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 in patients with APDS/PASLI (Activated phosphoinositide 3-kinase delta syndrome/ p110*-activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency)

Published: 02-05-2016
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This trial is, along with establishment of the safety, tolerability and pharmacokinetics and -dynamics of CDZ173 in the target population, designed to select the optimal dose to normalize the function of the PI3K protein in patients with APDS/PASLI...

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

Summary

ID

NL-OMON47748

Source
ToetsingOnline

Brief title
CCDZ173X2201

Condition

- Immunodeficiency syndromes

Synonym
Activated phosphoinositide 3-kinase delta syndrome/ p110□-activating mutation causing senescent T cells, lymphadenopathy and immunodeficiency

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
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

Part I:

- To assess the safety and tolerability of CDZ173 in patients with APDS/PASLI:

All safety parameters (including AEs, physical exam, vital signs, ECG, safety

laboratory (hematology, blood chemistry, urinalysis))

- To assess the dose-PD and PK/PD relationship of CDZ173 in patients with

APDS/PASLI for dose: Single and multiple dose concentrations CDZ173 and pAkt

inhibition in unstimulated and stimulated whole blood

Part II: Co-primary endpoint;

- Change from baseline in the log10 transformed sum of product of diameters

(SPD) in the index lesions selected as per the Cheson

methodology from MRI/CT imaging.

- Change from baseline in percentage of naïve B cells out of total B cells

Secondary outcome

* Part II: MRI/CT imaging * e.g. 3D volume of index and measurable non-index

lesions selected as per the Cheson methodology, and 3D

volume and bi-dimensional size of the spleen

* Part I and II: Single dose CDZ173 PK parameters (including but not limited to

Cmax and AUC) and trough evaluations after multiple dose

* Part I and II: SF-36 (Short Form 36) Survey and WPAI-CIQ (Work Productivity

Activity Impairment plus Classroom Impairment

Questionnaire)

* Part I and II: Visual analogue scales for PGA and PtGA (for Part II the PGA

is a key secondary endpoint)

* Part I and II:

- Creactive protein (CRP), Lactate dehydrogenase (LDH)

- For Part II additional: beta2 microglobulin, ferritin, fibrinogen and

erythrocyte sedimentation rate (ESR)

* Part I and II: Narratives

* Part II: All safety parameters, including AEs, physical exam, vital signs,

ECG, safety laboratory (hematology, blood chemistry, urinalysis)

Study description

Background summary

This study is designed to evaluate CDZ173, a selective PI3K* inhibitor, in patients with genetically activated PI3K*, i.e., patients with APDS/PASLI.

Mutations in the p110* 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 PI3K*. Less than 100 patients have been described to date. This rare disease has been named *Activated PI3K* Syndrome* (APDS) or *p110*-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 p110* that inhibits the overactive function of the mutated PI3K.

Study objective

This trial is, along with establishment of the safety, tolerability and pharmacokinetics and -dynamics of CDZ173 in the target population, designed to select the optimal dose to normalize the function of the PI3K protein in patients with APDS/PASLI.

* Part I: To assess the safety and tolerability as well as the dose-PD and PK/PD relationship of CDZ173 in patients with APDS/PASLI enabling dose selection for Part II.
* Part II: To assess the clinical efficacy of CDZ173 in patients with APDS/PASLI

Study design

Risk:
Adverse events IMP and study procedures.

Burden:
Part I:
A total of 6 patients have been enrolled worldwide (in USA and Europe), of which 1 patient in the Netherlands.

During the Screening Visit (Day -50 to Day -2) patients* eligibility will be assessed and then reviewed during the baseline visit. When still eligible, they will be randomized for the treatment period of 12 weeks. IMP will be taken

orally twice a day in three sub-periods of 4 weeks with dose escalation:
* Week 1-4: twice a day one capsule of 10 mg (in total 2 capsules a day, in total 20 mg/day)
* Week 5-8: twice a day three capsules of 10 mg (in total 6 capsules a dag, in total 60 mg/day)
* Week 8-12: twice a day one capsule of 70 mg (in total 2 capsules a day, in total 140 mg/day)

There will be 12 control visits at the clinic over a period of approx. 6 months. Three visits (V3, V6, V9) will cover a whole day. The other visits will take 2-3 hours.

Following the treatment period of 12 weeks, there will be a follow-up and conclusive visit after 4 weeks.

Part II:
30 patients will be enrolled worldwide, of which 3 in the Netherlands.

Screeningperiod of max. 7 weeks, followed by treatment period of 12 weeks; patients will receive:
- Placebo twice a day or
- CDZ173 70 mg twice a day

After treatmenmt stop follow-up period of 4 weeks, followed by end of trial visit.

In total 8 visits, duration approx. 5 months. Duration 1 visit (visit 3) 8 hours and other visits 4 hours.

Intervention

Part I:
* Week 1-4: twice a day one capsule of 10 mg (in total 2 capsules a day, in total 20 mg/day)
* Week 5-8: twice a day three capsules of 10 mg (in total 6 capsules a dag, in total 60 mg/day)
* Week 8-12: twice a day one capsule of 70 mg (in total 2 capsules a day, in total 140 mg/day)

Part II:
* Twice a day one capsule placebo (in total 2 capsules a day)
* Twice a day one capsule of 70 mg (in total 2 capsules a day, in total 140 mg/day)

Study burden and risks

Risk:
Adverse events IMP and study proecedures.

Burden:
Part I:
Study period: circa 6 months, 15 visits, varying from 2-9 hours per visit
Physical examination: 6 times
Blood sampling: 13 times, 15-80 ml per draw (total volume: 532 mL)
Urinalysis: 13 times
Vital signs: 13 times
ECG: 13 times
Scan CT/MRI: 2 times
Questionnaires: 4 times

Optional:
Farmacogenetic/-genomics sub-study (6 ml): 1x

Other: prohibited concomitant medication.

Part II:
Study period: circa 5 months, 8 visits, varying from (7x4hours and once 8 hours)
Physical examination: 8 times
Blood sampling: 8 times, max. 60 ml per colection (total volume: 300 mL)
Urinalysis: 8 times
Vital signs: 8 times
ECG: 8 times
Subjects 16 years or older: Scan CT/MRI: twice. Adolescents (12-15 years old:
MRI-Scan: twice
Completion questionnaires: 4 times
Completion diary during treatment period.
Wearing actibelt (measurement physical activity): twice during 9 consecutive days.

Optional:
Farmacogenetic/-genomics sub-study (3 ml): 1x.

Other: prohibited concomitant medication.

Contacts

Public
Novartis

Raapopseweg 1

Arnhem 6824 DP
NL
Scientific
Novartis

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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Male and female patients age 12 to 75 years of age (inclusive), who have a documented APDS/PASLI-associated genetic PI3K delta mutation.
Patients with mutations in either PIK3CD or PIK3R1 can be included.
* In part I and part II, patients must have nodal and/or extranodal lymphoproliferation, and clinical findings and manifestations compatible with APDS/PASLI such as a history of repeated oto-sinopulmonary infections and/or organ dysfunction (e.g., lung, liver). Additionally, in part II, patients must have at least one measurable nodal lesion on a CT or MRI scan.
* At screening, 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. Sitting vital signs should be within the following ranges:
* Systolic blood pressure, 90-160 mmHg
* Diastolic blood pressure, 50-95 mmHg
* Pulse rate, 40 - 100 bpm; up to 110 bpm in adolescents

Exclusion criteria

* Use of unstable 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) injections is acceptable
* Previous or concurrent use of immunosuppressive medication such as:
- use of an mTOR inhibitor (e.g., sirolimus, rapamycin, everolimus) or a PI3K* inhibitor (selective or non-selective PI3K inhibitors) within 6 weeks prior to first dosing, however short-term use for up to a total of 5 days is allowed but only up to 1 month prior to enrollment in the study.
- B cell depleters (e.g., rituximab) within 6 months prior to first dosing of study medication; if patients have received prior treatment with a B cell depleter, absolute B lymphocyte counts in the blood must have regained normal values.
- Belimumab or cyclophosphamide within 6 months prior to first dosing of study medication.
- Cyclosporine A, mycophenolate, 6-mercaptopurine, azathioprine or methotrexate within 3 months prior to first dosing of study medication.
- Glucocorticoids above 25 mg prednisone or equivalent per day within 2 weeks prior to first dosing of study medication.
- Other immunosuppressive medication where effects are expected to persist at start of dosing of study medication.
* Current use of medication known to be strong inhibitors 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 drugs that are metabolized by isoenzyme CYP1A2 and have a narrow therapeutic index (drugs whose exposure-response 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.

Study design

Design

Study phase:	3
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-06-2016
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	n.v.t.
Generic name:	Leniolisib

Ethics review

Approved WMO

Date:	02-05-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	23-06-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	23-06-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	04-10-2016
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:	17-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-04-2018
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:	11-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	20-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-05-2019
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:	12-11-2020
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)

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	EUCTR2014-003876-22-NL
ClinicalTrials.gov	NCT02435173
CCMO	NL57174.078.16