



Clinical trial results:

An open-label, non-randomized extension study to evaluate the long term safety, tolerability, efficacy and pharmacokinetics 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	2016-000468-41
Trial protocol	CZ NL IE GB FR DE IT
Global end of trial date	30 January 2025

Results information

Result version number	v1 (current)
This version publication date	16 August 2025
First version publication date	16 August 2025

Trial information

Trial identification

Sponsor protocol code	CCDZ173X2201E1
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02859727
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharming Technologies B.V.
Sponsor organisation address	Darwinweg 24, Leiden, Netherlands, 2333 CR
Public contact	Clinical Department, Pharming Technologies B.V., +31 71 5247400, clinical@pharming.com
Scientific contact	Clinical Department, Pharming Technologies B.V., +31 71 5247400, clinical@pharming.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 January 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 January 2025
Global end of trial reached?	Yes
Global end of trial date	30 January 2025
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

Discontinuation of study treatment for a patient occurred when study treatment was stopped earlier than the protocol planned duration. Discontinuation of study treatment could be decided by either the patient or the investigator.

Study treatment was required to be discontinued under the following circumstances:

- Patient decision – patients could choose to discontinue study treatment for any reason at any time.
- The investigator believed that continuation would negatively impact the safety of the patient or the risk/benefit ratio of study participation.
- Any protocol deviation that resulted in a significant risk to the patient's safety.
- Pregnancy (see protocol Section 8.6.7 and Section 9.7 [Appendix 16.1.1]).
- The patient experienced a drug-related SAE.
- Diarrhea of common terminology criteria for AE (CTCAE) Grade 2 or higher on 3 consecutive days.
- Diarrhea of CTCAE Grade 3 or higher.
- Diarrhea or abdominal pain with accompanying fever assessed to be related to a gastrointestinal infection.
- Grade 4 skin rashes as per protocol Section 6.8 (Appendix 16.1.1).
- Use of prohibited treatment as per protocol Section 5.2 (Appendix 16.1.1).

If discontinuation of study treatment occurred, investigator determined the primary reason for the patient's premature discontinuation of study treatment and recorded this information on the dosage administration CRF. Resumption of study treatment after a full safety review of the patient was possible, pending agreement between the investigator and the Sponsor.

Background therapy: -

Evidence for comparator:

NA

Actual start date of recruitment	08 September 2016
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	Netherlands: 2
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Russian Federation: 2

Country: Number of subjects enrolled	Belarus: 1
Country: Number of subjects enrolled	United States: 20
Worldwide total number of subjects	37
EEA total number of subjects	14

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)	0
Adolescents (12-17 years)	13
Adults (18-64 years)	24
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

37 participants were enrolled in the extension study . Of these, 26 participants received leniolisib in study CCDZ173X2201 and 11 participants had no previous exposure to leniolisib (9 participants received placebo in study CCDZ173X2201 and 2 participants were previously treated with PI3Kδ inhibitors other than leniolisib

Pre-assignment

Screening details:

Patients could be enrolled in this extension study either directly at the end of treatment (EOT) or end of study (EOS) visit of Study CCDZ173X2201 (Part 1 or Part 2) or later in time. Patients who were treated previously with PI3Kδ inhibitors other than leniolisib could be enrolled if they met the eligibility criteria at the screening visit.

Period 1

Period 1 title	Open Label extension (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open label study
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Arm description:

Open label treatment for total duration of study

Arm type	Experimental
Investigational medicinal product name	CDZ173
Investigational medicinal product code	
Other name	leniolisib
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:

HGC or FCT 70 mg twice daily

Number of subjects in period 1	Open label study
Started	37
Completed	3
Not completed	34
Adverse event, serious fatal	1
Physician decision	3
Consent withdrawn by subject	2
Adverse event, non-fatal	1
Study termination	25
Lost to follow-up	2

Baseline characteristics

Reporting groups

Reporting group title	Open Label extension
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Reporting group description: -

Reporting group values	Open Label extension	Total	
Number of subjects	37	37	
Age categorical Units: Subjects			
Adolescents (12-17 years)	13	13	
Adults (18-64 years)	24	24	
Age continuous Units: years			
arithmetic mean	22.7		
full range (min-max)	12 to 55	-	
Gender categorical Units: Subjects			
Female	16	16	
Male	21	21	

End points

End points reporting groups

Reporting group title	Open label study
Reporting group description:	
Open label treatment for total duration of study	

Primary: Safety

End point title	Safety ^[1]
End point description:	
To evaluate the long-term safety and tolerability of leniolisib in patients with APDS. All safety parameters (including adverse events [AEs], physical examination, vital signs, electrocardiogram [ECG], and safety laboratory [hematology, blood chemistry, urinalysis]).	
End point type	Primary
End point timeframe:	
Duration of study	

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: This is a one-arm trial for which no statistical analysis or hypotheses testing was planned. All Serious Adverse Events and Adverse Events experienced by 2 or more participants are added in the Adverse Events section.

End point values	Open label study			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: number of patients with adverse event				
Number of patients with Serious Adverse Events	10			
Number of patients with Adverse Events	34			

Statistical analyses

No statistical analyses for this end point

Secondary: To evaluate the long-term efficacy of leniolisib to modify health-related quality of life in patients with APDS.

End point title	To evaluate the long-term efficacy of leniolisib to modify health-related quality of life in patients with APDS.
End point description:	
Short form-36 (SF-36) survey and work productivity activity impairment and classroom impairment questionnaire (WPAI-CIQ), visual analogue scales for physician's global assessment (PGA) and patient's global assessment (PtGA), and patient narratives by the investigator.	
End point type	Secondary
End point timeframe:	
duration of study participation	

End point values	Open label study			
Subject group type	Reporting group			
Number of subjects analysed	37 ^[2]			
Units: scores				
median (full range (min-max))				
SF-36 general health score baseline	36.540 (18.95 to 60.32)			
SF-36 general health score after 1 year	46.050 (26.08 to 66.50)			
SF-36 general health score after 3 years	48.430 (29.41 to 60.70)			
SF-36 general health score after 4 years	48.430 (34.17 to 62.70)			
SF general health score after 5 years	47.240 (36.54 to 57.94)			

Notes:

[2] - baseline N= 37, 1 year N=37, 3 year N=27, 4 year N=22, 5 year N=10

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from time of signing Informed Consent until the End of Study visit.

Adverse event reporting additional description:

The occurrence of AEs must be sought by non-directive questioning of the patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits or through physical examination finding, laboratory test finding, or other assessments. Study patients will be instructed to take notes of any AE

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.0
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Reporting groups

Reporting group title	Number of patients with adverse event
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Reporting group description:

The long-term safety data with leniolisib included 37 participants with APDS treated for at least one year 31 participants (83.8%) for at least 2 years, and 10 participants (27.0%) had at least 5 years of leniolisib exposure.

Serious adverse events	Number of patients with adverse event		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 37 (27.03%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hodgkin's disease			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transitional cell carcinoma			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hypotension			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Orthostatic hypotension			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Facial pain			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory disorder			

subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			

subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Anal fissure			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			

subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthritis reactive			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Flank pain			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abscess			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute sinusitis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Parotitis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Periorbital cellulitis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Number of patients with adverse event		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 37 (91.89%)		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 37 (24.32%)		
occurrences (all)	9		
Influenza like illness			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Non-cardiac chest pain			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		
Oropharyngeal pain			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		
Cough			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		
Epistaxis			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Dysphonia			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		

Dyspnoea subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Productive cough subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Psychiatric disorders Illusion subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Investigations Weight increased subjects affected / exposed occurrences (all)	5 / 37 (13.51%) 5		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
SARS-CoV-2 test negative subjects affected / exposed occurrences (all)	15 / 37 (40.54%) 15		
Injury, poisoning and procedural complications Joint injury subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Ligament sprain subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Limb injury subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Nervous system disorders Headache			

subjects affected / exposed	8 / 37 (21.62%)		
occurrences (all)	8		
Migraine			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Paraesthesia			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Lymphadenopathy			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	5 / 37 (13.51%)		
occurrences (all)	5		
Abdominal pain			
subjects affected / exposed	5 / 37 (13.51%)		
occurrences (all)	5		
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		
Dental caries			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		
Abdominal pain upper			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Haematochezia			

subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Anal fissure			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Seborrhoeic dermatitis			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Keratosis pilaris			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Skin papilloma			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 37 (13.51%)		
occurrences (all)	5		
Back pain			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Flank pain			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Myalgia			

subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Infections and infestations			
COVID-19			
subjects affected / exposed	12 / 37 (32.43%)		
occurrences (all)	12		
Upper respiratory tract infection			
subjects affected / exposed	10 / 37 (27.03%)		
occurrences (all)	10		
Sinusitis			
subjects affected / exposed	6 / 37 (16.22%)		
occurrences (all)	6		
Otitis externa			
subjects affected / exposed	7 / 37 (18.92%)		
occurrences (all)	7		
Nasopharyngitis			
subjects affected / exposed	6 / 37 (16.22%)		
occurrences (all)	6		
Rhinitis			
subjects affected / exposed	5 / 37 (13.51%)		
occurrences (all)	5		
Gastroenteritis			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		
Pneumonia			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		
Respiratory tract infection			
subjects affected / exposed	5 / 37 (13.51%)		
occurrences (all)	5		
Bronchitis			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		
Oral herpes			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		

Pharyngitis			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		
Urinary tract infection			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		
Herpes zoster			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Otitis media			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		
Conjunctivitis			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Conjunctivitis allergic			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Folliculitis			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Herpes simplex			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Lyme disease			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Otitis media acute			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Paronychia			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		

Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Obesity			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 March 2017	Amendment 1: Minimum age lowered from 16 to 12, prolong the treatment period of patients beyond 9 months (up to 3 years)
20 October 2017	Amendment 2: Change of study purpose to provide access to the extension study not only for patients who participated in study CCDZ173X2201 but also for patients previously treated with PI3K δ inhibitors other than CDZ173
26 March 2018	Amendment 3: introduce a film-coated tablets (FCT) formulation of CDZ173
18 June 2018	Amendment 4: incorporate health authority recommendations for: 1) the management of potentially occurring skin rashes, 2) pregnancy monitoring, and 3) additional screening assessments and eligibility criteria for patients who did not participate in the core study CCDZ173X2201
15 March 2019	Amendment 5: eligibility criteria; prohibited medication and the option to use a low dose CT scan in adolescents between 12-15 years of age (inclusive) in sites when approved, Treatment period is extended to 5 years
24 June 2020	Amendment 6: address changes to trial conduct in the case of an epidemic or pandemic that limits or prevents on-site visits (eg COVID-19 pandemic).
22 October 2020	Amendment 7: align CCDZ173X2201E1 (extension study) with changes that were made to CCDZ173X2201 (core study)
07 June 2021	Amendment 8: the individual treatment period to 6 years duration
25 August 2021	Amendment 9: Administrative update
20 December 2021	Amendment 10: Transfer Sponsorship from Novartis to Pharming Technologies B.V.
13 December 2022	Amendment 11: results of an interim analysis of the CCDZX2210E1 and the update of the Investigators Brochure

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported