Clinical trial results:
Effect of Calcipotriol plus Betamethasone Dipropionate Gel on the HPA Axis and Calcium Metabolism in Adolescent Subjects (Aged 12 to 16 Years, 11 months) with Scalp and Body Psoriasis

Summary

EudraCT number	2013-001538-16
Trial protocol	GB DE FR RO
Global end of trial date	13 February 2018

Results information

Result version number	v2 (current)
This version publication date	14 November 2018
First version publication date	26 August 2018
Version creation reason	• New data added to full data set • Correction of full data set Changes made to data: - The number of subjects included in the analyses of pharmacokinetic endpoints was corrected from 33 to 32. - Data were added to the endpoints AUC(0-t) and AUC(0-infinity). Editorial changes made to align with comments received from clinicaltrials.gov. - Specifications of endpoint time frames. - Explanation the Psoriasis Area and Severity Index score and the range of this score.

Trial information

Trial identification

Sponsor protocol code	LP0076-1017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02038569
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LEO Pharma A/S
Sponsor organisation address	Industriparken 55, Ballerup, Denmark, 2750
Public contact	Clinical Disclosure Specialist, LEO Pharma A/S, +45 44945888, disclosure@leo-pharma.com
Scientific contact	Clinical Disclosure Specialist, LEO Pharma A/S, +45 44945888, disclosure@leo-pharma.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 February 2018
Global end of trial reached?	Yes
Global end of trial date	13 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the safety of once daily use of calcipotriol (50 mcg/g) plus betamethasone (0.5 mg/g) (as dipropionate) gel in adolescent subjects (aged 12 to 16 years, 11 months) with scalp and body psoriasis.

Protection of trial subjects:

This clinical trial was conducted in accordance with the revision current at the start of the trial of the World Medical Association’s Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. All subjects received written and verbal information concerning the clinical trial. This information emphasised that participation in the clinical trial was voluntary and that the subject could withdraw from the clinical trial at any time and for any reason. All subjects and their legally acceptable representatives were given an opportunity to ask questions and were given sufficient time to consider before consenting. Subjects who were not of legal age gave assent to their participation in the trial. The subject’s and legally acceptable representatives' signed and dated informed consent and assent to participate in the clinical trial were obtained prior to any trial related activities being carried out in accordance with ICH Good Clinical Practice (GCP) Section 4.8 and all applicable laws and regulations.
Overdosage with calcipotriol may be associated with hypercalcaemia, and clinically important hypercalcaemia could be managed at the investigator’s discretion with rehydration, biphosphonate administration or according to local instructions.
Overdosage with betamethasone dipropionate may result in suppression of the pituitary adrenal function, and could be treated symptomatically at the investigator's discretion.
There is a risk of allergic hypersensitivity reactions with administration of Cortrosyn®/Synacthen®. Prior to the injection, the physician administering the injection was prepared to treat any possible hypersensitivity reactions.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	07 March 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	Romania: 45

Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	125
EEA total number of subjects	98

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)	125
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Male or female, 12 to 16 years 11 months, psoriasis on body and scalp.
•10-35% BSA; ≥20% scalp; at least moderate severity for subjects performing HPA assessment.
•≥3% BSA; ≥10% scalp; at least mild severity for subjects not performing HPA assessment.
125 screened. 107 assigned to treatment, 1 lost to follow up and, 17 didn't meet entry criteria

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	LEO 80185

Arm description:

This arm contains all 107 subjects that were assigned to treatment and constitutes the full analysis set and the safety analysis set. 31 subjects in this arm performed additional hypothalamic-pituitary axis assessments and constitute the per protocol analysis set.

Arm type	Experimental
Investigational medicinal product name	LEO 80185
Investigational medicinal product code	
Other name	Daivobet® gel , Xamiol® gel, Dovobet gel ®, and Taclonex® Topical Suspension
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

LEO 80185 gel is formulated as a gel containing Calcipotriol 50 mcg/g (as hydrate) and Betamethasone 0.5 mg/g (as dipropionate).LEO 80185 gel was applied once daily to all affected areas of the scalp and body. For subjects aged 12 to less than 15 years with a body surface area below 1.3 m2, the maximum weekly dosage of LEO 80185 gel was 55 g gel per week. For subjects aged 12 to less than 15 years with a body surface area above 1.3 m2 and subjects older than 15 years with a body surface area below 1.3 m2, the maximum weekly dosage of LEO 80185 gel was 75 g gel per week. For subjects aged older than 15 years with a body surface area above 1.3 m2, the maximum weekly dosage of LEO 80185 gel was 100 g gel per week. No maximum weekly dosage of LEO 80185 gel was defined for subjects performing HPA assessments.

Number of subjects in period 1[1]	LEO 80185
Started	107
Completed	102
Not completed	5
Consent withdrawn by subject	3
Adverse event, non-fatal	1
Lost to follow-up	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The worldwide number of enrolled subjects include all subjects who provided consent for participation in the trial and were screened. Out of the 125 subjects who were screened, 107 subjects met all inclusion criteria and none of the exclusion criteria, and were assigned to treatment. These 107 subjects are included in the data for the baseline period.

Baseline characteristics

Reporting groups

Reporting group title	Overall period

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	107	107	
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)	107	107	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
All subjects included were between 12 years and 16 years 11 months.			
Units: years			
arithmetic mean	14.2		
standard deviation	± 1.4	-	
Gender categorical Units: Subjects			
Female	62	62	
Male	45	45	

Subject analysis sets

Subject analysis set title	Per protocol analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

For the analysis of the results from the ACTH-challenge test, the per protocol analysis set was defined by including the subjects performing HPA axis assessments from the full analysis set, but was to exclude the subjects who did not apply any LEO 80185 gel, met the inclusion criterion concerning evidence of adrenal function suppression at baseline, or provide any results for the ACTH-challenge test after receiving IMP.

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

107 subjects who applied LEO 80185 gel at least once and were included in the analysis of efficacy.

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

107 subjects who applied LEO 80185 gel at least once and for whom either the presence or confirmed absence of adverse events was available.

Reporting group values	Per protocol analysis set	Full analysis set	Safety analysis set
Number of subjects	31	107	107
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)	31	107	107
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
All subjects included were between 12 years and 16 years 11 months.			
Units: years			
arithmetic mean	14.2	14.2	14.2
standard deviation	± 1.2	± 1.4	± 1.4
Gender categorical Units: Subjects			
Female	17	62	62
Male	14	45	45

End points

End points reporting groups

Reporting group title	LEO 80185

Reporting group description:

This arm contains all 107 subjects that were assigned to treatment and constitutes the full analysis set and the safety analysis set. 31 subjects in this arm performed additional hypothalamic-pituitary axis assessments and constitute the per protocol analysis set.

Subject analysis set title	Per protocol analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

For the analysis of the results from the ACTH-challenge test, the per protocol analysis set was defined by including the subjects performing HPA axis assessments from the full analysis set, but was to exclude the subjects who did not apply any LEO 80185 gel, met the inclusion criterion concerning evidence of adrenal function suppression at baseline, or provide any results for the ACTH-challenge test after receiving IMP.

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

107 subjects who applied LEO 80185 gel at least once and were included in the analysis of efficacy.

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

107 subjects who applied LEO 80185 gel at least once and for whom either the presence or confirmed absence of adverse events was available.

Primary: Adverse Drug Reactions (ADRs)

End point title	Adverse Drug Reactions (ADRs)[1]

End point description:

Number of Adverse Drug Reactions (ADRs) defined as adverse events for which the investigator has not described the causal relationship to LEO 80185 gel as “not related”.

End point type	Primary

End point timeframe:

8 weeks.

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: No statistical analyses for this end point

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of adverse drug reactions				
Blood cortisol decreased	2			
Blood parathyroid hormone increased	1			
Acne	1			
Erythema	1			
Hyperparathyroidism	1			
Folliculitis	1			
Headache	1			

Statistical analyses

No statistical analyses for this end point

Primary: Subjects With Serum Cortisol Concentration of ≤18 mcg/dl at 30 Minutes After ACTH-challenge, Week 4

End point title	Subjects With Serum Cortisol Concentration of ≤18 mcg/dl at 30 Minutes After ACTH-challenge, Week 4[2]

End point description:

Subjects With Serum Cortisol Concentration of ≤18 mcg/dl at 30 Minutes After ACTH-challenge, Week 4

End point type	Primary

End point timeframe:

30 minutes after ACTH-challenge at Week 4

Notes:

[2] - 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: No statistical analyses for this end point

End point values	Per protocol analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: Number of subjects				
Serum cortisol equal to or below 18 mcg/dL	4			
Serum cortisol above 18 mcg/dL	27			

Statistical analyses

No statistical analyses for this end point

Primary: Subjects With Serum Cortisol Concentration of ≤18 mcg/dl at 30 Minutes After ACTH-challenge, Week 8

End point title	Subjects With Serum Cortisol Concentration of ≤18 mcg/dl at 30 Minutes After ACTH-challenge, Week 8[3]

End point description:

Subjects With Serum Cortisol Concentration of ≤18 mcg/dl at 30 Minutes After ACTH-challenge, Week 8

End point type	Primary

End point timeframe:

30 minutes after ACTH-challenge at Week 8

Notes:

[3] - 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: No statistical analyses for this end point

End point values	Per protocol analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: Number of subjects				
Serum cortisol equal to or below 18 mcg/dL	2			
Serum cortisol above 18 mcg/dL	27			
No assessment performed, withdrawn before Week 8	2			

Statistical analyses

No statistical analyses for this end point

Primary: Change in Albumin-corrected Serum Calcium From Baseline to Week 4

End point title	Change in Albumin-corrected Serum Calcium From Baseline to Week 4[4]

End point description:

Change in Albumin-corrected Serum Calcium From Baseline to Week 4

End point type	Primary

End point timeframe:

From baseline to Week 4

Notes:

[4] - 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: No statistical analyses for this end point

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	107[5]			
Units: mmol/L				
arithmetic mean (standard deviation)	-0.012 (± 0.131)			

Notes:

[5] - Data available for 100 subjects

Statistical analyses

No statistical analyses for this end point

Primary: Change in Albumin-corrected Serum Calcium From Baseline to Week 8

End point title	Change in Albumin-corrected Serum Calcium From Baseline to Week 8[6]

End point description:

Change in Albumin-corrected Serum Calcium From Baseline to Week 8

End point type	Primary

End point timeframe:

From baseline to Week 8

Notes:

[6] - 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: No statistical analyses for this end point

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	107[7]			
Units: mmol/L				
arithmetic mean (standard deviation)	-0.008 (± 0.125)			

Notes:

[7] - Data available for 87 subjects

Statistical analyses

No statistical analyses for this end point

Primary: Change in Albumin-corrected Serum Calcium From Baseline to End of Treatment

End point title	Change in Albumin-corrected Serum Calcium From Baseline to End of Treatment[8]

End point description:

Change in Albumin-corrected Serum Calcium From Baseline to End of Treatment, Defined as the Last Value Recorded after Baseline Up to and Including Week 8.

End point type	Primary

End point timeframe:

From baseline to end of treatment

Notes:

[8] - 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: No statistical analyses for this end point

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	107[9]			
Units: mmol/L				
arithmetic mean (standard deviation)	-0.003 (± 0.121)			

Notes:

[9] - Data available for 102 subjects

Statistical analyses

No statistical analyses for this end point

Primary: Change in 24-hour Urinary Calcium Excretion From Baseline to Week 4

End point title	Change in 24-hour Urinary Calcium Excretion From Baseline to Week 4[10]

End point description:

Change in 24-hour Urinary Calcium Excretion From Baseline to Week 4

End point type	Primary

End point timeframe:

From baseline to Week 4

Notes:

[10] - 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: No statistical analyses for this end point

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	107[11]			
Units: mmol/24hr				
arithmetic mean (standard deviation)	-0.493 (± 1.669)			

Notes:

[11] - Data available for 85 subjects

Statistical analyses

No statistical analyses for this end point

Primary: Change in 24-hour Urinary Calcium Excretion From Baseline to Week 8

End point title	Change in 24-hour Urinary Calcium Excretion From Baseline to Week 8[12]

End point description:

Change in 24-hour Urinary Calcium Excretion From Baseline to Week 8

End point type	Primary

End point timeframe:

From baseline to Week 8

Notes:

[12] - 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: No statistical analyses for this end point

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	107[13]			
Units: mmol/24hr				
arithmetic mean (standard deviation)	0.040 (± 1.638)			

Notes:

[13] - Data available for 72 subjects

Statistical analyses

No statistical analyses for this end point

Primary: Change in 24-hour Urinary Calcium Excretion From Baseline to End of Treatment

End point title	Change in 24-hour Urinary Calcium Excretion From Baseline to End of Treatment[14]

End point description:

Change in 24-hour Urinary Calcium Excretion From Baseline to End of Treatment, Defined as the Last Value Recorded after Baseline Up to and Including Week 8.

End point type	Primary

End point timeframe:

From baseline to end of treatment

Notes:

[14] - 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: No statistical analyses for this end point

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	107[15]			
Units: mmol/L				
arithmetic mean (standard deviation)	0.069 (± 1.593)			

Notes:

[15] - Data available for 85 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Events (AEs)

End point title	Adverse Events (AEs)

End point description:

Number of Adverse Events (AEs)

End point type	Secondary

End point timeframe:

8 weeks

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Adverse events				
Nasopharyngitis	6			
Rhinitis	2			
Folliculitis	1			
Hordeolum	1			
Impetigo	1			
Peritonsillar abscess	1			
Upper respiratory tract infection	1			
Viral infection	1			
Blood parathyroid hormone increased	5			
Blood cortisol decreased	2			
Eosinophil count increased	1			
Headache	8			

Balance disorder	1			
Dizziness	1			
Syncope	1			
Cough	2			
Oropharyngeal pain	2			
Dyspnoea	1			
Epistaxis	1			
Respiratory disorder	1			
Acne	1			
Erythema	1			
Pruritus	1			
Sunburn	1			
Abdominal pain upper	1			
Constipation	1			
Diarrhoea	1			
Back pain	1			
Muscle spasms	1			
Musculoskeletal chest pain	1			
Neck pain	1			
Dysmenorrhoea	3			
Arthropod sting	1			
Concussion	1			
Sleep disorder	1			
Suicide attempt	1			
Cardiovascular disorder	1			
Hyperparathyroidism	1			
Iron deficiency	1			
Wisdom teeth removal	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Serum Cortisol Concentration of ≤18 mcg/dl at Both 30 and 60 Minutes After ACTH-challenge at Week 4

End point title	Number of Subjects With Serum Cortisol Concentration of ≤18 mcg/dl at Both 30 and 60 Minutes After ACTH-challenge at Week 4

End point description:

Number of Subjects With Serum Cortisol Concentration of ≤18 mcg/dl at Both 30 and 60 Minutes After ACTH-challenge at Week 4

End point type	Secondary

End point timeframe:

30 and 60 minutes after ACTH-challenge at Week 4

End point values	Per protocol analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: Number of subjects				
Serum cortisol equal to or below 18 mcg/dL	0			
Serum cortisol above 18 mcg/dL	31			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Serum Cortisol Concentration of ≤18 mcg/dl at Both 30 and 60 Minutes After ACTH-challenge at Week 8

End point title	Number of Subjects With Serum Cortisol Concentration of ≤18 mcg/dl at Both 30 and 60 Minutes After ACTH-challenge at Week 8

End point description:

Number of Subjects With Serum Cortisol Concentration of ≤18 mcg/dl at Both 30 and 60 Minutes After ACTH-challenge at Week 8

End point type	Secondary

End point timeframe:

30 and 60 minutes after ACTH-challenge at Week 8

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: Number of subjects				
Serum cortisol equal to or below 18 mcg/dL	0			
Serum cortisol above 18 mcg/dL	29			
No assessment performed, withdrawn before Week 8	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Urinary Calcium:Creatinine Ratio From Baseline to Week 4

End point title	Change in Urinary Calcium:Creatinine Ratio From Baseline to Week 4

End point description:

Change in Urinary Calcium:Creatinine Ratio From Baseline to Week 4

End point type	Secondary

End point timeframe:

From baseline to Week 4

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	107[16]			
Units: mmol/g				
arithmetic mean (standard deviation)	-0.098 (± 1.642)			

Notes:

[16] - Data available for 85 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Urinary Calcium:Creatinine Ratio From Baseline to Week 8

End point title	Change in Urinary Calcium:Creatinine Ratio From Baseline to Week 8

End point description:

Change in Urinary Calcium:Creatinine Ratio From Baseline to Week 8

End point type	Secondary

End point timeframe:

From baseline to Week 8

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	107[17]			
Units: mmol/g				
arithmetic mean (standard deviation)	0.219 (± 1.700)			

Notes:

[17] - Data available for 72 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Serum Alkaline Phosphatase From Baseline to Week 4

End point title	Change in Serum Alkaline Phosphatase From Baseline to Week 4

End point description:

Change in Serum Alkaline Phosphatase From Baseline to Week 4

End point type	Secondary

End point timeframe:

From baseline to Week 4

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	107[18]			
Units: mmol/L				
arithmetic mean (standard deviation)	-0.4 (± 31.4)			

Notes:

[18] - Data available for 100 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Serum Alkaline Phosphatase From Baseline to Week 8

End point title	Change in Serum Alkaline Phosphatase From Baseline to Week 8

End point description:

Change in Serum Alkaline Phosphatase From Baseline to Week 8

End point type	Secondary

End point timeframe:

From baseline to Week 8

End point values	Safety analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	107[19]			
Units: mmol/L				
arithmetic mean (standard deviation)	-6.8 (± 42.6)			

Notes:

[19] - Data available for 87 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Evaluation AUC(0-t)

End point title	Pharmacokinetic Evaluation AUC(0-t)

End point description:

AUC(0-t) values for betamethasone dipropionate, betamethasone 17-propionate, calcipotriol, and MC1080. Betamethasone dipropionate was only detected above lower limit of quantification in 5 samples from 4 subjects, and no subjects had enough positive samples to allow calculation AUC(0-t) for betamethasone dipropionate. Betamethasone 17-propionate was only detected in 12 samples from 5 subjects, and only 2 subjects had enough positive samples to calculate AUC(0-t). The mean value of AUC(0-t) for these 2 subjects is presented for betamethasone 17-propionate. Calcipotriol and MC1080 were never detected above lower limit of quantification, therefore no PK parameters could be calculated

and no data have been entered for calcipotriol and MC1080.

End point type	Secondary

End point timeframe:

Week 4, blood samples taken before IMP was applied and 1, 3, and 5 hours after application of IMP

End point values	LEO 80185			
Subject group type	Reporting group			
Number of subjects analysed	32[20]			
Units: pg*h/mL				
arithmetic mean (standard deviation)				
Betamethasone dipropionate (n=4)	0 (± 0)			
Betamethasone 17-propionate (n=5)	325 (± 193.75)			
Calcipotriol (n=0)	0 (± 0)			
MC1080 (n=0)	0 (± 0)			

Notes:

[20] - PK in 32 subjects. Analysis set not defined. n=subjects with ≥1 sample where compound was detectable

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Evaluation AUC(0-infinity)

End point title	Pharmacokinetic Evaluation AUC(0-infinity)

End point description:

AUC(0-infinity) values for betamethasone dipropionate, betamethasone 17-propionate, calcipotriol, and MC1080. Betamethasone dipropionate was only detected above lower limit of quantification in 5 samples from 4 subjects, and no subjects had enough positive samples to allow calculation AUC(0-infinity) for betamethasone dipropionate. Betamethasone 17-propionate was only detected in 12 samples from 5 subjects, and only 2 subjects had enough positive samples to calculate AUC(0-infinity). The mean value of AUC(0-infinity) for these 2 subjects is presented for betamethasone 17-propionate. Calcipotriol and MC1080 were never detected above lower limit of quantification, therefore no PK parameters could be calculated and no data have been entered for calcipotriol and MC1080.

The terms AUC(0-infinity) and AUC(all) are interchangeable, AUC(0-infinity) was used in the protocol whereas AUC(all) was used in the report. AUC(0-infinity) has been used here to be consistent with the protocol.

End point type	Secondary

End point timeframe:

Week 4, blood samples taken before IMP was applied and 1, 3, and 5 hours after application of IMP

End point values	LEO 80185			
Subject group type	Reporting group			
Number of subjects analysed	32[21]			
Units: pg*h/mL				
arithmetic mean (standard deviation)				
Betamethasone dipropionate (n=4)	0 (± 0)			
Betamethasone 17-propionate (n=5)	325 (± 193.75)			
Calcipotriol (n=0)	0 (± 0)			

MC1080 (n=0)	0 (± 0)			

Notes:

[21] - PK in 32 subjects. Analysis set not defined. n=subjects with ≥1 sample where compound was detectable

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Evaluation C(max)

End point title	Pharmacokinetic Evaluation C(max)

End point description:

C(max) values for betamethasone dipropionate, betamethasone 17-propionate, calcipotriol, and MC1080. Betamethasone dipropionate was only detected above lower limit of quantification in 5 samples from 4 subjects and betamethasone 17-propionate was only detected in 12 samples from 5 subjects, therefore pharmakokinetic profiles could not be calculated. Presented C(max) values for betamethasone dipropionate and betamethasone 17-propionate are the highest value observed at any time point. Calcipotriol and MC1080 were never detected above lower limit of quantification, therefore no C(max) values are available for calcipotriol and MC1080. Non-calculated values have been entered as "0".

End point type	Secondary

End point timeframe:

Week 4, blood samples taken before IMP was applied and 1, 3, and 5 hours after application of IMP

End point values	LEO 80185			
Subject group type	Reporting group			
Number of subjects analysed	32[22]			
Units: pg/mL				
number (not applicable)				
Betamethasone dipropionate (n=4)	104			
Betamethasone 17-propionate (n=5)	126			
Calcipotriol (n=0)	0			
MC1080 (n=0)	0			

Notes:

[22] - PK in 32 subjects. Analysis set not defined. n=subjects with ≥1 sample where compound was detectable

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Evaluation T(max)

End point title	Pharmacokinetic Evaluation T(max)

End point description:

T(max) values for betamethasone dipropionate, betamethasone 17-propionate, calcipotriol, and MC1080. Betamethasone dipropionate was only detected above lower limit of quantification in 5 samples from 4 subjects and betamethasone 17-propionate was only detected in 12 samples from 5 subjects. Calcipotriol and MC1080 were never detected above lower limit of quantification. Therefore it was not possible to calculate T(max) for betamethasone dipropionate, betamethasone 17-propionate, calcipotriol, or MC1080. Non-calculated values have been entered as "0".

End point type	Secondary

End point timeframe:

Week 4, blood samples taken before IMP was applied and 1, 3, and 5 hours after application of IMP

End point values	LEO 80185			
Subject group type	Reporting group			
Number of subjects analysed	32[23]			
Units: hours				
number (not applicable)				
Betamethasone dipropionate (n=4)	0			
Betamethasone 17-propionate (n=5)	0			
Calcipotriol (n=0)	0			
MC1080 (n=0)	0			

Notes:

[23] - PK in 32 subjects. Analysis set not defined. n=subjects with ≥1 sample where compound was detectable

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Evaluation T(½)

End point title	Pharmacokinetic Evaluation T(½)

End point description:

T(½) values for betamethasone dipropionate, betamethasone 17-propionate, calcipotriol, and MC1080. Betamethasone dipropionate was only detected above lower limit of quantification in 5 samples from 4 subjects and betamethasone 17-propionate was only detected in 12 samples from 5 subjects. Calcipotriol and MC1080 were never detected above lower limit of quantification. Therefore it was not possible to calculate T(½) for betamethasone dipropionate, betamethasone 17-propionate, calcipotriol, or MC1080. Non-calculated values have been entered as "0".

End point type	Secondary

End point timeframe:

Week 4, blood samples taken before IMP was applied and 1, 3, and 5 hours after application of IMP

End point values	LEO 80185			
Subject group type	Reporting group			
Number of subjects analysed	32[24]			
Units: hours				
number (not applicable)				
Betamethasone dipropionate (n=4)	0			
Betamethasone 17-propionate (n=5)	0			
Calcipotriol (n=0)	0			
MC1080 (n=0)	0			

Notes:

[24] - PK in 32 subjects. Analysis set not defined. n=subjects with ≥1 sample where compound was detectable

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects With "Controlled Disease" According to the Investigator's Global Assessment of Disease Severity on the Body at End of Treatment

End point title	Subjects With "Controlled Disease" According to the Investigator's Global Assessment of Disease Severity on the Body at End of Treatment

End point description:

Subjects with "Controlled disease" (i.e., "Clear" or "Almost clear" for subjects with at least "Moderate" disease at baseline, "Clear" for subjects with "Mild" disease at baseline) according to the investigator's global assessment of disease severity on the body at end of treatment, defined as the last value recorded up to and including Week 8.

End point type	Secondary

End point timeframe:

End of treatment

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of subjects				
Controlled	62			
Non-controlled	45			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change in PASI From Baseline to End of Treatment

End point title	Percentage Change in PASI From Baseline to End of Treatment

End point description:

Percentage Change in PASI From Baseline to End of Treatment, Defined as the Last Value Recorded Up to and Including Week 8. Psoriasis area and severity index (PASI) assesses extent and severity of clinical signs of psoriasis vulgaris. Body surface is divided in 4 ares: head (incl. neck), arms (incl. hands), trunk (incl. flexures) and legs (incl. buttocks and feet). Each area is scored from 0-6 for extent of psoriasis and from 0-4 for redness, thickness, and scaliness, and an area PASI score is calculated. The total PASI score is calculated from each area's score. The PASI score ranges from 0 (clear skin) to 72 (maximum disease), a PASI score higher than 10 generally corresponds to moderate-to-severe disease.

End point type	Secondary

End point timeframe:

From baseline to end of treatment

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Percentage change in PASI				
arithmetic mean (standard deviation)	-78.7 (± 32.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects With "Controlled Disease" According to the Patient's Global Assessment of Disease Severity on the Body at End of Treatment

End point title	Subjects With "Controlled Disease" According to the Patient's Global Assessment of Disease Severity on the Body at End of Treatment

End point description:

Subjects with "Controlled disease" (i.e., "Clear" or "Almost clear" for subjects with at least "Moderate" disease at baseline, "Clear" for subjects with "Mild" disease at baseline) according to the patient's global assessment of disease severity on the body at end of treatment, defined as the last value recorded up to and including Week 8.

End point type	Secondary

End point timeframe:

End of treatment

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: Number of subjects				
Controlled	67			
Non-controlled	40			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs/SAEs were followed up until final outcome was determined. After a subject left the trial, investigator followed up all SAEs and AEs deemed possibly/probably related to IMP for 14± 2 days or until final outcome was determined, whichever came first.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	All subjects

Reporting group description:

This arm contains all 107 subjects that were assigned to treatment and constitutes the safety analysis set.

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 107 (0.93%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 107 (35.51%)		
Surgical and medical procedures			
Wisdom teeth removal			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Reproductive system and breast disorders			

Dysmenorrhoea subjects affected / exposed occurrences (all)	3 / 107 (2.80%) 3		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Respiratory disorder subjects affected / exposed occurrences (all)	 2 / 107 (1.87%) 2 2 / 107 (1.87%) 2 1 / 107 (0.93%) 1 1 / 107 (0.93%) 1 1 / 107 (0.93%) 1		
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all)	 1 / 107 (0.93%) 1		
Investigations Blood parathyroid hormone increased subjects affected / exposed occurrences (all) Blood cortisol decreased subjects affected / exposed occurrences (all) Eosinophil count increased subjects affected / exposed occurrences (all)	 4 / 107 (3.74%) 5 2 / 107 (1.87%) 2 1 / 107 (0.93%) 1		
Injury, poisoning and procedural complications			

Arthropod sting subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Concussion subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Cardiac disorders Cardiovascular disorder subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	6 / 107 (5.61%) 8		
Balance disorder subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Dizziness subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Syncope subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Constipation subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Diarrhoea subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		

Erythema			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Sunburn			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	6		
Rhinitis			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences (all)	2		
Folliculitis			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		

Hordeolum subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Impetigo subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Peritonsillar abscess subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Viral infection subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Metabolism and nutrition disorders Iron deficiency subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 November 2013	Clarifications concerning efficacy, pharmacokinetic, and laboratory assessments; calculation of body surface area concomitant medications, vitamin D supplementation; details concerning discontinuation and end of treatment.
12 June 2014	Specification of US sites assigned to perform HPA axis and PK assessments; clarification of the main inclusion criteria for all subjects; additional inclusion criteria for subjects not performing HPA axis and PK assessments; dose for HPA axis subgroup; limit of vitamin D analogues; Australia & New Zealand removed as participating countries; sites updated; simplification to SAE reporting.
16 February 2015	Extent of BSA; definitions of controlled disease based on baseline disease severity, inclusion of subjects with mild disease severity; update of LSLV; specifications of data handling; additional inclusion criteria for HPA/ non-HPA subjects.
14 August 2015	Inclusion of Central and Eastern European sites; allowing German sites to perform HPA axis and PK assessments.
24 November 2015	Inclusion of Romanian sites for HPA axis and PK assessments; update of LSLV; inclusion of Synacthen® information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported