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	2013-002861-20
Trial protocol	BG PL
Global end of trial date	25 August 2014

Results information

Result version number	v1 (current)
This version publication date	14 February 2016
First version publication date	14 February 2016

Trial information

Trial identification

Sponsor protocol code	2012-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Lek Pharmaceuticals d.d.
Sponsor organisation address	Verovškova 57, Ljubljana, Slovenia, 1526
Public contact	Head of Clinical Development, Lek Pharmaceuticals d.d., +386 15803385,
Scientific contact	Head of Clinical Development, Lek Pharmaceuticals d.d., +386 15803385 ,

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	17 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 August 2014
Global end of trial reached?	Yes
Global end of trial date	25 August 2014
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:

Safety assessments included adverse events (AEs), local tolerance, safety laboratory parameters (including determination of albumin-corrected calcium), vital signs, physical examination and cortisol measurement. This study was conducted in accordance with International Conference on Harmonisation of Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 January 2014
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	Poland: 187
Country: Number of subjects enrolled	Bulgaria: 257
Worldwide total number of subjects	444
EEA total number of subjects	444

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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	404

From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

multi-centre, randomised, double-blind, parallel-group, study in male and female patients

Pre-assignment

Screening details:

Patients underwent a screening phase with a maximum duration of 2 weeks prior to the baseline visit. Of 483 screened patients 445 were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	test

Arm description:

test product

Arm type	Experimental
Investigational medicinal product name	calcipotriol-betamethasone
Investigational medicinal product code	
Other name	Calcipotriol-Betamethasone Sandoz
Pharmaceutical forms	Ointment
Routes of administration	Cutaneous use

Dosage and administration details:

Strength: 50 µg/g, 0.5 mg/g. Topical cutaneous application once daily.

Arm title	reference

Arm description:

reference product

Arm type	Active comparator
Investigational medicinal product name	calcipotriol-betamethasone
Investigational medicinal product code	
Other name	Daivobet®
Pharmaceutical forms	Ointment
Routes of administration	Cutaneous use

Dosage and administration details:

Strength: 50 µg/g, 0.5 mg/g. Topical cutaneous application once daily.

Arm title	vehicle

Arm description:

placebo/vehicle product

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Cutaneous use

Dosage and administration details:
Topical cutaneous application once daily.

Number of subjects in period 1	test	reference	vehicle
Started	194	201	49
Completed	188	198	48
Not completed	6	3	1
Consent withdrawn by subject	3	1	-
Adverse event, non-fatal	-	-	1
Lost to follow-up	2	-	-
not able to continue due to long travel	-	1	-
Protocol deviation	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	test
Reporting group description:	
test product	
Reporting group title	reference
Reporting group description:	
reference product	
Reporting group title	vehicle
Reporting group description:	
placebo/vehicle product	

Reporting group values	test	reference	vehicle
Number of subjects	194	201	49
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	174	185	45
From 65-84 years	20	16	4
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	47.18	45.57	48.39
standard deviation	± 14.19	± 14.23	± 12.96
Gender categorical			
Units: Subjects			
Female	84	88	22
Male	110	113	27

Reporting group values	Total		
Number of subjects	444		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	404		

From 65-84 years	40		
85 years and over	0		

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	194		
Male	250		

End points

End points reporting groups

Reporting group title	test
Reporting group description: test product	
Reporting group title	reference
Reporting group description: reference product	
Reporting group title	vehicle
Reporting group description: placebo/vehicle product	

Primary: Mean percent change from baseline in modified Psoriasis Area and Severity Index (PASI) score, per protocol set

End point title	Mean percent change from baseline in modified Psoriasis Area and Severity Index (PASI) score, per protocol set
End point description:	
End point type	Primary
End point timeframe: baseline (score at randomization), end of week 4	

End point values	test	reference	vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	171	186	41	
Units: % change LS mean				
least squares mean (confidence interval 95%)	81.3 (78.13 to 84.46)	75.51 (72.53 to 78.5)	48.97 (42.86 to 55.08)	

Statistical analyses

Statistical analysis title	therapeutic equivalence compared to reference

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, an analysis of covariance (ANCOVA) was carried out using treatment and centre as factors and baseline PASI score as a covariate.

Comparison groups	test v reference

Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.69
upper limit	9.87
Variability estimate	Standard error of the mean
Dispersion value	2.08

Statistical analysis title	superiority of the test product to its vehicle
Statistical analysis description:	
This analysis was intended to provide supportive evidence and was considered descriptive.	
Comparison groups	test v vehicle
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	25.58
upper limit	39.07
Variability estimate	Standard error of the mean
Dispersion value	3.43

Primary: Mean percent change from baseline in modified Psoriasis Area and Severity Index (PASI) score, full analysis set

End point title	Mean percent change from baseline in modified Psoriasis Area and Severity Index (PASI) score, full analysis set
End point description:	

End point type	Primary
End point timeframe:	
baseline, end of week 4	

End point values	test	reference	vehicle	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	193	201	49	
Units: % change LS mean				
least squares mean (confidence interval 95%)	79.87 (76.87 to 82.88)	75.1 (72.17 to 78.02)	48.39 (42.66 to 54.12)	

Statistical analyses

Statistical analysis title	therapeutic equivalence compared to reference
Comparison groups	test v reference
Number of subjects included in analysis	394
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	8.78
Variability estimate	Standard error of the mean
Dispersion value	2.03

Statistical analysis title	superiority of the test product to its vehicle
Comparison groups	test v vehicle
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	25.12
upper limit	37.85
Variability estimate	Standard error of the mean
Dispersion value	3.24

Adverse events

Adverse events information	
Timeframe for reporting adverse events: AEs were recorded by the investigator at each visit until the end of the double-blind phase and at follow-up.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0
Reporting groups	
Reporting group title	test
Reporting group description: patients treated with test medication	
Reporting group title	reference
Reporting group description: patients treated with reference drug	
Reporting group title	vehicle
Reporting group description: patients receiving placebo/vehicle formulation	

Serious adverse events	test	reference	vehicle
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 194 (0.52%)	2 / 201 (1.00%)	0 / 49 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian germ cell teratoma benign			
subjects affected / exposed	1 / 194 (0.52%)	0 / 201 (0.00%)	0 / 49 (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
Transitional cell carcinoma			
subjects affected / exposed	0 / 194 (0.00%)	1 / 201 (0.50%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cataract operation			

subjects affected / exposed	0 / 194 (0.00%)	1 / 201 (0.50%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	test	reference	vehicle
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 194 (5.15%)	17 / 201 (8.46%)	8 / 49 (16.33%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 194 (0.00%)	1 / 201 (0.50%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Blood glucose increased			
subjects affected / exposed	0 / 194 (0.00%)	0 / 201 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 194 (0.00%)	1 / 201 (0.50%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 194 (0.00%)	1 / 201 (0.50%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Limb injury			
subjects affected / exposed	0 / 194 (0.00%)	1 / 201 (0.50%)	1 / 49 (2.04%)
occurrences (all)	0	1	1
Vascular disorders			
Venous insufficiency			
subjects affected / exposed	1 / 194 (0.52%)	0 / 201 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Burning sensation			
subjects affected / exposed	1 / 194 (0.52%)	0 / 201 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			

Application site erythema			
subjects affected / exposed	0 / 194 (0.00%)	0 / 201 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Application site pain			
subjects affected / exposed	2 / 194 (1.03%)	1 / 201 (0.50%)	0 / 49 (0.00%)
occurrences (all)	2	1	0
Application site pruritus			
subjects affected / exposed	1 / 194 (0.52%)	1 / 201 (0.50%)	2 / 49 (4.08%)
occurrences (all)	1	1	2
Influenza like illness			
subjects affected / exposed	0 / 194 (0.00%)	1 / 201 (0.50%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	1 / 194 (0.52%)	0 / 201 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 194 (0.52%)	0 / 201 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 194 (0.00%)	1 / 201 (0.50%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	1 / 194 (0.52%)	2 / 201 (1.00%)	2 / 49 (4.08%)
occurrences (all)	1	2	2
Miliaria			
subjects affected / exposed	1 / 194 (0.52%)	0 / 201 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 194 (0.00%)	1 / 201 (0.50%)	3 / 49 (6.12%)
occurrences (all)	0	1	3
Psoriasis			
subjects affected / exposed	2 / 194 (1.03%)	2 / 201 (1.00%)	0 / 49 (0.00%)
occurrences (all)	2	2	0
Rash macular			

subjects affected / exposed	0 / 194 (0.00%)	1 / 201 (0.50%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Skin exfoliation			
subjects affected / exposed	0 / 194 (0.00%)	1 / 201 (0.50%)	1 / 49 (2.04%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Leukocyturia			
subjects affected / exposed	0 / 194 (0.00%)	1 / 201 (0.50%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 194 (0.52%)	0 / 201 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 194 (0.00%)	1 / 201 (0.50%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 194 (0.00%)	1 / 201 (0.50%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Cystitis			
subjects affected / exposed	0 / 194 (0.00%)	0 / 201 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 194 (0.00%)	0 / 201 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 194 (0.00%)	1 / 201 (0.50%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Onychomycosis			
subjects affected / exposed	0 / 194 (0.00%)	1 / 201 (0.50%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 194 (0.00%)	0 / 201 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Sinusitis			

subjects affected / exposed occurrences (all)	0 / 194 (0.00%) 0	0 / 201 (0.00%) 0	1 / 49 (2.04%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 January 2014	Amendment was prepared as it became known after finalizing and submitting the study protocol to the regulatory authorities of both countries that the product needed for performing the planned adrenocorticotropic hormone (ACTH) challenge test was at that time not available in Europe due to manufacturing problems. An alternative test had to be introduced to replace the ACTH challenge test, i.e. measurement of cortisol excreted into urine over a period of 24 hours.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported