A randomized, double blind, placebo controlled multicenter dose ranging study to assess the safety and efficacy of multiple oral ZPL389 doses in patients with moderate to severe Atopic Dermatitis

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In this study we want to evaluate the safety and efficacy of the new drug ZPL389. ZPL389 is tested in various strengths in patients with moderate or severe atopic dermatitis. The effects of ZPL389 are compared with those of a placebo.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Epidermal and dermal conditions
Study type	Interventional

Summary

ID

NL-OMON48764

Source
ToetsingOnline

Brief title
CZPL389A2203 (ZEST)

Condition

- Epidermal and dermal conditions

Synonym
atopic eczema, Neurodermitis

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Atopic dermatitis, Chronic inflammatory skin disease, H4R antagonist, ZPL389

Outcome measures

Primary outcome

- To characterize the dose-response relationship of ZPL389 in subjects with

moderate to severe AD assessed by IGA response after 16 weeks of treatment

Secondary outcome

- To characterize the dose-response relationship of ZPL389 in subjects with

moderate to severe AD assessed using the percent change from

Baseline in Eczema Area and Severity Index (EASI) score after 16 weeks of

treatment

- To evaluate the efficacy across different dose levels as assessed by EASI and

IGA compared to placebo over time

- To assess the safety and tolerability of different doses of ZPL389 as

compared to placebo

Study description

Background summary

Atopic dermatitis is also called atopic eczema. It is a form of skin inflammation. Symptoms include itching, redness and swelling of the skin. The

skin spots can be moist and may have scabs on it. Two to ten percent of the adults and up to 20 percent of the children have AD, of which about 70% and 16% are moderate to severe. The usual treatment of AD consists of moisturizing cream, anti-inflammatory ointment (eg with corticosteroids), light therapy and anti-inflammatory pills ". Unfortunately, some of the patients have insufficient benefit from these existing treatments or can not tolerate them well. There is therefore a need for new medicines.

ZPL389 is a substance that attaches to a body protein called the histamine 4 receptor (H4R). Histamine is made by the body when it comes into contact with a substance for which it is hypersensitive. Histamine attaches itself to the H4R and therefore causes skin symptoms such as itching. ZPL389 is so firmly attached to the H4R that histamine can no longer attach itself to it. We therefore expect that ZPL389 can counteract the symptoms of atopic dermatitis.

So far, around 214 test subjects have been treated with ZPL389 in studies.

Study objective

In this study we want to evaluate the safety and efficacy of the new drug ZPL389. ZPL389 is tested in various strengths in patients with moderate or severe atopic dermatitis. The effects of ZPL389 are compared with those of a placebo.

Study design

This is a randomized, double-blind, placebo-controlled, multicenter dose ranging (5 parallel groups) study in at least
360 subjects with moderate to severe Atopic Dermatitis. An unbalanced randomization ratio will be used to randomize approximately 90 patients in the 30 mg / day, 50 mg / day and placebo arms. Approximately 45 patients will be randomized in the 3 mg / day and 10 mg / day arms.

The study consists of a screening period of 1 to 3 weeks (depending on current medication use and associated wash-out period) and a 16-week double-blind treatment period. After the end of treatment visit, subjects may be offered ongoing treatment in an
extension study, or enter the 4 week treatment-free follow up period.

The total duration of study is a maximum of 23 weeks. Subjects can participate in an extension study. Details of this extention study will be described in a separate pro

Intervention

Four dose levels were chosen to characterize the dose-response curve. An

unbalanced allocation of 2:1:1:2:2 for placebo: 3 mg: 10 mg: 30 mg: 50 mg with more subjects on placebo and the higher doses of ZPL389 is chosen to increase the precision of the estimate for the treatment effect at doses in the expected efficacious dose range.

Study burden and risks

The study lasts for a maximum of 24 weeks (almost half a year). The study consists of screening from 1 to 4 weeks, a treatment period of 16 weeks and a follow-up period of 4 weeks.

Based on 9 visits:
- Physical examination: 9x
- ECG: 9x
- Vital signs: 9x
- Blood test (9-27 ml): 9x
- Pregnancy test (if applicable) 7x
- Urine test: 9x
- Diary completion: daily
- Complete questionnaires: 6x

Optional:
- Measuring sleeping activity: every night during 1 week preceding 6 visits
- Farmacogenetics (1x bloodsdample collection)
- Tape-strips (3 visits)

Side effects of research medication and inconveniences research procedures. There is banned comedication.

Contacts

Public
Novartis

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Scientific
Novartis

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Females and males aged 18 years or older
- Chronic atopic dermatitis (according to AADConsensus Criteria), that has been present for at least 1 year before the Baseline visit.
- Moderate to severe atopic dermatitis defined as:
- Eczema Area and Severity Index (EASI) >=16 at Screening and Baseline
- IGA 3 or 4 at Screening and Baseline
- Body Surface Area involvement >=10% at Screening and Baseline
- Average peak pruritus score >=3 as assessed by NRS over the last 7 days prior to Baseline
- Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications for AD or for whom topical treatments are otherwise medically inadvisable
- Have applied a stable dose of bland topical emollient once daily for at least the 7 consecutive days immediately before the baseline visit

Exclusion criteria

- Any skin disease that, in the opinion of the investigator, would confound the diagnosis or evaluation of AD disease activity
- Risk factors for Torsades de Pointes (TdP)
- Resting QTcF >=450 msec (male) or >=470 msec (female) at Screening or Baseline or inability to determine the QTcF interval
- Cardiac or cardiac repolarization abnormality
- Subjects with pre-existing conditions that may confound ability to diagnose drug-induced liver injury (DILI) or subjects with factors that increase susceptibility to DILI
- Subjects who have a laboratory abnormality at Screening as follows:
- ALT/AST, ALP or TBL above upper limit of normal (ULN)
- Total white blood cell count (WBC) <2.5 x 109cells/L

- Absolute neutrophil count (ANC) <1.5 x 109/L (one re-test is allowed during the screening period)
- Hemoglobin <11.0 g/dL
- Platelets <100.0 x 109/L
- Potassium and magnesium outside normal range
- eGFR by MDR equation <60 mL/minute/1.73 m2
- Past medical history record of, or current infection with, human immunodeficiency virus (HIV)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	17-04-2019
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ZPL389
Generic name:	ZPL389

Ethics review

Approved WMO Date:	05-03-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-07-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-01-2019
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-08-2020
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	EUCTR2017-002176-75-NL
ClinicalTrials.gov	NCT03517566
CCMO	NL63968.078.18