A First-in-Human, Double-Blind, Randomised, Vehicle-Controlled Phase I/II Proof of Concept Study to Investigate the Safety, Tolerability, Pharmacokinetics and Efficacy of BEN2293 in Patients with Mild to Moderate Atopic Dermatitis.

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

Summary

ID

NL-OMON51714

Source
ToetsingOnline

Brief title
BEN2293 in patients with Mild to Moderate AD

Condition

- Epidermal and dermal conditions

Synonym
Atopic Dermatitis, Eczema

Research involving
Human

Sponsors and support

Primary sponsor: BenevolentAI Bio Limited
Source(s) of monetary or material Support: BenevolentAI

Intervention

Keyword: Atopic Dermatitis, BEN2293, Pharmacodynamics, Pharmacokinetics

Outcome measures

Primary outcome

Primary safety endpoints:

· Adverse events, local tolerance assessments, vital signs, 12-lead ECG,

laboratory safety tests (clinical chemistry, haematology and urinalysis).

Secondary outcome

Secondary PK endpoints:

· Plasma concentration-time profiles and PK parameters for BEN2293 and BEN6403

including maximum observed plasma concentration (Cmax), time corresponding to

the maximum observed plasma concentration (tmax), apparent terminal half-life

(t1/2), area under the plasma concentration vs. time curve (AUC) over a dosing

interval (AUC*) (Part A only).

· Accumulation ratio (Part A only).

Secondary efficacy endpoints:

· Time to itch reduction.

· Fraction of patients achieving itch reduction.

· Change from baseline in the Numerical Rating Score (NRS) for Pruritus (Worst

Itch over 24 hours).

· Change from baseline in the NRS for Pruritus (Current Itch).

· Change from baseline in the Eczema Area and Severity Index (EASI) score.

· Number of patients achieving improvement in EASI score.

· Change from baseline in BSA affected by AD in treated area(s).

· Change from baseline in validated Investigators Global Assessment (vIGA)

Score.

· Change from baseline in Patient Oriented Eczema Measure (POEM).

· Change from baseline in Dermatology Life Quality Index (DLQI).

· Change from baseline in EQ-5D.

· Change from baseline in Patient-Reported Outcomes Measurement Information

System (PROMIS).

· Change from baseline in Insomnia Severity Index ([ISI] for Part A, Cohorts 3

and 4 and Part B only).

Study description

Background summary

Atopic dermatitis (AD), also known as atopic eczema, is the most common chronic inflammatory skin disease of children and adults with a lifetime prevalence of 15% to 20% in developed countries. The condition is characterised by intense, chronic pruritus (itch), eczematous skin lesions (erythematous patches with exudation, blistering and crusting), xerosis (dry skin) and, at later stages, lichenification (thickening of the skin and an increase in skin markings). The disease is characterised by a remitting and recurring course with the majority of patients presenting with mild to moderate disease severity. Although not life-threatening, AD is associated with a significant reduction in quality of life (QoL) for patients. In particular, the intense chronic itch and skin discomfort can lead to sleep disturbance, diminished self-esteem, anxiety, depression and poor performance at school and work.

Atopic dermatitis is a heterogeneous disease thought to be triggered by environmental factors in genetically susceptible individuals. Atopic dermatitis lesions typically show a cellular infiltrate that mainly consists of CD4+ T cells, which are considered the key drivers of AD cutaneous inflammation, together with an increased number of dendritic cell subsets, mast cells, and eosinophils. Histologically, the epidermal nerve fibre density is higher in the skin of AD patients than in healthy controls. The intense itch characteristic of AD is caused by elongation of sensory nerves into the epidermis leading to increases epidermal nerve fibre density (hyperinnervation), together with increased sensory nerve fibre responsiveness to pruritogens (hypersensitivity).

Approximately 90% of patients present with mild to moderate AD and 5% to 10% with severe disease. Disease severity usually correlates with the intensity of pruritus. Topical treatments are widely used in patients with mild to moderate AD as they minimise the risk of adverse events (AEs) compared to systemic therapies. Currently, topical treatments for AD are limited, consisting of emollients, corticosteroids, calcineurin antagonists, and a phosphodiesterase type 4 inhibitor (Eucrisa®; currently marketed in the USA and Canada). However, all classes of products are associated with side effects which limit chronic continuous use. Long term use of topical corticosteroids causes skin atrophy, striae, petechiae, acne and systemic effects. In addition, topical corticosteroid treatment regimens are often associated with poor treatment compliance as a result of *steroid phobia* in patients and/or doctors due to concerns about skin atrophy and other adverse reactions. The calcineurin inhibitors tacrolimus and pimecrolimus have been associated with application site burning and irritation. Model systems have linked calcineurin antagonists to carcinogenicity, resulting in the inclusion of a warning in the prescribing information from the European Medicines Agency for both Protopic®/Protopy® (tacrolimus) and Elidel® (pimecrolimus) for potential increased risk of malignancy and a US Food and Drug Administration (FDA) black-box warning for this class of medication. Eucrisa is a topical ointment approved in the USA and Canada. Application site pain and burning sensation are the most common AEs in clinical trials and post-marketing safety reports. As a result of the limitations associated with currently available topical therapies, there is a large unmet need for an efficacious and safe alternative topical therapy for the treatment of patients with AD

Study objective

Primary
The primary objective of this study is to assess the safety and tolerability of BEN2293, administered as multiple topical doses to increasing body surface area (BSA), in patients with mild to moderate AD.

Secondary
Pharmacokinetics
· To investigate the plasma PK of BEN2293 and metabolite BEN6403 following

multiple topical doses to mild to moderate AD patients.
Efficacy
· To investigate the effect of BEN2293 on pruritus in patients with mild to moderate AD.
· To investigate the effect of BEN2293 on AD in patients with mild to moderate AD.

Study design

This is a randomised, adaptive design, double-blind, placebo-controlled, first-in-human, two-part study to investigate the safety, tolerability, PK and preliminary efficacy of multiple topical doses of BEN2293 in patients with mild to moderate AD.
Part B is a randomised, double-blind, placebo-controlled, parallel group study to investigate a single dose regimen of topical doses of BEN2293 versus placebo administered for 28 days in patients with mild to moderate AD. CHDR will only participate in Part B of the study.

Intervention

BEN2293 (0.25% or 1.0% w/w) or matching placebo

Study burden and risks

The risk assessment of BEN2293 is based mainly on the preclinical studies conducted to date, but also takes into account important safety and preliminary plasma PK data from Part A of this study. In this study, safety will be monitored closely both by subjective reporting and by objective means i.e., serial assessments of vital signs, clinical laboratory evaluations data, physical examinations, local tolerability and 12-lead electrocardiogram (ECG).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients meeting the following criteria will be included in the study:
1. Males and females with mild to moderate AD (based on vIGA) free from other clinically significant illness or disease that may adversely affect the safety of the patient or the integrity of the study as determined by medical history, physical examination, safety laboratory and other assessments.
2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.
3. Patient is aged between 18 to 65 years, inclusive.
4. Patient has a body mass index (BMI) of 18.0 to 35.0 kg/m2, inclusive.
5. Body weight of >=50 kg.
6. History of AD for at least 6 months diagnosed by a dermatologist or GP.
7. Previous or current successful treatment with topical corticosteroids.
8. A vIGA score of 2 (mild) to 3 (moderate) at both Screening and Day -1 (Part A) and at Screening, Day -3 and Day 1 (Part B).
9. Atopic dermatitis affecting between >=1% to <=30% BSA of treatable skin (not including face, scalp, genital area, palms of hands or soles of feet) at Screening and Day -1 for all cohorts in Part A and at Screening, Day -3 and Day 1 for Part B.
10. History of AD associated pruritus with an itch score (NRS) of >=4.
· For Part A, the mean of the pruritus NRS scores (worst itch over the last 24 hours) obtained on Day -3, Day -2 and Day -1 during the emollient only washout phase will be used to assess inclusion.
· For Part B, the mean of the pruritus NRS scores (worst itch over the last 24 hours) obtained on Day -5, Day -4 and Day -3 (pre-dose) during the emollient only washout phase, and the mean of these scores on each day of the run-in phase (Day -2, Day -1 and Day 1 [pre-dose]) will be used to assess

inclusion at Day -3 and Day 1, respectively. Where the run-in phase is extended by 1 day, the mean NRS for all NRS scores reported over that time (minimum of 3) will be used to determine eligibility. Where patients are unable to provide 3 consecutive days of NRS scores for calculation of the average score to determine eligibility, a minimum of 3 scores taken over a maximum of 4 days will be used to calculate the average.
11. Patients must be willing to stop applying their daily emollients and instead use the study emollient and shower cream from at least 7 days prior to Day 1 in Part A and 10 days prior to Day 1 in Part B, and throughout their participation in the study.
12. Males must use a condom during the trial and for 3 months after their final dose study medication. In addition, their female partner of child-bearing potential must be established on an additional method of highly effective contraception (see Section 6.3.1) prior to dosing until 3 months following final dosing.
13. Female patients of child-bearing potential must be established on a highly effective method of contraception prior to dosing until 3 months after last dose (see Section 6.3.1 for highly effective method of contraception) in combination with male partner*s use of a condom during the trial and for 3 months after the last dose.
14. Female patients must have a negative pregnancy test at Screening and Day -1 (Part A only) and at Screening, Day -3 and Day 1 (Part B only).
15. Participant has a minimum of one AD area in a site suitable for biopsy.
16. Written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.

Exclusion criteria

Patients with any of the following will be excluded from study participation:
1. Atopic dermatitis of such severity that the patient could not comply with the demands of the study and/or the patient is not a suitable candidate for a placebo-controlled study, as per Investigator*s discretion.
2. Any skin tattoo, scar, cuts, bruises, or other skin damage, including excessive UV exposure, at the possible IMP application sites.
3. Patients who have AD lesions affecting >3% untreatable areas (face, scalp, genitals, palms of hands or soles of feet) (Cohorts 3 and 4 in Part A and Part B only).
4. Patients who have a source of itch solely or significantly from untreatable areas (face, scalp, genitals, palms of hands or soles of feet) (Cohorts 3 and 4 in Part A and Part B only).
5. Have concomitant skin disease or infection (e.g., acne, impetigo) or presence of skin comorbidities in the study area to be dosed that may interfere with study assessments.
6. Patients who are excessively hirsute in areas of skin to be dosed with study ointment.

7. Patients who are unwilling to stop hair removal by any means (including shaving, waxing or depilatory creams) to skin areas to be dosed with study ointment for 2 weeks prior to Day -1 and throughout the duration of the study.
8. History of drug and/or alcohol abuse within the last 2 years, or intake of >21 units of alcohol weekly, or a positive alcohol breath test at Screening or Day -1 (Part A) and at Screening, Day -3 or Day 1 (Part B). One unit is equivalent to a 285 mL glass of full-strength beer or one (30 mL) measure of spirits or one small glass (100 mL) of wine.
9. Regular use of tobacco and/or nicotine containing products within 3 months of Day 1, until the end of the study. Social smokers may be included in the study as long as they are able to abstain from smoking/vaping during residential stays (Part A only). Patients with a positive urine cotinine test at Screening or Day -1 will not be eligible (Part A only). Use of tobacco and/or nicotine containing products (up to 20 cigarettes per day, or equivalent) is permitted for patients in Part B.
10. Clinically relevant history of abnormal physical or mental health interfering with the study as determined by medical history and physical examinations as judged by the Investigator (including [but not limited to], neurological, psychiatric, endocrine, cardiovascular, gastrointestinal, hepatic, or renal disorder).
11. Positive urine test for drugs of abuse at Screening or Day -1 (Part A) and at Screening or Day -3 (Part B).
12. Positive test for hepatitis B surface antigen (HBsAg), anti-hepatitis C antibody (anti-HCV), human immunodeficiency virus I and II (anti-HIV I/II) or SARS-CoV-2 at Screening.
13. Clinically relevant abnormal laboratory results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis), 12-lead ECG and vital signs, or physical findings at Screening or Day -1 (Part A) and at Screening or Day -3 (Part B). In case of uncertain or questionable results, tests performed during Screening, Day -1 or Day -3 may be repeated once to confirm eligibility or judged to be clinically irrelevant.
14. Part B only: Patients treated within 28 days of Day 1 with tricyclic antidepressants (e.g., amitriptyline), anticonvulsants (e.g., carbamazepine, gabapentin) or similar drugs that may interfere with itch sensation.
15. Any other concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study as outlined in this Protocol, or that would, in the opinion of the Investigator, pose an unacceptable risk to the patient in this study. Patients with asthma and hay fever can be included provided they are stable and not receiving oral steroids or antihistamines. Patients with conditions that have been stable for at least 3 months may be included, subject to the requirements above. Patients who have previously tested positive for SARS-CoV-2 virus will not be excluded, as long as they do not test positive at Screening and are COVID-19 symptom free.

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):	11-08-2022
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BEN2293
Generic name:	N.a.

Ethics review

Approved WMO Date:	01-06-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	14-07-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	21-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-11-2022
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	EUCTR2020-003143-28-NL
ClinicalTrials.gov	NCT04737304
CCMO	NL81355.056.22

Study results

Date completed:	17-01-2023
Results posted:	01-12-2023

First publication
29-09-2023

URL result
URL

Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File