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

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Immunodeficiency syndromes
Study type	Interventional

Summary

ID

NL-OMON54847

Source
ToetsingOnline

Brief title
CCDZ173X2201E1

Condition

- Immunodeficiency syndromes

Synonym
Activated phosphoinositide 3-kinase delta syndrome/ p110δ-activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency

Research involving
Human

Sponsors and support

Primary sponsor: Pharming Group
Source(s) of monetary or material Support: Novartis Pharma B.V. (sponsor / verrichter van het onderzoek)

Intervention

Keyword: APDS / PASLI, Efficacy, Safety

Outcome measures

Primary outcome

To evaluate the long term safety and tolerability of CDZ173 in patients with

APDS/PASLI

Secondary outcome

- To evaluate the long term efficacy of CDZ173 to modify healthrelated quality

of life in patients with APDS/PASLI.

- To evaluate the long term efficacy of CDZ173 by means of biomarkers

reflecting the efficacy of CDZ173 to reduce systemic inflammatory components of

the disease in patients with APDS/PASLI.

- To characterize the pharmacokinetics (trough concentrations) of CDZ173 in

patients with APDS/PASLI.

- To evaluate the pharmacokinetics and relative bioavailability of CDZ173

film-coated tablets compared to CDZ173 hard-gelatin capsules

Study description

Background summary

This study is designed to evaluate CDZ173, a selective PI3Kδ inhibitor, in patients with genetically activated PI3Kδ, i.e., patients with APDS/PASLI. Mutations in the p110δ subunit of the PI3K kinase that recruit the kinase PI3K to the plasma membrane independent of exogenous activation have been recently described, hence resulting in a gain-of-function of PI3Kδ. Less than 100 patients have been described to date. This rare disease has been named *Activated PI3Kδ Syndrome* (APDS) or *p110δ-activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency* (PASLI). The clinical phenotype frequently includes massive lymphoproliferation/lymphadenopathy, recurrent oto-sino-pulmonary infections, increased risk for autoimmune diseases, inability of successful vaccination, and risk of lymphomas. Current treatment options are only symptomatic. CDZ173 is a small molecule inhibitor of p110δ that inhibits the overactive function of the mutated PI3K.

Study objective

This study is an open-label, non-randomized extension to study CCDZ173X2201. It aims to provide treatment with CDZ173 to patients with APDS/PASLI who participated in study CCDZ173X2201 or who were treated previously with PI3Kδ inhibitors other than CDZ173, and to obtain long term safety, tolerability, efficacy and pharmacokinetic data of CDZ173 in this patient population.

Study design

Patients can be enrolled in this extension study either directly at the EOT or EOS visit of the study CCDZ173X2201 or later in time. Patients who were treated previously with PI3Kδ inhibitors other than CDZ173 can be enrolled if they meet the eligibility criteria at the screening visit.

The study will be composed of a screening period of max. 7 days, following by a treatment period of 6 years during which the subject will take the study drug twice daily. In total there will be 18 control visits in approx. 6 years and 9 months, including a follow-up period of 3 months (following the treatment period) and a final control visit. All visits will take approx. 2 hours.

In case patients will be enrolled in this extension study directly at the end-of-study (EOS) visit of the study CCDZ173X2201, this visit counts as the

screening visit for the extension study. In this case, the total number of visits comes down to 18.

Intervention

Dosing regime of 70 mg twice daily

Study burden and risks

Study period: circa 6 years and 9 months, 18 visits, approx. 2 hours per visit. In case patients will be enrolled in this extension study directly at the end-of-study (EOS) visit of the study CCDZ173X2201, this visit counts as the screening visit for the extension study. In this case, the total number of visits comes down to 18.

Based on 18 visits:
Physical examination: 17 times; Blood sampling: 18 times (15-65 ml per draw (total volume < 200 mL)); Urinalysis: 17 times; Vital signs: 18 times; ECG: 17 times; Optional CT- / MRI-/ US-Scan: 1 time; Assessment disease activity: 16 times, saliva assessment: 4 times

Other: Prohibited concomitant medication.

Contacts

Public
Pharming Group

Darwinweg 24
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NL
Scientific
Pharming Group

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)

Inclusion criteria

• Patients must have completed the study CCDZ173X2201 EOT/EOS visit, or were treated previously with PI3Kδ inhibitors other than CDZ173.
• Patients who are deemed by the Investigator to benefit from PI3K inhibitor therapy.
• Patients or their legal representatives (for patients under the age of 18 years) must be able to communicate well with the Investigator, to understand and comply with the requirements of the study.
• Documented APDS/PASLI-associated genetic PI3K delta mutation.
Patients with mutations in either PIK3CD or PIK3R1 can be included.
Other protocol-defined inclusion criteria may apply

Exclusion criteria

• Patients who withdrew consent from the study CCDZ173X2201
• Use of other investigational drugs, except CDZ173, within 5 half -lives of enrollment, or within 30 days, whichever is longer.
• Concurrent use of immunosuppressive medication
• Administration of any live vaccines (including 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 should be excluded.
• Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation.
• 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 and for 2 days after last dose of study medication.
• Uncontrolled chronic or recurrent infectious disease (with the exception of those that are considered to be characteristic of APDS/PASLI). , For patients who did not participate in study CCDZ173X2201 but were treated previously with PI3Kδ inhibitors other than CDZ173, the following additional exclusion criteria apply:

• Vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position after the patient has rested for at least three minutes.
• Patient must have a minimum body weight of 45 kg
• Evidence of tuberculosis infection as defined by a positive QuantiFERON TB test (or comparable test) at screening. If presence of latent tuberculosis is established then treatment according to local
country guidelines must have been completed before patients can be considered for enrollment.
• Use of unstable dosing regimen with i.v. Ig / s.c. Ig in the last 6 months before screening. Stable maintenance immunoglobulin regimen, as per local practice, such as regular injections with a consistent dosing interval (e.g., monthly) is acceptable
• History of acquired immunodeficiency diseases, or a positive HIV (ELISA and Western blot) test result at screening.
• A positive Hepatitis B surface antigen or Hepatitis C test (by PCR) result at screening.
Other protocol-defined exclusion criteria may apply

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-12-2016
Enrollment:	5
Type:	Actual

Medical products/devices used

Registration:	No

Product type:	Medicine
Brand name:	CDZ173 (Leniolisib)
Generic name:	CDZ173 (Leniolisib)

Ethics review

Approved WMO Date:	19-09-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-10-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-11-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-05-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	17-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-06-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-11-2020

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-06-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-04-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-05-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	08-08-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-11-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-03-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-04-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-10-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-11-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-000468-41-NL
ClinicalTrials.gov	NCT02859727
CCMO	NL58812.078.16