Phase I study of M528101

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON29502

Source
Nationaal Trial Register

Brief title
CHDR2016

Health condition

Atopic dermatitis

Sponsors and support

Primary sponsor: Maruho
Source(s) of monetary or material Support: Sponsor

Intervention

Outcome measures

Primary outcome

To evaluate safety and tolerability of M528101 after topical administration
To evaluate systemic exposure of M528101 after topical administration and establish PK profile if possible

Secondary outcome

To evaluate efficacy of M528101 after topical administration

To evaluate M5281 metabolites in blood and urine samples

Study description

Background summary

In many dermatological diseases, pruritus (or itch) is one of the impactful and burdensome symptoms patients face every day. Although pruritus by itself is seen as a benign symptom, pruritus can have adverse effects on the patients' wellbeing and daily life. In addition, chronic itch is often accompanied by several unpleasant sensations such as pain or a burning sensation. The mechanisms that underlie pruritus are not well known and are compounded by the subjective nature of itch.
In dermatological conditions, itch is mainly caused by inflammation or skin damage. Changes in barrier function of the skin can lead to itch by endogenous mediators or exogenous allergens that come into contact with the skin. The primary sensory nerve fibers that innervate the skin are categorized into three groups based on the degree of myelination, diameter, and conduction velocity. The thick myelinated Aβ fibers transmit
tactile sensation, whereas the thinly myelinated Aδ and unmyelinated C-fibers are mainly involved in the conduction of thermal and pain/itch sensation. Itch is transmitted predominately by these
unmyelinated, slow conducting C-fibers. These fibers extend to the dermo-epidermal junction with free endings penetrating into the epidermis where sensation is detected. The cell bodies for these fibers are in the dorsal root ganglia (DRG), just outside the spinal cord. From here, both sensations involve secondary transmission neurons that ascend via the contralateral spinothalamic tract to the thalamus (Garibyan et al 2013).
Pruritogens interact with receptors or ion channels on the nerve fibers. The receptors that are often involved are G-protein coupled receptors (GPCR). GPCRs detect and respond to a diverse range of
ligands or stimuli and are the target of many drugs. GPCRs that are relevant to itch respond to histamine, prostaglandins, neuropeptides, and proteases. When a pruritogen activates a GPCR, this results in a rise of cytosolic calcium levels partly via voltage-gated sodium channels (NaV) (Kühn et al 2020).
Upon membrane depolarization, voltage-gated sodium channels (NaV) are opened, triggering the initiation and propagation of action potentials. For their indispensable role in the generation and propagation of action potentials, these NaV channels have been suggested as potential drug targets for blunting sensory perceptions. Case studies revealed that gain-of-function mutations in NaV channels can cause paroxysmal itch in affected patients (Devigili et al 2014, Faber et al 2012,Salvatierra et al 2018, Woods et al 2015).
The current first-in-human study will evaluate the safety/tolerability, pharmacokinetics and efficacy of M528101 in healthy volunteers and AD patients.

Study objective

This is a FIH study for M528101. We expect that the compound is safe and tolerable.

Study design

Part A and B: Screening up to 42 days before dosing, day 1, 2, 3, 4
Part C: Screening up to 42 days before dosing, day 1, 2, 5, 8, 11, 13, 14, 15, 16, 17, 22

Intervention

Investigational product: M528101
Control: placebo

Contacts

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Eligibility criteria

Inclusion criteria

Inclusion Criteria part A
Subjects who meet all of the following criteria are eligible to participate in this study:
1. Healthy male subjects, 18 to 45 years of age, inclusive. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, blood serology and urinalysis;
2. Body mass index (BMI) between 18 and 30 kg/m2, inclusive, and with a minimum weight of 50 kg;
3. Subjects must use effective contraception for the duration of the study;
4. Able and willing to give written informed consent and to comply with the study restrictions;
5. Subject has a negative result of COVID-19 test at Day -1.

Inclusion Criteria part B and C
1. Male subjects with mild to moderate AD (IGA 2 or 3) 18 to 65 years of age, inclusive;

Healthy status is defined by absence of evidence of any active or chronic disease except for atopic dermatitis following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, blood serology and urinalysis;
2. Diagnosed with AD according to the Hanifin & Rajka criteria;
3. Body mass index (BMI) between 18 and 30 kg/m2, inclusive, and with a minimum weight of 50 kg;
4. Subjects must use effective contraception for the duration of the study;
5. Suitable target lesions defined as eczema lesions of 3- 10% BSA (excluding the head, face and genitals);
In part C, the first 6 subjects have eczema lesions with 3 to 5% BSA and 3 subjects have 8 to 10% BSA;
6. Subject has a negative result of COVID-19 test at Day -1;
(ranging from 0 to 10) of the past 24-hours.

Exclusion criteria

Exclusion Criteria part A
1. Any disease associated with immune system impairment, including auto-immune diseases, allergies, HIV and transplantation patients;
2. History of pathological scar formation (keloid, hypertrophic scar);
3. Excessive sun exposure or a tanning booth within 21 days prior to Day 1;
4. Participation in an investigational drug or device study within 3 months prior to screening or more than 4 times a year;
5. Loss or donation of blood over 500 mL within three months prior to screening. Or the donation of plasma within 14 days prior to screening;
6. Current smoker and/or regular user, of other nicotine-containing products (e.g., patches). Regular users are defined as someone who smokes more than 10 cigarettes per day;
7. History of or current drug or substance abuse considered significant by the PI (or medically qualified designee), including a positive urine drug screen;
8. Subject has a body temperature of ≥38.0 °C at screening and/or Day 1;
9. Have known history of atopy;
10. No prescription medications and OTC medications will be permitted within 21 days prior to study drug administrations, or less than 5 half-lives (whichever is longer, and during the course of the study;
11. Have any current and / or recurrent pathologically, clinically significant skin condition at the
treatment area (i.e. atopic dermatitis).

Exclusion Criteria part B and C
1. Any disease associated with immune system impairment, including auto-immune diseases, allergies, HIV and transplantation patients;
2. History of pathological scar formation (keloid, hypertrophic scar);
3. Excessive sun exposure or a tanning booth within 21 days prior to Day 1;
4. Participation in an investigational drug or device study within 3 months prior to screening

or more than 4 times a year;
5. Loss or donation of blood over 500 mL within three months prior to screening. Or the donation of plasma within 14 days prior to screening;
6. Current smoker and/or regular user of other nicotine-containing products (e.g., patches). Regular users are defined as someone who smokes more than 10 cigarettes per day;
7. History of or current drug or substance abuse considered significant by the PI (or medically qualified designee), including a positive urine drug screen;
8. Subject has a body temperature of ≥38.0 °C at screening and/or Day 1;
9. Any topical anti-AD drugs on the lesional sites within 7 days prior to Day 1, for all other systemic anti-AD drugs a washout period of 4 weeks or 5 half-lives (whichever is longer) is required, or planned to use during the course of the study;
10. Requirement of immunosuppressive or immunomodulatory medication within 28 days or 5 half-lives (whichever is longer) prior to Day 1 or planned to use during the course of the study;
11. Use of antihistamines within 14 days prior to Day 1.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-03-2021
Enrollment:	36
Type:	Anticipated

IPD sharing statement

Plan to share IPD: No

Plan description
N.A.

Ethics review

Positive opinion
Date: 30-08-2021
Application type: First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 50835
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL9695
CCMO	NL76048.056.20
OMON	NL-OMON50835

Study results

Summary results
N.A.