A randomized, single-blind, saline-controlled, dose-finding, study to characterize the pruritus and inflammatory response to intradermal histamine in healthy volunteers and patients with atopic dermatitis

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Primary objectives • To characterize the histamine dose response on pruritus• To profile the response to intradermal histamine by:o Clinical measureso Biophysical measureso Imagingo Molecular and cellular responsesSecondary objective • Comparison to...

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

Summary

ID

NL-OMON54996

Source
ToetsingOnline

Brief title
Characterization of a pruritus challenge model

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: AD, Challenge, Pruritus

Outcome measures

Primary outcome

Tolerability / safety endpoints

• Monitoring adverse events

• Monitoring HR, BP and temperature

• Local tolerance (Visual Analog Scale (VAS) pruritus)

Pharmacodynamic endpoints

The injection sites will be monitored for a period of up to 180 min. Safety assessments and non-invasive efficacy assessments (imaging) will be performed at baseline, directly after histamine and saline administration after 10, 30 and 60 minutes.

Imaging measurements (Part A + Part C)

- Perfusion by Laser speckle contrast imaging (LSCI)

- Erythema by Antera 3D camera

- Wheal and flare by Antera 3D camera

- Wheal and flare by clinical evaluation (erythema grading scale)

- Erythema by colorimetry (DSM III)

Biochemical measurements

- Skin biopsies (Part C). Readout measures may comprise, but are not limited to:

o Immunohistochemistry:

- Eosinophils

- Monocytes/macrophages

- Mast cells

- IgE, IgG

o qPCR (exploratory):

- NAV 1.1 to 1.9 expression

Subject reported outcomes

Itch intensity is assessed on a horizontal bar from 0 to 100 representing the visual analogue scale (VAS) in both parts following each provocation every minute up to 15 minutes. After 15 minutes, itch will be assessed with a frequency of 5 minutes up to 30 min after challenge. The burning sensation is evaluated similarly.

Pain intensity is assessed on a 100 mm visual analogue scale (VAS) in both parts following each provocation pre-dose, post-dose, after 10 and 30 minutes of histamine challenge

Itch intensity is assessed on a horizontal bar from 0 to 100 representing the visual analogue scale (VAS) in all three parts. After every histamine/NaCl administration itch is assessed every minute up to 15 minutes. After 15

minutes, itch will be measured with a frequency of 5 minutes up to 30 min after challenge. Additionally, itch will also be assessed after 45 min and 60 min of challenge (only part A and part B).
Pain intensity is assessed on a 100 mm visual analogue scale (VAS) in each part of the study. The intensity is measured pre-dose, post-dose, after 10, 30, 45 and 60 minutes of histamine challenge in Part A and B.

In case the subject still experiences substantial itch or pain at the end of a round, the physician decides whether this is clinically relevant and provides permission for next dosing/histamine challenge.

The following outcomes are included to evaluate itch sensitization with the different histamine doses and the difference between HV and AD patients.

- Maximum itch / peak itch
- Time to maximum itch
- Time to complete itch subsidence
- AUCitch

Secondary outcome

N.a.

Study description

Background summary

In many dermatological diseases, pruritus (or itch will be used interchangeably) 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. The ion channels that appear to be primarily involved are members of the transient receptor potential (TRP) family. As an example, TRPV1 detects capsaicin, the active ingredient in chili peppers.
Various drugs with different mechanisms of action are currently in development. These drugs have the potential to lead to targeted therapy of peripheral itch independent of blocking inflammation. For clinical drug development efficient and effective pruritus provoking challenge models in humans are needed. For these purposes a variety of different compounds including cowhage, capsaicin and histamine have been tested. Ample experience has been obtained with histamine also being used as positive control of the skin prick test in allergy testing sued routinely in clinical practice. However, hardly any bioquantitative measurements have been performed to characterize the itch response following histamine injection.
The aim of this study is to characterize the dose-pruritogenic response upon intradermal histamine injection in healthy volunteers and patients with atopic dermatitis. This setup will create a challenge model that temporarily induces skin itch which enables future application as proof-of-pharmacology or drug profiling in drug developmental programs. As histamine is known as low potent pruritogenic agent the study will also enroll atopic dermatitis patients where lesional site will be evaluated to study the difference in pruritus response in patients. With the application oral antihistamine, the reversal of a fixed

histamine-dose effect can be investigated in both populations.

Study objective

Primary objectives
• To characterize the histamine dose response on pruritus
• To profile the response to intradermal histamine by:
o Clinical measures
o Biophysical measures
o Imaging
o Molecular and cellular responses
Secondary objective
• Comparison to itch induction in healthy volunteers and patients with atopic dermatitis
• To assess safety and tolerability of intradermal histamine challenge

Study design

This is a randomized, single-blind, saline-controlled, dose-finding, study to characterize the pruritus and immune response to intradermal histamine in healthy volunteers and patients with atopic dermatitis.
The study is divided into three parts: in part A, the optimal dose of histamine is explored in healthy volunteers and in atopic dermatitis patients to enhance the characterization of the pruritus challenge. Part B will be carried out to explore itch response by administration of histamine dihydrochloride via intradermal injection and skin prick test. In these two parts the optimal administration method and dose will be determined. In part C, oral antihistamine is used as a positive control to assess reversal of the histamine-induced pruritus challenge.

Intervention

Investigational product: Histamine dihydrochloride
Non-investigational product: Cetirizine 10 mg
or placebo

Study burden and risks

The overall aim of this study is to characterize a model for pruritus upon intradermal histamine injection in healthy volunteers and patients with atopic dermatitis. In addition, the reversal effect of histamine challenge will be examined by applying systemic antihistamine. No medical benefit can be expected from this study for the participating subjects.

Contacts

Public
Maruho Co., Ltd

Chudoji Awatacho 93 .
Shimogyo-ku, Kyoto 600-8815
JP
Scientific
Maruho Co., Ltd

Chudoji Awatacho 93 .
Shimogyo-ku, Kyoto 600-8815
JP

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

All participants
1. Body mass index (BMI) between 18 and 30 kg/m2, inclusive, and with a minimum weight of 50 kg;
2. Fitzpatrick skin type I-II (Caucasian);
3. All 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.

Healthy volunteers
5. 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;

AD patients
6. Male and female subjects with mild to moderate AD (IGA 2 or 3) 18 to 65 years of age,
inclusive. The health status is verified by absence of evidence of any clinically significant
active or uncontrolled chronic disease other than AD following a detailed medical history and
a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, blood serology and urinalysis;
7. Diagnosed with AD according to the Hanifin & Rajka diagnostic criteria;
8. Suitable target of the affected skin defined as an eczema lesion of at least 1% BSA for each lesions (volar forearms and/or preferably upper back, total 3 lesions)
9. IGA 2 or 3
10. VAS itch of <=30 at screening and prior to first administration of target lesions

Exclusion criteria

All participants
1. Diseases associated with immune system impairment, including auto-immune diseases, HIV and transplantation patients;
2. History of pathological scar formation (keloid, hypertrophic scar);
3. Excessive sun exposure or a tanning booth within 3 weeks of enrollment
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);
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. Use of antihistamines within 3 weeks prior to start of the study;
9. Subjects who show skin reaction to Skin marker;
10. Subject has a body temperature of >=38.0 °C at any visit.

Healthy volunteers
11. Subjects suffering from chronic itch defined as presence of pruritic symptoms lasting more than 6 weeks;
12. Have known history of atopy;
13. Have any current and / or recurrent pathologically, clinically significant skin condition at the treatment area (i.e. atopic dermatitis);

AD patients
14. Requirement of immunosuppressive or immunomodulatory medication within 30 days prior to enrollment or planned to use during the course of the study;
15. Pregnant, a positive pregnancy test, intending to become pregnant, or breastfeeding.;

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	31-12-2019
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Allergopharma skin prick test
Generic name:	Histaminedihydrochloride
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	09-12-2019
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-12-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-06-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-03-2021
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: 28663
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2019-004261-40-NL
CCMO	NL71946.056.19

Study results

Date completed: 11-08-2021

Results posted: 14-11-2022

First publication
07-11-2022