mastoiditis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Injury, poisoning and procedural complications						
Alcohol poisoning	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Investigations						
Lipase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Metabolism and nutrition disorders						
Failure to thrive	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Nervous system disorders						
Coma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Pulmonary hypertension	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Social circumstances						
Dependence on oxygen therapy	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)

Other Adverse Events by System Organ Class

Time Frame	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. For the subset of participants in Part II that rolled over to the extension study (CCDZ173X2201E1) directly after the last treatment dose in Part II, AEs were reported from the start of treatment to end of treatment, assessed up to maximum duration of 85 days.
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.
Source Vocabulary for Table Default	MedDRA (24.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	0%

	Part I: CDZ173 10 mg N = 6	**Part I: CDZ173 30 mg N = 6**	**Part I: CDZ173 70 mg N = 6**	**Part I: Total N = 6**	**Part II: CDZ173 70 mg N = 21**	**Part II: Placebo N = 10**
Arm/Group Description	Participants received CDZ173 10 mg b.i.d. from Day 1 to Day 28.	Participants received CDZ173 30 mg b.i.d. from Day 29 to Day 56.	Participants received CDZ173 70 mg b.i.d. from Day 57 to Day 84.	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.	Participants received CDZ173 70 mg b.i.d. from Day 1 to Day 85.	Participants received Placebo b.i.d. from Day 1 to Day 85.
Total participants affected	2 (33.33%)	2 (33.33%)	4 (66.67%)	4 (66.67%)	18 (85.71%)	9 (90.00%)

Cardiac disorders						
Sinus tachycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Tachycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Congenital, familial and genetic disorders						
Methylenetetrahydrofolate reductase gene mutation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Ear and labyrinth disorders						
Deafness	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
External ear pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Hypoacusis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Vertigo	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Eye disorders						
Conjunctivitis allergic	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Episcleritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Gastrointestinal disorders						
Abdominal discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (10.00%)
Abdominal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Abdominal pain upper	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Aphthous ulcer	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Constipation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Dental caries	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Diarrhoea	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	2 (9.52%)	0 (0.00%)
Dyspepsia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)

Gastrooesophageal reflux disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Haematochezia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Nausea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	3 (30.00%)
Toothache	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Vomiting	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (10.00%)
General disorders and administration site conditions						
Asthenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	2 (20.00%)
Fatigue	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.52%)	1 (10.00%)
Pyrexia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.52%)	0 (0.00%)
Vascular device occlusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Infections and infestations						
Acute sinusitis	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Clostridium difficile colitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Conjunctivitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Fungal skin infection	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Gastroenteritis	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	1 (4.76%)	0 (0.00%)
Gastrointestinal infection	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Groin infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Lower respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Nasal herpes	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Nasopharyngitis	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	1 (10.00%)
Oral candidiasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)

Oral herpes	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Otitis externa	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Pneumonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Rhinitis	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Sinusitis	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	4 (19.05%)	0 (0.00%)
Upper respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.52%)	2 (20.00%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Vulvovaginal candidiasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Vulvovaginal mycotic infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Injury, poisoning and procedural complications						
Contusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Iliotibial band syndrome	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Joint injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Musculoskeletal injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Road traffic accident	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Sunburn	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Investigations						
Amylase increased	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (4.76%)	0 (0.00%)
Aspartate aminotransferase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Blood creatine phosphokinase increased	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)

Body temperature increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Lipase increased	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Pancreatic enzymes increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Protein urine present	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
SARS-CoV-2 test positive	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Weight increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (10.00%)
Metabolism and nutrition disorders						
Decreased appetite	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Hypokalaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Musculoskeletal and connective tissue disorders						
Back pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.52%)	0 (0.00%)
Bursitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Flank pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Musculoskeletal chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Neck pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.52%)	0 (0.00%)
Nervous system disorders						
Dizziness	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (10.00%)
Headache	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (16.67%)	5 (23.81%)	2 (20.00%)
Paraesthesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Somnolence	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Syncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)

Taste disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Psychiatric disorders						
Depressed mood	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Renal and urinary disorders						
Anuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Pollakiuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Reproductive system and breast disorders						
Adnexa uteri cyst	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Menstrual disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Respiratory, thoracic and mediastinal disorders						
Asthma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Cough	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (10.00%)
Dyspnoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Epistaxis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Oropharyngeal pain	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders						
Alopecia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.52%)	0 (0.00%)
Dermatitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)
Dermatitis atopic	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Eczema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.52%)	0 (0.00%)
Hyperhidrosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Pruritus	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	1 (4.76%)	0 (0.00%)
Rash maculo-papular	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)

Seborrhoeic dermatitis	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Vascular disorders						
Hypotension	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	0 (0.00%)
Vasculitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)

Other Relevant Findings

Not applicable

Conclusion:

Treatment of six APDS patients with CDZ173 was well tolerated and showed consistent laboratory and clinical improvement, including normalization of immune dysfunction and reduction of lymphoproliferation. The results of Part I justify progression into Part II of the study at the selected dose of 70 mg bid CDZ173 in a 2:1 placebo controlled trial.

The results of Part II demonstrated clinical efficacy of CDZ173 70 mg bid over placebo in reduction of lymph proliferation and improvement in cellular immune dysfunction. The drug was safe and well tolerated in APDS1 and APDS2 patients aged <18 years and ≥18 years.

Date of Clinical Trial Report

14-Feb-2022