Sponsor Novartis
Generic Drug Name BFH772
Therapeutic Area of Trial Psoriasis
Approved Indication Investigational
Study Number CBFH772A2201
Title A single center, phase I, partially blinded, placebo-controlled, first-in-man study to evaluate the safety, tolerability and Proof of Mechanism (PoM) of a single administration of BFH772 in healthy volunteers, and Proof of Concept (PoC) study to evaluate the safety, tolerability, and pharmacodynamics of multiple topical administrations of BFH772 in patients with psoriasis
Phase of Development Phase I
Study Start/End Dates 17Dec2008/02Feb/2010
Study Design/Methodology Single center, randomized, partially blinded, placebo-controlled safety and tolerability study of two different formulations (cream and ointment) of 0.2% and 1% and placebo of BFH772: Single dose in healthy volunteers in part 1 Multiple dose in psoriasis patients in part 2
Centres 1 center in Germany
Publication No publication

Objectives

- Safety and tolerability of single and multiple doses of BFH772 in two different formulations in healthy and psoriatic subjects.
- Efficacy of topically applied BFH772 to treat psoriasis as assessed by plaque PASI scoring at week 4.

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

BFH772 cream 2mg/g (0.2%)
BFH772 cream 10 mg/g (1%)
Matching placebo for cream
BFH772 ointment 2mg/g (0.2%)
BFH772 ointment 10 mg/g (1%)
Matching placebo for ointment
Cohort 1: 2 subjects received a single application of BFH772 cream at both strengths and placebo
Cohort 2: 2 subjects received a single application of BFH772 ointment at both strengths and placebo
Part 1: 6 subjects received a single application of BFH772 cream and ointment at both strengths and placebos
Part 2: 15 subjects received multiple applications of BFH772 cream and ointment at 1% and placebos
Cohorts 1, 2 and part 1: The formulations were applied as approximately 5mg/cm^2 of skin area
Part 2: the formulations were applied twice daily for 4 weeks to a total surface area treated of maximum 32 cm^2

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

Calcipotriol/Betamethasone combo (Psorcutan®) in part 2 of the study.
Part 2: the formulations were applied twice daily for 4 weeks to a total surface area treated of maximum 32 cm^2

Criteria for Evaluation

Primary variables

Safety cohorts and part 1:

There was no primary variable.

Part 2:

Plaque PASI score at Day 29 (week 4). The plaque PASI score is a composite score made up of three assessments:

- Erythema
- Induration
- Scaling

Each assessment was scored using a 5-point scale (0 – 4). The plaque PASI score was defined as the sum of these three assessments.

Safety and tolerability

All safety and tolerability (vital signs, ECG, hematology, blood chemistry, urinalysis) including local tolerability were evaluated.

Other

Pharmacokinetics:

Blood samples were collected to measure plasma BFH772 concentration in order to determine the systemic exposure at the following timepoints:

Safety cohorts and part 1

- Day 1: Pre-dose; 4 h and 24 h post dose

Part 2

- Day 1: Pre-dose; 4h post dose.
- Days 2, 3, 8, 15, and 22: predose (morning dose)
- Day 29: pre-dose; 4h, and 24h after the last dose
- At study completion.

Skin samples were collected to measure skin BFH772 concentration

Part 2

Five skin biopsies were taken at Day 29 from psoriatic lesions of each treated areas and half of the biopsy taken from the two active BFH772 treated areas only (longitudinal split) will be used for pharmacokinetics. Another two skin biopsies of 4 mm diameter will be taken from a non-diseased, active treatment area.

Statistical Methods

Safety cohorts and part 1

Descriptive statistics were used to summarize the safety data (including local tolerability assessments), investigator-assessed erythema, reflectometry, and pharmacokinetic concentrations. For each parameter, summary statistics were calculated by, where applicable, treatment and time-point.

Part 2

Descriptive statistics were used to summarize the plaque PASI score by treatment and time point.

A Bayesian linear mixed model for the time course of plaque PASI score over 4 weeks was used to compare the two BFH772 formulations and the active control treatment to placebo. Using the estimated adjusted treatment means for plaque PASI at week 4 , the following ratios were calculated:

- BFH772 [cream] / Placebo [cream]
- BFH772 [ointment] / Placebo [ointment]
- Positive Control / (Average of Placebo [cream] & Placebo [ointment])

and posterior probability distributions for each of these ratios were generated.

The probability of the ratios being less than certain cut-offs were calculated. These cut-offs included:

- The probability that the treatment ratio is less than 0.75 (i.e. greater than a 25% reduction)
- The probability that the treatment ratio is less than 1.0 (i.e. greater than a 0% reduction)

There was an interim analysis after part 1 was completed and prior to the start of part 2 of the study. Its objective was to determine the dosages for part 2 of the study based on safety and PK data from part 1.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria.

Safety cohorts and part 1: Healthy volunteers were included in the study who met the following criteria:

- Healthy Caucasian male and female (of non-childbearing potential) subjects aged 18 to 45 years of age included, and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening.
- Subjects had to weigh at least 50 kg to participate in the study, and had to have a body mass index (BMI) within the range of 18 to 29 kg/m^2.

- Able to communicate well with the investigator, to understand and comply with the requirements of the study. Understand and sign the written informed consent.

Part 2: Patients were included in the study who met the following criteria:

- Male and female (of non-childbearing potential) patients aged 18 to 75 years of age included at the time of the screening visit, having passed screening examinations.
- Diagnosis of stable mild to moderate plaque psoriasis (BSA involvement < 10% or PASI < 10; category "mild to moderate" on PGA as according to the EMA (CHMP 2004) (Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis, with or without arthritis); diagnosed or history of psoriasis for at least 6 months prior to screening.

Exclusion criteria.

Safety cohorts and part 1: main exclusion criteria were:

- 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. If needed, (i.e. an incidental and limited need) paracetamol is acceptable, but must be documented in the Concomitant medications / Significant non-drug therapies page of the CRF.
- Participation in any clinical investigation within four (4) weeks prior to initial dosing or longer if required by local regulations, and for any other limitation of participation based on local regulations.
- Donation or loss of 400 mL or more of blood within eight (8) weeks prior to initial dosing, or longer if required by local regulation.
- Significant illness within two (2) weeks prior to initial dosing.
- A past medical history of clinically significant ECG abnormalities.
- Recent (within the last three [3] years) and/or recurrent history of autonomic dysfunction (e.g., recurrent episodes of fainting, palpitations, etc).
- History of clinically significant drug allergy or history of atopic allergy (asthma, urticaria, eczematous dermatitis). A known hypersensitivity to the study drug or drugs similar to the study drug.
- Total WBC count which falls outside the range of 4500–11,000/µL (or that of the local laboratory 4 400-11 300 /µL), or platelets <100,000/µl at screening.
- History of abnormal skin reactivity to UV light. Unusual exposure to UV light in the previous 3 weeks to study start (screening), including tanning, sun beds etc.

Part 2: main exclusion criteria were:

- Currently have any of the nonplaque forms of psoriasis: erythrodermic, guttate, or pustular.
- Currently have drug-induced psoriasis (new onset or exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium).
- Used any investigational drug within the previous 4 weeks.
- Currently use beta blockers
- Recent previous treatment with anti-TNF therapy (or other biological therapy), immunosuppressive agents such as cyclosporine, mycophenolate, pimecrolimus or tacrolimus. The fol-

lowing washout period will be required for such patients to be eligible to participate in the trial:

- 2 months washout prior to screening for etanercept, adalimumab, efalizumab, infliximab or any other biologic therapy or UVB / PUVA therapy.
- 1 month washout prior to screening for cyclosporine, mycophenolate, tacrolimus and any systemic immunosuppressants including, but not limited to, methotrexate and azathioprine
- Within 1 month of randomization, received any systemic medications/treatments that could affect psoriasis or PASI evaluation including, but not limited to, oral or injectable corticosteroids, retinoids, vitamin D analogs, psoralens, sulfasalazine, fumaric acid derivatives, or phototherapy.
- Within 1 month of randomization, used topical medications/treatments at the skin sites to be chosen for topical treatment with BFH772 that could affect psoriasis of PASI evaluation including, but not limited to corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, pimecrolimus, tacrolimus and trimethylpsoralens.

Number of Subjects

	Safety cohorts and part 1				Part 2	
	Cohort 1 N = 2 n (%)	**Cohort 2 N = 3 n (%)**	**Part 1 N = 6 n (%)**	**Total N = 11 n (%)**	**Part 2 N = 15 n (%)**	**Total N = 15 n (%)**
Subjects						
Completed	2 (100.0%)	3 (100.0%)	6 (100.0%)	11 (100.0%)	15 (100.0%)	15 (100.0%)

Demographic and Background Characteristics

Safety cohorts & part 1

		Cohort 1 N=2	Cohort 2 N=3	Part 1 N=6	All treatments N=11
Age (years)	Mean (SD)	40.5 (0.71)	37.3 (6.11)	35.2 (5.15)	36.7 (5.02)
	Median	40.5	36.0	36.5	38.0
	Range	40 - 41	32 - 44	29 - 41	29 - 44
Gender - n(%)	Male	2 (100.0 %)	3 (100.0 %)	6 (100.0 %)	11 (100.0 %)
Race - n(%)	Caucasian	2 (100.0 %)	3 (100.0 %)	6 (100.0 %)	11 (100.0 %)
Ethnicity - n(%)	Other	2 (100.0 %)	3 (100.0 %)	6 (100.0 %)	11 (100.0 %)
Weight (kg)	Mean (SD)	75.85 (2.192)	90.17 (18.817)	82.43 (7.108)	83.35 (11.057)
	Median	75.85	92.00	82.00	79.00
	Range	74.3 - 77.4	70.5 - 108.0	73.8 - 93.6	70.5 - 108.0
Height (cm)	Mean (SD)	180.0 (4.24)	185.3 (8.02)	182.2 (4.96)	182.6 (5.54)
	Median	180.0	186.0	182.5	183.0
	Range	177 - 183	177 - 193	175 - 188	175 - 193
BMI (kg/m2)	Mean (SD)	23.415 (0.4313)	26.027 (3.2815)	24.838 (1.8292)	24.904 (2.1608)
	Median	23.415	26.590	25.285	24.770
	Range	23.11 - 23.72	22.50 - 28.99	21.56 - 26.48	21.56 - 28.99

Part 2

		All treatments N=15
Age (years)	Mean (SD)	47.0 (8.62)
	Median	47.0
	Range	31 - 61
Gender - n(%)	Male	14 (93.3 %)
	Female	1 (6.7 %)
Race - n(%)	Caucasian	15 (100.0 %)
Ethnicity - n(%)	Other	15 (100.0 %)
Weight (kg)	Mean (SD)	89.31 (16.235)
	Median	89.80
	Range	56.3 - 129.2
Height (cm)	Mean (SD)	177.5 (6.62)
	Median	180.0
	Range	163 - 185
BMI (kg/m2)	Mean (SD)	28.145 (3.7806)
	Median	28.220
	Range	21.19 - 38.16

Primary Objective Result(s)

Part 2: Plaque PASI score at baseline and week 4

	Baseline (n, mean ± sd)	Week 4 (n, mean ± sd)
BFH772 1% cream	n=15, 5.8 ± 1.26	n=15, 5.1 ± 2.36
Placebo to BFH772 1% cream	n=15, 6.0 ± 1.20	n=15, 4.9 ± 1.83
BFH772 1% ointment	n=15, 5.9 ± 1.10	n=15, 3.7 ± 1.94
Placebo to BFH772 1% ointment	n=12, 6.2 ± 1.40	n=12, 4.6 ± 1.62
Active control treatment	n=13, 6.3 ± 1.03	n=13, 1.5 ± 0.78

The posterior probability that the treatment ratio for week 4 plaque PASI score was less than 0.75 (i.e. greater than 25% reduction) was 0% for BFH772 cream / placebo cream, 13.7% for BFH772 ointment / placebo ointment and 100% for positive control / average of placebo cream and placebo ointment. Results for the positive control confirmed assay sensitivity, i.e., the ability of study design and conduct to observe a treatment effect.

Safety Results

All subjects completed the study. No severe adverse events were reported.

Application of BFH772 cream and ointment was well tolerated and showed no potential for skin irritation.

Adverse events by system organ classes - n(%) of subjects (all patients) – Safety cohorts & part 1

	Cohort 1 N=2 n(%)	Cohort 2 N=3 n(%)	Part 1 N=6 n(%)	All treatments N=11 n(%)
Patients with AE(s)	0	0	1 (16.7%)	1 (9.1%)
System organ class				
Injury, poisoning and procedural complications	0	0	1 (16.7%)	1 (9.1%)
Respiratory, thoracic and mediastinal disorders	0	0	1 (16.7%)	1 (9.1%)

Adverse events by system organ classes - n(%) of subjects (all patients) - Part 2

	All treatments N=15 n(%)
Patients with AE(s)	4 (26.7%)
System organ class	
Injury, poisoning and procedural complications	3 (20.0%)
General disorders and administration site conditions	2 (13.3%)

Other Relevant Findings

BFH772 concentrations were below limit of quantification in plasma.
BFH772 concentrations in skin were identical for both cream and ointment formulations.

Date of Clinical Trial Report:

Date Inclusion on Novartis Clinical Trial Results Database: 7-Feb-2011