A single-center, open-label study to evaluate the absorption, distribution, metabolism and excretion (ADME) and pharmacokinetics of ZPL389 following a single oral dose of [14C]ZPL389 in healthy male subjects.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin and subcutaneous tissue disorders NEC
Study type	Interventional

Summary

ID

NL-OMON46218

Source
ToetsingOnline

Brief title
ADME ZPL389

Condition

- Skin and subcutaneous tissue disorders NEC

Synonym
atopic dermatitis

Research involving

Human

Sponsors and support

Primary sponsor: Novartis Pharma AG
Source(s) of monetary or material Support: Farmaceutische industrie.

Intervention

Keyword: ADME, PK, ZPL389

Outcome measures

Primary outcome

To determine the rates and routes of excretion of [14C] ZPL389 - related

radioactivity, including mass balance of total drug-related radioactivity in

urine and feces.

To determine the pharmacokinetics of total radioactivity in blood and plasma.

To characterize the plasma pharmacokinetics of ZPL389.

Secondary outcome

To assess the safety and tolerability of a single 100 mg oral dose of [14C]

ZPL389 administered to healthy male subjects.

Study description

Background summary

ZPL389 is a new compound that may eventually be used for the treatment of inflammatory diseases such as atopic dermatitis. This is a type of eczema that begins early in life during infancy and childhood. And often precedes asthma and allergic disorders. The symptoms of this chronic inflammatory disease are itching, dry scaly skin, redness, swelling and cracked skin, and sores.

Histamine is a substance in your body that is, among other things, involved in the immune response, inflammation and allergies. If histamine is released in the body this can result in the well-known allergy reactions like sneezing, runny nose and itching, but histamine also plays a role in the itching and other skin problems in eczema.

ZPL389 is a, so-called, histamine 4 receptor antagonist, which means that ZPL389 blocks histamine from activating cells with a histamine 4 receptor. Activation of this receptor can result in inflammatory responses and it is thought that, by blocking this receptor, the inflammatory response can be reduced and thus be beneficial in treating chronic inflammatory diseases such as atopic dermatitis.

Study objective

The purpose of this study is to investigate how safe the new compound ZPL389 is and how well it is tolerated when it is administered to healthy volunteers. ZPL389 has been administered to humans before. It has also been previously tested in the laboratory and on animals.

It will also be investigated how quickly and to what extent ZPL389 is absorbed and eliminated from the body (pharmacokinetics). ZPL389 will be labeled with 14 Carbon (14C) and is thus radioactive. In this way ZPL389 can be traced in blood, urine and feces. In addition, the effects of ZPL389 on the body will be investigated.

In addition, the effect of genetic information on how volunteers body responds to ZPL389 will be investigated (pharmacogenetics).

Study design

The study will consist of 1 period during which the volunteer will stay in the research center for 21 days (20 nights). This will be followed by at least 1 and a maximum of 5 overnight visit(s). These visits will take place on Day 26, 33, 40, 54 and 68. End of study visit on Day 68-69 is fixed.

Day 1 is the day of administration of the study compound. The volunteer is expected at the research center at 14:00 h in the afternoon before the day of administration of the study compound (on Day -1). You will leave the research center on Day 20 of the study.

Entry: Day -1
Administration of the study compound: Day 1
Discharge: Day 20
Overnight visits*: Day 26-27, Day 33-34, Day 40-41, Day 54-55
End-of- study visit: Day 68-69

Follow-up phone call (or email): 30 days after the last visit + Day 120

*It is possible that the volunteer does not have to return for (all) the overnight visits, this depends on the radioactivity levels in urine and feces.

For the (possible) overnight visits the volunteers are expected in the research center at 11:00 h in the morning of Day 26, 33, 40, 54, and 68 and the volunteer an leave in the afternoon the next day. The number of overnight visits will depend on the amount of radioactivity left in urine and feces. The amount of radioactivity in urine and feces will be measured daily from Day 1 onwards. If, from Day 20 onwards, the radioactivity levels in urine and feces are below the pre-defined levels for 2 consecutive days, the volunteer will not have to return for additional overnight visits.

The volunteer should be aware that for the overnight visits the volunteer needs to collect urine and feces during the 24 hours before the visit and bring these to the research center. And also during these visits urine and feces will be collected.

During the end-of-study visit on Day 68-69 volunteers health will be checked for the last time during which the volunteer will stay 1 night at the research center. The volunteers are expected in the research center at 11:00 h in the morning of Day 68, and the volunteer can leave in the afternoon the next day. This visit will consist of a physical examination including measurement of blood pressure, heart rate, and body temperature, weight, a heart trace, several blood and urine tests and questions about their wellbeing.

The volunteer should be aware that for the end-of-study visit urine and feces should be collected during the 24 hours before the visit and to bring these to the research center. And also during this visit urine and feces will be collected.

The volunteer will receive a follow-up phone call or email approximately 30 days after the last visit to the research center. The volunteer will be asked questions about their wellbeing. The volunteer will also be contacted on Day 120 to check continued compliance with the 120-day condom use requirement

Intervention

100 mg radioactive labeled ZPL389 will be given as oral capsules with 240 milliliters (mL) of (tap) water.

During the first 4 hours after administration of the study compound the volunteer is not be allowed to lie down (except when indicated as such by one of the investigators), as this may influence the uptake of the study compound.

One of the investigators will inspect volunteers hands and mouth after the

study compound intake.

Study burden and risks

The study compound may cause side effects.

ZPL389 has been administered to man before and has been studied extensively in the laboratory and in animals.

ZPL389, up to doses of 400 mg, has been investigated in 264 subjects (100 healthy volunteers, 12 subjects with asthma, 65 patients with atopic dermatitis and 87 patients with psoriasis). ZPL389 was found to be safe and well tolerated.

The effect of ZPL389 were studies in patients with atopic dermatitis. 65 patients received ZPL389 and 33 patients received placebo. The side effects were similar between the placebo and the ZPL389 group.
The most common side effects were:
•nasopharyngitis (common cold); this occurred in 12 subjects (18%) in the ZPL389 group and in 8 subjects (24%) in the placebo group.
•headache; this occurred in 7 subjects (11%) in the ZPL389 group and in 4 subjects (12%) in the placebo group.

In a study investigating the effects of ZPL389 in psoriasis patients (87 patients receiving ZPL389 and 42 patients receiving placebo) side effects were similar between the ZPL389 and placebo group.
The most common side effects were:
•nasopharyngitis (common cold); this occurred in 5 subjects (5.7%) in the ZPL389 group and in 2 subjects (4.8%) in the placebo group.
•headache; this occurred in 5 subjects (5.7%) in the ZPL389 group and in 3 subjects (7.1%) in the placebo group.

The study compound may also have side effects that are still unknown.

Possible discomforts due to procedures
Drawing blood and/or insertion of the indwelling cannula may be painful or cause some bruising. In total, we will take about 475 milliliters (mL) of blood from the volunteer. This amount does not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken each time.

To make a heart tracing, electrodes (small, plastic patches) will be pasted at specific locations on the arms and legs. Prolonged use of these electrodes can cause skin irritation (rash and itching).

Exposure to radiation
This study involves using radioactive markers. The additional amount of radiation volunteer will be exposed to in this study is 0.93 mSv (milliSievert

[a unit for radioactivity]). To compare: the background radiation in the Netherlands is ~2.5 mSv per year.

Procedures: pain, minor bleeding, bruising, possible infection

Contacts

Public
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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Healthy male subjects
18-55 yrs, inclusive
BMI: 18.0-30.0 kg/m2
Weigth at least 50kg
Non-smoking

Exclusion criteria

Suffering from hepatitis B, hepatitis C, cancer or HIV/AIDS. In case of participation in another drug study within 90 days before the start of this study or being a blood donor within 60 days from the start of the study. In case of donating more than 1.5 liters of blood in the 10 months prior the start of this study.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-10-2018
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO Date:	03-10-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-10-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2018-001877-26-NL
CCMO	NL67514.056.18