A first-in-human study to evaluate safety and tolerability of repeated topical administrations of BPR277 ointment in healthy volunteers, and safety, tolerability, and preliminary efficacy of multiple topical administrations of BPR277 in patients with atopic dermatitis and Netherton syndrome (CBPR277X2101)

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Primary: (part 3) Potential of BPR277 1% ointment b.i.d. to improve the clinical severity of lesional skin in the majority of NS patients at end of treatment versus baseline of >= 2 points, dose range and regimen relationship on clinical severity...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin and subcutaneous tissue disorders NEC
Study type	Interventional

Summary

ID

NL-OMON40034

Source
ToetsingOnline

Brief title
CBPR277X2101

Condition

- Skin and subcutaneous tissue disorders NEC

Synonym
Netherton syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Novartis Pharma BV
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: atopic dermatitis, BPR277, Netherton

Outcome measures

Primary outcome

Total lesional sign score

Secondary outcome

Lesional itch VAS, investigator and patient global assessment, safety.

Study description

Background summary

This study is designed as a First-in-Human study with subsequent parts for proof of concept of BPR277 in adult atopic dermatitis (AD) and Netherton Syndrome (NS) patients. The purpose of this exploratory study is to investigate tolerability, PK in subjects and patients as well as determine preliminary efficacy of BPR277 1% ointment, when applied topically. This study consists of 3 parts: in healthy subjects (1), patients with AD (2) and patients with NS (3). In the Netherlands only part 3 (cohort AA and AB) will be performed.
NS is a rare autosomal recessive disease with an estimated incidence of 1-9/100 000 births and characterized by congenital ichthyosiform erythroderma and hair shaft defects. The large majority of NS patients develop atopic manifestations. In NS the activity of proteases in the upper layers of the skin, including

Klk7, is increased. Augmented Klk7 activity ultimately results in barrier breakdown and disease manifestations. Treatment is symptomatic (emollients). Use of topical steroids and topical immunomodulators has been described as beneficial in some cases, but these agents are not indicated for long-term use or treatment of large surface areas as the skin barrier defect allows increased systemic drug absorption.
BPR277 is a naturally occurring depsipeptide isolated from myxobacteria and a highly potent Klk7 inhibitor with favorable skin penetration properties. Pharmacological models in pigs and mice have shown that BPR277 is able to enhance repair of a disturbed skin barrier and exhibits anti-inflammatory activities after topical application in both acute and subchronic models of skin inflammation. Thus, the potential clinical utility of BPR277 includes the topical treatment of various skin diseases with impaired barrier function where dysregulated Klk7 activity has been demonstrated.

Study objective

Primary: (part 3) Potential of BPR277 1% ointment b.i.d. to improve the clinical severity of lesional skin in the majority of NS patients at end of treatment versus baseline of >= 2 points, dose range and regimen relationship on clinical severity of lesional skin (TLSS-NS) in NS patients of two regimens of BPR277 (BPR277 1% ointment, applied b.i.d. and q.d.), safety and tolerability.
Secondary: Systemic steady state PK, BPR277 concentrations in the skin and the urinary excretion of BPR277 after repeated topical administration.

Study design

Multicenter open-label first-in-human study.
This study consists of 3 parts: in healthy subjects (1), patients with AD (2) and patients with NS (3). In the Netherlands only part 3 (cohorts AA and AB) will be performed.
The remaining information is focused on part 3.
• Cohort A: Patients (n=7) enrolled in Part 3 Cohort A (which was conducted in parallel to Part 2) received treatment with 1% BPR277 ointment and 0% vehicle administered b.i.d. over a 250 cm2 treatment area for 4 weeks.
• Cohort AA: Patients in Part 3AA will receive 1% BPR277 ointment and 0% vehicle administered b.i.d. over approximately 100 cm2 to up to 500 cm2 treatment area for 4 weeks. Between 4-10 patients are expected to be enrolled.
• Cohort AB: Patients in Part 3AB will receive 1% BPR277 ointment and 0% vehicle administered q.d. (preferentially in the evening) over approximately 100cm2 to up to a 500 cm2 treatment area for 4 weeks. Between 4-10 patients are also expected to be enrolled.

Intervention

Treatment with BPR277.

Study burden and risks

Risk: Adverse effects of study medication.
Burden: Study duration approx. 7 weeks. 6 visits. Duration 2-3 h.
Physical examination 4 times.
Blood draw during 5 visits, 5-20 ml per occasion.
Optional pharmacogenetic blood testing (10 ml).
Pregnancy test (if relevant) 3 times.
Skin tests (tape) 4x
Skin pH measurement 4x.
Skin biopsy 2x + 2 optional (pharmacokinetic substudy).
Stratum corneum sample (each treatment area) 2 times.
Photogrphs of skin lesions 5 times.
ECG 4 times.
Medication diary daily.
Questionnaires severity of symptoms (5x), quality of life (2x), satisfaction with end result (1x).

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

• Male and female patients with Netherton syndrome, 18 to 65 years of age inclusive.
• Confirmed diagnosis of Netherton syndrome (SPINK5 mutation and/or LEKTI deficiency in the skin).
• Total lesional sign score NS (TLSS-NS) of 5-9 for each selected treatment area at baseline.
• Each treatment area must have a minimum of approximately 250 cm2 of lesional skin within a maximum of approximately 1500 cm2. The TLSS-NS values of both treatment areas need to be similar and, if possible, should not differ (±) by more than 1 point between the two areas at baseline.

Exclusion criteria

• History of abnormal skin reactivity to UV light. Unusual exposure to UV light in the previous 3 weeks to study start (screening), including tanning and sun beds.
• Pregnant or nursing (lactating) women.
• Women of child-bearing potential not using acceptable contraceptive methods.
• Recent previous treatment with phototherapy, biological therapy, immunosuppressive agents (see protocol page 62 for details).

Study design

Design

Study phase:	2
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):	22-10-2013
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BPR277
Generic name:	BPR277

Ethics review

Approved WMO Date:	09-07-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-09-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-11-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
Other	clinicaltrials.gov;NCT01428297
EudraCT	EUCTR2011-000917-38-NL
CCMO	NL42450.041.12