Clinical trial results:
A multi-centre, randomised, double-blind, parallel-group phase III study to investigate the efficacy, safety, and tolerability of a generic calcipotriol-betamethasone ointment formulation compared to Daivobet® and vehicle in the treatment of adult patients with chronic stable plaque psoriasis.

Summary

EudraCT number	2016-001568-12
Trial protocol	BG
Global end of trial date	04 May 2017

Results information

Result version number	v1 (current)
This version publication date	08 February 2020
First version publication date	08 February 2020

Trial information

Trial identification

Sponsor protocol code	16-02/CalciBet-S

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Project number (CRO): CDD16001

Notes:

Sponsors

Sponsor organisation name	Dermapharm AG
Sponsor organisation address	Lil-Dagover Ring 7, Gruenwald, Germany, 82031
Public contact	Clinical Research Department, Dermapharm AG, Clinicaltrials.Dermapharm@dermapharm.com
Scientific contact	Clinical Research Department, Dermapharm AG, Clinicaltrials.Dermapharm@dermapharm.com

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	16 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 May 2017
Global end of trial reached?	Yes
Global end of trial date	04 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that topical treatment with the generic calcipotriol-betamethasone ointment formulation is therapeutically equivalent to the originator product Daivobet® ointment in the treatment of chronic stable plaque psoriasis as determined by the percentage reduction in modified Psoriasis Area and Severity Index (PASI).

Protection of trial subjects:

The study was conducted in accordance with the principles of ICH GCP, the declaration of Helsinki, as well as all other applicable local ethical and legal requirements. The reference product Daivobet® ointment is already registered and commercially available for years in Europe. For the purpose of approval the efficacy and safety of this drug has already been proven in clinical trials. The test drug had not been tested in clinical trials before. One possible risk have resulted from the theoretical assumption of lack of efficacy. In addition a certain, although small proportion of patients were treated with placebo. Any patient with lack of efficacy and/or deterioration of symptoms could stop treatment with study drug at any moment based on the clinical judgement of the investigator. In addition to this every patient could withdraw from the study on his/ her own request and without giving reasons. The planned procedures within the trial represented no special risk to the patients as, apart of blood sampling for laboratory evaluations, there were no further invasive procedures planned.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 October 2016
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	Bulgaria: 439
Worldwide total number of subjects	439
EEA total number of subjects	439

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	375
From 65 to 84 years	64
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Multi-centric study in Bulgaria; first volunteer enrolled: 17-Nov-2016; date of last completion: 04-May-2017

Pre-assignment

Screening details:

Diagnosis and main criteria for inclusion:
male or female patients ≥ 18 years of age; clinical diagnosis of chronic stable (at least 6 months) plaque psoriasis amenable to topical treatment; psoriasis affecting less than 30% of the body surface area (BSA); a modified PASI score of ≥ 5 to ≤ 15 at baseline.

Period 1

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

Blinding implementation details:

The study medications was masked to look the same. The test, reference, and vehicle ointment formulations were almost identical in smell and appearance. The investigators and the staff at clinical sites, patients, as well as CRO and sponsor personnel involved in the monitoring or conduct of the study were blinded to the drug codes, except in the case of an emergency.

Arms

Are arms mutually exclusive?	Yes
Arm title	Test product

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Calcipotriol Combi Ointment
Investigational medicinal product code	D05AX52
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Cutaneous use

Dosage and administration details:

once daily, maximum daily dose of 15 g ointment

Arm title	Reference product

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Daivobet 50 µg/g + 0.5 mg/g Ointment
Investigational medicinal product code	D05AX52
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Cutaneous use

Dosage and administration details:

once daily, maximum daily dose of 15 g ointment

Arm title	Vehicle

Arm description: -

Arm type	Placebo

Investigational medicinal product name	Test product vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Cutaneous use

Dosage and administration details:

once daily, maximum daily dose of 15 g ointment

Number of subjects in period 1	Test product	Reference product	Vehicle
Started	194	195	50
Completed	191	192	48
Not completed	3	3	2
Adverse event, non-fatal	-	1	-
Non-compliance	-	-	1
Lost to follow-up	1	1	-
Protocol deviation	2	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	439	439	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	375	375	
From 65-84 years	64	64	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	193	193	
Male	246	246	

End points

End points reporting groups

Reporting group title	Test product
Reporting group description: -	
Reporting group title	Reference product
Reporting group description: -	
Reporting group title	Vehicle
Reporting group description: -	

Primary: Primary endpoint

End point title	Primary endpoint
End point description:	
Percent change of modified PASI to baseline after 4 weeks of treatment - ANCOVA and 95% confidence intervals of treatment diffs., FAS, LOCF applied	
End point type	Primary
End point timeframe:	
Baseline to end of week 4	

End point values	Test product	Reference product	Vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	193	195	50	
Units: % change of mean				
least squares mean (confidence interval 95%)	71.81 (68.53 to 75.09)	68.96 (65.71 to 72.21)	46.55 (40.84 to 52.27)	

Statistical analyses

Statistical analysis title	Therapeutic equivalence
Statistical analysis description:	
For the primary efficacy outcome measure, mean percent change in modified PASI score between baseline and end of week 4 of the double-blind treatment phase, analysis of covariance (ANCOVA) was carried out using treatment and centre as factors and baseline PASI score as a covariate. The decision of therapeutic equivalence was based on two one-sided tests against the lower and the upper limit of the equivalence range, each with a local one-sided type I error rate of α=0.025.	
Comparison groups	Test product v Reference product
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	2.85

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.12
upper limit	6.81
Variability estimate	Standard error of the mean
Dispersion value	2.02

Statistical analysis title	Superiority of test product to vehicle
Statistical analysis description:	
The analysis was intended to provide supportive evidence with regard to assay sensitivity.	
Comparison groups	Test product v Vehicle
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Superiority of reference product to vehicle
Statistical analysis description:	
This analysis was intended to provide supportive evidence with regard to assay sensitivity.	
Comparison groups	Reference product v Vehicle
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Secondary: Change at the end of week 1	
End point title	Change at the end of week 1
End point description:	
Percent change of modified PASI to baseline after 1 week of treatment - ANCOVA and 95% confidence intervals of treatment diffs., FAS, LOCF applied	
End point type	Secondary
End point timeframe:	
Baseline to end of week 1	

End point values	Test product	Reference product	Vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	193	195	50	
Units: % change of mean				
least squares mean (confidence interval 95%)	29.22 (26.84 to 31.60)	27.93 (25.57 to 30.29)	20.10 (15.95 to 24.25)	

Statistical analyses

Statistical analysis title	Therapeutic equivalence
Comparison groups	Test product v Reference product
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	4.17
Variability estimate	Standard error of the mean
Dispersion value	1.47

Statistical analysis title	Superiority of test product to vehicle
Comparison groups	Test product v Vehicle
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Superiority of reference product to vehicle
Comparison groups	Reference product v Vehicle
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	ANCOVA

Secondary: Mean percent change in BSA at the end of treatment

End point title	Mean percent change in BSA at the end of treatment

End point description:

End point type	Secondary

End point timeframe:

From baseline to end of week 4

End point values	Test product	Reference product	Vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	193	195	50	
Units: % change of mean				
least squares mean (confidence interval 95%)	46.33 (41.14 to 51.52)	45.49 (40.33 to 50.65)	28.55 (18.35 to 38.75)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From baseline to the end of follow-up.	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0
Reporting groups	
Reporting group title	Test product
Reporting group description: all patients who have administered the test medication at least once	
Reporting group title	Reference product
Reporting group description: All patients who had administered the reference product at least once	
Reporting group title	Vehicle
Reporting group description: All patients who have administered the vehicle product at least once.	

Serious adverse events	Test product	Reference product	Vehicle
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 194 (0.52%)	1 / 195 (0.51%)	0 / 50 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Surgical and medical procedures			
Spinal operation			
subjects affected / exposed	1 / 194 (0.52%)	0 / 195 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 194 (0.00%)	1 / 195 (0.51%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	Test product	Reference product	Vehicle
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 194 (2.58%)	4 / 195 (2.05%)	3 / 50 (6.00%)
Investigations			
Hepatic enzyme abnormal			
subjects affected / exposed	0 / 194 (0.00%)	1 / 195 (0.51%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 194 (0.52%)	0 / 195 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Myocardial ischaemia			
subjects affected / exposed	0 / 194 (0.00%)	1 / 195 (0.51%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 194 (0.00%)	1 / 195 (0.51%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Contact dermatitis			
subjects affected / exposed	1 / 194 (0.52%)	0 / 195 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	0 / 194 (0.00%)	1 / 195 (0.51%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Pruritus			
subjects affected / exposed	0 / 194 (0.00%)	2 / 195 (1.03%)	1 / 50 (2.00%)
occurrences (all)	0	2	1
Psoriasis			
subjects affected / exposed	0 / 194 (0.00%)	1 / 195 (0.51%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Skin burning sensation			
subjects affected / exposed	0 / 194 (0.00%)	1 / 195 (0.51%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Renal pain			

subjects affected / exposed	1 / 194 (0.52%)	0 / 195 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Renal colic			
subjects affected / exposed	0 / 194 (0.00%)	0 / 195 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 194 (0.52%)	0 / 195 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	0 / 194 (0.00%)	1 / 195 (0.51%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 194 (0.52%)	0 / 195 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Hyperuricaemia			
subjects affected / exposed	1 / 194 (0.52%)	0 / 195 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Dyslipidaemia			
subjects affected / exposed	0 / 194 (0.00%)	1 / 195 (0.51%)	0 / 50 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: