Clinical Pharmacology Review

NDA Number	207,589/S-005/S-006/S007 (Related IND: 114,063)
Link to EDR	*\\CDSESUB1\evsprod\NDA207589\207589.enx (eCTD 0052)*
Submission Date	January 28, 2019
Submission Type	Efficacy/Labeling supplements
Brand Name	ENSTILAR®
Generic Name	Calcipotriene/betamethasone dipropionate foam, 0.005%/0.064% for topical use
Related Indication	For the topical treatment of plaque psoriasis in patients 12 years of age and older
Applicant	LEO Pharma Inc.
Primary Reviewer	Cindy (Liping) Pan, Ph.D.
Secondary Reviewer	Chinmay Shukla, Ph.D.
OCP Division	Division of Clinical Pharmacology 3 (DCP 3)
OND Division	CDER/ODEIII/DDDP

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1. EXECUTIVE SUMMARY

ENSTILAR® (LEO 90100) was approved in 2015 for the topical treatment of plaque psoriasis in patients 18 years of age and older. ENSTILAR® Foam is a combination of calcipotriene, a vitamin D analog, and betamethasone dipropionate, a corticosteroid (0.005%/0.064%). They both mediate their effect via binding to nuclear receptors and exert a variety of different pharmacodynamic actions.

At the time of original approval, there was a Pediatric Research Equity Act (PREA) Post-marketing requirement (PMR) to evaluate LEO 90100 in adolescents (2958-1) and a Post-marketing commitment (PMC) to conduct a vasoconstriction study (2958-2) as shown below:

2958-1 An open-label study to assess the effect of Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064% on calcium metabolism in 100 evaluable pediatric subjects aged 12 years to 16 years and 11 months with plaque psoriasis of the scalp and body. Pharmacokinetics (PK) of Enstilar® Foam and assessment of hypothalamic-pituitary axis (HPA) suppression will be conducted in a sub-set of 30 subjects with at least moderate plaque psoriasis under maximal use conditions.

2958-2 Conduct a single point vasoconstriction assay (VCA) trial in healthy subjects with adequate bracketing using visual assessment to determine the topical corticosteroid potency classification for Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064%.

In the current supplemental NDA, the Applicant submitted the final study report to fulfill the aforementioned PMR (2958-1). The study report for the PMC (2958-2) was reviewed by Dr. Luke Oh and the PMC was considered fulfilled (*see Clinical Pharmacology Review in DARRTS dated 07/27/2018*). Labeling revisions to reflect both PMR and PMC study results has been submitted in this application.

1.1 Recommendation

The Office of Clinical Pharmacology, Division of Clinical Pharmacology III has reviewed the final study report of the PMR (2958-1) and have concluded that the Applicant has fulfilled this PMR.

2. SUMMARY OF MAXIMAL USE PK STUDY LP0053-1108

Title: 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.

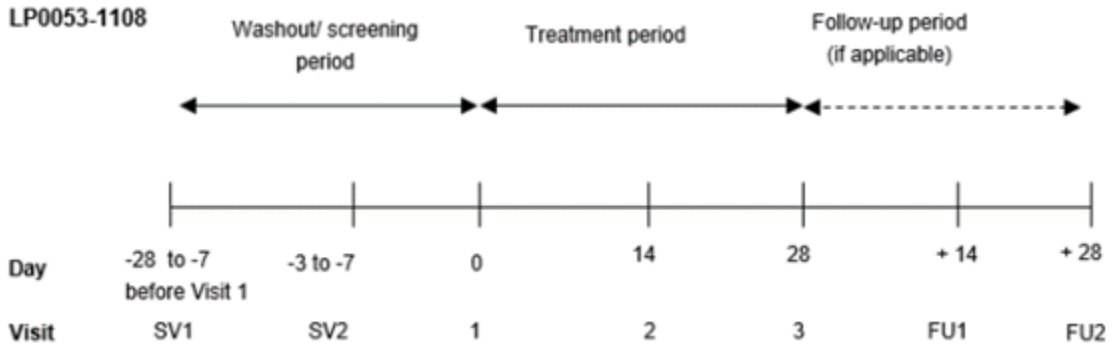
2.1 Study Objective

The primary objective of this open-label, non-controlled, 4-week trial was to evaluate the safety of once daily use of LEO 90100 in adolescent subjects (aged 12 to <17 years) with plaque psoriasis on the body and scalp.

2.2 Study Design

This was an open-label trial in adolescent subjects with plaque psoriasis on the body and scalp. A total of 106 subjects were assigned to treatment, of whom 34 subjects were treated under maximal use conditions (HPA axis cohort). These subjects had more sever disease, at least 10% of body surface area (BSA) affected on the body and at least 20% of the scalp area affected. The trial consisted of screening, treatment and follow-up (FU) periods (Figure 1).

Figure 1 Trial Design



(Source of data: Clinical Trial Report LP0053-1108, Panel 1)

Dosing regimen

- HPA axis cohort (maximal use study) (n=34)
  - Once daily to body and scalp psoriasis lesions for 4 weeks
  - No limitation in the weekly dose
- Non-HPA axis cohort (n=72)
  - Once daily until the psoriasis lesions had cleared at Week 2
  - Retreatment if the psoriasis re-appeared
  - Weekly doses
    - Subjects aged of 12 to 15 with a BSA≤1.3 m^2, 60 g
    - Subjects aged of 12 to 15 with a BSA>1.3 m^2, 90 g
    - Subjects aged of >15 with a BSA≤1.7 m^2, 90 g
    - Subjects aged of >15 with a BSA>1.7 m^2, 120 g

Reviewer's comments: *The maximum dosage approved for adults is 60 g every 4 days.*

2.3 Pharmacokinetic and Pharmacodynamic Sampling

For Subjects under maximal use conditions or in the HPA axis cohort,

- Blood samples were collected for PK analysis of LEO 90100 as:
  - Prior to study drug application on Days 14 (Visit 2) and 28 (Visit 3)
  - 1, 3, and 5 hours after study drug application on Day 28
- 24-hour urine samples were collected to evaluate the effect of LEO 90100 on calcium metabolism at 3 days prior to study drug application, and on Day 28.

- Blood samples were collected to evaluate the effect of LEO 90100 on HPA axis function prior to the ACTH Challenge test, and 30 and 60 minutes after the ACTH Challenge test.

Reviewer comment: *The 30-minute sample after ACTH challenge test was used to assess the results of HPA axis suppression.*

2.4 Pharmacokinetic results

Betamethasone dipropionate (BDP) could be quantified in at least 1 sample from 12 subjects (36% of subjects in the PK analysis set) and its metabolite (betamethasone 17-propionate) in 6 subjects (18% of subjects in the PK analysis set) (Table 1). The PK parameters of BDP and its metabolite betamethasone 17-propionate (B17P) were only characterized in Subject (b) (6) and Subject (b) (6), respectively. No PK parameters could be reliably estimated in other subjects. The highest observed concentrations of BDP and B17P were 480 pg/mL and 91.7 pg/mL, respectively (Table 1). Neither calcipotriol nor its metabolite MC1080 were quantifiable in any of the samples (Table 1).

Table 1 Pharmacokinetics of BDP and Calcipotriol and their Metabolites

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.

(Source of data: Clinical Trial Report LP0053-1108, Panel 46))

2.4 Labeling recommendations

Labeling recommendations on Section 12 of the label of NDA 207589 are summarized in Table 2. The text in red is proposed by the Applicant. The ~~strikethrough in red text~~

indicates recommended deletion by the reviewer. The texts in blue are recommended addition to the labeling by the reviewer.

Table 2 Reviewer's recommendations on labeling

Proposed labeling by the Applicant	Reviewer's labeling recommendations
12 CLINICAL PHARMACOLOGY 12.2 Pharmacodynamics *Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression* (b) (4) [redacted]	12 CLINICAL PHARMACOLOGY 12.2 Pharmacodynamics *Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression* (b) (4) [redacted] HPA axis suppression as indicated by a 30-minute post-stimulation cortisol level of ≤18 mcg/dL was evaluated in both adult (N=35) and a subset of pediatric subjects aged 12 to 17 years (N=33) following once daily application of Enstilar Foam on the body and scalp for 4 weeks. Enstilar Foam was applied to adult subjects with moderate to severe plaque psoriasis affecting a mean body surface area of 18% (range 12 to 28%) and mean scalp area of 50% (range 30 to 100%). The mean ± SD weekly dose used was 62 ± 28 grams. HPA axis suppression was not observed in any subjects after 4 weeks of treatment. Lack of adrenal suppression observed in this trial does not rule out the risk of HPA axis suppression *[see Warnings and Precautions (5.3)]*. Enstilar Foam was applied to pediatric subjects aged 12 to 17 years with moderate plaque psoriasis affecting a mean body surface area of 16% (range from 10% to 21%) and mean scalp area of 56% (range from 25% to 90%). The mean ± SD weekly dose used was 47 ± 22 grams. HPA axis suppression was observed in 3 (9%) of the subjects.

Effects on Calcium Metabolism In a trial, calcium metabolism was evaluated in [redacted] 106 subjects aged 12 to 17 years with plaque psoriasis of the scalp and body [redacted] once daily application of Enstilar® Foam for 4 weeks. No cases of hypercalcemia and no clinically relevant changes in urinary calcium were reported. *Vasoconstrictor Assay* Enstilar® Foam is [redacted] as demonstrated by studies in healthy subjects when compared with other topical corticosteroids. However, similar blanching scores do not necessarily imply therapeutic equivalence. 12.3 Pharmacokinetics Absorption [redacted]	*Effects on Calcium Metabolism* In a trial, calcium metabolism was evaluated in [redacted] 106 subjects aged 12 to 17 years with plaque psoriasis of the scalp and body [redacted] once daily application of Enstilar® Foam for 4 weeks. No cases of hypercalcemia and no clinically relevant changes in urinary calcium were reported. *Vasoconstrictor Assay* Enstilar Foam is [redacted] in the range of mid to potent corticosteroid as demonstrated by studies in healthy subjects when compared with other topical corticosteroids. However, similar blanching scores do not necessarily imply therapeutic equivalence. 12.3 Pharmacokinetics Absorption The PK of Enstilar Foam was investigated in both adult (N = 35) and a subset of pediatric subjects with plaque psoriasis aged 12 to 17 years (N=33) following once daily application of Enstilar Foam on the body and scalp for 4 weeks. [redacted] Enstilar Foam was applied to pediatric subjects aged 12 to 17 years with moderate plaque psoriasis affecting a mean body surface area of 16% and mean scalp area of 56%. Following application of a mean ± SD weekly dose of 47 ± 22 grams of Enstilar Foam, ~~C~~calcipotriene and its metabolite MC1080 were below the lower limit of quantification in all plasma samples. Betamethasone dipropionate was quantifiable in 12 of 33 (36%) subjects with the C_{max} ranging from 31.1 - 480 pg/mL. The metabolite of betamethasone dipropionate (B17P) was quantifiable in 6 of 33 (18%) subjects with the C_{max} ranging from 30.8 – 91.7 pg/mL. [redacted]

3. QUESTION-BASED CLINICAL PHARMACOLOGY REVIEW

Refer to the *Clinical Pharmacology Review (Reference ID 4297604; dated 07/27/2017)* for detailed information of study design, results, and labeling recommendations of the Vasoconstriction Study (Study LP0053-1276) which fulfilled the PMC 2958-2 (NDA 207589/S-007). The current clinical pharmacology review focuses on the PK, effect of LEO 90100 on HPA suppression and calcium metabolism in adolescent subjects with psoriasis under maximal use conditions based on the full clinical study report of Study LP0053-1108 (PMR 2958-1, NDA207589/S-005).

3.1 How does the systemic exposure of BDP and calcipotriol and their metabolites in adolescent subjects compare with adults?

A comparison PK data between adults and adolescents following LEO 90100 application under maximal use conditions is summarized in Table 3 (the adult PK data is obtained from the original NDA review).
The PK results suggest systemic exposure to BDP and calcipotriol and their metabolites in both adolescent and adult psoriasis patients treated under maximal use conditions were low. Note that the AUC values for BDP and B17P were considerably higher in one adolescent subject (1250 h*pg/mL) and one adult subject (4254 h*pg/mL), respectively (Table 3).

Table 3 Comparison PK data between adults and adolescents following LEO 90100 application under maximal use conditions

	Adults (n=35) [a]				Adolescents (n=33) [a]		
Analyte	n	C_{max} (pg/mL)	AUC_{last} (h*pg/mL)		n	C_{max} (pg/mL)	AUC_{∞} [b] (h*pg/mL)
BDP	5	33.7 - 81.1	16.9 – 82.5		12	31.1 – 480	1250
B17P	27	30.2 - 1133	18.5 – 4254		6	30.8 – 91.7	501
Calcipotriol	1	N.C	N.C		0	N/A	N/A
MC1080	3	23.3 - 26.6	55.3 – 65.5		0	N/A	N/A

a: mean weekly dose 62 grams (range 58 to 467 grams/4wk) for adults, 47 grams (range 9 to 345 grams/4wk) for adolescents
b: AUC data from 2 different subjects for BDP (n=1) and betamethasone 17-propionate (n=1)
B17P=betamethasone 17-propionate, BDP=betamethasone dipropionate, N.C=a parameter that could not be reliably estimated, N/A=not applicable
LLOQ: 30 pg/mL for BDP and B17P, 50 pg/mL for calcipotriol and 20 pg/mL for MC1080

(Source of data: reviewer's summary based on the data from CTRs of LP0053-1108 and LEO 90100-30)

3.2 What are the study population and drug usage information in Study LP0053-1108?

A total of 106 subjects received LEO 90100 were included in the Full Analysis Set used for efficacy evaluation and the safety analysis. A subset of 34 subjects were treated under maximal use conditions. Of the 34 subjects, 33 subjects were included in the PK analysis set (Per Protocol Analysis Set) (Table 4). The demographic data and the average weekly drug usage information are summarized in Table 4 and Table 5.

Table 4 Demographic data

Baseline characteristics	Full Analysis Set (n=106)	Per Protocol Analysis Set (n=33)
Age (years)		
Mean	14.2	14.2
SD	1.4	1.3
Median	14.0	14.0
Minimum	12	12
Maximum	16	16
Number	106	33
BMI (kg/m^2)		
Mean	21.69	20.56
SD	4.25	3.28
Median	20.95	20.70
Minimum	15.5	16.1
Maximum	40.6	30.3
Number	106	33
Height (cm)		
Mean	165.79	168.00
SD	9.77	9.33
Median	165.00	167.00
Minimum	138.0	147.0
Maximum	190.0	190.0
Number	106	33
Weight (kg)		
Mean	60.01	58.51
SD	14.41	12.83
Median	58.00	56.80
Minimum	36.0	40.0
Maximum	123.0	88.0
Number	106	33
Duration of psoriasis (years)		
Mean	4.3	3.5
SD	2.9	2.4
Median	3.0	3.0
Minimum	1	1
Maximum	12	8
Number	106	33

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(Source of data: Panel 23 of CTR LP0053-1108, page 75)

Table 5 Average weekly usage of LEO 90100

Visit interval Average weekly amount (g)	Safety Analysis Set (n=106)	Per Protocol Analysis Set (n=33)
Visit 1 to Visit 2 (2 weeks)		
Mean	46.2	55.5
SD	29.0	25.4
Median	48.0	55.5
Minimum	0.5	1.8
Maximum	100.8	97.6
Number	93	32
Visit 2 to Visit 3 (2 weeks)		
Mean	32.6	39.4
SD	27.1	22.5
Median	25.4	39.3
Minimum	0.0	1.6
Maximum	118.1	90.3
Number	89	32
Total treatment period		
Mean	39.9	47.0
SD	26.4	22.2
Median	39.7	46.8
Minimum	0.4	2.1
Maximum	104.8	86.3
Number	85	31

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Cross-reference: erratum Table 3-46

(Source of data: Panel 26 of CTR erratum LP0053-1108, page 10)

Reviewer comments: *The dose used in the maximal use cohort (n = 33) is within the upper range as shown in Table 5.*

3.3 What are the hypothalamic-pituitary-adrenal (HPA) axis suppression results of LEO 90100 in adolescent subjects with psoriasis in Study LP0053-1108?

HPA axis suppression indicated by a 30-minute post-stimulation (adrenocorticotrophic hormone [ACTH] challenge test) serum cortisol level of ≤ 18 mcg/dL was evaluated in a subset of pediatric subjects aged 12 to 17 years (n=33) following once daily application of LEO 90100 on the body and scalp for 4 weeks. LEO 90100 was applied to pediatric subjects with moderate plaque psoriasis affecting a mean body surface area of 16% and mean scalp area of 56% with the mean ± SD weekly dose of 47 ± 22 grams.

Of the 33 subjects who had the ACTH challenge test, 3 subjects (9%) were considered to show adrenal suppression after 30 minutes of ACTH challenge test at Week 4 (Table 6). Note that none of the 3 subjects with HPA axis suppression had quantifiable PK analytes.

Table 6 Subjects with serum cortisol concentration ≤ 18 mcg/mL after ACTH challenge

Subject#	Cortisol concentration (mcg/dL)			Amount of IMP (g)[1]
	Time (min)	Baseline	Week 4	%
(b) (6)	0	16.0	13.0	N/A
	30	18.0	15.0	
	60	21.0	16.0	
	0	13.7	7.6	8.8
	30	19.4	17.6	
	60	21.7	21.5	
	0	7.5	12.1	343.9
	30	20.4	16.5	
	60	21.6	25.4	

IMP=investigational medicinal product, N/A=not available
[1] total amount IMP (grams) used from baseline to Week 4
(Source of data: Reviewer's summary based on Panel 35 of CTR erratum LP0053-1108, page 14)

Reviewer comments: *The Applicant also measured serum cortisol at 60 minutes post ACTH challenge (Table 6). This data will not be considered as informative because of inconsistent standard for interpretation.*

3.4 What are the calcium metabolism results of LEO 90100 in adolescent subjects with psoriasis in Study LP0053-1108?

Effects of once daily LEO 90100 for 4 weeks on calcium metabolism were evaluated in a total of 106 pediatric subjects aged 12 years to 17 years with plaque psoriasis of the scalp and body in Study LP0053-1108. No clinically relevant changes in serum (Table 7) and urinary calcium (Table 8) were observed.

Table 7 Albumin-corrected serum calcium concentrations

	Albumin-corrected serum calcium (mmol/L)	
	Baseline (n=104)	Week 4 (n=103)
Mean	2.237	2.222
SD	0.092	0.116
Median	2.240	2.250
Minimum	1.88	1.87
Maximum	2.49	2.41

(Source of data: Reviewer's summary based on Table 3-4 of CTR LP0053-1108, page 181)

Table 8 24-hour urinary calcium excretion in HPA set (n=34)

	Calcium excretion rate (mmol/24hr)	
	Baseline (n=24)	**Week 4 (n=23)**
Mean	2.866	2.538
SD	1.554	1.938
Median	2.570	1.770
Minimum	0.33	0.30
Maximum	6.10	7.08

(Source of data: Reviewer's summary based on Table 3-16 of CTR LP0053-1108, page 192)

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