



## Clinical trial results:

**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**

### Summary

EudraCT number	2011-000917-38
Trial protocol	DE NL
Global end of trial date	13 February 2014

### Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	08 August 2015

### Trial information

#### Trial identification

Sponsor protocol code	CBPR277X2101
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01428297
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

Notes:

### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 February 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 February 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

There were three parts to this study:

Part 1 : A partially blinded intra-individual, vehicle controlled cohort to demonstrate tolerability (systemic and local) of repeated twice daily applications of BPR277 ointment in healthy volunteers

Part 2 : A double blind, inter-individual vehicle controlled cohort to evaluate tolerability and whether BPR277 1% ointment b.i.d. could maintain a treatment effect induced by topical corticosteroids in Atopic Dermatitis (AD) patients.

Part 3 : A double blind and intra-individual controlled cohorts to assess tolerability and the potential of BPR277 1% ointment (applied b.i.d in Part 3 Cohorts A & AA or q.d in Part 3 Cohort AB) to improve the clinical severity of lesional skin (TLSS-NS) in Netherton Syndrome (ND) patients

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

It is recommended, in particular in Parts 2 and 3A, AA & AB, to use a low potent TCS, such as hydrocortisone 2.5%, for the rest of the body if emollients are not sufficient, but if medically needed the investigator may need to use higher strengths or topical calcineurin inhibitors (pimecrolimus, tacrolimus). If the flare is restricted to areas outside the treatment area, do not apply the rescue medication to the selected treatment area and at least 10cm around.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 May 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United States: 37
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 31
Worldwide total number of subjects	79
EEA total number of subjects	42

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	79
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Study consists of three parts. Healthy volunteers will be recruited for Part 1, subjects with Atopic Dermatitis for Part 2 and subjects with Netherton Syndrome (NS) for Part 3.

### Pre-assignment

Screening details:

Each of the three Parts of the study had it's own unique screening period designed to screen for the appropriate subjects for the treatment period (Part 1 - Healthy Volunteers (HV), Part 2 - Atopic Dermatitis (AD) and Part 3 - Netherton Syndrome (NS).

### Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	HV Part 1 Cohort 1A

Arm description:

For Cohort A an area of 100 cm<sup>2</sup> (10x10 cm) on the volar side of one forearm, including the antecubital fossa, will be treated with the 1% BPR277 ointment and two separate areas of 25 cm<sup>2</sup> (5x5 cm) on the lower back will be treated with either 1% BPR277 ointment or vehicle ointment.

Arm type	Experimental
Investigational medicinal product name	BPR277
Investigational medicinal product code	BPR277
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Subjects in Part 1 Cohort 1A were randomized to one of the following sequences:

- Sequence 1: 1% BPR277 on 100cm<sup>2</sup> forearm + 1% BPR277 on 25cm<sup>2</sup> lower back right side + Vehicle on 25cm<sup>2</sup> lower back left side
- Sequence 2: 1% BPR277 on 100cm<sup>2</sup> forearm + Vehicle on 25cm<sup>2</sup> lower back right side + 1% BPR277 on 25cm<sup>2</sup> lower back left side

<b>Arm title</b>	HV Part 1 Cohort 1B
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Arm description:

For Cohort B an area of 1250 cm<sup>2</sup> of one arm was treated with the 1% BPR277 ointment and two separate areas of 25 cm<sup>2</sup> on the lower back were treated with 0.2% BPR277 ointment or vehicle.

Arm type	Experimental
Investigational medicinal product name	BPR277
Investigational medicinal product code	BPR277
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Subjects in Cohort 1B were randomized to one of the following sequences:

- Sequence 1: 1% BPR277 on 1250cm<sup>2</sup> arm + 0.2% BPR277 on 25cm<sup>2</sup> lower back right side + Vehicle on 25cm<sup>2</sup> lower back left side

- Sequence 2: 1% BPR277 on 1250cm2 arm + Vehicle on 25cm2 lower back right side + 0.2% BPR277 on 25cm2 lower back left side

<b>Arm title</b>	Atopic Dermatitis Part 2 1% BPR277
Arm description: Patients applied 0.5 g b.i.d. of either 1% BPR277 ointment or its vehicle (corresponding to 10 mg/d of BPR277 for the active group) over 4 weeks to a 250 cm2 selected treatment area.	
Arm type	Experimental
Investigational medicinal product name	BPR277
Investigational medicinal product code	BPR277
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

**Dosage and administration details:**

A qualifying 250 cm2 area of skin containing at least 50% AD affected skin (i.e., at least 125 cm2 affected with atopic dermatitis lesions at screening) was chosen. The study drug was applied twice daily (morning and evening) for 4 weeks.

<b>Arm title</b>	Atopic Dermatitis Part 2 Vehicle
Arm description: Patients applied 0.5 g b.i.d. of either 1% BPR277 ointment or its vehicle (corresponding to 10 mg/d of BPR277 for the active group) over 4 weeks to a 250 cm2 selected treatment area.	
Arm type	Experimental
Investigational medicinal product name	BPR277
Investigational medicinal product code	BPR277
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

**Dosage and administration details:**

A qualifying 250 cm2 area of skin containing at least 50% AD affected skin (i.e., at least 125 cm2 affected with atopic dermatitis lesions at screening) was chosen. The study drug was applied twice daily (morning and evening) for 4 weeks.

<b>Arm title</b>	Netherton Syndrome Cohort 3A BID 250 cm2
Arm description: BID 250 cm2 In Cohort 3A, patients were randomly allocated to one of the two following sequences to enable randomization of the location of treatment: <ul style="list-style-type: none"> <li>• Sequence 1: 1% BPR277 b.i.d on Area 1 + Vehicle on Area 2</li> <li>• Sequence 2: Vehicle b.i.d on Area 1+ 1% BPR277 on Area 2</li> </ul>	
Arm type	Experimental
Investigational medicinal product name	BPR277
Investigational medicinal product code	BPR277
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

**Dosage and administration details:**

The patient was instructed on how to apply the study drug (1% BPR277 ointment or vehicle as per randomization). Patient was supervised for the first application to the selected treatment areas on Day 1 to ensure patient did not mix up treatment applications. Patients were dispensed three tubes on Day 1 and 15, and two tubes on Day 8 and 22. The study drug was applied twice daily (morning and evening) for 4 weeks.

<b>Arm title</b>	Netherton Syndrome Cohort 3AA BID 500 cm2
Arm description: BID 500 cm2 In Cohort 3AA, patients were randomly allocated to one of the two following sequences to enable randomization of the location of treatment: <ul style="list-style-type: none"> <li>• Sequence 1: 1% BPR277 b.i.d on Area 1 + Vehicle b.i.d. on Area 2</li> <li>• Sequence 2: Vehicle b.i.d. on Area 1+ 1% BPR277 b.i.d. on Area 2</li> </ul>	
Arm type	Experimental
Investigational medicinal product name	BPR277
Investigational medicinal product code	BPR277
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use
Dosage and administration details: The patient was instructed on how to apply the study drug (1% BPR277 ointment or vehicle as per randomization). Patient was supervised for the first application to the selected treatment areas on Day 1 to ensure patient did not mix up treatment applications. Patients were dispensed three tubes on Day 1 and 15, and two tubes on Day 8 and 22. The study drug was applied twice daily (morning and evening) for 4 weeks.	
<b>Arm title</b>	Netherton Syndrome Cohort 3AB QD 500 cm2

Arm description: QD 500 cm2 In Cohort 3AB, patients were randomly allocated to one of the two following sequences to enable randomization of the location of treatment: <ul style="list-style-type: none"> <li>• Sequence 1: 1% BPR277 q.d. on Area 1 + Vehicle q.d. on Area 2</li> <li>• Sequence 2: Vehicle q.d. on Area 1 + 1% BPR277 q.d. on Area 2</li> </ul>	
Arm type	Experimental
Investigational medicinal product name	BPR277
Investigational medicinal product code	BPR277
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use
Dosage and administration details: In Cohort 3AB patients applied 1% BPR277 ointment once a day (q.d.) over 4 weeks (corresponding to 10 mg/d of BPR277 applied to a surface of approximately 500 cm2) and vehicle similarly.	

<b>Number of subjects in period 1</b>	HV Part 1 Cohort 1A	HV Part 1 Cohort 1B	Atopic Dermatitis Part 2 1% BPR277
Started	6	6	25
Completed	6	6	25
Not completed	0	0	0
Consent withdrawn by subject	-	-	-
Lost to follow-up	-	-	-

<b>Number of subjects in period 1</b>	Atopic Dermatitis Part 2 Vehicle	Netherton Syndrome Cohort 3A BID 250 cm2	Netherton Syndrome Cohort 3AA BID 500 cm2
Started	24	7	5
Completed	23	7	5
Not completed	1	0	0

Consent withdrawn by subject	1	-	-
Lost to follow-up	-	-	-

<b>Number of subjects in period 1</b>	Netherton Syndrome Cohort 3AB QD 500 cm2
Started	6
Completed	5
Not completed	1
Consent withdrawn by subject	-
Lost to follow-up	1

## Baseline characteristics

### Reporting groups

Reporting group title	HV Part 1 Cohort 1A
Reporting group description: For Cohort A an area of 100 cm <sup>2</sup> (10x10 cm) on the volar side of one forearm, including the antecubital fossa, will be treated with the 1% BPR277 ointment and two separate areas of 25 cm <sup>2</sup> (5x5 cm) on the lower back will be treated with either 1% BPR277 ointment or vehicle ointment.	
Reporting group title	HV Part 1 Cohort 1B
Reporting group description: For Cohort B an area of 1250 cm <sup>2</sup> of one arm was treated with the 1% BPR277 ointment and two separate areas of 25 cm <sup>2</sup> on the lower back were treated with 0.2% BPR277 ointment or vehicle.	
Reporting group title	Atopic Dermatitis Part 2 1% BPR277
Reporting group description: Patients applied 0.5 g b.i.d. of either 1% BPR277 ointment or its vehicle (corresponding to 10 mg/d of BPR277 for the active group) over 4 weeks to a 250 cm <sup>2</sup> selected treatment area.	
Reporting group title	Atopic Dermatitis Part 2 Vehicle
Reporting group description: Patients applied 0.5 g b.i.d. of either 1% BPR277 ointment or its vehicle (corresponding to 10 mg/d of BPR277 for the active group) over 4 weeks to a 250 cm <sup>2</sup> selected treatment area.	
Reporting group title	Netherton Syndrome Cohort 3A BID 250 cm <sup>2</sup>
Reporting group description: BID 250 cm <sup>2</sup> In Cohort 3A, patients were randomly allocated to one of the two following sequences to enable randomization of the location of treatment: <ul style="list-style-type: none"> <li>• Sequence 1: 1% BPR277 b.i.d on Area 1 + Vehicle on Area 2</li> <li>• Sequence 2: Vehicle b.i.d on Area 1+ 1% BPR277 on Area 2</li> </ul>	
Reporting group title	Netherton Syndrome Cohort 3AA BID 500 cm <sup>2</sup>
Reporting group description: BID 500 cm <sup>2</sup> In Cohort 3AA, patients were randomly allocated to one of the two following sequences to enable randomization of the location of treatment: <ul style="list-style-type: none"> <li>• Sequence 1: 1% BPR277 b.i.d on Area 1 + Vehicle b.i.d. on Area 2</li> <li>• Sequence 2: Vehicle b.i.d. on Area 1+ 1% BPR277 b.i.d. on Area 2</li> </ul>	
Reporting group title	Netherton Syndrome Cohort 3AB QD 500 cm <sup>2</sup>
Reporting group description: QD 500 cm <sup>2</sup> In Cohort 3AB, patients were randomly allocated to one of the two following sequences to enable randomization of the location of treatment: <ul style="list-style-type: none"> <li>• Sequence 1: 1% BPR277 q.d. on Area 1 + Vehicle q.d. on Area 2</li> <li>• Sequence 2: Vehicle q.d. on Area 1 + 1% BPR277 q.d. on Area 2</li> </ul>	

Reporting group values	HV Part 1 Cohort 1A	HV Part 1 Cohort 1B	Atopic Dermatitis Part 2 1% BPR277
Number of subjects	6	6	25
Age categorical Units: Subjects			
Adults (18-64 years)	6	6	25
Gender categorical Units: Subjects			
Female	3	3	12
Male	3	3	13

Reporting group values	Atopic Dermatitis	Netherton Syndrome	Netherton Syndrome
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	Part 2 Vehicle	Cohort 3A BID 250 cm2	Cohort 3AA BID 500 cm2
Number of subjects	24	7	5
Age categorical Units: Subjects			
Adults (18-64 years)	24	7	5
Gender categorical Units: Subjects			
Female	13	3	1
Male	11	4	4

<b>Reporting group values</b>	Netherton Syndrome Cohort 3AB QD 500 cm2	Total	
Number of subjects	6	79	
Age categorical Units: Subjects			
Adults (18-64 years)	6	79	
Gender categorical Units: Subjects			
Female	3	38	
Male	3	41	

## End points

### End points reporting groups

Reporting group title	HV Part 1 Cohort 1A
Reporting group description: For Cohort A an area of 100 cm <sup>2</sup> (10x10 cm) on the volar side of one forearm, including the antecubital fossa, will be treated with the 1% BPR277 ointment and two separate areas of 25 cm <sup>2</sup> (5x5 cm) on the lower back will be treated with either 1% BPR277 ointment or vehicle ointment.	
Reporting group title	HV Part 1 Cohort 1B
Reporting group description: For Cohort B an area of 1250 cm <sup>2</sup> of one arm was treated with the 1% BPR277 ointment and two separate areas of 25 cm <sup>2</sup> on the lower back were treated with 0.2% BPR277 ointment or vehicle.	
Reporting group title	Atopic Dermatitis Part 2 1% BPR277
Reporting group description: Patients applied 0.5 g b.i.d. of either 1% BPR277 ointment or its vehicle (corresponding to 10 mg/d of BPR277 for the active group) over 4 weeks to a 250 cm <sup>2</sup> selected treatment area.	
Reporting group title	Atopic Dermatitis Part 2 Vehicle
Reporting group description: Patients applied 0.5 g b.i.d. of either 1% BPR277 ointment or its vehicle (corresponding to 10 mg/d of BPR277 for the active group) over 4 weeks to a 250 cm <sup>2</sup> selected treatment area.	
Reporting group title	Netherton Syndrome Cohort 3A BID 250 cm <sup>2</sup>
Reporting group description: BID 250 cm <sup>2</sup> In Cohort 3A, patients were randomly allocated to one of the two following sequences to enable randomization of the location of treatment: <ul style="list-style-type: none"><li>• Sequence 1: 1% BPR277 b.i.d on Area 1 + Vehicle on Area 2</li><li>• Sequence 2: Vehicle b.i.d on Area 1+ 1% BPR277 on Area 2</li></ul>	
Reporting group title	Netherton Syndrome Cohort 3AA BID 500 cm <sup>2</sup>
Reporting group description: BID 500 cm <sup>2</sup> In Cohort 3AA, patients were randomly allocated to one of the two following sequences to enable randomization of the location of treatment: <ul style="list-style-type: none"><li>• Sequence 1: 1% BPR277 b.i.d on Area 1 + Vehicle b.i.d. on Area 2</li><li>• Sequence 2: Vehicle b.i.d. on Area 1+ 1% BPR277 b.i.d. on Area 2</li></ul>	
Reporting group title	Netherton Syndrome Cohort 3AB QD 500 cm <sup>2</sup>
Reporting group description: QD 500 cm <sup>2</sup> In Cohort 3AB, patients were randomly allocated to one of the two following sequences to enable randomization of the location of treatment: <ul style="list-style-type: none"><li>• Sequence 1: 1% BPR277 q.d. on Area 1 + Vehicle q.d. on Area 2</li><li>• Sequence 2: Vehicle q.d. on Area 1 + 1% BPR277 q.d. on Area 2</li></ul>	
Subject analysis set title	AD PD Analysis Set - BPR277
Subject analysis set type	Sub-group analysis
Subject analysis set description: All subjects with any evaluable PD parameter data and without protocol deviations impacting the PD analysis were included in the PD analysis sets. In part 2 however there was a "2nd PD population" excluding one patient who received the incorrect treatment.	
Subject analysis set title	AD PD Analysis Set - Vehicle
Subject analysis set type	Sub-group analysis
Subject analysis set description: All subjects with any evaluable PD parameter data and without protocol deviations impacting the PD analysis were included in the PD analysis sets. In part 2 however there was a "2nd PD population" excluding one patient who received the incorrect treatment.	
Subject analysis set title	NS PD BPR277 b.i.d.
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Protocol deviations were reported for 2 subjects in Cohort 3A which excluded them from the PD analysis.

Subject analysis set title	NS PD Vehicle b.i.d.
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Protocol deviations were reported for 2 subjects in Cohort 3A which excluded them from the PD analysis.

Subject analysis set title	NS PD BPR277 q.d.
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Cohort AB for q.d. dosing with 1 patient not included because lost to follow up.

Subject analysis set title	NS PD Vehicle q.d.
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Cohort AB for q.d. dosing with 1 patient not included because lost to follow up.

Subject analysis set title	NS Total BPR277
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who received BPR277 from all 3 cohorts minus 2 patients with protocol deviations and 1 lost to follow-up.

Subject analysis set title	NS Total Vehicle
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who received Vehicle from all 3 cohorts minus 2 patients with protocol deviations and 1 lost to follow-up.

**Primary: Demonstrate tolerability (systemic and local) of repeated twice daily topical applications of BPR277 in adult subjects, and in patients with AD and NS (all parts).**

End point title	Demonstrate tolerability (systemic and local) of repeated twice daily topical applications of BPR277 in adult subjects, and in patients with AD and NS (all parts). <sup>[1][2]</sup>
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End point description:

Refer to safety section.

End point type	Primary
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End point timeframe:

Adverse events were collected from first dose of study medication until resolution. Serious Adverse Events were collected from signing of Informed Consent through 30 days post drug.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only summary statistics.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only arms of comparable dose were included as per planned analysis.

End point values	HV Part 1 Cohort 1A	Atopic Dermatitis Part 2 1% BPR277	Atopic Dermatitis Part 2 Vehicle	Netherton Syndrome Cohort 3A BID 250 cm2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 <sup>[3]</sup>	0 <sup>[4]</sup>	0 <sup>[5]</sup>	0 <sup>[6]</sup>
Units: Incidence of Adverse Events				

Notes:

[3] - Refer to Safety Section.

[4] - Refer to Safety Section

[5] - Refer to Safety Section.

[6] - Refer to Safety Section.

End point values	Netherton Syndrome Cohort 3AA BID 500 cm2	Netherton Syndrome Cohort 3AB QD 500 cm2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[7]</sup>	0 <sup>[8]</sup>		
Units: Incidence of Adverse Events				

Notes:

[7] - Refer to Safety Section.

[8] - Refer to Safety Section

## Statistical analyses

No statistical analyses for this end point

**Primary: Part 2, evaluate whether BPR277 ointment b.i.d. maintained a treatment effect, induced by topical corticosteroids, by assessing that the TLSS increase was at most half of that of its vehicle in AD patients.**

End point title	Part 2, evaluate whether BPR277 ointment b.i.d. maintained a treatment effect, induced by topical corticosteroids, by assessing that the TLSS increase was at most half of that of its vehicle in AD patients.
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End point description:

The Total Lesional Sign Score (TLSS) was assessed at each week for the treatment areas. For each patient the slope of the score versus time curve was calculated in order to estimate the rate of increase of score with time, i.e. the rate of relapse.

End point type	Primary
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End point timeframe:

4 weeks

End point values	AD PD Analysis Set - BPR277	AD PD Analysis Set - Vehicle		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	22		
Units: Rate of increase of TLSS				
arithmetic mean (standard error)	0.13 (± 0.029)	0.08 (± 0.029)		

## Statistical analyses

Statistical analysis title	Treatment Comparison
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Statistical analysis description:

A positive sign of efficacy was considered to be a difference of at least 0.5 in the slope of the score versus time curve between BPR277 and vehicle with at least 70% level of proof. Additionally there should be evidence that there was some difference between BPR277 and vehicle with at least 90% level of proof.

Comparison groups	AD PD Analysis Set - BPR277 v AD PD Analysis Set - Vehicle
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Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other <sup>[9]</sup>
P-value	> 0.1 <sup>[10]</sup>
Method	Bayesian credibility interval
Parameter estimate	Slope
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	0.15

Notes:

[9] - The probability is calculated from the simulated posterior distributions of  $\theta$  (BPR277) and  $\theta$  (Vehicle) which are constructed from Bayesian analysis with a non-informative Jeffery's prior distribution.

95% BCI = 95% Bayesian credibility interval

[10] - Vehicle p = 0.1% BPR277 p = 7.8%

The probability is calculated from the simulated posterior distributions of  $\theta$  (1% BPR277) and  $\theta$  (Vehicle) which are constructed from Bayesian analysis with a non-informative Jeffery's prior distribution.

### Primary: Netherton Syndrome Summary of clinical response (2 points)

End point title	Netherton Syndrome Summary of clinical response (2
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End point description:

Lesions treated with BPR277 and with vehicle were evaluated separately. A lesion was considered as having a clinical response if the reduction in TLSS-NS score at the end of treatment compared to baseline was  $\geq 2$  points.

Posterior probability > 0.5; 95% BCI = 95% Bayesian credibility interval.

End point type	Primary
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End point timeframe:

At week 4.

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The summary of the treatments is presented. Posterior probability > 0.5; 95% BCI = 95% Bayesian credibility interval was used.

End point values	NS PD BPR277 b.i.d.	NS PD Vehicle b.i.d.	NS PD BPR277 q.d.	NS PD Vehicle q.d.
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	10	5	5
Units: Responders				
number (not applicable)				
Responders	6	0	1	1
Responders (percent)	60	0	20	20
Pr ( $p \geq 0.5$   data)	0.739	0.001	0.08	0.08
95% BCI Lower	0.302	0	0.016	0.016
95% BCI Upper	0.852	0.182	0.622	0.622

End point values	NS Total	NS Total		
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	BPR277	Vehicle		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: Responders				
number (not applicable)				
Responders	7	1		
Responders (percent)	47	7		
Pr ( $p \geq 0.5$   data)	0.398	0.001		
95% BCI Lower	0.236	0.005		
95% BCI Upper	0.708	0.26		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Summary of BPR277 exposure data AUC0-24h,ss (h\*ng/mL)

End point title	Summary of BPR277 exposure data AUC0-24h,ss (h*ng/mL) <sup>[12]</sup>
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End point description:

- Evaluate systemic steady state pharmacokinetics in human after topical administration of BPR277 ointment.
- Determine BPR277 concentrations in the skin and the urinary excretion of BPR277 after repeated topical administration of BPR277 ointment in adult HV subjects and patients with AD and NS (for NS only in Part 3A).
- Assess the ability of repeated topical applications of BPR277 to restore the skin barrier function in AD and NS patients as demonstrated by the change in Transepidermal Water

Reported values of <LLOQ as 0. Reported ~ 1 as 1.

End point type	Secondary
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End point timeframe:

Part 1

- Days 1, 3, 5, 8, and 11 predose, day 22
- Day 14: pre-dose and 1, 3, 7, and 12 h after the morning dose

Part 2 and Cohort 3A

- Days 1, 8, 15 and 22 predose, day 43
- Day 29: pre-dose and 1, 3, 7, and 12 h after the morning dose

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only arms of comparable dose were included (250 cm<sup>2</sup>). Vehicle and 500 cm<sup>2</sup> were excluded.

Secondary endpoint.

End point values	HV Part 1 Cohort 1A	HV Part 1 Cohort 1B	AD PD Analysis Set - BPR277	NS PD BPR277 b.i.d.
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	23	10
Units: h*ng/mL				
number (not applicable)				
AUC0-24h,ss (h*ng/mL)	0	0	1	1

## Statistical analyses

No statistical analyses for this end point

### Secondary: Summary of BPR277 exposure data - Median skin concentration (ng/g)

End point title	Summary of BPR277 exposure data - Median skin concentration (ng/g) <sup>[13]</sup>
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End point description:

- Evaluate systemic steady state pharmacokinetics in human after topical administration of BPR277 ointment.
- Determine BPR277 concentrations in the skin and the urinary excretion of BPR277 after repeated topical administration of BPR277 ointment in adult HV subjects and patients with AD and NS (for NS only in Part 3A).
- Assess the ability of repeated topical applications of BPR277 to restore the skin barrier function in AD and NS patients as demonstrated by the change in Transepidermal Water

End point type	Secondary
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End point timeframe:

Part 1

- Days 1, 3, 5, 8, and 11 predose, day 22
- Day 14: pre-dose and 1, 3, 7, and 12 h after the morning dose

Part 2 and Cohort 3A

- Days 1, 8, 15 and 22 predose, day 43
- Day 29: pre-dose and 1, 3, 7, and 12 h after the morning dose

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Secondary endpoint.

End point values	HV Part 1 Cohort 1A	HV Part 1 Cohort 1B	AD PD Analysis Set - BPR277	NS PD BPR277 b.i.d.
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	23	10
Units: ng/g				
number (not applicable)				
Median skin concentration	1050	1070	4870	1810

## Statistical analyses

No statistical analyses for this end point

### Secondary: Summary of BPR277 exposure data - Median fraction of dose in urine (%)

End point title	Summary of BPR277 exposure data - Median fraction of dose in urine (%) <sup>[14]</sup>
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End point description:

- Evaluate systemic steady state pharmacokinetics in human after topical administration of BPR277 ointment.
- Determine BPR277 concentrations in the skin and the urinary excretion of BPR277 after repeated topical administration of BPR277 ointment in adult HV subjects and patients with AD and NS (for NS only in Part 3A).
- Assess the ability of repeated topical applications of BPR277 to restore the skin barrier function in AD and NS patients as demonstrated by the change in Transepidermal Water Values
- <LLOQ were reported as 0 and analyzed as 0 for Median fraction of dose in urine.

End point type	Secondary
End point timeframe:	
Part 1 • Days 1, 3, 5, 8, and 11 predose, day 22 • Day 14: pre-dose and 1, 3, 7, and 12 h after the morning dose. Part 2 and Cohort 3A • Days 1, 8, 15 and 22 predose, day 43 • Day 29: pre-dose and 1, 3, 7, and 12 h after the morning dose	

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only arms of comparable dose were included as per planned analysis.

End point values	HV Part 1 Cohort 1A	HV Part 1 Cohort 1B	AD PD Analysis Set - BPR277	NS PD BPR277 b.i.d.
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	6	6	23	10
Units: Percent				
median (full range (min-max))				
Median fraction of dose in urine (%)	0 (0 to 0.015)	0 (0 to 0.00199)	0.011 (0 to 0.169)	0.001 (0 to 0.042)

## Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic
<b>Dictionary used</b>	
Dictionary name	MedDRA
Dictionary version	16.0
<b>Reporting groups</b>	
Reporting group title	Part 1 - Cohort A
Reporting group description: Part 1 - Cohort A	
Reporting group title	Part 2 - 1% BPR277
Reporting group description: Part 2 - 1% BPR277	
Reporting group title	Part 3 - Cohort AB
Reporting group description: Part 3 - Cohort AB	
Reporting group title	Part 3 - Cohort A
Reporting group description: Part 3 - Cohort A	
Reporting group title	Part 3 - Cohort AA
Reporting group description: Part 3 - Cohort AA	
Reporting group title	Part 2 - Vehicle
Reporting group description: Part 2 - Vehicle	

Serious adverse events	Part 1 - Cohort A	Part 2 - 1% BPR277	Part 3 - Cohort AB
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Part 3 - Cohort A	Part 3 - Cohort AA	Part 2 - Vehicle
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 5 (0.00%)	0 / 24 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Part 1 - Cohort A	Part 2 - 1% BPR277	Part 3 - Cohort AB
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	9 / 25 (36.00%)	4 / 6 (66.67%)
Investigations			
Blood uric acid increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Procedural site reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sports injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Burning sensation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Migraine			
subjects affected / exposed	0 / 6 (0.00%)	0 / 25 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 6 (16.67%)	2 / 25 (8.00%)	1 / 6 (16.67%)
occurrences (all)	1	3	1
General disorders and administration			

site conditions Malaise subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 25 (0.00%) 0	1 / 6 (16.67%) 1
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 25 (0.00%) 0	0 / 6 (0.00%) 0
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 25 (0.00%) 0	0 / 6 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 25 (0.00%) 0	0 / 6 (0.00%) 0
Skin and subcutaneous tissue disorders Dermatitis subjects affected / exposed occurrences (all)  Dermatitis atopic subjects affected / exposed occurrences (all)  Ingrowing nail subjects affected / exposed occurrences (all)  Pruritus subjects affected / exposed occurrences (all)  Erythema subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0  0 / 6 (0.00%) 0  0 / 6 (0.00%) 0  0 / 6 (0.00%) 0  0 / 6 (0.00%) 0	0 / 25 (0.00%) 0  3 / 25 (12.00%) 4  0 / 25 (0.00%) 0  1 / 25 (4.00%) 1  0 / 25 (0.00%) 0	0 / 6 (0.00%) 0  0 / 6 (0.00%) 0  1 / 6 (16.67%) 1  0 / 6 (0.00%) 0  0 / 6 (0.00%) 0
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)  Myalgia	0 / 6 (0.00%) 0  0 / 6 (0.00%) 0	0 / 25 (0.00%) 0  0 / 25 (0.00%) 0	0 / 6 (0.00%) 0  0 / 6 (0.00%) 0

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 25 (0.00%) 0	0 / 6 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 25 (4.00%) 1	0 / 6 (0.00%) 0
Infections and infestations Incision site infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 25 (0.00%) 0	2 / 6 (33.33%) 4
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	6 / 25 (24.00%) 7	0 / 6 (0.00%) 0
Otitis media subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 25 (0.00%) 0	1 / 6 (16.67%) 1
Rhinitis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 25 (4.00%) 1	0 / 6 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 25 (0.00%) 0	0 / 6 (0.00%) 0
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 25 (0.00%) 0	1 / 6 (16.67%) 1

<b>Non-serious adverse events</b>	Part 3 - Cohort A	Part 3 - Cohort AA	Part 2 - Vehicle
Total subjects affected by non-serious adverse events subjects affected / exposed	6 / 7 (85.71%)	3 / 5 (60.00%)	7 / 24 (29.17%)
Investigations Blood uric acid increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 5 (20.00%) 1	0 / 24 (0.00%) 0
Injury, poisoning and procedural complications Procedural site reaction subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 5 (20.00%) 1	0 / 24 (0.00%) 0

Contusion subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 5 (20.00%) 1	0 / 24 (0.00%) 0
Sports injury subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 5 (20.00%) 1	0 / 24 (0.00%) 0
Nervous system disorders Burning sensation subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0	0 / 24 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 5 (0.00%) 0	0 / 24 (0.00%) 0
Migraine subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0	0 / 24 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 5 (20.00%) 2	2 / 24 (8.33%) 2
General disorders and administration site conditions Malaise subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 5 (0.00%) 0	0 / 24 (0.00%) 0
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 5 (20.00%) 1	0 / 24 (0.00%) 0
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0	0 / 24 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Rhinoirrhoea subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 5 (0.00%) 0	1 / 24 (4.17%) 1
Skin and subcutaneous tissue disorders			

Dermatitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Dermatitis atopic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 5 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Ingrowing nail			
subjects affected / exposed	0 / 7 (0.00%)	0 / 5 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Erythema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 5 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Incision site infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 5 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 7 (28.57%)	0 / 5 (0.00%)	3 / 24 (12.50%)
occurrences (all)	2	0	3
Otitis media			
subjects affected / exposed	0 / 7 (0.00%)	0 / 5 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Rhinitis			

subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 7 (0.00%)	0 / 5 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 January 2012	<p>For Part 2 conducted in AD patients:</p> <ul style="list-style-type: none"><li>• The location options for the treatment area were expanded. Additional particular body locations were permissible to ensure a broad AD population was eligible for the study.</li><li>• The TEWL assessment was no longer required at the antecubital fossa location, due to the expansion of treatment area location options. The TEWL was now required within the treatment area and outside the treatment area.</li><li>• An additional 2 day extension was allowed for the TCS pre-treatment period to permit greater flexibility in scheduling patient visits.</li><li>• A global clinical assessment (IGA-WB) on the whole body (minus the study treatment area) was included to follow the evolution of the overall disease outside the treated area.</li></ul> <p>For Parts 2 and 3 of the study, conducted in patients:</p> <ul style="list-style-type: none"><li>• The unblinding procedure during exploratory interim analyses was clarified, including a list of team members who might have been unblinded at these times.</li><li>• The conditions (i.e. temperature, humidity, and standard deviation) of the TEWL assessment were clarified / updated.</li><li>• The time window for the skin tape stripping procedure and PK blood sampling was clarified.</li></ul>
25 July 2012	<ul style="list-style-type: none"><li>• Addition of two new cohorts (B &amp; C) to Part 3 of the study in NS patients in order to gather additional safety and efficacy data when BPR277 ointment was applied over larger areas of the skin surface (approximately 1500 cm<sup>2</sup>) at different concentrations (vehicle, 0.2% and 1%) and treatment regimens (b.i.d. and q.d.).</li><li>• Biomarker data would continue to be gathered in these additional cohorts, including tape strips and skin biopsies to understand more about BPR277's mechanism of action. A pharmacogenetic blood sample was also proposed for all patients in Part 3, which was optional in Cohort A.</li><li>• As NS is a rare disease and the topical application of BPR277 ointment over 4 weeks was considered well tolerated, it was proposed that NS patients who participated in Part 3A be allowed to be screened for entry into either of the newly added cohorts provided that &gt;6 months had elapsed since their last application of BPR277.</li></ul>



25 February 2013	<ul style="list-style-type: none"> <li>• The study design was adjusted to take an approach that confirmed previous results from the first cohort in Netherton syndrome and included an additional dose-regimen (b.i.d and q.d) aspect. This modified study design meant that the 0.2% BPR277 formulation would not be investigated, as originally planned in amendment 3. Instead, the 1% BPR277 formulation (versus vehicle) was studied when applied on up to 500cm<sup>2</sup> of lesional skin using b.i.d and q.d dosing regimens.</li> <li>• Additional biomarkers (such as the RNA-based assessment in skin biopsy) and by using novel, non-invasive techniques including epidermal barrier and skin lipid analysis were introduced to further explore the mechanism of action of this kallikrein 7 inhibitor.</li> </ul>
20 June 2013	Testing for the presence of the SPINK5 gene mutation and/or LEKTI deficiency in the skin was incorporated, in order to confirm the diagnosis of Netherton syndrome.

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported