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

Enstilar

Calcipotriol and betamethasone dipropionate

DK/W/0027/pdWS/004

Marketing Authorisation Holder:

LEO Pharma A/S

Rapporteur:	DK
Finalisation procedure (day 120):	11 September, 2019

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Enstilar
INN (or common name) of the active substance(s):	One gram of cutaneous foam contains 50 micrograms of calcipotriol (as monohydrate) and 0.5 mg of betamethasone (as dipropionate).
MAH:	LEO Pharma A/S
Currently approved Indication(s)	Topical treatment of psoriasis vulgaris in adults.
Pharmaco-therapeutic group (ATC Code):	D05AX52
Pharmaceutical form(s) and strength(s):	Cutaneous foam 50 microg/g+0.5 mg/g

I. EXECUTIVE SUMMARY

SmPC changes are proposed in sections 4.2, 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:

Proposed change in Section 4.2 Posology and method of administration

Paediatric population
The safety and efficacy of Enstilar® foam in children below 18 years have not been established. Currently available data in children aged 12 to 17 years are described in sections 4.8 and 5.1.
~~No data are available.~~

Proposed additional text in 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 106 adolescent subjects were treated in one open-label clinical trial.
See section 5.1 for further details regarding this trial.

Proposed additional text in Section 5.1 Pharmacodynamic properties

Paediatric population
The effects on calcium metabolism were investigated in an uncontrolled, open-label, 4-week trial in 106 adolescents aged 12 to 17 years with scalp and body psoriasis. The subjects used up to 105 g Enstilar® per week. No cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in a subset of 33 subjects with extensive plaque psoriasis involving at least 20% of the scalp and 10% of the body surface area. After 4 weeks of treatment with Enstilar®, 2 subjects had a cortisol level ≤18 mcg/dL at 30 minutes after ACTH challenge, but had normal response at 60 minutes. A third subject had minimal cortisol response to the ACTH challenge test at baseline resulting in inconclusive results after the treatment. None of these cases had any clinical manifestations.

III. INTRODUCTION

On December 19, 2018, the MAH submitted a completed paediatric study for Enstillar, 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:

Proposed change in Section 4.2 Posology and method of administration

Paediatric population
The safety and efficacy of Enstilar® foam in children below 18 years have not been established.
Currently available data in children aged 12 to 17 years are described in sections 4.8 and 5.1.
No data are available.

Proposed additional text in 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 106 adolescent subjects were treated in one open-label clinical trial.
See section 5.1 for further details regarding this trial.

Proposed additional text in Section 5.1 Pharmacodynamic properties
Paediatric population
The effects on calcium metabolism were investigated in an uncontrolled, open-label, 4-week trial in 106 adolescents aged 12 to 17 years with scalp and body psoriasis. The subjects used up to 105 g Enstilar® per week. No cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in a subset of 33 subjects with extensive plaque psoriasis involving at least 20% of the scalp and 10% of the body surface area. After 4 weeks of treatment with Enstilar®, 2 subjects had a cortisol level ≤18 mcg/dL at 30 minutes after ACTH challenge, but had normal response at 60 minutes. A third subject had minimal cortisol response to the ACTH challenge test at baseline resulting in inconclusive results after the treatment. None of these cases had any clinical manifestations.

IV. SCIENTIFIC DISCUSSION

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

The investigational medicinal product used in the submitted study was Enstilar, or LEO 90100, a fixed combination product containing calcipotriol 50 mcg/g, a vitamin D analogue, and betamethasone dipropionate (BDP) 0.5 mg/g, a potent steroid.

LEO 90100 has been approved in all European Economic Area (EEA) countries (2016), USA (2015), Canada (2016), Australia (2016), New Zealand (2018), Switzerland (2016) and South Korea (2016) (trade names Enstilar® and Enstilum®).

The indication in EU is topical treatment of psoriasis vulgaris in adults.

There is no specific paediatric formulation.

IV.2 Clinical aspects

1. Introduction

The MAH submitted a final report(s) for:

Trial LP0053-1108: Safety and effect of LEO 90100 aerosol foam on the hypothalamic-pituitary-adrenal (HPA) axis and calcium metabolism in adolescent subjects (aged 12 to <17 years) with plaque psoriasis.

In the New Drug Application approval, FDA waived paediatric trial requirement in children aged 0 to 11 years 11 months because this age group has a higher body surface area (BSA) to body mass ratio than adolescents and adults, which increases the potential for adverse drug reactions due to absorption of topically applied compounds through the skin. However, FDA required a post-approval trial in paediatric subjects aged 12 to 16 years 11 months with psoriasis vulgaris on the body and scalp to assess the effect of LEO 90100 on calcium metabolism in 100 evaluable subjects and assessment of HPA axis suppression and pharmacokinetics in a subset of 30 subjects under maximal use conditions.

2. Clinical study(ies)

Trial LP0053-1108: Safety and effect of LEO 90100 aerosol foam on the HPA axis and calcium metabolism in adolescent subjects (aged 12 to <17 years) with plaque psoriasis.

- **Description**

Trial LP0053-1108 was an international, multi-center, prospective, open-label, non-controlled, single-group, 4-week trial in adolescent subjects (aged 12 to <17 years) with psoriasis vulgaris on the body and scalp. Subjects were treated with LEO 90100 once daily for up to 4 weeks.

The trial was conducted at 26 centers in 4 countries (the Netherlands, Poland, Romania, and the US).

- **Methods**

- Objective(s)

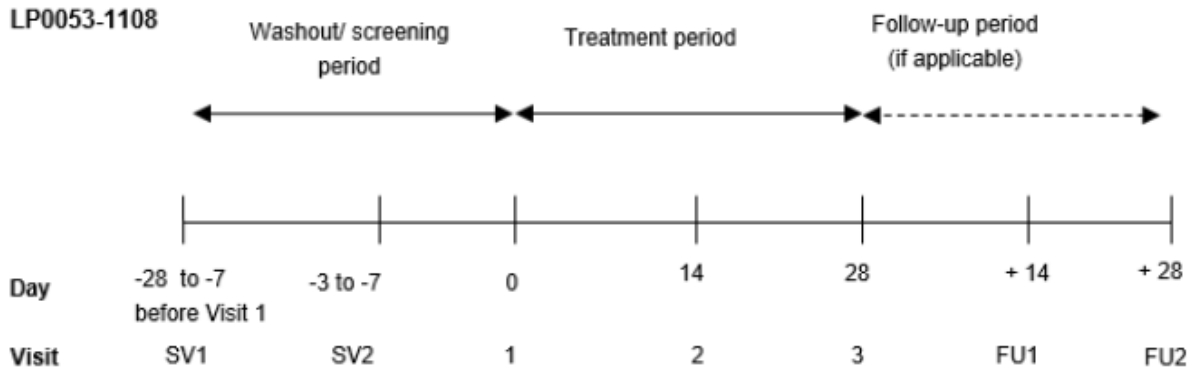
The primary objective was to evaluate the safety of once daily use of LEO 90100 in adolescent subjects with plaque psoriasis on the body and scalp.
Secondary objective was to evaluate the efficacy.

- Study design

This was an international, multi-center, prospective, open-label, non-controlled, single-group, 4-week trial in adolescent subjects (aged 12 to <17 years) with plaque psoriasis on the body and scalp. A subset of the subjects, referred to as the HPA axis cohort, was treated under maximal use conditions and were to have HPA axis testing, PK assessments, and analysis of 24-hour urine.

The trial consisted of 3 periods (wash-out, treatment, and follow-up [if applicable]) as illustrated in Panel 1.

Panel 1 Trial design



Washout / Screening Period: Depending on the prior use of treatments that were prohibited, but allowed with washout, the washout / screening period lasted between 7 to 28 days prior to the first administration of LEO 90100 (visit 1). There were two screening visits, SV1 and SV2. Depending on the subject's use of prohibited treatments, SV1 was up to 3 weeks before SV2; SV2 was 3 to 7 days before visit 1.
Treatment Period: The treatment period lasted for up to 4 weeks and included three visits: visit 1 (Day 0), visit 2 (Day 14; hereinafter 'Week 2'), and visit 3 (Day 28; hereinafter 'Week 4'). LEO 90100 was to be applied once daily to body and scalp psoriasis lesions.
Follow-up: If applicable, the investigator was to collect additional data after completion of the treatment ('follow-up visits'):
Visit FU1 was 14 days after the last visit in the treatment period; this visit was only required for subjects who at the last on-treatment visit had an ongoing SAE, or any ongoing non-serious AE(s) classified as possibly or probably related to the IMP, or an albumin-corrected serum calcium value above reference range. If the latter was the case, a new blood sample was to be collected.
Visit FU2 was 28 days after the ACTH-challenge test performed at Week 4; this visit was only required if the serum cortisol concentration was ≤18 mcg/dL 30 minutes after ACTH-challenge. Therefore, this visit was only applicable for subjects in the HPA axis cohort.

For the ACTH-challenge test, 2 separate commercial solutions for injection containing cosyntropin products were to be used for the 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 SmPC.

- Study population /Sample size

Eligible subjects had psoriasis vulgaris on the body and scalp of at least mild severity according to the physician's global assessment of disease severity (PGA) (using a 5-level scale: clear, almost clear, mild, moderate, severe)

The HPA cohort had more severe disease, which was at least moderate disease according to the PGA on body and scalp, at least 10% BSA affected, and at least 20% of the scalp area affected. Furthermore, a normal HPA axis function at SV2 (serum cortisol concentration above 5 mcg/dL before ACTH challenge and serum cortisol concentration above 18 mcg/dL 30 minutes after ACTH challenge).

No formal sample size calculation has been performed. However, the following consideration regarding the sample size was made: For AEs with a true (theoretical) frequency of at least 2%, the probability of observing at least 1 case among the 100 subjects was at least 86.7%.

The sample size was outlined in the paediatric investigation plan, and accepted by the FDA as an adequate sample size.
The trial was to be conducted in 100 evaluable adolescents to evaluate the safety and effect of LEO 90100 on calcium metabolism. In a subset of 30 with at least moderate plaque psoriasis treated under maximal use conditions, evaluation of HPA axis suppression and PK was required.

- Treatments

LEO 90100 was applied once daily to body and scalp psoriasis lesions. Subjects in the HPA axis cohort were to continue the treatment, even if their lesions had cleared at Week 2. For subjects in the non-HPA axis cohort, the following treatment principle applied: If the psoriasis lesions had cleared at Week 2 (according to the investigator), the subject was allowed to discontinue treatment but should stay in the trial. During periods of discontinuation of treatment, those cleared subject were to restart treatment if the psoriasis re-appeared.

For subjects in the non-HPA axis cohort, the maximum weekly dose was determined by the subject's age and the BSA at visit 1 and ranged from 60 g per week to 120 g per week. For subjects in the HPA axis cohort who were treated under maximum use conditions, the weekly dose was not limited.

- Outcomes/endpoints

Primary endpoints:

Adverse events
Subjects with serum cortisol concentration of ≤18 mcg/dL at 30 minutes after ACTH-challenge at Week 4
Change in albumin-corrected serum calcium from baseline (SV2) to Week 4
Change in calcium excretion from baseline (SV2) to Week 4 in 24-hour urine
Change in calcium:creatinine ratio from baseline (SV2) to Week 4 in 24-hour urine

Secondary endpoints:

Safety:
Subjects with serum cortisol concentration of ≤18 mcg/dL at both 30 and 60 minutes after ACTH-challenge at Week 4
Change in calcium:creatinine ratio from baseline (SV2) to Week 4 in spot urine

Efficacy:
Subjects with 'treatment success' (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 PGA on the body at Week 4
Subjects with 'treatment success' (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 PGA on the scalp at Week 4
Percentage change in PASI from baseline (visit 1) to Week 4
Subjects with 'treatment success' (i.e., 'clear' or 'very mild') according to the subject's global assessment of disease severity on the body at Week 4

Subjects with ‘treatment success’ (i.e., ‘clear’ or ‘very mild’) according to the subject’s global assessment of disease severity on the scalp at Week 4
Change in itch as assessed by the VAS from baseline (visit 1) to Week 4

- Statistical Methods

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

All subjects assigned to treatment were included in the full analyses set (FAS) and were analyzed for efficacy.

For the analysis of the results from the ACTH-challenge test, a per protocol analysis set was defined by including subjects from the FAS who were in the HPA axis cohort, and by excluding subjects who: 1) Received no treatment with the IMP; 2) Provided no results for the ACTH-challenge test at Week 4; 3) Did not fulfil the inclusion criterion concerning evidence of adrenal function at baseline.

A safety analysis set was defined by excluding subjects from the FAS who either received no treatment with IMP or for whom no post-baseline safety evaluations were available.

For the analysis of PK data, a PK analysis set was defined by including subjects from the FAS for whom PK measurements were available, and by excluding subjects who: 1) Received no treatment with the IMP; 2) Did not provide PK data at Week 4.

➢ Results

- Recruitment/ Number analysed

A total of 117 subjects were screened and 106 subjects were assigned to treatment: 72 subjects in the non-HPA axis cohort and 34 subjects in the HPA axis cohort; 103 subjects completed the trial.

- Baseline data

Sixty-one (57.5%) of the subjects were girls; the mean age of the 106 subjects was 14.2 years (median 14.0; range 12 to 16 years). The majority of the subjects (96.2%) were white and 97.2% reported their ethnicity as ‘not Hispanic or Latino’.

For all subjects, the mean duration of psoriasis was 4.3 years (median 3.0, range 1-12 years).

According to the PGA, the majority of subjects had moderate disease on the body (76.4%) and scalp (72.6%). The mean total extent of psoriasis on the body and scalp was 13.2% of BSA. The mean Psoriasis Area and Severity Index (PASI) score at baseline was 8.61 (median 8.45; range 2.0 to 20.7). According to the subject’s global assessment of disease severity, the majority of subjects had moderate disease on the body (66.0%) and scalp (63.2%).

No noteworthy differences between the FAS and the per protocol analysis set were observed for the demographic data presented above.

- Efficacy results

Physician's global assessment of disease severity on the body and scalp

The proportion of subjects achieving treatment success according to the PGA (clear or almost clear with at least a 2-step improvement) on the body and scalp are shown in the table below.

	LEO 90100 (n=106)			
	Body		Scalp	
Visit Treatment Success[1]	Number of subjects	%	Number of subjects	%
Visit 2 (Week 2)				
Yes	31	30.1	42	40.8
No	72	69.9	61	59.2
Total	103	100.0	103	100.0
Visit 3 (Week 4)				
Yes	74	71.8	78	75.7
No	29	28.2	25	24.3
Total	103	100.0	103	100.0
95% CI (% Treatment success)[2]		63.2 to 80.5		67.4 to 84.0
End of Treatment				
Yes	74	69.8	78	73.6
No	32	30.2	28	26.4
Total	106	100.0	106	100.0
95% CI (% Treatment success)[2]		61.1 to 78.6		65.2 to 82.0

05JUL18:12:18:41 LP0053 1108 t2pga_vis_suc.doc

1) Treatment success is defined as a PGA score of 'clear' or 'almost clear' for subjects with at least 'moderate' disease at baseline and 'clear' for subjects with 'mild' disease at baseline.
2) 95% CI based on a binomial distribution for the proportion of subjects with 'treatment success' at week 4 and end of treatment

At Week 4, 71.8% of the subjects achieved treatment success on the body and 75.7% achieved treatment success on the scalp. The treatment success rate was comparable between subjects aged 12 to 14 years and 15 to <17 years.

Physician's assessment of the extent and severity of clinical signs of plaque psoriasis (PASI)

The mean PASI decreased (improved) over time, from 8.61 at baseline to 1.40 at Week 4.

The table below shows the percentage change in PASI from baseline to each visit and EoT: FAS

Visit Percentage change in PASI	LEO 90100 (n=106)
Baseline	
Mean	8.61
SD	3.98
Median	8.45
Minimum	2.0
Maximum	20.7
Number	106
Percentage change at Visit 2 (Week 2)	
Mean	-59.09
SD	22.34
Median	-60.78
Minimum	-100.0
Maximum	0.0
Number	103
Percentage change at Visit 3 (Week 4)	
Mean	-82.05
SD	17.87
Median	-85.19
Minimum	-100.0
Maximum	-4.8
Number	103
95% CI (mean)[1]	-85.54 to -78.55
Percentage change at End of Treatment	
Mean	-79.89
SD	21.75
Median	-85.05
Minimum	-100.0
Maximum	0.0
Number	106
95% CI (mean)[1]	-84.08 to -75.70

04JUL18:14:52:28 LP0053 1108 t11_pchpasi_visit.doc

1) 95% CI for mean change in PASI based on a normal distribution for week 4 and end of treatment

By Week 2, a mean decrease of 59.1% in PASI score was observed; by Week 4, the mean decrease was 82.0%.

Subject's global assessment of disease severity and Subject's assessment of itch and itch-related sleep loss.

Eighty-six (83.5%) subjects achieved treatment success on the body while 81.6% achieved treatment success on the scalp at week 4.
The mean itch intensity at baseline as assessed on a 100 mm VAS was 39.3. The mean change in itch intensity from baseline to Week 4 was -32.5.
The mean itch-related sleep loss at baseline as assessed on the 100 mm VAS was 14.3. The mean change in itch-related sleep loss from baseline to Week 4 was -11.6.

- Safety results

Adverse events

In total, 22 (20.8%) subjects reported 32 AEs (Table 3-49, below).

Table 3–49: Adverse events by MedDRA primary system organ class: safety analysis set

	LEO 90100 (n=106)		
System Organ Class[1]	Number of AEs	Number of subjects	%
Infections and infestations	18	18	17.0
Skin and subcutaneous tissue disorders	6	5	4.7
General disorders and administration site conditions	2	2	1.9
Musculoskeletal and connective tissue disorders	2	2	1.9
Eye disorders	1	1	0.9
Injury, poisoning and procedural complications	1	1	0.9
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1	0.9
Surgical and medical procedures	1	1	0.9
Total	32	22	20.8

04JUL18:13:21:28 LP0053 1108 t49_aesoc.doc

The most frequent AEs were upper respiratory tract infection (8 [7.5%] subjects), nasopharyngitis, (4 [3.8%] subjects), and acne (2 [1.9%] subjects). All other AEs were reported by one subject only.

Serious adverse events and withdrawals
No deaths, other SAEs, or AEs leading to withdrawal were reported in this trial, and no severe AEs were reported.

Adverse drug reactions
A total of 6 related AEs in 5 subjects were reported: the causality for 5 events (acne, erythema, skin reaction, application site pain, product physical consistency issue) in 5 subjects was assessed as possibly or probably related to the IMP by the investigator; the causality for one event (myopia) was assessed as ‘unknown’ by the investigator. One of these related AEs (product physical consistency issue) was a product complaint.

Rebound effect
Two patients experienced rebound effect of the scalp lesions 42 days after the last application of the IMP.

Vital signs and physical examinations.
There were no clinically significant abnormalities in vital signs or physical examinations

Adrenal suppression - ACTH challenge (Primary endpoint)
Serum cortisol concentrations after ACTH challenge at SV2 (baseline) and Week 4 are tabulated in Panel 34.

Panel 34 Serum cortisol concentration at time 0 and 30 and 60 minutes after ACTH challenge at baseline and Week 4: per protocol analysis set

Visit	Statistic	Minutes after ACTH challenge test		
		0	30	60
Baseline	Mean	13.52	24.15	27.73
	SD	3.92	3.48	4.25
	Median	14.00	24.20	27.70
	Minimum	5.6	18.0	21.0
	Maximum	20.0	33.1	36.1
	Number	33	33	33
Week 4	Mean	13.85	23.61	27.71
	SD	5.53	4.42	4.94
	Median	14.60	23.30	27.70
	Minimum	4.4	15.0	16.0
	Maximum	30.3	37.6	44.0
	Number	33	33	33

Of the 33 subjects who had the ACTH challenge test, three subjects (9.1%) had serum cortisol concentration ≤18 mcg/dL 30 minutes after ACTH challenge at Week 4. These three subjects were all considered to show signs of mild adrenal suppression. The individual data for subjects with serum cortisol concentration ≤18 mcg/dL are tabulated in Panel 35.

Panel 35 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.

Subject	Visit	Sample time	Serum cortisol concentration (mcg/dL)	Change in serum cortisol concentration from time 0 (mcg/dL)	Total extent of psoriasis (%)	Amount of IMP(g)[1]
LEO90100						
PL08002	Baseline	0 min	16.0		21.0	N/A
		30 min	18.0	2.0		
		60 min	21.0	5.0		
	Week 4	0 min	13.0		9.0	
		30 min	15.0	2.0		
		60 min	16.0	3.0		
PL08007	Baseline	0 min	13.7		15.5	21.5
		30 min	19.4	5.7		
		60 min	21.7	8.0		
	Week 4	0 min	7.6		5.4	
		30 min	17.6	10.0		
		60 min	21.5	13.9		
RO05001	Baseline	0 min	7.5		22.0	838.69
		30 min	20.4	12.9		
		60 min	21.6	14.1		
	Week 4	0 min	12.1		11.0	
		30 min	16.5	4.4		
		60 min	25.4	13.3		
	FU2	0 min	12.8			
		30 min	21.9	9.1		
		60 min	24.7	11.9		

04JUL18:13:34:40 LP0053 1108 t3_cortlpp.doc

1) Total amount IMP used from baseline to Week 4.

The HPA axis suppression was reversible for 2 of the 3 subjects since they had normal serum cortisol concentration (>18 mcg/dL) 60 minutes after the ACTH challenge. One subject (3.0%) had serum cortisol concentration ≤18 mcg/dL 60 minutes after the ACTH challenge at Week 4.

Subjects with suppression at Week 4 (serum cortisol concentration ≤18 mcg/dL 30 minutes after ACTH challenge) were supposed to come back to the trial site 28 days later to have an additional ACTH challenge test (visit FU2); however, only 1 of the 3 subjects completed a FU2 visit and had an additional ACTH challenge test. At the FU2 visit, the subject had normal cortisol levels at both 30 and 60 minutes after ACTH challenge.

Calcium metabolism

The change from baseline to Week 4 is summarized in Panel 36.

Panel 36 Change in albumin-corrected serum calcium from baseline to Week 4: safety analysis set

Albumin-corrected serum calcium (mmol/l) Visit	LEO 90100 (n=106)
Calcium Corrected (mmol/L)	
Baseline	
Mean	2.237
SD	0.092
Median	2.240
Minimum	1.88
Maximum	2.49
Number	104
Change at Week 4	
Mean	-0.016
SD	0.119
Median	0.000
Minimum	-0.52
Maximum	0.26
Number	101
Lower 95% confidence limit (mean)	-0.039
Upper 95% confidence limit (mean)	0.008

05JUL18:12:42:23 LP0053 1108 t5_chalb.doc

Cross-reference: Table 3-5

The level of albumin-corrected serum calcium was classified as ‘low’, ‘normal’ or ‘high’, depending on whether the value was below, within, or above the reference range. Six subjects shifted from low (baseline) to normal (week 4) while 9 subjects shifted from normal to low.

Furthermore, no clinically relevant changes in calcium excretion in 24-hour urine, or calcium:creatinine ratio in 24-hour urine and spot urine samples were observed.

No clinically significant changes in other clinical laboratory parameters were observed.

Pharmacokinetics

A total of 33 subjects in the HPA axis cohort provided data and were included in the PK analysis set.
A validated bioanalytical assay was used for the quantification of calcipotriol, betamethasone propionate (BPD), and the metabolites MC1080 and betamethasone 17-propionate in the plasma samples (Panel 46):

Panel 46 Subjects with 1 or more observations above LLOQ per analyte at any time-point

Analyte	LEO 90100 (n=33[a])		
	n (%)	C_{max} (pg/mL) range	Comments
BDP	12 (36)	31.1 to 480	22 observations above LLOQ. All PK parameters could be calculated for 1 subject[b] (C_{max}=480 pg/mL, AUC_{all}=1219 pg*h/mL, AUC_{inf}=1250 pg*h/mL, $T_{½}$=0.5 h)
Betamethasone 17-propionate	6 (18)	30.8 to 91.7	11 observations above LLOQ. All PK parameters could be calculated for 1 subject[b] (C_{max}=61.9 pg/mL, AUC_{all}=314.4 pg*h/mL, AUC_{inf}=500.7 pg*h/mL, $T_{½}$=3.2 h)
Calcipotriol	0 (0)	N/A	No observations above LLOQ.
MC1080	0 (0)	N/A	No observations above LLOQ.

a) The total number of observations were:
(4 analytes × 5 time-points × 33 subjects) = 660

b) The subjects for whom PK parameters could be calculated (BDP, betamethasone 17-propionate) were 2 different subjects.

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

Abbreviations: BDP, betamethasone dipropionate; LLOQ; lower limit of quantification; N/A, not applicable.

BDP could be quantified in at least one sample from 12 subjects (36% of subjects in the PK analysis set) and its metabolite (betamethasone 17-propionate) in 6 subjects (18%). It was only possible to characterise the pharmacokinetic profile for BDP and betamethasone 17-propionate in two subjects, each in one subject. Neither calcipotriol nor its metabolite MC1080 were quantifiable in any of the samples.
None of the three subjects with HPA axis suppression had quantifiable PK analytes.

3. Discussion on clinical aspects

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

Enstilar Cutanous Foam® (LEO 90100), is a fixed combination product containing calcipotriol 50 mcg/g, a vitamin D analogue, and betamethasone dipropionate (BDP) 0.5 mg/g, a potent steroid, approved for topical treatment of psoriasis vulgaris in adults.

Enstilar® 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.

Trial LP0053-1108 was an international, multi-center, prospective, open-label, non-controlled, single-group, phase-2 trial in 106 adolescent subjects (aged 12 to <17 years) with psoriasis vulgaris on the body and scalp treated with LEO 90100 once daily for up to 4 weeks evaluating safety, a potential suppressive effect on the hypothalamic-pituitary-adrenal (HPA) axis, effect on calcium metabolism, PK and as secondary endpoint efficacy.
All subjects had body psoriasis of at least mild (mainly mild to moderate) disease severity as assessed by the PGA, with a minimum body involvement of at least 2% BSA (mean: 10.4%);

further, all subjects had mild to severe scalp psoriasis, with a minimum scalp involvement of at least 10% of the scalp area (mean: 50.6%).

Out of the 106 subjects, 22 subjects (20.8%) reported 32 AEs which were mostly mild in nature. No SAEs, AEs leading to withdrawal, or severe AEs were reported. A total of six events (reported in 5 subjects) were considered related to the IMP. As two of these AEs (acne and erythema) do not appear from the approved SmPC it should be included (OC).

The 33 subjects included in the HPA axis cohort had at baseline a mean BSA involvement of 18.5% on body and scalp, moderate disease severity on both body and scalp, and a mean PASI score of 10.5. They did not have a maximum weekly dose limit; and used a mean weekly amount of 114.7 g during the total treatment period – compared to 97.4 g in all subjects. So in conclusion, the HPA axis cohort had more severe disease than the average and they used more of the IMP; however, it is not clear if the cohort fulfilled the request from the FDA. The applicant should comment. (OC)

Three of the subjects in the HPA axis cohort demonstrated adrenal suppression after 30 minutes. However, two of the three subjects had normalised cortisol levels after 60 minutes; and the 3rd subject should most probably not have been included in the study, since the serum cortisol at baseline at the screening visit was exactly 18 mcg/dL. So in conclusion, the influence of treatment with the IMP on the HPA axis seems to be negligible.

Pharmacokinetics were also evaluated in the HPA axis cohort. The results show that the systemic absorption of the product is marginal. However, in a similar study in 32 adolescents using the gel formulation of the same combination product (LP0076-1017), BDP could be quantified in only four (13%) subjects compared to 12 (36%) in the actual study. This difference is significant, and the applicant should discuss the potential clinical impact (OC).

No influence on the calcium metabolism was observed.

Efficacy was evaluated as a secondary endpoint. At Week 4, 71.8% of the subjects achieved treatment success according to the PGA on the body and 75.7% achieved treatment success on the scalp. The mean PASI decreased (improved) over time, from 8.61 at baseline to 1.40 at Week 4; a change of -82.0%. The mean area affected by psoriasis on the body decreased from 10.4% of BSA at baseline to 3.2% at Week 4. The mean affected area on the scalp decreased from 50.6% at baseline to 11.7% at Week 4.The success rate was higher than or at least as high as among 564 adults treated in 3 clinical studies (45-54.6%) according to the approved Enstilar SmPC.

V. PPDAR REQUEST FOR SUPPLEMENTARY INFORMATION

Major Objections

No Major Objections have been identified.

Other Concerns

1. Two AEs possibly/probably related to the product (acne and erythema) do not appear from the approved SmPC. These AEs should be included.

2. The applicant should clarify what happened to three of the children? Results at week 2 and 4 are presented for 103 patients; however, at end of treatment there were 106.

3. The applicant should clarify how many patients stopped treatment during the 4 weeks and how many restarted treatment.

4. The HPA axis cohort had more severe disease than the average and they used more of the IMP; it is, however, not clear if the cohort fulfilled the request from the FDA. The applicant should comment.

5. In a similar study in 32 adolescents using the gel formulation of the same combination product (LP0076-1017), BDP could be quantified in only four (13%) subjects compared to 12 (36%) in the actual study. This difference is significant ($p<0.05$), and the applicant should discuss the potential clinical impact.

VI. ASSESSMENT OF RESPONSE TO QUESTIONS

QUESTION 1
Two AEs possibly/probably related to the product (acne and erythema) do not appear from the approved SmPC. These AEs should be included.

RESPONSE 1
LEO Pharma A/S (LEO) considers that the events acne and erythema should not be specified in Section 4.8 of the SmPC for the following reasons:

 The approved indication for LEO 90100 is “Topical treatment of psoriasis vulgaris in adults.” The safety profile described in the tabulated list of adverse reactions in section 4.8 of the SmPC are based on the adverse reactions reported in adults. The population in which the events of erythema and acne were reported in the present trial LP0053-1108 were adolescents.

 The frequency of reported events of acne in LP0053-1108 was low: reported in two subjects; one event in one subject was assessed by the investigator as possibly or probably related to LEO 90100. Of note, acne is commonly seen in an adolescent population.
 The frequency of reported events of erythema in this trial, LP0053-1108 was low (one subject with one event). In addition, erythema is already listed as a class effect of calcipotriol in the section 4.8 of the SmPC. Also, onset of erythema can be considered as a manifestation of underlying psoriasis rather than a side effect of treatment with LEO 90100 based on post marketing reports in file at LEO.

 LEO Global safety has reviewed cases of erythema and acne reported in completed clinical trials as well as spontaneous cases recorded in LEO Global safety database (covering cases received cumulatively up to 30 Apr 2019). These data did not suggest a causal relationship to LEO 90100. Of note, most of the cases contained limited information or plausible alternative explanations.

In conclusion, LEO does not think there is enough data to support inclusion of erythema and acne in the table in Section 4.8 of the SmPC, due to the low frequency of reported events, limited data from post-marketing experience, and lack of suggestive causal relationship with LEO 90100. LEO will monitor these events as part of routine signal detection performed for LEO 90100. If any change in the reporting pattern of erythema and acne is observed, a re-evaluation for a potential labelling update will be made. Therefore, LEO made a proposal to amend Section 4.8 of the SmPC with "No clinically relevant differences between the safety profiles in adult and adolescent populations have been observed."

Assessor's comment: It is due to the low frequency of reported events, limited data from post-marketing experience, and lack of suggestive causal relationship with LEO 90100 acceptable not to include erythema and acne as AEs in section 4.8 of the SmPC. **Issue solved**.
It is, however, a little peculiar that the applicant as the first argument against inclusion emphasizes that the product is approved for adults, not for adolescents, but still wants to amend Section 4.8 of the SmPC with "No clinically relevant differences between the safety profiles in adult and adolescent populations have been observed."

QUESTION 2
The applicant should clarify what happened to three of the children? Results at week 2 and 4 are presented for 103 patients; however, at end of treatment there were 106.

RESPONSE 2
Of the 106 subjects assigned to treatment, 3 subjects withdrew from the trial (reason unspecified) prior to attending the Week 2 visit (Visit 2) (M5.3.5.2 LP0053-1108 CTR Table 1-2). Therefore, the number of subjects available for analysis at Week 2 (Visit 2) and Week 4 (Visit 3) was 103.
The end of treatment value was defined as the last value recorded up to and including Week 4 (Visit 3). Therefore, all end of treatment results are based on the 106 subjects assigned to treatment, not only the 103 subjects who completed the trial.

Assessor's comment: Three subjects withdrew from the trial prior to Visit 2, however end of treatment results were based on "the last value recorded up to and including week 4" from all 106 subjects. The last values recorded for the 3 withdrawn subjects must then be identical to the Visit 1 (treatment start) value. **Issue solved.**

QUESTION 3
The applicant should clarify how many patients stopped treatment during the 4 weeks and how many restarted treatment.

RESPONSE 3
According to the clinical trial protocol, subjects whose psoriasis lesions had cleared (investigator assessed) at Week 2 (Visit 2) were allowed to discontinue treatment but stayed in the trial. These subjects were to restart the treatment upon re-appearance of psoriasis during the

discontinuation period. However, subjects in the HPA axis cohort were to continue the treatment, even if their lesions had cleared at Week 2 (Visit 2) (M5.3.5.2 LP0053-1108 CTR Section 5.3.1).

The eCRF for the LP0053-1108 was designed to only collect the information on the number of days a subject missed treatment, including the reason(s) for missing the treatment (M5.3.5.2 LP0053-1108 CTR Appendix 1.2). This could mean a subject might have missed treatment on some days or stopped treatment for some days at any timepoint between Week 2 (Visit 2) and Week 4 (Visit 3). Therefore, based on the data collected in the eCRF, it is not possible to determine how many subjects stopped treatment during the 4 weeks and then restarted.

However, between Week 0 (Visit 1) and Week 2 (Visit 2), three subjects withdrew from the trial (see Response 2; M5.3.5.2 LP0053-1108 CTR Table 1-2) and these subjects stopped treatment and did not restart treatment.

Assessor's comments: Due to the design of the study it was not possible for the applicant to answer the question. The issue will not be pursued.

QUESTION 4
The HPA axis cohort had more severe disease than the average and they used more of the IMP; it is, however, not clear if the cohort fulfilled the request from the FDA. The applicant should comment.

RESPONSE 4
Subjects in the per protocol analysis set (n=33 [subjects in the HPA axis cohort minus 1]) had more severe disease than the safety analysis set (n=106).

According to the protocol, for subjects in the HPA axis cohort who were treated under maximum use conditions, the weekly dose was not limited. It was the investigator's responsibility to ensure the subject had sufficient IMP to apply once daily to all affected areas on body and scalp (M5.3.5.2 LP0053-1108 CTR Section 5.3.1).

The mean total amount of IMP used during the entire treatment period was higher for the per protocol analysis set (192.0 g) than for safety analysis set (163.2 g) (M5.3.5.2 LP0053-1108 CTR erratum Table 3-45).

We believe that we have met the FDA's request to treat the subgroup undergoing ACTH challenge under maximal use conditions. However, the dossier with the results of the LP0053-1108 trial is under review by the FDA.

Assessor's comment: The applicant repeats what has also been noted in the question that the subjects in the per protocol analysis set had more extensive disease and used more IMP than the safety analysis set; however whether it fulfills the request from FDA remains to be confirmed. The issue will not be pursued; however, it would be appropriate if the amendment to the European and American SmPCs will be identical.

QUESTION 5
In a similar study in 32 adolescents using the gel formulation of the same combination product (LP0076-1017), BDP could be quantified in only four (13%) subjects compared to 12 (36%) in the actual study. This difference is significant ($p<0.05$), and the applicant should discuss the potential clinical impact.

RESPONSE 5
LEO agrees that the proportion of subjects with BDP concentrations above LLOQ may seem to differ between the 2 trials in adolescents. However, we believe the apparent difference in number of subjects with observations above LLOQ (12 vs 4, for adolescents) is stochastic.

The proportion of subjects with BDP concentration above LLOQ were identical among adolescents and adults for the gel formulation. Also, the Median Cmax is identical for both formulations in adolescents and adults as observed in the clinical trials. However, for Enstilar, a higher proportion of adolescents with BDP concentration above LLOQ was observed than adults (Panel 1).

Taking the low concentrations (pg/ml) into consideration (M5.3.5.2 LP0053-1108 CTR Appendix 2.8 Listing 8-6) and the random pattern when these concentrations appear, it can be considered that there is no pattern in the observed values of BDP systemic exposure (Panel 1).

Furthermore, there was no impact on the HPA axis in the LP0053-1108 trial as evidenced by the ACTH challenge test (M5.3.5.2 LP0053-1108 CTR Section 8.3.2).

Based on the above, we believe that there is no potential clinical impact as the systemic exposure does not seem to be higher for the foam formulation than gel formulation.

Panel 1 **C_{max} (pg/ml) of BDP by population**

	Enstilar	**Gel formulation**
Adolescents	**LP0053-1108 N=33**	**LP0076-1017 N=32**
Mean	59.9	20.7
SD	94.4	17.8
Median	15.0	15.0
Maximum	480	104
Number (percentage) > LLOQ	12 (36.4%)	4 (12.5%)
Adults	**LEO 90100-30[1] N=35**	**LEO 80185-G24[2] N=40**
Mean	20.3	68.6
SD	14.8	316
Median	15.0	15.0
Maximum	81.1	2020
Number (percentage) > LLOQ	5 (14.3%)	5 (12.5%)

Abbreviations: LLOQ = lower limit of quantification; SD = standard deviation

1. LEO 90100-30 evaluated the pharmacokinetic profile of Cal and BDP foam under maximal usage conditions in subjects with extensive psoriasis vulgaris (total involvement 15-30% of body surface area with at least 30% of the scalp involved)
2. LEO 80185-G24 evaluated the pharmacokinetic profile of Cal and BDP gel under maximal usage conditions in subjects with extensive psoriasis vulgaris (total involvement 15-30% of body surface area)

Assessor's comment: Taking the low concentrations (pg/ml) into consideration we agree that the higher frequency of quantifiable BDP in this foam study compared to the gel study most probably is without any clinical impact. **Issue solved.**

VII. FPDAR REQUEST FOR SUPPLEMENTARY INFORMATION

No further comments from RMS, but the following question from DE had been received:

Question 1 from DE
It is expected that the proposed and implemented changes (4.2, 4.8 esp.) will be adequately reflected in the corresponding sections of the PIL (citation from AR: “No PL changes are proposed”).

VIII. ASSESSMENT OF RESPONSE TO QUESTIONS

Question 1 from DE
It is expected that the proposed and implemented changes (4.2, 4.8 esp.) will be adequately reflected in the corresponding sections of the PIL (citation from AR: “No PL changes are proposed”).

Response 1
The following text is stated in the currently approved PIL: “Enstilar is not recommended for the use in children below the age of 18 years”. Therefore, no changes were made to the PIL. Enstilar® does not have an indication for use in children, and the current text in the PIL is therefore valid.

Assessor´s comment (DE):
Issue resolved.

The assessor from DE had accepted the response from the applicant, and no further issues are outstanding.

IX MEMBER STATES Overall Conclusion AND RECOMMENDATION

- **Overall conclusion**

The applicant has appropriately responded to the questions posed. The response do not change the overall conclusion of the study submitted. The benefit-risk for Enstilar 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:

Proposed change in Section 4.2 Posology and method of administration

Paediatric population
The safety and efficacy of Enstilar® foam in children below 18 years have not been established. Currently available data in children aged 12 to 17 years are described in sections 4.8 and 5.1.
~~No data are available.~~

Proposed additional text in 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 106 adolescent subjects were treated in one open-label clinical trial.
See section 5.1 for further details regarding this trial.

Proposed additional text in Section 5.1 Pharmacodynamic properties

Paediatric population
The effects on calcium metabolism were investigated in an uncontrolled, open-label, 4-week trial in 106 adolescents aged 12 to 17 years with scalp and body psoriasis. The subjects used up to 105 g Enstilar® per week. No cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in a subset of 33 subjects with extensive plaque psoriasis involving at least 20% of the scalp and 10% of the body surface area. After 4 weeks of treatment with Enstilar®, 2 subjects had a cortisol level ≤18 mcg/dL at 30 minutes after ACTH challenge, but had normal response at 60 minutes. A third subject had minimal cortisol response to the ACTH challenge test at baseline resulting in inconclusive results after the treatment. None of these cases had any clinical manifestations.