A phase I/IIa, single-centre, randomized, double-blind, placebo-controlled, parallel treated dose-ranging study with a safety run-in period to assess the safety and efficacy of topical XZ.700 in patients with mild to moderate atopic dermatitis

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Primary ObjectiveTo evaluate the safety and tolerability of topical XZ.700 in patients with mild to moderate atopic dermatitisSecondary ObjectivesTo investigate the PD effects of XZ.700 in patients with mild to moderate atopic dermatitis To evaluate...

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

Summary

ID

NL-OMON54877

Source
ToetsingOnline

Brief title
XZ.700 in patients with mild to moderate atopic dermatitis

Condition

- Epidermal and dermal conditions

Synonym
Atopic Dermatitis / Eczema

Research involving

Human

Sponsors and support

Primary sponsor: Micreos Human Health
Source(s) of monetary or material Support: Ministerie van OC&W,Micreos Human Health

Intervention

Keyword: Atopic dermatitis, Eczema, XZ.700

Outcome measures

Primary outcome

Tolerability / safety endpoints

- Adverse events (AE)

- Laboratory safety testing (blood and urine)

- 12-Lead ECGs

- Vital signs

- Physical examination

- Skin irritation by local irritation grading scale (Part A only)

Adherence

* Electronic diary with photo capture function to monitor treatment compliance

Secondary outcome

Pharmacodynamic endpoints

Pharmacodynamic effects of XZ.700 will be assessed at the time points indicated

in the Visit and Assessment Schedule (Table 1 & 2) by:

- Multispectral imaging (erythema and roughness of target lesion)

- Laser speckle contrast imaging (LSCI, blood flow of target lesion)

- 2D photo documentation of the target lesion

- Microbiome of skin lesions (of target lesion and non-lesional skin)

- Bacterial colonization of skin lesions (S. aureus cultures of target lesion

and non-lesional skin)

- Local (biopsy) biomarkers may comprise, but are not limited to: IL-13, IL-4,

IL-5, IL-33, TSLP, IL-31, IL-22, eotaxin

- Transepidermal water loss of lesional and non-lesional skin

- Blood-based biomarkers

Efficacy endpoints

Efficacy of XZ.700 will be assessed at the time points indicated in the Visit

and Assessment Schedule (Table 1 & 2):

* SCORAD; EASI, IGA, lesion count, lesion clearance

* Target lesion oSCORAD, TSS and surface area (BSA in cm2)

* Patient-reported itch (twice daily NRS by e-diary / mobile app and POEM)

* DLQI

Study description

Background summary

The pathophysiology of atopic dermatitis (AD) is complex and still not completely understood. Genetic susceptibility, environmental factors, epidermal barrier abnormalities, immunological disturbances and dysbiosis of the skin microbiota all play a role in the disease and the variability of these mechanisms may explain the heterogeneous character of AD. It remains hard to discern which of these mechanisms are primary events (causing AD), secondary events (resulting from AD), or both (Weidinger et al., 2018).
Staphylococcus aureus (S. aureus) is an important player regarding dysbiosis in

AD. Colonization with this pathogen combined with a lower general microbial diversity is apparent in approximately 70-90% of the AD patients (Totte et al., 2016). Several factors contribute to enhanced S. aureus adhesion to AD skin. After adhesion S. aureus may cause or exacerbate inflammation by binding of its superantigens (SAgs) to MHCII molecules which induces an excessive production of T cell cytokines (Spaulding et al., 2013), next to being conventional allergens that can generate an IgE response. In addition, S. aureus produces alpha toxin, which causes lysis of keratinocytes and aureolysin which inactivates antimicrobial peptides (Geoghegan et al., 2018).
Based on the hypothesis that dysbiosis plays an important role in the pathogenesis of AD the microbiome and especially S. aureus might be a target for novel therapies (Geoghegan et al., 2018, Nakatsuji et al., 2017). A novel topical treatment targeting the perturbed microbiome is XZ.700. XZ.700 is a recombinant chimeric endolysin that specifically targets S. aureus. Endolysins are phage derived enzymes that are produced at the end of the reproduction cycle of bacteriophages in the bacteria to lyse the peptidoglycan cell wall and to allow the newly assembled phages to leave the host-cell. XZ.700 is produced via recombinant technology. It is highly specific against the S. aureus species (both MSSA and MRSA) and unlikely to induce bacterial resistance, allowing it to be used for the long-term treatment of chronic skin diseases such as AD.
This first-in-human study is intended to evaluate the safety and tolerability of XZ.700 as well as exploring the pharmacodynamic effects in patients with mild to moderate AD. Clinical efficacy will be investigated by means of clinical outcomes (i.e. clearance of the target lesion, target lesion oSCORAD, target lesion TSS) and local biomarkers will be assessed.

Study objective

Primary Objective
To evaluate the safety and tolerability of topical XZ.700 in patients with mild to moderate atopic dermatitis

Secondary Objectives
To investigate the PD effects of XZ.700 in patients with mild to moderate atopic dermatitis
To evaluate the efficacy of three dose levels of topical XZ.700 in patients with mild to moderate atopic dermatitis

Study design

Phase I/IIa, single-centre, randomized, double blind, placebo controlled, parallel treated dose-ranging study with a safety run-in period. The study will entail two Parts. . The aim of part A is to closely observe the safety through daily assessments of both the non lesional and lesional skin whereas Part B is only focussing on lesional skin.

Part A (safety run-in):
- 12 atopic dermatitis patients with 2 treatment areas
- Treatment area 1: healthy appearing, uninvolved, non-lesional skin of preferably the upper back, 20x20cm (approx. 2.3% body surface area (BSA)), 7 days twice per day (BID) in-clinic treatment (for Part A interim safety analysis).
- Treatment area 2: lesional skin involvement of approximately 1%*BSA*10% for 14 days BID followed by an end of treatment (EOT) visit at Day 15 and an end of study (EOS) visit at Day 22. One target lesion of BSA*0,5% (preferably elbow or knee-fold) is selected for pharmacodynamic measurements. Treatment area two will consist of all lesions.(for Part A interim safety analysis and, together with Part B, overall safety, efficacy and pharmacodynamic analysis)

Safety will be assessed by the investigator on an ongoing basis and if needed action will be taken to warrant the safety of the patients. After completion of the D22 visit of the last patient of Part A, a unblinded interim analysis will be performed. The full interim analysis together with the decision to proceed to Part B of the study will be provided to the Ethics Committee for assessment.

The study may continue as planned when:
- There are no Serious Adverse Events (SAEs) assessed related to the study drug by the investigator
- There are no adverse events graded severe and assessed as related to the study drug by the investigator
- There are no assessments of more than 8 points on the local irritation grading scale
- The criteria of section 8.11, interim analysis after Part A, have been fulfilled

In case any of the foregoing events occur in Part A, the study will be temporarily halted, treatment allocation of the subjects will be unblinded and a critical review of the safety data will be performed. In that case, approval from the Ethics Committee will be obtained prior to restarting the study with Part B.

Part B:
- 24 atopic dermatitis patients (that will be grouped together with Part A for overall safety, efficacy and pharmacodynamic analysis)
- Treatment of all lesions of 1%*BSA*15% for 14 days BID treatment followed by an EOT visit at Day 15 and an EOS visit at Day 22. One target lesion of BSA*0.5% (preferably elbow or knee-fold) is selected for pharmacodynamic measurements. First treatment is in-clinic, all other treatments will be performed by the subjects (at home or at clinic)

Intervention

XZ.700 or placebo

Study burden and risks

The current study is the first investigation with XZ.700 in humans. The drug is a large molecule with 52kDa in size and applied via the topical route of administration. Hence only negligible exposure of the drug is expected in the systemic circulation and mainly local effects are expected. XZ.700 is a very similar endolysin to the EU marketed SA.100. Since its introduction 7 years ago no major safety issues were reported. The patients in this trial do have a mild to moderate disease where any safety or tolerability issues can be assessed in a well-monitored manner, i.e. daily administration site inspections, vital signs monitoring and in-house observation. After completion of Part A a blinded safety evaluation will be performed to continue into the outpatient-clinic Part B with administrations at home. This warrants additional measures to mitigate the risks of potential safety or tolerability issues. A multiple dose design will be performed, as explained in detail in section 1.4.6 of the protocol, with frequent administration site assessment and negligible systemic exposure to XZ.700 based on ample SA.100 experience as well as negligible XZ.700 penetration as observed in ex vivo experiments.
Measurements are predominantly non-invasive, the minimally invasive techniques are venepuncture and 4mm small skin punch biopsies (no suture necessary).
No additional risk for infection to SARS-CoV-2 can be determined due to participation in the trial due to the various extra measures applied.
In summary, the risk to participate in the trial can be assessed as acceptable.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Male and female subjects with mild to moderate AD (IGA 2 or 3) 18 to 65 years (during covid-19 restriction period subjects will be included from 18 to 54 years of age inclusive) of age, inclusive. The health status is verified by absence of evidence of any clinically significant active or uncontrolled chronic disease other than AD that potentially may influence the adherence to the study and/or assessments in the study, following a detailed medical history and a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, virology and urinalysis;
2. Diagnosed with AD according to the Hanifin criteria (Hanifin 1980);
3. Suitable target lesion (preferably the antecubital fossa) defined as an eczema lesion of 0,5%*BSA*5% (excluding the face and hands) with at least mild erythema and mild induration at screening and baseline day 1;
4. Target lesion is cultured positive for S. aureus on two consecutive occasions during the screening period;
5. Extent of lesional, atopic dermatits affected skin for 1%*BSA*15%; at screening and baseline (day 1);
6. Willing to refrain from washing the target lesion 12 hours before every study visit that includes microbiology samples;
7. Willing to use microbiome friendly wash solution as provided by sponsor and refrain from other products for washing from screening until end-of-study;
8. Willing to refrain from all topical products for lesional skin during the treatment period;
9. Subjects and their Partners of childbearing potential must use effective contraception, for the duration of the study and for 3 months after the last dose;
10. Able to Participate and willing to give written informed consent and to comply with the study restrictions;
11. Has the ability to communicate well with the Investigator in the Dutch language.

Exclusion criteria

1. Any current and / or recurrent clinically significant skin condition which will interfere with the clinical findings of the study as assessed by the investigator;
2. Ongoing use of prohibited atopic dermatitis treatments. Washout periods prior to baseline (first dose of the study drug) are as follows:
- All atopic dermatitis lesions: any topical medication (prescription or over-the-counter [OTC]): 14 days. For emollients target lesion only: 7 days. On other atopic dermatitis lesions use of emollients is allowed, however must be discontinued prior to Day 1.
- Cyclosporine/oral steroids/azathioprine/mycophenolate mofetil/other systemic AD drugs: 4 weeks
- Phototherapy: 3 weeks
- Biologics: 5 half-lives of the drug
- Systemic antibiotics: 14 days
3. Tanning due to sunbathing, excessive sun exposure or a tanning booth within 3 weeks of enrolment and/or not willing to refrain from these during the study;
4. Known hypersensitivity to the investigational compound or its excipients;
5. Pregnant, a positive pregnancy test, intending to become pregnant, or breastfeeding;
6. Participation in an investigational drug or device study within 3 months prior to screening or more than 4 times a year;
7. Loss or donation of blood over 500 mL within three months (males) or four months (females) prior to screening;
8. A positive drug and/or alcohol test at screening (rescreening is allowed).
9. Subject has a body temperature of >38.0 °C at any visit, only during SARS-CoV-2 measures;
10. Only during SARS-CoV-2 measures: Subject has a BMI of >30 kg/m2

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:	Recruitment stopped
Start date (anticipated):	16-09-2020
Enrollment:	36
Type:	Actual

Ethics review

Approved WMO Date:	30-06-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-07-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-06-2021

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-09-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-09-2021
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: 21515
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2020-002767-56-NL
CCMO	NL74232.056.20
Other	NL8876
OMON	NL-OMON21515