NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharma AG

Generic Drug Name

BPR277

Trial Indication(s)

Healthy volunteers, Atopic Dermatitis (AD), Netherton Syndrome (NS)

Protocol Number

CBPR277X2101

Protocol Title

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

Clinical Trial Phase

I/IIa

Phase of Drug Development

IIa

Study Start/End Dates

25-May-11 to 13-Feb-14

Reason for Termination (If applicable)

NA

Study Design/Methodology

This was a multicenter, double-blind, randomized placebo-controlled study to investigate the safety, tolerability, and preliminary efficacy of BPR277. The study consisted of 3 parts, with part 3 further divided into two separate parts, 3A, and 3AA/AB. In Part 1 BPR277 was administered to healthy volunteers. This study part was a partially blinded intra-individual, vehicle controlled, single center, FIH study in two subsequent cohorts of 6 subjects each. In the first cohort (cohort A), 16 subjects received active and vehicle on two separate areas on the lower back for 2 weeks. In addition, active was applied b.i.d. on skin of the forearm.

Part 2 was a double blind, vehicle controlled, multicenter study in two parallel groups of 24 adult AD patients. After an initial treatment with a topical corticosteroid on a selected area, patients applied either BPR277 or its vehicle b.i.d. over 4 weeks. In total 49 AD patients were included in the study with 24 patients receiving active drug
Part 3 was a double blind, vehicle controlled, multicenter study in 3 cohorts of NS patients with confirmed diagnosis. Patients applied the study medications b.i.d. to the two treatment areas for 4 weeks. 7 NS patients were included in Part 3A. Part 3AA and AB with a total of 11 NS patients included, two dosage regimen of BPR277 were tested and compared to vehicle.

Centers

17 centers in United States, Germany, France, and Netherlands

Publication

None

Objectives:

Primary objective:

- 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).
- In 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.
- In Part 3A, assess the potential of BPR277 ointment b.i.d. to improve the clinical severity of lesional skin (TLSS-NS) in the majority of NS patients at end of treatment versus baseline of ≥ 2 points.
- In Part 3 (Cohorts AA & AB), assess the potential of BPR277 (ointment, applied either b.i.d. or q.d.) to improve the clinical severity of lesional skin (TLSS-NS) in NS patients.

Secondary objectives:

- 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).

Test Product (s), Dose(s), and Mode(s) of Administration

BPR277 was provided as ointment with matching vehicles ointments for topical administration.

Statistical Methods

Data for each part of the study was analyzed separately.

Analysis sets: All subjects who received at least one dose of study drug were included in the safety analysis population. All subjects with evaluable PK parameter data were included in the PK analysis set. All subjects with any evaluable PD parameter data were included in the PD analysis set. Subjects and lesions were analyzed according to the treatment received.

All end-points, including primary, were summarized using descriptive statistics together and presented graphically. Summaries are presented by time and treatment. Additionally, A mixed model was fitted for TLSS vs treatment*day interaction. Plasma and urine concentrations were expressed in mass per volume units. All concentrations below the lower limit of quantification (LLOQ) or missing data were labeled as such in the concentration data listings. Concentrations below LLOQ were treated as zero in summary statistics and for the calculation of pharmacokinetic parameters.

The relationship between the skin exposure to BPR277 and biomarker readouts in comparable biopsies as well as BPR277 concentrations in tape strips and biomarker readouts in comparable tape strips were explored via graphical presentation.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion criteria:

Healthy volunteers:

- Healthy male and female subjects of non-childbearing potential, 18 to 65 years of age inclusive and in good health

Atopic dermatitis patients:

- Male and female subjects, 18 to 65 years of age inclusive and having passed screening examinations
- Presence of atopic dermatitis confirmed by Itchy skin condition in the past 12 months (must have)
  Plus three or more of the following:
  - History of involvement of the skin creases
  - Personal history of asthma or hay fever
  - History of generally dry skin in the past year
  - Onset before age of 2 years
  - Visible flexural dermatitis
- Diagnosis of at least moderate atopic dermatitis by the IGA and a minimum target area (right or left) situated on the forearm including the antecubital fossa with a corresponding baseline total lesional sign score (TLSS)

Netherton syndrome patients:

- Patients with Netherton syndrome, male and female subjects, 18 to 65 years of age inclusive and having passed screening examinations
- Confirmed diagnosis of Netherton syndrome (SPINK5 mutation or LEKTI deficiency in the skin).
- Minimum total lesional sign score NS (TLSS-NS) of 5-9 for two selected target areas at baseline. The TLSS-NS values need to be similar between the two areas at baseline.

Key Exclusion criteria:

Healthy volunteers:

- History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes or history of serious allergic reaction.
- Use of any prescription drugs, herbal supplements, within four (4) weeks prior to initial dosing, and/or over-the-counter (OTC) medication, dietary supplements (vitamins included) within two (2) weeks prior to initial dosing.

Atopic dermatitis patients:

- History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes or history of serious allergic reaction.
- 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 must use highly effective contraception (as further defined in study protocol)
- Use of topical prescription treatment for eczema within 1 week prior to initial dosing of topical corticosteroids (TCS).
- Recent previous treatment with systemic treatment including phototherapy. A washout period will be required for such patients to be eligible to participate in the trial.

Netherton syndrome patients:

- History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes or history of serious allergic reaction.
- 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 must use highly effective contraception (as further defined in study protocol)
- Use of topical prescription treatment within 2 week prior to initial dosing of study drug.
- Recent previous treatment with systemic treatment. A washout period will be required for such patients to be eligible to participate in the trial.

Participant Flow Table

Subject disposition Part 2

	BPR277 N=25 n (%)	Vehicle N=24 n (%)	Total N=49 n (%)
Subjects			
Randomized	25 (100)	24 (100)	49 (100)
Completed pre-treatment period	25 (100)	24 (100)	49 (100)
Completed study period	25 (100)	23 (96)	48 (98)
Discontinued	0	1 (4)	1 (2)
Main cause of discontinuation			
Subject withdrew consent	0	1 (4)	1 (2)

Subject disposition Part 3

	Cohort A N=7 n (%)	Cohort AA N=5 n (%)	Cohort AB N=6 n (%)	Total N=18 n (%)
Subjects				
Randomized	7 (100)	5 (100)	5 (83)	17 (94)
Discontinued	0	0	1 (17)	1 (6)
Main cause of discontinuation				
Lost to follow-up	0	0	1 (17)	1 (6)

Number (percent) of subjects in the analysis sets Part 1

All subjects enrolled in Part 1 of the study were included in the PK, PD and safety analysis sets.

Number (percent) of subjects in the analysis sets Part 2

Population	BPR277 N=25 n (%)	Vehicle N=24 n (%)	Total N=49 n (%)
Subjects randomized	25 (100)	24 (100)	49 (100)
Safety analysis set	25 (100)	24 (100)	49 (100)
PK analysis set	23 (92)	23 (96)	46 (94)
PD analysis set	23 (92)	23 (96)	46 (94)

Number (percent) of subjects in the analysis sets Part 3

All eighteen NS patients enrolled in Part 3 of the study were included in the safety analysis set. Two patients were excluded from the PK and PD analysis sets

Baseline Characteristics

Demographic summary by cohort in Part 1 (Safety analysis set)

		Cohort A N=6	Cohort B N=6	Total N=12
Age (years)	Mean (SD)	43 (12.9)	43 (17.4)	43 (14.6)
	Range	29, 60	20, 61	20, 61
Gender – n (%)	Male	3 (50%)	3 (50%)	6 (50%)
	Female	3 (50%)	3 (50%)	6 (50%)
Race – n (%)	Caucasian	6 (100%)	6 (100%)	12 (100%)
Weight (kg)	Mean (SD)	78.4 (8.87)	76.8 (17.40)	77.6 (13.19)
	Range	65.9, 89.2	59.5, 105.4	59.5, 105.4
Height (cm)	Mean (SD)	172 (11.4)	168 (10.5)	170 (10.7)
	Range	154, 183	153, 180	153, 183
BMI (kg/m^2)	Mean (SD)	26.5 (2.84)	27.1 (4.68)	26.8 (3.70)
	Range	23.0, 30.9	23.1, 33.6	23.0, 33.6

BMI = body mass index

Demographic summary by cohort for AD patients in Part 2 (Safety analysis set)

		BPR277 N=25	Vehicle N=24	Total N=49
Age (years)	Mean (SD)	39 (13.2)	32 (12.1)	35 (13.1)
	Range	19, 61	18, 64	18, 64
Gender – n (%)	Male	13 (52%)	11 (46%)	24 (49%)
	Female	12 (48%)	13 (54%)	25 (51%)
Race – n (%)	Caucasian	22 (88%)	17 (71%)	39 (80%)
	Black	1 (4%)	4 (17%)	5 (10%)
	Asian	1 (4%)	2 (8%)	3 (6%)
	Other	1 (4%)	1 (4%)	2 (4%)
Weight (kg)	Mean (SD)	77.6 (16.32)	76.8 (18.57)	77.2 (17.28)
	Range	50.9, 107.4	50.0, 115.0	50.0, 115.0
Height (cm)	Mean (SD)	170 (9.8)	170 (13.0)	170 (11.4)
	Range	147, 190	150, 198	147, 198
BMI (kg/m^2)	Mean (SD)	26.7 (4.56)	26.4 (4.80)	26.6 (4.64)
	Range	17.8, 35.1	18.5, 38.0	17.8, 38.0

BMI = body mass index

Demographic summary for all NS patients - Part 3

		Cohort A N=7	Cohort AA N=5	Cohort AB N=6	Total N=18
Age (years)	Mean (SD)	25 (9.5)	33 (14.6)	26 (9.2)	27 (11.0)
	Range	18, 45	19, 52	18, 39	18, 52
Gender - n (%)	Male	4 (57%)	4 (80%)	3 (50%)	11 (61%)
	Female	3 (43%)	1 (20%)	3 (50%)	7 (39%)
Race - n (%)	Caucasian	7 (100%)	5 (100%)	5 (83%)	17 (94%)
	Other	0	0	1 (17%)	1 (6%)
Weight (kg)	Mean (SD)	73.3 (7.51)	67.2 (7.51)	76.6 (10.19)	72.7 (9.70)
	Range	59.1, 83.0	52.1, 83.3	58.9, 88.9	52.1, 88.9
Height (cm)	Mean (SD)	167 (3.5)	164 (10.3)	161 (8.1)	164 (7.5)
	Range	163, 172	152, 178	152, 173	152, 178
BMI (kg/m^2)	Mean (SD)	26.3 (3.06)	24.8 (3.00)	29.7 (3.10)	27.0 (3.51)
	Range	21.7, 31.1	20.4, 28.1	25.3, 33.7	20.4, 33.7

Summary of Efficacy

Primary Outcome Result(s)

TLSS for Part 2:

Results of the statistical analysis of rate of change in TLSS for AD patients (Part 2) over time (PD analysis set)

		Rate of increase (change in TLSS/day)		Treatment comparison θ(Vehicle)- θ(BPR277) (95% BCI)	Posterior probability of Pr(θ(Vehicle)- θ(BPR277))	
Patient	Treatment	N	Mean (SE)		>0.5	>0
AD	BPR277	23	0.13 (0.029)	-0.40 (-0.94, 0.15)	0.1%	7.8%
	Vehicle	22	0.08 (0.029)			

θ = mean slope of the score versus time curve

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

95% BCI = 95% Bayesian credibility interval

Clinical Efficacy for Part 3
Summary of the statistical analysis of clinical response (2 points) for NS patients at week 4 (PD analysis set)

Treatment	N	Responders	Pr (p≥0.5|data)*	95% BCI
BPR277 b.i.d.	10	6 (60%)	0.739	0.302, 0.852
Vehicle	10	0	<0.0001	0.000, 0.182
BPR277 q.d.	5	1 (20%)	0.080	0.016, 0.622
Vehicle	5	1 (20%)	0.080	0.016, 0.622
Total BPR277	15	7 (47%)	0.398	0.236, 0.708
Vehicle	15	1 (7%)	0.0001	0.005, 0.260

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

Secondary Outcome Result(s)

PK/PD endpoints:
Summary of BPR277 exposure data

Study Part	AUC0-24h,ss (h*ng/mL)	Median skin concentration (ng/g)	Median fraction of dose in urine (%)
1A	All samples < LLOQ	1050	Mostly < LLOQ
1B	All but 2 samples < LLOQ	1070	0.000108
2	~ 1	4870	0.0113
3A	~ 1	1810	0.00128

Summary of Safety
Safety Results
Incidence of AEs by primary system organ class in Part 1 (Safety analysis set) - n (percent) of patients (Safety analysis set)

	Cohort A N=6 n (%)	Cohort B N=6 n (%)
Subjects with AE(s)	3 (50.0)	0 (0.0)
Primary system organ class		
Respiratory, thoracic and mediastinal disorders	1 (17.0)	0 (0.0)
Nervous system disorders	1 (17.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (17.0)	0 (0.0)

Under one group, a subject with multiple occurrences of an adverse event is counted only once in the AE category. Under one group, a subject with multiple adverse events within a body system is counted only once in the total row.
N = number of subjects studied. n = number of subjects with at least one AE in the category
only adverse events occurring at or after first drug intake are included.

Incidence of AEs by primary system organ class experienced by greater or equal 2 patients in Part 2 (Safety analysis set)

	BPR277 N=25 n (%)	Vehicle N=24 n (%)	Total Treated N=49 n (%)
Subjects with AE(s)	15 (60.0)	12 (50.0)	27 (55.0)
Primary system organ class			
Infections and infestations	11 (44.0)	5 (21.0)	16 (33.3)
Skin and subcutaneous tissue disorders	4 (16.0)	2 (8.0)	6 (12.0)
Respiratory, thoracic and mediastinal disorders	2 (10.0)	2 (20.0)	5 (10.3)
Nervous system disorders	1 (4.0)	3 (30.0)	4 (8.0)
Gastrointestinal disorders	2 (8.0)	2 (8.0)	4 (8.0)
General disorders and administration site conditions	2 (8.0)	1 (4.0)	3 (6.0)
Musculoskeletal and connective tissue disorders	1 (4.0)	2 (8.0)	3 (6.0)

Under one group, a subject with multiple occurrences of an adverse event is counted only once in the AE category. Under one group, a subject with multiple adverse events within a body system is counted only once in the total row.
N = number of subjects studied. n = number of subjects with at least one AE in the category
only adverse events occurring at or after first drug intake are included.

Incidence of AEs by primary system organ class and preferred term in Part 3 (Safety analysis set)

	Cohort A N= 7 n (%)	Cohort AA N=5 n (%)	Cohort AB N=6 n (%)
Subjects with AE(s)	6 (86.0)	3 (60.0)	6 (67.0)
Primary system organ class			
Infections and infestations	3 (43.0)	1 (20)	3 (50.0)
Nervous system disorders	2 (29.0)	1 (20.0)	2 (33.3)
Skin and subcutaneous tissue disorders	2 (29.0)	1 (20.0)	1 (17.0)
Injury, poisoning and procedural complications	0 (0.0)	3 (60.0)	0 (0.0)
Immune system disorders	0 (0.0)	1 (20.0)	0 (0.0)
Eye disorders	1 (14.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	1 (17.0)
Musculoskeletal and connective tissue disorders	1 (14.0)	1 (14.0)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	1 (17.0)
Metabolism & nutrition disorders	0 (0.0)	0 (0.0)	1 (17.0)

Under one group, a subject with multiple occurrences of an adverse event is counted only once in the AE category. Under one group, a subject with multiple adverse events within a body system is counted only once in the total row.
N = number of subjects studied. n = number of subjects with at least one AE in the category
only adverse events occurring at or after first drug intake are included.

Conclusion:

• BPR277 ointment was well tolerated in both diseased (AD & NS) and normal skin (HV, from Part 1 of the study) and no tolerability or other safety concern emerged.

•No positive treatment effect was seen in AD patients after treatment of 1% BPR277 for 4 weeks

• Although treated for only 4 weeks, 7 out of 15 NS patients who were treated per protocol showed a clinical response from baseline to BPR277 and at least a 2 point difference versus vehicle.

• Systemic exposure was very low after treatment with BPR277 ointment.

• Plasma and urine data suggest that permeation of BPR277 through diseased skin may be 1-2 orders of magnitude higher than through healthy skin.

• Skin exposure data suggest that twice daily dosing leads to higher skin exposure compared to once daily application on diseased skin.

Date of Clinical Trial Report

12-Dec-2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

13-Feb-2015

Date of Latest Update

Reason for Update