Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Daivobet / Xamiol
Calcipotriol / Betamethasone dipropionate

DK/W/0027/pdWS/003

Marketing Authorisation Holder:
LEO Pharma A/S

Rapporteur:	DK
Finalisation procedure (day 120):	10 August 2019

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Daivobet / Xamiol
INN (or common name) of the active substance(s):	Calcipotriol / Betamethasone dipropionate
MAH:	LEO Pharma A/S
Currently approved Indication(s)	Topical treatment of scalp psoriasis in adults. Topical treatment of mild to moderate “non-scalp” plaque psoriasis vulgaris in adults.
Pharmaco-therapeutic group (ATC Code):	D05AX52
Pharmaceutical form(s) and strength(s):	Gel, 50 micrograms/0.5 mg/g gel

I. EXECUTIVE SUMMARY

SmPC changes are proposed in sections 4.8 and 5.1.
No PL changes are proposed.

II. RECOMMENDATION

The following wording should be implemented by a type IB variation submitted within 30 days after the end of the procedure in order to update the product information:

Change in '4.8 Undesirable effects' (currently approved text to be amended)

Paediatric population
~~No new adverse events and no new adverse reactions were seen in 109 adolescents aged 12-17 years with scalp psoriasis treated with Daivobet gel for 8 weeks. However, due to the size of the studies, no firm conclusion can be drawn as to the safety profile of Daivobet gel in adolescents compared to that in adults. See section 5.1.~~

No clinically relevant differences between the safety profiles in adult and adolescent populations have been observed. A total of 216 adolescent subjects were treated in three open label clinical trials.
See Section 5.1 for further details regarding the trials.

Proposed change in '5.1 Pharmacodynamic properties' (addition)

Paediatric population

Scalp
Effects on calcium metabolism were investigated in two uncontrolled open 8-week *trials* ~~studies~~ including in total 109 adolescents aged 12-17 years with scalp psoriasis who used up to 69 g per week of Daivobet gel. No cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in 30 patients; one patient showed a decrease in cortisol response to ACTH challenge after 4 weeks of treatment, which was mild, without clinical manifestations, and reversible.

Scalp and body
Effects on calcium metabolism was investigated in one uncontrolled open 8-week trial in 107 adolescents aged 12-17 years with scalp and body psoriasis who used up to 114.2 g per week of Daivobet gel. No cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in 31 patients; ~~there were 5~~ five patients ~~who~~ showed a decrease in cortisol response to ACTH challenge where 2 of the 5 patients showed only borderline decreases. Four of the patients showed the decrease after 4 weeks of treatment and 2 showed ~~the~~ decrease after 8 weeks including 1 patient showing a decrease at both periods. These events were mild, without clinical manifestations, and reversible.

III. INTRODUCTION

On 19 October 2019, the MAH submitted a completed paediatric study for Daivobet/Xamiol, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH proposed the following regulatory action: Change of the text in 4.8 and addition to the text in 5.1 of the SmPC.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study(ies)

The investigational medicinal product used was Daivobet® gel; a two-compound gel containing calcipotriol 50 mcg/g (a vitamin D3 analogue) and betamethasone 0.5 mg/g (as dipropionate; a corticosteroid).
Daivobet® gel is launched in different markets under the following trademarks: Daivobet®, Dovobet®, Taclonex®, and Xamiol®. In the clinical trial reports the LEO product code, LEO 80185 gel is used.
Daivobet® gel was initially approved via the decentralised procedure for the treatment of scalp psoriasis in adults on 15-Aug-2008. Subsequently in 2009, the product was also approved for the use of mild to moderate “non-scalp” plaque psoriasis vulgaris in adults.

There is no specific paediatric formulation.

IV.2 Clinical aspects

1. Introduction

The MAH submitted a final report for:

Trial LP0076-1017: 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

2. Clinical study(ies)

- **Description**

This trial was undertaken as a post-marketing commitment request from the FDA.
LP0076-1017 was an 8-week, multi-centre, prospective, non-controlled, open-label, single-group, phase 2 trial in adolescent subjects (12 to <17 years) with psoriasis vulgaris on the scalp and body treated with LEO 80185 once daily that evaluated safety and effect on calcium metabolism. It was an international trial with centres in US, Canada, France, Poland, Germany, the United Kingdom, and Romania. For assigned US, German, and Romanian sites assessment of a potential suppressive effect on the hypothalamic-pituitary-adrenal (HPA) axis and pharmacokinetic assessments were also included.

➢ Methods

- Objective(s)

The primary objective of the trial was to evaluate safety of once daily dosing of LEO 80185, including investigations of hypothalamic-pituitary-adrenal (HPA) axis suppression, adverse drug reactions (ADRs), and calcium metabolism.

The secondary objective was the evaluation of efficacy.

- Study design

This was an international, multi-centre, prospective, non-controlled, open, single-group, 8-week trial in adolescent subjects (aged 12 to 16 years, 11 months) with scalp and body psoriasis.
The subjects received topical treatment with calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate) gel once daily for up to 8 weeks.

The trial consisted of 3 periods:

1) Washout: Depending on the prior use of disallowed treatments, the washout/screening period lasted between 7 to 56 days prior to the first administration of LEO 80185 (Visit 1).
2) Treatment: The treatment period lasted for up to 8 weeks with up to 5 visits: Visit 1 (day 0), Visit 2 (day 14), Visit 3 (day 28), Visit 4 (day 42) and Visit 5 (day 56). Visits 2 through 5 should have been performed within ±2 days of the scheduled time relative to Visit 1.
3) Follow-up: If applicable, there was a follow-up (FU) period consisting of visit FU1 (14 days after the last visit in the treatment period) and/or visit FU2 (28 days after the ACTH-challenge test performed at Visit 3 or Visit 5).

For the ACTH-challenge tests, 2 separate commercial solutions for injection containing cosyntropin products were used for the respective US and European sites: CORTROSYN® and Synacthen®.
CORTROSYN® was used in accordance with the U.S. Prescribing Information for the marketed product and Synacthen® was used in accordance with the European Summary of Product Characteristics.

- Study population /Sample size

The FDA required the trial to be conducted in 100 evaluable paediatric subjects (ages 12 to 16 years, 11 months) with psoriasis vulgaris on the scalp and body, to evaluate the safety and effect of LEO 80185 on calcium metabolism. In a subset of a least 30 subjects treated under maximal use conditions, evaluation of the hypothalamic-pituitary-adrenal axis (HPA) and pharmacokinetics was required.
No formal sample size calculation evaluating the power of the trial were performed.

For adverse events with a true (theoretical) frequency of at least 2% the probability of observing at least one case among the 100 subjects was at least 86.7%.

The trial subjects were included in 30 centres in Canada, Germany, France, United Kingdom, Poland, Romania, and US.

- Treatments

LEO 80185 was applied once daily to scalp and body psoriasis lesions. Subjects were instructed to discontinue treatment on individual lesions if/when a lesion has cleared.
Subjects whose scalp and body psoriasis cleared after 4-week treatment were to stop treatment with IMP and leave the trial.
Subjects who had psoriasis after 4 weeks of treatment continued treatment for an additional 4-week period.
For those subjects whose psoriasis cleared at Visit 2 or Visit 4, according to the (sub)investigator, should have discontinued treatment but remained in the trial. During periods of discontinuation of treatment those cleared subject were to restart treatment if the psoriasis reappeared.

- Outcomes/endpoints

Adverse drug reactions (ADRs)
Subjects with serum cortisol concentration of ≤18 mcg/dL at 30 minutes after ACTH challenge at Week 4 and at Week 8.
Change in albumin-corrected serum calcium from baseline (SV2) to Week 4, Week 8, and end of treatment.
Change in 24-hour urinary calcium excretion from baseline (SV2) to Week 4, Week 8, and end of treatment.

Secondary endpoints:

Safety:
Adverse events (AEs)
Subjects with serum cortisol concentration of ≤18 mcg/dL at both 30 and 60 minutes after ACTH-challenge at Week 4 and at Week 8.
Change in urinary calcium:creatinine ratio from baseline (SV2) to Week 4 and Week 8.
Change in serum alkaline phosphatase (ALP) from baseline (SV2) to Week 4 and Week 8.
AUC0-t, AUC0-∞, Cmax, Tmax, and T1/2 were to be calculated (when possible) at Week 4 for each assayed compound.

Efficacy:
Subjects with controlled disease (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.
Percentage change in Psoriasis area severity index (PASI) from baseline to end of treatment.
Subjects with controlled disease (clear or very mild) according to the patient's global assessment of disease severity on the body at end of treatment.

- Statistical Methods

As this is an open-label, non-controlled trial there is no specific statistical analyses.

The analysis of safety was based on the safety analysis set according to the defined response criteria, except the analysis of the results from the ACTH-challenge test, which was based on the per protocol analysis set.

All subjects who applied any IP was included in the full analysis set and analysed for efficacy.

➢ Results

- Recruitment/ Number analysed

A total of 125 subjects were screened and 107 subjects were assigned to the treatment (Safety Analysis Set). Out of these 107 subjects, 31 subjects (Per Protocol Analysis Set) provided results for the ACTH-challenge test and 32 subjects provided samples for pharmacokinetic assessments.

- Baseline data

Sixty-two (57.9%) of the subjects were girls and the mean age was 14.2 years of age (median 14.0; range 12 to 16 years). The majority of the subjects were white (90.7%), non-Hispanic/Latino (93.5%), had Fitzpatrick skin types II, III, or IV (over 90%), and the mean BMI was 22.32 kg/m² (median 21.45; range 15.1 to 38.5 kg/m²).

According to the Investigator's global assessment of disease severity, the majority (87; 81.3%) of subjects had body psoriasis of moderate intensity; 14 (13.1%) had mild body psoriasis, and 6 (5.6%) had severe body psoriasis.

The mean extent of psoriasis on the scalp was 55.1% of the scalp area (median 50.0; range 10-100% of the scalp area) and the mean total extent of psoriasis on the scalp and body was 14.9% of BSA (median 13.0; range 4 to 68% of BSA).

For all subjects, the mean duration of psoriasis was 4.1 years (median 3.0; range 1 to 15 years).

- Efficacy results

Investigator's global assessment (IGA) of disease severity

Controlled disease (investigator's global assessment on the body) by visit and at end of treatment: full analysis set:

Visit Controlled disease (body)	LEO 80185 (n=107) Number of subjects	%
Visit 2 (Week 2)		
Controlled	15	14.4
Non-controlled	89	85.6
Total	104	100.0
Visit 3 (Week 4)		
Controlled	45	43.3
Non-controlled	59	56.7
Total	104	100.0
Visit 4 (Week 6)		
Controlled	46	51.1
Non-controlled	44	48.9
Total	90	100.0
Visit 5 (Week 8)		
Controlled	49	54.4
Non-controlled	41	45.6
Total	90	100.0
End of Treatment		
Controlled	62	57.9
Non-controlled	45	42.1
Total	107	100.0

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Out of the 107 subjects, 57.9% had *controlled disease* on the body (Table above) and 69.2% had *controlled disease* on the scalp (Table not shown here) as assessed by the IGA at the end of treatment. There were no clinically relevant differences between sexes or between the age groups (12 to 14 years, 15 to 17 years).

Psoriasis area severity index (PASI)

Percentage change in PASI from baseline to each visit and end of treatment: full analysis set:

Visit Percentage change in PASI	LEO 80185 (n=107)
Visit 2 (Week 2)	
Mean	-49.4
SD	24.8
Median	-51.1
Minimum	-98.9
Maximum	17.6
Number	104
Visit 3 (Week 4)	
Mean	-69.7
SD	28.2
Median	-78.0
Minimum	-100.0
Maximum	44.1
Number	104
Visit 4 (Week 6)	
Mean	-75.5
SD	27.5
Median	-84.3
Minimum	-100.0
Maximum	31.8
Number	90
Visit 5 (Week 8)	
Mean	-78.4
SD	31.3
Median	-90.8
Minimum	-100.0
Maximum	34.8
Number	90
End of Treatment	
Mean	-78.7
SD	32.4
Median	-91.4
Minimum	-100.0
Maximum	34.8
Number	107
95% CI (mean)	-84.9 to -72.5

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The mean percentage change in PASI was a 78.7% decrease by end of treatment with a 69.7% improvement in PASI already at Week 2.

Patient's global assessment of disease severity and patient assessment of itching

Sixty-seven (62.6%) of the 107 patients reported *controlled disease* on the body and 74 (69.2%) on the scalp at the end of treatment. The subjects experienced a relief in itching and improvement in sleep already at Week 2.

- Safety results

Safety was assessed by adverse events at all visits and by vital signs and clinical laboratory tests (haematology, biochemistry, urinalysis, and ACTH-challenge test [in a subset of 31 patients]) at Screening Visit 2, Week 4, and Week 8.

Common adverse events

In total, 38 subjects (35.5%) reported 62 AEs. 1 AE was *serious* and considered not related (*attempted suicide*), and 8 AEs were reported as adverse drug reactions. There was 1 AE leading to withdrawal: *blood cortisol decreased* at 30 minutes after ACTH stimulation at Week 4.

Panel 33 **Overall summary of adverse events: safety analysis set**

	LEO 80185 (n=107)	
Adverse event category	Number of adverse events	Number of subjects (%)
All adverse events	62	38 (35.5)
Adverse drug reactions	8	7 (6.5)
Serious adverse events	1	1 (0.9)
Adverse events leading to withdrawal from trial	1	1 (0.9)

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1) Only treatment emergent adverse events are included

Table 3–33: Adverse events by MedDRA primary system organ class: safety analysis set

	LEO 80185 (n=107)		
System Organ Class[1]	Number of AEs	Number of subjects	%
Infections and infestations	14	13	12.1
Investigations	8	7	6.5
Nervous system disorders	11	7	6.5
Respiratory, thoracic and mediastinal disorders	7	7	6.5
Skin and subcutaneous tissue disorders	4	4	3.7
Gastrointestinal disorders	3	3	2.8
Musculoskeletal and connective tissue disorders	4	3	2.8
Reproductive system and breast disorders	3	3	2.8
Injury, poisoning and procedural complications	2	2	1.9
Psychiatric disorders	2	2	1.9
Cardiac disorders	1	1	0.9
Endocrine disorders	1	1	0.9
Metabolism and nutrition disorders	1	1	0.9
Surgical and medical procedures	1	1	0.9
Total	62	38	35.5

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Serious adverse events
There was 1 serious adverse event of a *suicide attempt*. The subject was treated with IMP in 2016 and completed treatment according to protocol. The subject attempted suicide by overdosing on a combination of ibuprofen, diphenhydramine hydrochloride, and tinidazole/norfloxacin approximately 70 days after first dose of IMP and after finishing treatment.

At the follow-up visit, the subject came in for redraw of parathyroid hormone, which was elevated at V5 (Day 56) visit. The subject had overdosed on painkillers but did not go to the hospital that night. At the visit, the vitals were normal and the subject was sent to the emergency department for evaluation and later transferred to a psychiatric facility. The subject was hospitalised for 3 days after the suicide attempt and discharged. During this hospitalisation a urine test confirmed the ingestion of the drug combinations as well as measurement of acetaminophen levels. The outcome of the event was reported as recovered with sequelae due to ongoing therapy and treatment for depression.

The relevant medical history and current medical conditions recorded were anxiety, depression, and psoriasis. The concomitant medication recorded were folic acid, montelukast sodium, and salbutamol. The causality was assessed as not related by both the investigator and LEO Pharma A/S.

Adverse drug reactions
A total of 8 adverse events in 7 subjects (6.5%) were considered *possibly* or *probably* related. Of those adverse drug reactions there were 3 of *moderate* intensity: *blood parathyroid hormone increased*, *erythema*, and *folliculitis*. The remaining were considered *mild.*
Of note, any potential adverse clinical effect on the parathyroid hormone following treatment would have caused a decrease and not an increase.

Panel 35 **Adverse drug reactions by MedDRA primary system organ class and preferred term: safety analysis set**

	LEO 80185 (n=107)		
System Organ Class Preferred Term[1]	Number of AEs	Number of subjects	%
Investigations			
Blood cortisol decreased	2	2	1.9
Blood parathyroid hormone increased	1	1	0.9
SOC total	3	3	2.8
Skin and subcutaneous tissue disorders			
Acne	1	1	0.9
Erythema	1	1	0.9
SOC total	2	2	1.9
Endocrine disorders			
Hyperparathyroidism	1	1	0.9
SOC total	1	1	0.9
Infections and infestations			
Folliculitis	1	1	0.9
SOC total	1	1	0.9
Nervous system disorders			
Headache	1	1	0.9
SOC total	1	1	0.9
Total number of adverse events	8	7	6.5

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1) Only treatment emergent adverse events are included

Withdrawal due to adverse events
One subject was withdrawn due to low value of plasma cortisol at 30 minutes after ACTH stimulation at Week 4 according to protocol.

Vital signs and physical examination
There were no clinically significant abnormalities in vital signs. The 1 clinically significant abnormality recorded in physical examinations was Down syndrome.

Adrenal suppression (Primary endpoint)
The table below shows serum cortisol concentration at 30 minutes after ACTH challenge at baseline, Week 4 and Week 8 for the Per Protocol Analysis Set.

Serum Cortisol Concentration (mcg/dL)	LEO 80185 (n=31)
30 min after ACTH challenge test	
Screening 2	
Mean	22.32
SD	3.96
Median	23.60
Minimum	10.0
Maximum	27.9
Number	31
Week 4	
Mean	22.22
SD	4.73
Median	22.80
Minimum	8.6
Maximum	31.2
Number	31
Week 8	
Mean	23.58
SD	4.12
Median	23.40
Minimum	13.2
Maximum	31.2
Number	29

Five (16.1%) of the 31 subjects included in the Per Protocol Analysis Set showed a decrease in cortisol response to ACTH challenge at 30 minutes. Two subjects (6.5%) showed mild decreases: 17.4 and 17.8 mcg/dL at week 4 and 8 respectively. Four subjects (12.9%) showed a decrease after 4 weeks of treatment and 2 (6.5%) showed a decrease after 8 weeks, including 1 subject showing a decrease at both periods (Weeks 4 and 8). One (3.2%) of the subjects who showed signs of suppression at Week 4 was withdrawn. None of the subjects had a decrease in cortisol response at 60 minutes. See individual data in Table 3-4 below.

Table 3–4: Individual data for subjects with serum cortisol concentration <=18 mcg/dL at either 30 minutes or 60 minutes after ACTH challenge: per protocol analysis set

CRF number	Visit	Sample time	Serum cortisol concentration (mcg/dL)	Change in serum cortisol concentration from time 0 (mcg/dL)	Extent of BSA psoriasis (%)	Amount of IP used visit 1 to 3 (g)	Amount of IP used visit 3 to 5 (g)
LEO 80185							
7062	Baseline	0 min	12.1		21		
						65.31	
		30 min	25.9	13.8			
		60 min	26.6	14.5			
	Week 4 (Visit 3)	0 min	16.3		11		
		30 min	15.0	-1.3			
		60 min	33.1	16.8			
	Week 8 (Visit 5)	0 min	13.6		3		
		30 min	13.2	-0.4			
		60 min	34.3	20.7			
7087	Baseline	0 min	8.7		22		
						266.18	
		30 min	24.2	15.5			
		60 min	27.2	18.5			
	Week 4 (Visit 3)	0 min	8.7		10		
		30 min	8.6	-0.1			
		60 min	29.1	20.4			
7104	Baseline	0 min	7.2		21		
						133.7	121.06
		30 min	10.0	2.8			
		60 min	27.4	20.2			
	Week 4 (Visit 3)	0 min	10.8		15		
		30 min	12.7	1.9			
		60 min	24.2	13.4			
	Week 8 (Visit 5)	0 min	8.0		5		
		30 min	21.5	13.5			
		60 min	28.9	20.9			
7133	Baseline	0 min	6.5		28		
						132.47	
		30 min	18.6	12.1			
		60 min	22.7	16.2			
	Week 4 (Visit 3)	0 min	4.7		18		
		30 min	17.4	12.7			
		60 min	20.0	15.3			
7143	Baseline	0 min	14.0		22		
						166.51	90.46
		30 min	20.3	6.3			
		60 min	23.2	9.2			
	Week 4 (Visit 3)	0 min	11.7		16		
		30 min	22.9	11.2			
		60 min	27.9	16.2			
	Week 8 (Visit 5)	0 min	4.8		1		
		30 min	17.8	13.0			
		60 min	21.9	17.1			

Calcium metabolism

No cases of hypercalcaemia were reported (Panel 37) and there were no clinically relevant increases in urinary calcium or other parameters of calcium metabolism.

Panel 37 **Albumin-corrected serum calcium categorised as low, normal or high at Week 4, Week 8 and end of treatment shown against baseline category: safety analysis set**

Visit Albumin-corrected serum calcium	Baseline category[1]	LEO 80185 (n=107) End of period category[1] Low	Normal	High
Week 4 (Visit 3)	Low	2	4	0
	Normal	8	86	0
Week 8 (Visit 5)	Low	2	3	0
	Normal	6	76	0
End of Treatment	Low	2	4	0
	Normal	6	90	0

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1) Number of subjects with laboratory parameters below, within or above the reference range.

There were no clinically relevant changes in the further clinical laboratory assessment.

Pharmacokinetics

A validated bioanalytical assay was used for the quantification of calcipotriol, betamethasone dipropionate (BDP) and the metabolites MC1080 and betamethasone 17-propionate (B17P) in the plasma samples from 32 subjects.

Betamethasone dipropionate could be quantified in only four (4) subjects (13%) and its metabolite (betamethasone 17-propionate) in five (5) subjects (16%). Neither calcipotriol nor its metabolite (MC1080) were quantifiable in any of the samples, see table below.

Subjects with one or more observations above LLOQ per analyte at any timepoint

Analyte	LP0076-1017 (N=32)[a]		
	n (%)	C_{max} (pg/mL)[b]	Comments
BDP	4(13)	104	5 observations were above LLOQ. Unable to calculate AUC or $T_{½}$.
B17P	5(16)	126	12 observations above LLOQ. AUC_{all} was calculated for 2 subjects (188 and 462 pg*h/mL)
Calcipotriol	0(0)	n.d	-
MC1080	0(0)	n.d	-

[a]1 subject had only one sample taken but is included in the analysis

[b]Highest observed value in any subject

Total number of observations were 624 (156 observations for each of the 4 analytes).

BDP= betamethasone dipropionate; B17P= betamethasone 17-propionate; MC1080 is the metabolite of calcipotriol.

LLOQ for the 4 analytes: 30.0 pg/mL for betamethasone dipropionate and betamethasone 17-propionate, 50.0 pg/mL for calcipotriol, and 20.0 pg/mL for MC1080. AUC calculations were performed using Pheonix 8.0 (data on file).

3. Discussion on clinical aspects

This trial was undertaken as a post-marketing commitment request from the FDA.

Daivobet® gel (LEO 80185) is a fixed combination product containing calcipotriol 50 mcg/g, a vitamin D3 analogue, and betamethasone dipropionate 0.5 mg/g, approved for topical treatment of psoriasis vulgaris in adults.

Daivobet Gel is approved for use only in adults; the MAH applies with this submission only for a few amendments to the SmPC, no indication or posology in adolescent and children is applied for. As off-label use in adolescents is probable / to be expected, it is of value to investigate the safety of the product in this age group, with special focus on the HPA axis.

LP0076-1017 was an 8-week, multi-centre, prospective, non-controlled, open-label, single-group, phase 2 trial in 107 adolescent subjects (12 to <17 years) with psoriasis vulgaris on the scalp and body treated with LEO 80185 once daily evaluating safety, a potential suppressive effect on the hypothalamic-pituitary-adrenal (HPA) axis, effect on calcium metabolism, PK and as secondary endpoint efficacy.

According to the CSR, the patients “were to have received between 55 and 100 g of IMP per week for treatment, based on age and BSA”. However, the mean weekly amount of LEO 80185 used during the entire treatment period was 30.8 g/week. The MAH has not discussed this issue; MAH states in the Conclusion that “The number of subjects for this trial design was in line with discussions with the FDA as an adequate sample size for investigations into calcium metabolism (100 subjects) and for HPA axis and PK evaluations (30 subjects); however, no comments about the amount of Daivobet used. **(LoQ)**

For the 31 subjects whose adrenal response to ACTH challenge was measured, 5 subjects (16.1%) had a serum cortisol ≤18 mcg/dL 30 minutes after the ACTH stimulation test. No subjects showed suppression at 60 minutes. Of these 5 subjects, 3 were considered to show signs of adrenal suppression. PK samples from these 3 subjects had quantifiable analytes; B17P was detectable in 2 subjects and BDP was detected in only 1 subject.

It is well known that potent steroids may have an impact on the HPA axis and a warning is included in the approved SmPC 4.4 Special warnings and precautions for use. Hence, the finding in this study is not unexpected; however, it should be clarified if these 3 patients had a more extensive disease with a larger amount of Daivobet Gel used than the average use. **(LoQ)**

In the CSR a full list of all observed adverse events has been presented. Of the 107 subjects, 38 subjects (35.5%) reported 62 adverse events; 1 of these was an SAE (suicide attempt) and was considered *unrelated*. One subject was withdrawn due to low value of plasma cortisol at 30 minutes after ACTH stimulation. The *mild* and *moderate* adverse events were roughly equally distributed. A total of 8 events (reported in 7 subjects) were considered *possibly* or *probably related*.

As stated by the MAH, there were no reported cases of hypercalcaemia. However, at Week 4, 8 patients and at Week 8 and at End of Treatment, 6 patients changed from a normal albumin-corrected serum calcium to a low value. These numbers (8 and 6 patients) correspond to 7.5% and 5.6% respectively, of the study population The MAH should clarify if this is the same 6 patients throughout the study. **(OC)** Further, possible reasons for and clinical consequences of this change should be discussed by the Applicant. **(OC)**
There were no clinically relevant changes in the other clinical laboratory assessment.

Efficacy was evaluated as a secondary endpoint. The percentage of subjects with *controlled disease* according to IGA and PGA was comparable; 57.9% had *controlled disease* of the body (IGA) versus 62.6% (PGA) at end of treatment. The mean percentage change in PASI was a 78.7% decrease by end of treatment with a 69.7% improvement in PASI already at Week 2.

Comparing the results with those in adults it is surprising that 54.4% had controlled disease at week 8 (57.9% at end of treatment); according to the SmPC 31.7% of 296 adult psoriasis patients had controlled disease at week 8 after once daily use of Daivobet gel on non-scalp regions of the body. This should be discussed by the MAH. **(OC)** In contrast, the efficacy in the treatment of scalp psoriasis seems equal among adults and adolescents: 69.8% and 66.7% respectively at week 8.

V. PPDAR REQUEST FOR SUPPLEMENTARY INFORMATION

Major Objections
No Major Objections have been identified.

Other Concerns
1) The treatment plan is not clear: should the patients leave the trial if the psoriasis had cleared at week 4? Should these patients then re-enter the study in case of relapse? Looking at the result-tables it seems as if 90 patients remained in the trial until week 8, active psoriasis or not. Please clarify.

2) Effect on scalp psoriasis is not listed as an efficacy endpoint. However, results are presented. Please clarify.

3) The figures in the table *"Controlled disease (investigator's global assessment on the body) by visit and at end of treatment: full analysis set:"* (and other corresponding tables) need some further explanation.
(A) 45 out of 104 patients had controlled disease at week 4. So it is expected that only 59 continued to 8 weeks treatment. However, 49 out of 90 had controlled disease at week 8. Does this mean that 31 out of the 45 (90 – 59) had to re-start treatment? According to the CSR "Subjects whose scalp and body psoriasis cleared after 4-week treatment were to stop treatment with IMP and leave the trial." So this was the case for only 14 (104 – 90) patients? The MAH should clarify. **(OC)**
(B) Furthermore, comparing the results with those in adults it is surprising that 54.4% had controlled disease at week 8 (57.9% at end of treatment); according to the SmPC 31.7% of 296 adult psoriasis patients had controlled disease at week 8 after once daily use of Daivobet gel on non-scalp regions of the body. In contrast, the efficacy in the treatment of scalp psoriasis seems equal among adults and adolescents: 69.8% and 66.7% respectively at week 8. The MAH should discuss. **(OC)**

4) Comparing the efficacy results with those in adults it is surprising that 54.4% had controlled disease at week 8 (57.9% at end of treatment); according to the SmPC 31.7% of 296 adult psoriasis patients had controlled disease at week 8 after once daily use of Daivobet gel on non-scalp regions of the body. The MAH should discuss: Was the disease less severe in the adolescents? Did the adolescents use more of the IMP?

5) The extent (BSA) and the severity of the disease and the amount of IMP used in the 3 patients with s-cortisol < 18 mcg/dL 30 min after ACTH challenge should be clarified.

6) As FDA required that the subset of a least 30 subjects who should be included in the ACTH challenge test should be treated under maximal use conditions, the MAH should inform about the amount used by this subset. Panel 22 shows the average weekly amount of IMP used, but only for the safety analysis set.

7) (A) The MAH should comment on the low value of 8.6 mcg/dL (week 4, 30 min) in subject 7087 and on the low baseline 30 min value of 10.0 mcg/dL in subject 7104 – an inclusion criterium for the subset for ACTH challenge was: Subjects with a normal HPA axis function at SV2 including serum cortisol concentration above 5 mcg/dL before ACTH challenge and serum cortisol concentration above 18 mcg/dL 30 minutes after ACTH challenge.
(B) The MAH should discuss the value of this study in the light of patients using much less of the IMP as intended (30.8 g/week and 55-100 g/week, respectively).

8) (A) As stated by the MAH, there were no reported cases of hypercalcaemia. According to the Shift table (Panel 37), 8 (Week 4) to 6 (Week 8 and at End of Treatment) patients changed from a normal albumin-corrected serum calcium to a low value. These numbers (8 and 6 patients) correspond to 7.5% and 5.6% respectively, of the study population The MAH should clarify if this is the same 6 patients throughout the study.
(B) Further, possible reasons for and clinical consequences of this change should be discussed by the Applicant.

VI. ASSESSMENT OF RESPONSE TO QUESTIONS

QUESTION 1
The treatment plan is not clear: should the patients leave the trial if the psoriasis had cleared at week 4? Should these patients then re-enter the study in case of relapse? Looking at the result-tables it seems as if 90 patients remained in the trial until week 8, active psoriasis or not. Please clarify.

MAH's RESPONSE 1
Subjects whose scalp and body psoriasis cleared (according to the [sub]investigator) after 4-weeks treatment, were to stop treatment with IMP and leave the trial. The subjects who were clear at Week 4 were not to re-enter the trial.

A total of 12 subjects of the 104 subjects who attended the Week 4 visit had cleared psoriasis and left the trial as per protocol. Further 2 patients withdrew from the trial; 1 due to unacceptable adverse event and 1 'voluntarily'. 90 subjects remained in the trial until Week 8.

Subjects whose psoriasis cleared at Week 2 or 6 (according to the [sub]investigator) were to stay in the trial but discontinue treatment; however, these subjects were able to restart treatment if the psoriasis had reappeared.

Assessor's comment
The treatment plan has been clarified.
Conclusion: Issue solved.

QUESTION 2
Effect on scalp psoriasis is not listed as an efficacy endpoint. However, results are presented. Please clarify.

MAH's RESPONSE 2
The present phase 2 trial was undertaken in response to a Post Marketing Requirement (PMR) from the FDA issued with the approval of the treatment of plaque psoriasis of the body in the adult population. LP0076-1017 was conducted in adolescent patients with plaque psoriasis of the scalp and body ages 12 to 16 years, 11 months to evaluate the safety and effect of Daivobet® gel on calcium metabolism. In addition, evaluation of the hypothalamic-pituitary axis and pharmacokinetics in a subset of subjects treated under maximal use conditions was required.

Prior to initiation of LP0076-1017 there were 2 post-approval commitment trials conducted in adolescent subjects using Daivobet® gel. Both trials were 8-week, multi-centre, prospective, non-controlled, open, single-group, phase 2 trials in adolescent subjects (aged 12 to 17 years) with psoriasis vulgaris on the scalp using Daivobet® gel once daily. Trial MBL 0801 was a national trial (centres in the US) and Trial MBL 0412 INT was an international trial (centres in Canada, France, and the United Kingdom). These data were submitted and approved as part of an sNDA for an adolescent indication (age 12-17 years) for the treatment of plaque psoriasis of the scalp. In the EU, the data from these 2 trails were submitted as part of the article 46 DK/W/0027/pdWS/002.

Efficacy of Daivobet® gel on body and scalp psoriasis was assessed in this trial. As effect of Daivobet® gel on the scalp psoriasis had already been established in the 2 trials in adolescents mentioned above, the efficacy endpoints in this trial involved only assessments of body psoriasis to avoid large number of endpoints. However, the scalp was treated with Daivobet® gel and the effect on scalp psoriasis was assessed in the trial according to the protocol. Therefore, all efficacy results, as specified in the protocol, were presented in the clinical trial report even though the effect on the scalp was not specified as an endpoint.

Assessor's comment:
The MAH has clarified why results of scalp psoriasis were reported though not specified as an efficacy endpoint. The explanation is accepted.
Conclusion: Issue solved.

QUESTION 3
The figures in the table *"Controlled disease (investigator's global assessment on the body) by visit and at end of treatment: full analysis set:"* (and other corresponding tables) need some further explanation.

(A) 45 out of 104 patients had controlled disease at week 4. So it is expected that only 59 continued to 8 weeks treatment. However, 49 out of 90 had controlled disease at week 8. Does this mean that 31 out of the 45 (90 – 59) had to re-start treatment? According to the CSR *"Subjects whose scalp and body psoriasis cleared after 4-week treatment were to stop treatment with IMP and leave the trial."* So this was the case for only 14 (104 – 90) patients? The MAH should clarify.

(B) Furthermore, comparing the results with those in adults it is surprising that 54.4% had controlled disease at week 8 (57.9% at end of treatment); according to the SmPC 31.7% of

296 adult psoriasis patients had controlled disease at week 8 after once daily use of Daivobet gel on non-scalp regions of the body. In contrast, the efficacy in the treatment of scalp psoriasis seems equal among adults and adolescents: 69.8% and 66.7% respectively at week 8. The MAH should discuss.

MAH's RESPONSE 3

A) *Controlled* disease (according to investigator's global assessment (IGA)) was defined as *clear* or *almost clear* disease for subjects with at least *moderate* disease at baseline and *clear* disease for subjects with *mild* disease at baseline. However, only subjects with *clear* disease (according to the IGA) on the body and scalp at Week 4 were allowed to leave the trial. 12 subjects (out of 104 subjects attending Week 4 visit) were *clear* at Week 4 and left the trial as per protocol. Further 2 subjects withdrew from the trial; 1 due to unacceptable adverse event and 1 voluntarily. 90 subjects remained in the trial until Week 8 of which 49 had *controlled* disease at Week 8 (LP0076-1017 CTR Figure 1-1 and LP0076-1017 CTR Table 2-2).

B) LP0076-1017 was an uncontrolled, open-label trial with the majority of subjects having more severe disease (moderate and severe). It is noted that due to the presence of residual redness of the skin in those with *controlled* disease, it may be more difficult going from mild disease to clear than going from moderate disease to almost clear and could explain the higher proportion of subjects with *controlled* disease (Panel 1).

Panel 1 **Comparison of trial populations and mean weekly Daivobet® gel used (LP0076-1017 and MBL 0202 INT)**

Trial (location) no. subjects	Baseline severity (IGA) no. subjects (%)	Subjects with controlled disease (IGA) Week 8 (LOCF)	Mean weekly IMP used
MBL 0202 INT (body) 126 subjects	Mild: 31 (25%) Moderate: 95 (75%)	40 (31.7%)	22.7g
LP0076-1017 (body+scalp) 107 subjects	Mild: 14 (13%) Moderate: 87 (81%) Severe: 6 (6%)	62 (57.9%)	30.8g

Further, it is possible that the more treatments patients have tried the more resistant to treatment they may become and it is likely that the adolescent subjects had shorter treatment experience with other medications as compared with the adult patients. Additionally, it could be suggested that the mean weekly amount used 22.7 g (adults) versus 30.8 g (adolescents) indicate better adherence to treatment, considering the relatively smaller body surface area in adolescents. In the efficacy evaluations, after treatment with Daivobet® gel of scalp psoriasis in adults, a different definition of *controlled* disease was used, omitting a 2-step improvement. Furthermore, controlled disease (IGA) on the scalp at Week 8 (LOCF) in adults is based on data in 1108 subjects from 2 pooled phase 3, pivotal, randomised, controlled trials. In the 2 pooled uncontrolled, open-label trials in adolescents with scalp psoriasis 83 out of 109 subjects (76.1%) achieved *controlled* disease (IGA) at Week 8 (LOCF). Overall, it was expected that *controlled* disease (IGA) on the scalp in adolescents in LP0076-1017 was to be higher based on the trial design and from the results in previous trials in adolescents (please refer to Response 2 for additional information).

Assessor's comments:
A) The question posed was obviously due to the Assessor's "temporarily" oversight of the definitions of *controlled* and *clear.*
Conclusion: Issue solved.
B) The MAH has presented some possible explanations for the difference in efficacy among adolescents and adults. The explanations are hypothetical; however, they are acceptable.
Conclusion: Issue solved.

QUESTION 4
Comparing the efficacy results with those in adults it is surprising that 54.4% had controlled disease at week 8 (57.9% at end of treatment); according to the SmPC 31.7% of 296 adult psoriasis patients had controlled disease at week 8 after once daily use of Daivobet gel on non-scalp regions of the body. The MAH should discuss: Was the disease less severe in the adolescents? Did the adolescents use more of the IMP?

MAH's RESPONSE 4
Please refer to Response 3 for the disease severity and IMP usage of the adolescents as compared with the adult data presented in the SmPC.

Assessor's comment:
This Q4 is the same as Q3B, so an editorial mistake)
Conclusion: Issue solved.

QUESTION 5
The extent (BSA) and the severity of the disease and the amount of IMP used in the 3 patients with s-cortisol <18 mcg/dL 30 min after ACTH challenge should be clarified.

MAH's RESPONSE 5
There were 5 subjects with s-cortisol <18 mcg/dL 30 min after ACTH challenge; however, 2 subjects had borderline decreases and are not discussed (17.4 mcg/dL (Subject 7133) and17.8 mcg/dL (Subject 7143)). Panel 2 shows the disease severity, extent of BSA, and amount of IMP used for the 3 subjects in question.

Panel 2 **Individual data for 3 subjects with serum cortisol concentration <=18 mcg/dL at either 30 minutes or 60 minutes after ACTH challenge: per protocol analysis set**

CRF number	Visit	Sample time	Serum cortisol conc (mcg/dL)	Disease severity (IGA) body/scalp	Extent of BSA (%)	IMP used	
						Baseline to Week 4(g)	Week 4 to Week 8 (g)
7062	Baseline	0 min	12.1	mod/mod	21	65.31	
		30 min	25.9				
		60 min	26.6				
	Week 4 (Visit 3)	0 min	16.3	mild/mild	11		
		30 min	15.0				
		60 min	33.1				
	Week 8 (Visit 5)	0 min	13.6	alm clear/alm clear	3		
		30 min	13.2				
		60 min	34.3				
7087	Baseline	0 min	8.7	mod/mod	22	266.18	
		30 min	24.2				
		60 min	27.2				
	Week 4 (Visit 3)	0 min	8.7	mild/clear	10		
		30 min	8.6				
		60 min	29.1				
7104	Baseline	0 min	7.2	mod/mod	21	133.7	121.06
		30 min	10.0				
		60 min	27.4				
	Week 4 (Visit 3)	0 min	10.8	mild/mild	15		
		30 min	12.7				
		60 min	24.2				
	Week 8 (Visit 5)	0 min	8.0	mild/mild	5		
		30 min	21.5				
		60 min	28.9				

Mod = moderate, alm clear = almost clear Cross references LP0076-1017 Table 3-4 and Appendix 2,6, Listing 6-1

Assessor's comment:
As it appears from the assessment above [*"It should be clarified if these 3 patients had a more extensive disease with a larger amount of Daivobet Gel used than the average use"*], the purpose of this question was to clarify if a more extensive disease with a larger amount of IMP used could explain the low s-cortisol. The MAH has just shown the figures (again) without any further discussion. In conclusion, neither the extent of disease nor the amount of IMP used seem to explain the low s-cortisol observed. The issue will not be further pursued.
Conclusion: Issue solved.

QUESTION 6
As FDA required that the subset of a least 30 subjects who should be included in the ACTH challenge test should be treated under maximal use conditions, the MAH should inform about the amount used by this subset. Panel 22 shows the average weekly amount of IMP used, but only for the safety analysis set.

MAH's RESPONSE 6
The amount of IMP used by the subjects in the safety analysis set and per protocol analysis set (HPA-axis/PK subgroup) is summarised in Panel 3. The average weekly amount is in Panel 4.

Panel 3 **Amount of IMP used (g): safety analysis set and per protocol analysis set**

Visit interval Amount used[1] (g)	Safety Analysis Set (n=107)	Per Protocol Analysis Set (n=31)
Visit 1 to Visit 3 (4 weeks)		
Mean	136.2	157.0
SD	89.2	70.3
Median	127.7	162.9
Minimum	5.4	18.7
Maximum	431.1	266.2
Number[2]	92	31
Visit 3 to Visit 5 (4 weeks)		
Mean	103.5	107.0
SD	87.0	58.6
Median	82.9	96.3
Minimum	0.1	7.6
Maximum	433.3	239.0
Number[2]	80	27
Visit 1 to End of Treatment		
Mean	247.2	268.1
SD	172.8	114.4
Median	217.2	263.2
Minimum	12.0	26.3
Maximum	864.3	490.4
Number[2]	75	27

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1) Calculated by subtracting the weight of the used bottles from the mean normal weight of full bottles. Negative weights have been set to zero.
2) Only subjects who returned all dispensed bottles provide data.

Panel 4 **Average weekly amount of IMP used: safety analysis set and per protocol analysis set**

Visit interval Average weekly amount[1] (g)	Safety Analysis Set (n=107)	Per Protocol Analysis Set (n=31)
Visit 1 to Visit 3 (4 weeks)		
Mean	32.5	36.9
SD	21.5	16.1
Median	30.6	38.0
Minimum	1.4	4.2
Maximum	111.8	61.2
Number[2]	92	31
Visit 3 to Visit 5 (4 weeks)		
Mean	26.7	27.7
SD	22.2	16.3
Median	22.2	24.9
Minimum	0.0	2.2
Maximum	116.6	67.1
Number[2]	80	27
Visit 1 to End of Treatment		
Mean	30.8	33.2
SD	21.6	14.7
Median	26.6	32.1
Minimum	1.6	3.3
Maximum	114.2	61.8
Number[2]	75	27

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1) Calculated by subtracting the weight of the used bottles from the mean normal weight of full bottles. Negative weights have been set to zero.
2) Only subjects who returned all dispensed bottles provide data.

Assessor's comments:
The MAH has now presented the amount of IMP used by both analysis sets: According to Panel 3 above the Per Protocol Analysis Set used more IMP during the first 4 weeks than the Safety Analysis Set (157.0 vs 136.2 g (mean)); at the end of treatment the relative difference is less (268.1 vs 247.2 g (mean)). The MAH has not discussed whether these differences were significant or, more important, if the amount used by the Per Protocol Analysis Set fulfilled the definition of "maximal use conditions". **(OC)**

Conclusion: Issue not resolved.

The MAH should discuss if the amount used by the Per Protocol Analysis Set fulfilled the definition of *"maximal use conditions"*. **(OC)**

QUESTION 7
A) The MAH should comment on the low value of 8.6 mcg/dL (week 4, 30 min) in Subject 7087 and on the low baseline 30 min value of 10.0 mcg/dL in Subject 7104 – an inclusion criterium for the subset for ACTH challenge was: Subjects with a normal HPA axis function at SV2 including serum cortisol concentration above 5 mcg/dL before ACTH challenge and serum cortisol concentration above 18 mcg/dL 30 minutes after ACTH challenge.

B) The MAH should discuss the value of this study in the light of patients using much less of the IMP as intended (30.8 g/week and 55-100 g/week, respectively).

MAH's RESPONSE 7

A) Post-clinical phase, data cleaning revealed 6 subjects included in the HPA-axis subgroup who did not fulfil inclusion criterion at Screening Visit 2 (SV2) prior to treatment with Daivobet® gel. These subjects had serum cortisol results below the threshold for inclusion and therefore should not have been included, yet 5 of these 6 subjects completed the trial.

As these subjects had evaluable data, they were included in the per protocol analysis set (LP0076-1017 CTR Section 7.2.4) as current literature suggest that the test for adrenal insufficiency may employ a too short timeframe for diagnosis of suppression (Zueger T, 2014; Cartaya J, 2015).

Specifically concerning the 2 subjects referred to in Question 7 details are given below:

Subject 7087 showed transient decrease in cortisol given that the value was normalised at 60 minutes (Panel 2). The Subject voluntarily left the trial after Week 4 and no results for Week 8 are available. The Subject used 266.2 g IMP during 4 weeks and this was Subject who used the most of IMP in HPA axis subgroup (mean 157.0 g); see Panel 3 and Panel 4 in response to Question 6.

Subject 7104 also had a low value (12.7 mcg/dL) at 30 minutes after ACTH challenge at Week 4 but normal values at 60 minutes after ACTH challenge at Week 4 and 30 and 60 minutes after ACTH challenge at Week 8 (Panel 2).

B) For subjects not performing HPA axis and PK assessments, the maximum weekly dose, and the number of bottles dispensed at each dispensing visit (Visit 1, 2, 3 and 4) was dependent on the subject's age and BSA at Visit 1 (Panel 5).

Panel 5 **Criteria for dose of subjects not performing HPA axis**

Age range (years)	BSA[a]	Maximum weekly dose Daivobet® gel	Number of bottles dispensed[b]
12 to < 15	≤ 1.3 m^2	55g	2
12 to < 15	> 1.3 m^2	75g	3
> 15	BSA ≤ 1.7 m^2	75g	3
> 15	BSA > 1.7 m^2	100g	4

Cross-reference: LP0076-1017 CTR Panel 12

[a]BSA calculated using the Mosteller formula (BSA (m^2) = ([Height (cm) x Weight (kg)] / 3600) ½ (Mosteller RD, 1987))

[b]Bottles distributed at dispensing visits

For subjects performing HPA axis and PK assessments the subjects were given enough IMP to treat all affected areas of scalp and body once daily to achieve maximal use conditions. The maximum daily dosage approved for adults is 15 g in the EU, which corresponds to an approximate maximum weekly dose of 100 g. The overall weekly amount of Daivobet® gel used in trial LP0076-1017 was not less than intended and similar to what

was seen in adults with body psoriasis in the MBL 0202 INT trial (a mean weekly amount of Daivobet® gel of 22.7g; Panel 1).

Assessor's comments:
A) It is agree that the results of the ACTH challenge are acceptable and that the deviations from the inclusion criteria are insignificant. However, the MAH might have taken into account that "current literature suggest that the test for adrenal insufficiency may employ a too short timeframe for diagnosis of suppression" before designing the trial. This will however, not be pursued.

B) The MAH and this Assessor may interpret "maximal use conditions" differently and the MAH should discuss if the amount used by the Per Protocol Analysis Set fulfilled the definition of *"maximal use conditions"*. **(OC**

Conclusion: Issue not solved.

The MAH should discuss if the amount used by the Per Protocol Analysis Set fulfilled the definition of *"maximal use conditions"*. **(OC)**

QUESTION 8
A) As stated by the MAH, there were no reported cases of hypercalcaemia. According to the Shift table (Panel 37), 8 (Week 4) to 6 (Week 8 and at End of Treatment) patients changed from a normal albumin-corrected serum calcium to a low value. These numbers (8 and 6 patients, respectively) correspond to 7.5% and 5.6% respectively, of the study population. The MAH should clarify if this is the same 6 patients throughout the study.

(B) Further, possible reasons for and clinical consequences of this change should be discussed by the MAH.

MAH's RESPONSE 8
A) These are not the same 6 subjects. Only 1 of these 6 subjects (Subject 7082) had a low value at Weeks 4 and 8 (baseline value = 2.22 mmol/L, Week 4 value = 2.11 mmol/L, Week 8 value = 1.99 mmol/L [reference range for normal = 2.15 to 2.55 mmol/L]). Details of the subjects with abnormal laboratory measurements are in LP0076-1017 Appendix 2.8, Listing 8-3.

B) The low albumin-corrected, serum calcium values observed in this trial are considered to be due to normal fluctuations in the individual subjects and not a clinical effect of the IMP. Further, as calcipotriol is a vitamin D analogue its potential side effect would be increased levels of calcium in the serum and urine, the opposite to the cases presented here. Parathyroid hormone (PTH) is released from the parathyroid gland when calcium levels are too low, which could lead to hyperparathyroidism, after prolonged periods of low calcium levels which is opposite to the expected adverse effect that Daivobet® gel would cause. Overall, the sporadic low levels of calcium in this trial are of no clinical relevance.

Assessor's comment:
The MAH has sufficiently described the number of patients with and the possible reason for the changes in serum calcium values. This is endorsed.
Conclusion: Issue solved.

MAH's RESPONSE to Assessor's comments to the SmPC (page 20 of this AR):
MAH accepts to make the editorial amendments in section 5.1 as indicated above (strike through and underlined) in the section with the subheading 'Scalp and body'.
Regarding 4.8 'vision, blurred' has been marked with 2 stars (has been corrected from 5 stars).
'Application site pain' is marked with 5 stars which is correct.

Assessor's comment:
The MAH has amended the SmPC as requested; this is endorsed.
Conclusion: Issue solved.

QUESTION 10 (Day 85 comment from UK)
It is noted that the proposed SmPC wording in Section 4.8 and Section 5.1 will state:

Section 4.8 Undesirable effects

Paediatric population
No clinically relevant differences between the safety profiles in adult and adolescent populations have been observed. A total of 216 adolescent subjects were treated in three open label clinical trials.

See Section 5.1 for further details regarding the trials.

Section 5.1 Pharmacodynamic properties

Paediatric population

Scalp and body
Effects on calcium metabolism was investigated in one uncontrolled open 8-week trial in 107 adolescents aged 12-17 years with scalp and body psoriasis who used up to 114.2 g per week of Daivobet gel. No cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in 31 patients; five patients showed a decrease in cortisol response to ACTH challenge where 2 of the 5 patients showed only borderline decreases. Four of the patients showed decrease after 4 weeks of treatment and 2 showed the decrease after 8 weeks including 1 patient showing a decrease at both periods. These events were mild, without clinical manifestations, and reversible.

Although Section 4.8 mentions 'a total of 216 adolescent subjects in 3 trials', section 5.1 only appears to discuss one trial involving 107 adolescents. To maintain consistency between the two sections, we suggest that section 5.1 reflects findings from the 3 trials and the total of 216 adolescent subjects.

We also suggest that the information regarding 'Paediatric population' in Section 4.2 is reviewed. Given that there is data on the use of Daivobet gel in paediatric patients, it is envisaged that statements reflecting the available paediatric data are included in Section 4.2.

MAH's RESPONSE 10
Section 4.8 mentions 3 trials and a total of 216 adolescent subjects. The 3 trials are the following: MBL 0801; MBL 0412 INT; LP0076-1017.

The trials MBL 0801 and MBL 0412 INT included subjects (total 109) with scalp psoriasis and the trials were submitted in 2013 as part of the procedure DK/W/0027/pdWS/002. The authority approved description of the trials MBL 0801 and MBL 0412 INT are described in section 5.1 with the subheading 'Scalp'.

The trial LP0076-1017 included subjects (107 subjects) with scalp and body psoriasis and the trial is submitted with the current procedure DK/W/0027/pdWS/003. The proposed description of this trial is described in section 5.1 with the subheading 'Scalp and body'.

Thus, section 4.8 describes the outcome of the 3 trials together (216 subjects) whereas section 5.1 describes the scalp studies in one subheading (109 subjects), submitted in 2013 as part of the procedure DK/W/0027/pdWS/002, and the recent scalp and body study in another subheading (107 subjects).

For clarification, the SmPC texts are provided below (proposed texts in italic, already authority approved text is not in italic, proposed deleted texts in strike through):

Section 4.8 Undesirable effects

Paediatric population
~~No new adverse events and no new adverse reactions were seen in 109 adolescents aged 12-17 years with scalp psoriasis treated with Daivobet gel for 8 weeks. However, due to the size of the studies, no firm conclusion can be drawn as to the safety profile of Daivobet gel in adolescents compared to that in adults. See section 5.1.~~

No clinically relevant differences between the safety profiles in adult and adolescent populations have been observed. A total of 216 adolescent subjects were treated in three open label clinical trials.

See Section 5.1 for further details regarding the trials.

Section 5.1 Pharmacodynamic properties

Paediatric population

Scalp
Effects on calcium metabolism were investigated in two uncontrolled open 8-week *trials* ~~studies~~

including in total 109 adolescents aged 12-17 years with scalp psoriasis who used up to 69 g per week of Daivobet gel. No cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in 30 patients; one patient showed a decrease in cortisol response to ACTH challenge after 4 weeks of treatment, which was mild, without clinical manifestations, and reversible.

Scalp and body
Effects on calcium metabolism was investigated in one uncontrolled open 8-week trial in 107 adolescents aged 12-17 years with scalp and body psoriasis who used up to 114.2 g per week of Daivobet gel. No cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in 31 patients; ~~there were~~ ~~5~~ five patients ~~who~~ showed a decrease in cortisol response to ACTH challenge where 2 of the 5 patients showed only borderline decreases. Four of the patients showed ~~the~~ decrease after 4 weeks of treatment and 2 showed ~~the~~ decrease after 8 weeks

including 1 patient showing a decrease at both periods. These events were mild, without clinical manifestations, and reversible.

Section 4.2 was updated as part of the procedure DK/W/0027/pdWS/002 (2013) with the following wording:

Paediatric population: The safety and efficacy of Daivobet gel in children below 18 years have not been established. Currently available data in children aged 12 to 17 years are described in section 4.8 and 5.1, but no recommendation on a posology can be made.

The wording in section 4.2 is in accordance with the CMDh Annotated QRD template for MR/DC Procedures and the wording is already included in the authority approved SmPC.

Assessor's comment:
The proposed changes in the SmPC are endorsed. Indeed, there is no need for "Paediatric population" twice in section 4.8.
Conclusion: Issue solved.

VII. FPDAR REQUEST FOR SUPPLEMENTARY INFORMATION

The MAH should discuss if the amount used by the Per Protocol Analysis Set fulfilled the definition of *"maximal use conditions''*.

VIII. ASSESSMENT OF RESPONSE TO QUESTIONS

Question 1: The MAH should discuss if the amount used by the Per Protocol Analysis Set fulfilled the definition of *"maximal use conditions"*.

RESPONSE 1
LEO considers that the amount of LEO 80185 used in the Per Protocol Analysis Set (HP Aaxis subgroup) did fulfill the definition of maximal use conditions as the subjects were given sufficient amounts of LEO 80185 to treat all affected areas of the scalp and body once daily.

The population in this trial was in accordance with the commitment to FDA to investigate the safety and efficacy of LEO 80185 treatment in 100 evaluable adolescent subjects with psoriasis vulgaris on the scalp and body. The commitment also included the evaluation of calcium metabolism in all subjects as well as investigations in a subset of at least 30 subjects, treated under maximal use conditions, to determine any effect of treatment on the hypothalamic-pituitary (HPA) axis and pharmacokinetics (PK).

Eligible subjects for the HPA-axis subgroup (per protocol analysis set) were to have psoriasis vulgaris of at least moderate severity and involving 10 to 35% of body surface area (excluding face and sensitive areas) and at least 20% of the scalp area.

The maximum daily dosage approved for adults is 15 g in the EU, which corresponds to an approximate maximum weekly dose of 100 g. In this trial, the maximum weekly dosage was up to 100 g per week depending on body surface area (BSA) and age.

For the subjects not performing HPA axis assessments, the dosing was according to the approved labelling instructions with specific guidance given with respect to age range and BSA (Panel 1).

Panel 1 Criteria for dose of subjects not performing HPA-axis assessments in trial LP0076-1017

Age range (years)	BSA[1]	Maximum weekly dose LEO 80185	Number of bottles dispensed[2]
12 to <15	≤1.3 m^2	55 g	2
12 to <15	>1.3 m^2	75 g	3
>15	BSA ≤ 1.7 m^2	75 g	3
>15	BSA > 1.7 m^2	100 g	4

[1]BSA calculated using the Mosteller formula (BSA (m^2) = ([Height (cm) × Weight (kg)] / 3600)^{½} (Mosteller RD, 1987)).
[2]Bottles including 60 g of LEO 80185 distributed at dispensing visits.
BSA = body surface area, HPA = hypothalamic-pituitary-adrenal.

For comparison, the amount of LEO 80185 used by the subjects in the safety analysis set and per protocol analysis set (HPA-axis subgroup) during the treatment intervals is summarised in Panel 2.

Panel 2 Amount of LEO 80185 used (g): safety analysis set and per protocol analysis set

Visit interval Amount used[1] (g)	Safety Analysis Set (n=107)	Per Protocol Analysis Set (n=31)
Visit 1 to Visit 3 (4 weeks)		
Mean	136.2	157.0
SD	89.2	70.3
Median	127.7	162.9
Minimum	5.4	18.7
Maximum	431.1	266.2
Number[2]	92	31
Visit 3 to Visit 5 (4 weeks)		
Mean	103.5	107.0
SD	87.0	58.6
Median	82.9	96.3
Minimum	0.1	7.6
Maximum	433.3	239.0
Number[2]	80	27
Visit 1 to End of Treatment		
Mean	247.2	268.1
SD	172.8	114.4
Median	217.2	263.2
Minimum	12.0	26.3
Maximum	864.3	490.4
Number[2]	75	27

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1) Calculated by subtracting the weight of the used bottles from the mean normal weight of full bottles. Negative weights have been set to zero.
2) Only subjects who returned all dispensed bottles provide data.

Compliance with treatment instructions was assessed by questioning the subject at all on-treatment visits whether he/she used the LEO 80185 as prescribed. Exposure to LEO 80185 was assessed by weighing the returned bottles and calculating the amount used. It is noted that weighing of cans is not a precise measure of exposure; however, as seen in Panel 2, subjects in the per protocol analysis set used higher amounts of LEO 80185 compared to those in safety set.

The mean amount used in the per protocol analysis set during the first 4 weeks of treatment was 157.0 grams and during the entire treatment period was 268.1 grams; in the safety analysis set the mean amount used during the first 4 weeks was 136.2 grams and during the entire treatment period was 247.2 grams (Panel 2). No analysis was planned to compare the amount of LEO 80185 used by subjects in the safety analysis set versus the per protocol analysis set. As per the statistical analysis plan, only descriptive presentations of LEO 80185 used was planned and hence these results are presented. Overall, it is reasonable to conclude that all subjects had used sufficient amounts of LEO 80185 to meet the maximal use criteria as defined in the protocol.

Assessor's comments:
We agree *"the population in this trial was in accordance with the commitment to FDA to investigate the safety and efficacy of LEO 80185 treatment in 100 evaluable adolescent subjects with psoriasis vulgaris on the scalp and body."* We also agree that the study included the evaluation of calcium metabolism in all subjects as well as investigations in a subset of at least 30 subjects, to determine any effect of treatment on the hypothalamic-pituitary axis and pharmacokinetics. We just questioned whether these 30 patients were *"treated under maximal use conditions"*. In the previous assessment of Q5, we noticed that "The extent of BSA was for the Safety Analysis Set at baseline 13.3%, for the Per Protocol Analysis Set 18% (Panel 27, CSR)" and that *"The amount of IMP used by the Safety Analysis Set during the first 4 weeks of treatment was 136.2 g (Table 3-29, CSR), while the Per Protocol Analysis Set used 157.0 g (Panel 3 below (Q6)".*

The Applicant has in the response to the LoOI repeated these amounts and states that *"No analysis was planned to compare the amount of LEO 80185 used by subjects in the safety analysis set versus the per protocol analysis set"*; however, we did not ask whether the per protocol analysis set had more IMP than the safety analysis set.

In conclusion, as there seems to be no clear definition of "maximal use conditions", and therefore the issue will not be pursued.

Conslusion: Issue reolved.

IX MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The study showed an acceptable safety profile, an expected minor impact on the HPA axis, no influence on the calcium metabolism and an efficacy at least comparable to the efficacy in adults.

The benefit-risk for Daivobet gel (one gram of gel contains 50 micrograms of calcipotriol (as monohydrate) and 0.5 mg of betamethasone (as dipropionate)) with the indications *"Topical treatment of scalp psoriasis in adults"* and *"Topical treatment of mild to moderate "non-scalp" plaque psoriasis vulgaris in adults"* remains positive.

- **Recommendation**

The following wording should be implemented by a type IB variation submitted within 30 days after the end of the procedure in order to update the product information:

Change in '4.8 Undesirable effects' (currently approved text to be amended)

Paediatric population
~~No new adverse events and no new adverse reactions were seen in 109 adolescents aged 12-17 years with scalp psoriasis treated with Daivobet gel for 8 weeks. However, due to the size of the studies, no firm conclusion can be drawn as to the safety profile of Daivobet gel in adolescents compared to that in adults. See section 5.1.~~

No clinically relevant differences between the safety profiles in adult and adolescent populations have been observed. A total of 216 adolescent subjects were treated in three open label clinical trials.
See Section 5.1 for further details regarding the trials.

Proposed change in '5.1 Pharmacodynamic properties' (addition)

Paediatric population

Scalp
Effects on calcium metabolism were investigated in two uncontrolled open 8-week *trials* ~~studies~~ including in total 109 adolescents aged 12-17 years with scalp psoriasis who used up to 69 g per week of Daivobet gel. No cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in 30 patients; one patient showed a decrease in cortisol response to ACTH challenge after 4 weeks of treatment, which was mild, without clinical manifestations, and reversible.

Scalp and body

Effects on calcium metabolism was investigated in one uncontrolled open 8-week trial in 107 adolescents aged 12-17 years with scalp and body psoriasis who used up to 114.2 g per week of Daivobet gel. No cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in 31 patients; ~~there were 5~~ five patients ~~who~~ showed a decrease in cortisol response to ACTH challenge where 2 of the 5 patients showed only borderline decreases. Four of the patients showed the decrease after 4 weeks of treatment and 2 showed ~~the~~ decrease after 8 weeks including 1 patient showing a decrease at both periods. These events were mild, without clinical manifestations, and reversible.