Phase I, Randomized, double-blind, vehicle-controlled study to evaluate the safety, tolerability, PK and efficacy of M528101 in Healthy Volunteers and AD subjects

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This Phase 1, First in Human study is designed to assess the safety and systemic exposure (pharmacokinetics (PK)) of single dose (Part A,B) and multiple dose (thrice daily) for 14 days (Part C) topical M528101 Liquid 0.3% in healthy volunteers (Part…

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

Summary

ID

NL-OMON50835

Source
ToetsingOnline

Brief title
Phase I study of M528101

Condition

- Epidermal and dermal conditions

Synonym
Atopic Dermatitis, Eczema

Research involving
Human

Sponsors and support

Primary sponsor: Maruho Co,Ltd
Source(s) of monetary or material Support: Maruho

Intervention

Keyword: Atopic Dermatitis, Pharmacokinetics, Pruritus, Topical

Outcome measures

Primary outcome

Primary endpoints are safety, tolerability and PK after IMP is administered

once a day in part A and B and three times a day for 14 days in Part C.

Secondary outcome

Pharmacodynamic endpoints

• Change from baseline in EASI total score in part C.

• Change from baseline in SCORAD total score and each component signs and

symptoms of AD in part C (erythema, induration/papulation, exudation,

excoriation, lichenification).

• Change from baseline in treatable BSA in part C.

• Change in NRS itch score (Peak pruritus NRS, average NRS) from Baseline to

Day 14 for Part C.

• Time course change in NRS itch score in Part B.

• Time course change in NRS itch score (Daytime 12 hr itch and nighttime 12 hr

itch) in Part C.

• Change of nighttime duration of scratching in Part C.

• Change in NRS sleeplessness in Part C.

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).
M5281 is a dual inhibitor for voltage-gated sodium channel (NaV) 1.7 and NaV1.8, which was initially developed by RaQualia Pharma Inc. M5281 is currently being developed as a topical product for treatment of pruritus and

pain.
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 Phase 1, First in Human study is designed to assess the safety and systemic exposure (pharmacokinetics (PK)) of single dose (Part A,B) and multiple dose (thrice daily) for 14 days (Part C) topical M528101 Liquid 0.3% in healthy volunteers (Part A) and subjects with mild to moderate atopic dermatitis (AD) (Part B, C).

Primary objectives
• 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 objectives
• To evaluate efficacy of M528101 after topical administration
• To evaluate M5281 metabolites in blood and urine samples

Study design

Design
This is a single-center, randomized, vehicle-controlled, double-blind, Phase 1 study to assess the safety and PK of single dose (Part A,B) and multiple dose (thrice daily) for 14 days (Part C) topical M528101 in healthy adults (Part A) and patients with mild to moderate AD (Part B, C)
The study is divided into three parts: part A, B and C. In total nine (9) healthy male volunteers and twenty-seven (27) male subjects with mild to moderate AD will be enrolled. The subjects will have total treatable body surface area (BSA) of 3% to 10%.

Part A will serve to evaluate safety and tolerability of a single dose 0.3% M528101 or placebo in a cohort of healthy volunteers.

Part B will evaluate safety and tolerability of a single dose of 0.3% M528101 or placebo in a cohort of subjects with atopic dermatitis.

Part C will evaluate safety and tolerability of multiple doses 0.3%M528101or placebo. In this part, the first 6 subjects will have a maximum treated BSA of approximately 5%.

Intervention

0.3% M528101

Study burden and risks

The pharmacological and toxicological profile of M528101 observed in pre-clinical studies suggest that administration to humans in a carefully monitored study is acceptable. In addition, several non-selective sodium channel blockers with systemic rout of administration have known well-established safety profile.

There are no anticipated benefits for subjects participating in the part A of the study, other than the benefit of medical evaluation at screening and throughout the study. For participants (AD patients) in part B and C, there might be relief of itch if M528101 is efficacious. Additionally, the eczema of subjects will be monitored closely.

The study design has been used previously in first-in-man studies and is accepted by
scientists and regulatory authorities. All initial study drug administrations will be done in the clinic under medical supervision. The subjects participating in part A or B (FIH in healthy volunteers and in AD patients) receiving study drug for the first time will remain in the clinic for at least 24 hours after study drug administration. Thus, the subjects can be closely monitored for any adverse event during the different treatments. In addition, after part A, B and during part C, a blinded safety analysis will be performed. The responsible person of Maruho Clinical Development Department (and sponsor*s medical monitor) and the principal investigator or designee will decide in mutual agreement on the proceeding to part B or Part C or continue of Part C. Therefore, providing the protocol is adhered to, careful observation and medical management will minimize any associated risk in this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

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;
3. 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.

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)>=18 kg/m2, with a minimum 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;

7. Average Pruritus (AP) NRS *3 at Screening and AP NRS*5 at Day1. The AP NRS score for each visits will be determined by a single AP NRS assessment (ranging from 0 to 10) of the past 24-hours.

Inclusion Criteria Part C only
8. Average of daily AP NRS*5 at Day 1 The average of daily AP NRS score will be determined based on the average of Daily AP NRS scores (score ranging from 0 to 10) of the past three days.

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 start of the study (Day 1).

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):	09-02-2021
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	M5281
Generic name:	NA

Ethics review

Approved WMO Date:	04-01-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-02-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-11-2021
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

ID: 29502

Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2020-005223-36-NL
CCMO	NL76048.056.20

Study results

Date completed: 27-04-2022

Results posted: 18-04-2023

First publication
31-03-2023