A 6-part first-in-human study of LOU064 consisting of a 4 part randomized, double-blind, placebo-controlled SAD and MAD study to investigate the safety and tolerability in healthy volunteers, subjects with atopic diathesis and subjects with atopic dermatitis, an open-label food effect study and a double-blind formulation effect study in healthy volunteers

Published: 06-12-2018
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To explore the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of LOU064 over a treatment period of 4 weeks in a cohort of subjects with atopic dermatitis.

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

Summary

ID

NL-OMON46164

Source
ToetsingOnline

Brief title
Safety, tolerability, and efficacy of LOU064

Condition

- Epidermal and dermal conditions

Synonym
Atopic dermatitis, eczema

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Atopic dermatitis, Bruton's tyrosine kinase, Eczema

Outcome measures

Primary outcome

Safety assessments:

Adverse events

Physical examination and anamnesis including a bruising log

Test for occult blood in stool and urine

Laboratory assessments including standard coagulation tests and platelets

Vital signs

ECG

Secondary outcome

PK: Cmax, Tmax, AUClast, AUCinf, T1/2, Vz/F and CL/F from the blood

concentration-time data.

PD: BTK occupancy in whole blood, ex-vivo anti-IgE activation of Basophils

(Basotest) and skin prick test to a known allergen.

Dermatology assessments to determine the potential effectiveness of LOU064 on skin symptoms in AD.

Study description

Background summary

LOU064 is a selective covalent irreversible inhibitor of BTK and among a new generation of designed covalent enzyme inhibitors. The immunomodulatory action of LOU064 is mediated by its inhibition of BTK in the targeted pathways (e.g. mast cell and basophils degranulation via Fc*R) Atopic dermatitis (AD) is a common chronic, relapsing inflammatory, itchy skin disease affecting children and adult with a lifetime prevalence of 10*20% in children, and 1*3% in adults. It is thought to be caused by a variety of factors including genetic, environmental, and immunologic factors. Often AD is classified as intrinsic (or *non-allergic*) with low or normal IgE levels or the more frequent extrinsic (or *allergic*) AD which is characterized by high or very high IgE levels. Exposure to allergens, either from food or the environment, such as dust mites or pollens, can trigger flares in many AD patients and IgE levels are thought to be correlated to the disease severity. Blocking BTK downstream from the intracellular Fc*R-pathway triggered by the interaction with IgE may be a reliable therapeutic approach for diseases where IgE play a role.

Study objective

To explore the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of LOU064 over a treatment period of 4 weeks in a cohort of subjects with atopic dermatitis.

Study design

Part 6 is a double-blind, placebo-controlled multiple dose study in subjects with atopic dermatitis with a 4-week treatment period (twice daily dosing of LOU064 100mg) and 3-week follow-up period in 16 subjects.

Intervention

100mg LOU064 or matching placebo BID

Study burden and risks

Testing a cohort of subjects with a disease that is potentially addressed by

LOU064 is of particular interest because it is relevant to assess the impact of influencing the target in a patient population and whether this may have an influence on the PK and PD
parameters different from those in healthy volunteers. Also, given the accumulated safety data in doses up to 6-fold the single and 3-fold the daily dose for 12 days, the risk for toxicity in this population is low.

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

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female healthy subjects with an age range between 18 and 65 years (inclusive), and in good general health as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening. To participate in Part 6, subjects

must additionally have chronic atopic dermatitis (AD) according to American Academy of Dermatology Consensus Criteria (Eichenfield et al 2014), that has been present for at least 1 year before the baseline visit and defined as:
* Eczema Area and Severity Index (EASI) * 12 at screening and baseline
* IGA (Investigator*s Global Assessment) * 3 on a 5-point scale at screening and baseline
* BSA (Body Surface Area) involvement * 8% at screening and baseline
* Subjects have applied a stable dose of bland topical emollient at least twice daily for at least 7 consecutive days immediately before the baseline visit
Subjects must weigh at least 50 kg and must have a body mass index (BMI) within the range of 18 18-35 kg/m2 inclusive (part 6).

Exclusion criteria

2. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
7. Use of any systemic prescription drugs (including CYP3A inducers and inhibitors, and drugs with arrhythmogenic potential)
9. 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
16. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study.
18. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
19. A positive Hepatitis B test result (Hepatitis B surface antigen/Hepatitis B core antibody) or Hepatitis C test result.
20. Subjects with a latent TB infection as indicated by the absence of any signs of active TB disease but with a positive IGRA.
36. Subjects previously enrolled and dosed in any part of this study are not eligible to re-enroll in the same or another part.

Study design

Design

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

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	08-03-2019
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	LOU064
Generic name:	NA

Ethics review

Approved WMO Date:	06-12-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-12-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-10-2019
Application type:	Amendment
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	EUCTR2015-003750-40-NL
CCMO	NL68204.056.18

Study results

Date completed: 05-02-2020

Results posted: 29-09-2020

First publication
14-08-2020