Clinical Pharmacology Review

NDA #:	022185/S-27
Submission Date:	September 29, 2018
Brand Name:	Taclonex
Generic Name:	Calcipotriene and betamethasone dipropionate topical suspension, 0.005%/0.064%
Dosage Form:	Topical Suspension
Reviewer:	Jihye Ahn, Pharm.D.
Secondary Reviewer:	Chinmay Shukla, Ph.D.
OCP Division:	Division of Clinical Pharmacology - 3
OND Division:	Division of Dermatology and Dental Products
Applicant:	LEO Pharma Inc.
Relevant IND(s):	67835
Submission Type:	Efficacy Supplement
Indication:	Topical treatment of plaque psoriasis of the scalp and body in patients 12 years and older

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1. Executive Summary

Taclonex® Topical Suspension is a fixed combination product with two active ingredients of calcipotriene 0.005% and betamethasone dipropionate 0.064% in a suspension formulation. Presently, this drug is indicated for the topical treatment of plaque psoriasis of the scalp and body in patients 18 years and older, and plaque psoriasis of the scalp in patients aged 12 to 17 years.

The applicant submitted a clinical study report for Study LP0076-1017 to fulfill the post-marketing requirement (PMR) established under Pediatric Research Equity Act (PREA)

which was issued with the approval letter of efficacy supplement (S-10). Study LP0076-1017 is a phase 2, open label, and 8-week trial which evaluated pharmacokinetics (PK), and effects on HPA axis suppression and calcium metabolism following once daily use of LEO 80185 (i.e. already marketed Taclonex Topical Suspension) in 107 adolescent subjects aged 12 to < 17 years with scalp and body psoriasis.

The ultimate goal of this submission is to extend the indication to include treatment of psoriasis on the body in patients ages 12 to < 17 years and update the labeling pursuant to Pregnancy and Lactation Labeling Final Rule (PLLR).

1.1. Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III has reviewed the results of Study LP0076-1017 and finds NDA 022185/S-27 acceptable pending agreement on recommended labeling changes.

1.2. Post-Marketing Requirement

None

1.3. Summary of Clinical Pharmacology and Biopharmaceutics Findings

From a Clinical Pharmacology perspective, the study results support the systemic safety of the LEO 80185 following once daily application to the scalp and body of subjects 12 to < 17 years of age with psoriasis.

The mean levels (SD) of albumin-corrected serum calcium levels were 2.25 (0.085) mmol/L at baseline. Following administration LEO 80185 once daily, the mean changes from baseline for albumin corrected calcium levels were -0.012 (0.13) at Week 4, and -0.008 (0.13) at Week 8. The mean changes for 24-hour urine calcium excretion from baseline were -0.49 (1.67) at Week 4, and 0.04 (1.64) mmol/24hr at Week 8. Overall, the albumin-corrected serum calcium levels and urine calcium excretion seemed to remain similar throughout the treatment period.

HPA axis suppression and pharmacokinetics were assessed in a subset of 31 subjects with moderate or severe psoriasis involving a mean (SD) of 18% (4.7) of body and 62.4% (26.4) of scalp, in total 18.4% (10-29%) of the body surface area (including scalp). The subjects in this subset applied mean 157 g of LEO 80185 during the first 4 weeks of treatment period. HPA axis suppression was observed in a total of 5 subjects (16.1%); specifically, HPA axis suppression was observed in 4 subjects (12.9%) after 4 weeks of treatment and 2 subjects (6.5%) after 8 weeks. One subject had HPA axis suppression at both periods (Weeks 4 and 8). PK samples were analyzed using a validated bioanalytical assay. Betamethasone dipropionate (BDP) was quantifiable in five PK samples from four subjects (13%) and betamethasone 17-propionate (B17P), a metabolite of BDP, was

quantified in 12 PK samples from 5 subjects (16%). Neither calcipotriol nor its metabolite MC1080 were quantifiable in any of the PK samples.

2. Labeling Recommendation

The following changes are recommended for section 12. Clinical Pharmacology. Additions are noted as **double underline** and deletions are noted as ~~strikethrough~~.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Taclonex® Topical Suspension combines the pharmacological effects of calcipotriene hydrate as a synthetic vitamin D_3 analog and betamethasone dipropionate as a synthetic corticosteroid. However, while their pharmacologic and clinical effects are known, the exact mechanisms of their actions in plaque psoriasis are unknown.

12.2 Pharmacodynamics

Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression:

HPA axis suppression was evaluated in four trials (Trial A, B, C, and D) following the application of Taclonex® Topical Suspension. **In all these trials, adrenal suppression (b) (4) by a 30-minite post-stimulation cortisol level <18 mcg/dL.**

In Trial A, HPA axis suppression was evaluated in adult subjects (N=32) with extensive psoriasis involving at least 30% of the scalp and, in total, 15-30% of the body surface area. Treatment consisted of once daily application of Taclonex® Topical Suspension on the scalp in combination with Taclonex® Ointment on the body for 4 to 8 weeks. Adrenal suppression (b) (4) was observed in 5 of 32 subjects (15.6%) after 4 weeks of treatment and in 2 of 11 subjects (18.2%) who continued treatment for 8 weeks.

In Trial B, HPA axis suppression was evaluated in adult subjects (N=43) with extensive psoriasis involving 15-30% of the body surface area (including the scalp). Treatment consisted of once daily application of Taclonex® Topical Suspension to the body (including the scalp in 36 out of 43 subjects) for 4 to 8 weeks. Adrenal suppression (b) (4) was observed in 3 out of 43 subjects (7.0%) after 4 weeks of treatment and in none of the 36 subjects who continued treatment for 8 weeks.

In Trial C, HPA axis suppression was evaluated in subjects 12 to 17 years (N=30) with plaque psoriasis of the scalp involving at least 20% of the scalp area. Treatment consisted of once daily application of Taclonex® Topical Suspension to the affected area on the scalp for up to 8 weeks. Adrenal suppression (b) (4) was observed in 1 of 30 evaluable subjects (3.3%) after 4 weeks of treatment and in no subjects who continued treatment for 8 weeks.

In Trial D, HPA axis suppression was evaluated in a subset of subjects aged 12 to 17 years (N=31) with plaque psoriasis of the scalp and body involving 10 **to 29** (b) (4) % of the body surface area. (b) (4) Adrenal suppression (b) (4) was observed in 5 of 31 subjects: 3 subjects after 4 weeks of treatment, 1 subject after 8 weeks, and 1 subject after both 4 and 8 weeks. (b) (4)

Effects on Calcium Metabolism

In Trial A, (b) (4) (b) (4)

(b) (4)

(b) (4) elevated urinary calcium levels outside the normal range were observed in two subjects (one at 4 weeks and one at 8 weeks).

In Trial B, (b) (4)

(b) (4) there was no change in mean serum or urinary calcium levels. Elevated urinary calcium levels outside the normal range were observed in two subjects (one at 4 weeks and one at 8 weeks).

In Trial C **(N=109) including 31 subjects with at least 20% scalp involvement and 78 subjects with at least 10% scalp involvement no cases of hypercalcemia and no clinically relevant changes in urinary calcium were reported.** (b) (4)

In Trial D (N=107), (b) (4)

no cases of hypercalcemia and no clinically relevant changes in urinary calcium were reported.

12.3 Pharmacokinetics

Absorption

(b) (4)

The systemic effect of Taclonex® Topical Suspension in psoriasis was investigated in Trials A, **B,** and D (b) (4)

In Trial A, the serum levels of calcipotriene and betamethasone dipropionate and their major metabolites were measured after 4 and 8 weeks of once daily application of Taclonex® Topical Suspension on the scalp in combination with Taclonex® Ointment on the body. Calcipotriene and betamethasone dipropionate were below the lower limit of quantification in all serum samples of the 34 subjects evaluated. However, one major metabolite of calcipotriene (MC1080) was quantifiable in 10 of 34 (29.4%) subjects at week 4 and in 5 of 12 (41.7%) subjects at week 8. The major metabolite of betamethasone dipropionate, betamethasone 17-propionate (B17P) was also quantifiable in 19 of 34 (55.9%) subjects at week 4 and 7 of 12 (58.3%) subjects at week 8. The serum concentrations for MC1080 ranged from 20-75 pg/mL. The clinical significance of this finding is unknown.

In Trial B, the plasma levels of calcipotriene and betamethasone dipropionate and their major metabolites were measured after 4 weeks of once daily application of Taclonex® Topical Suspension (b) (4) Calcipotriene and its metabolite MC1080 were below the lower limit of quantification in all plasma samples. Betamethasone dipropionate was quantifiable in 4 of 43 (9.3%) subjects. The metabolite of betamethasone dipropionate (B17P) was quantifiable in 16 of 43 (37.2%) subjects. The plasma concentrations of betamethasone dipropionate ranged from 30.9- 63.5 pg/mL and that of its metabolite betamethasone 17-propionate ranged from 30.5-257 pg/mL. The clinical significance of this finding is unknown.

In Trial D, the plasma levels of calcipotriene and betamethasone dipropionate and their major metabolites were measured after 4 weeks of once daily application of Taclonex® Topical Suspension (b) (4) Calcipotriene and its metabolite MC1080 were below the lower limit of quantification in all plasma samples. Betamethasone dipropionate was quantifiable in 4 of 32 (13%) subjects. The metabolite of betamethasone dipropionate (B17P) was quantifiable in 5 of 32 (16%) subjects. The plasma concentrations of betamethasone dipropionate ranged from 41.4- 104 pg/mL and that of its metabolite betamethasone 17-propionate ranged from 30.1-126 pg/mL. The clinical significance of this finding is unknown.

Metabolism
Calcipotriene:
Calcipotriene metabolism following systemic uptake is rapid and occurs in the liver. The primary metabolites of calcipotriene are less potent than the parent compound.

Calcipotriene is metabolized to MC1046 (the α,ß-unsaturated ketone analog of calcipotriene), which is metabolized further to MC1080 (a saturated ketone analog). MC1080 is the major metabolite in plasma. MC1080 is slowly metabolized to calcitroic acid.

Betamethasone dipropionate:
Betamethasone dipropionate is metabolized to betamethasone 17-propionate and betamethasone, including the 6ß-hydroxy derivatives of those compounds by hydrolysis. Betamethasone 17-propionate (B17P) is the primary metabolite.

3. Detailed Review

3.1. Relevant history

Following table presents the approved/proposed indication in previous and current submissions.

	Indications	Relevant Review Note
Original NDA	Approved on 5/9/2008 for treatment of moderate to severe psoriasis vulgaris of the scalp in adults age 18 years and older	Following PMR was included in the approval letter. "Conduct a study in pediatric patients ages 12 to 17 years of TACLONEX SCALP®. Topical Suspension for the treatment of scalp psoriasis. Enrollment should be sufficient to allow for 100 evaluable patients. Evaluate the effect of TACLONEX SCALP® Topical Suspension on calcium metabolism in all subjects and on the hypothalamic-pituitary axis in a subset of 30 patients."
Suppl. 10	Approved on 10/17/2012 to include the additional indication for plaque psoriasis of the body	Following PMR was included in the approval letter. "Conduct a trial in 100 evaluable pediatric patients with plaque psoriasis of the scalp and body ages 12 to 16 years, 11 months, to evaluate the safety and effect of Taclonex® (calcipotriene and betamethasone dipropionate) Topical Suspension, 0.005%/0.064% on calcium metabolism. Evaluate the hypothalamic-pituitary axis and pharmacokinetics of the two drug components, calcipotriene and betamethasone dipropionate, in a subset of at least 30 patients treated with Taclonex® Topical Suspension under maximal use conditions."
Suppl. 18	Approved on 8/29/2014 for an extension of the approved indication to include patients ages 12 to 17 years with plaque psoriasis of the	Fulfilled the pediatric study requirement that was included in the approval letter dated 5/9/2008 for the original NDA submission.

	scalp	
Suppl. 27 (current)	Proposed indication: Topical treatment of plaque psoriasis of the scalp and body in patients 12 years and older	To fulfill the pediatric study requirement that was included in the approval letter dated 10/17/2012 for supplemental NDA (S-10).

3.2. Detail Review of Study LP0076-1017

Study LP0076-1017 was a phase 2, international (7 countries), multi-center (30 centers), non-controlled, open, single-group, and 8-week trial. The objective of this trial was to evaluate pharmacokinetics, safety and efficacy of once daily use of LEO 80185 gel containing calcipotriol 50 mcg/g (as hydrate) and betamethasone 0.5 mg/g (as dipropionate) in adolescent subjects aged 12 to 16 years, 11 months with scalp and body psoriasis. Primary response endpoints are listed below:

- Adverse drug reactions
- 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 to Week 4, Week 8, and end of treatment
- Change in 24-hour urinary calcium excretion from baseline to Week 4, Week 8, and end of treatment

As the secondary response endpoints, the applicant assessed treatment emergent adverse events, 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 to Week 4 and Week 8, change in serum alkaline phosphatase (ALP) from baseline to Week 4 and Week 8. The applicant also assessed efficacy response endpoints such as subjects with controlled disease and percent change in PASI from baseline.

This review is primarily focused on pharmacokinetics (PK) and pharmacodynamic (PD) effects on HPA axis suppression and calcium metabolism following once daily administration of LEO 80185 gel as these responses support systemic safety. For further evaluation of safety and efficacy, refer to Medical Review authored by Dr. Melinda McCord.

Study Subjects and Baseline Characteristics
Full analysis set included 107 subjects who were assigned to treatment and received LEO 80185. A subset of 33 subjects in the full analysis set were assigned to perform HPA axis suppression and PK assessments and referred as Per protocol (PP) analysis set or

HPA axis subgroup. The final PP analysis set comprised 31 subjects as the applicant excluded 2 subjects: one subject who withdrew after Visit 1 and the other subject who did not provide any results for the ACTH-challenge test after receiving the study product as the subject was clear at Visit 3 (Week 4) and Visit 5 (Week 8). The applicant also noted that 6 of these subjects who were assigned to perform HPA axis/PK assessments did not meet the inclusion criterion as regard to ACTH-challenge test at baseline. The applicant noted that 5 of these 6 subjects completed the trial, hence were included PP analysis set. Definition of the data sets used for analysis is following:

- Safety analysis set (N=107): All subjects who applied any LEO 80185 and for whom the presence or confirmed absence of adverse events was available
- Per Protocol (PP) analysis set (N=31): Subjects from the safety analysis set who provided results from the HPA-axis challenge.

Summary of study subject demographics is provided in Table 1. Demographic characteristics were not notably different between Safety analysis set and PP analysis set, except for geographic region (country). PP analysis set included majority (71%) of subjects who were in Romania, and the rest (29%) who were in the US. It is noted that there were sufficient number of subjects in the lowest age group in both Safety analysis set, and PP analysis set.

Table 1. Key Demographics

		Safety Analysis Set		Per Protocol Analysis Set	
		No. of subjects	%	No. of subjects	%
Sex	Female	62	57.9%	17	54.8%
	Male	45	42.1%	14	45.2%
	Total	107	100.0%	31	100.0%
Age (years)	12	16	15.0%	3	9.7%
	13	17	15.9%	6	19.4%
	14	27	25.2%	10	32.3%
	15	23	21.5%	7	22.6%
	16	24	22.4%	5	16.1%
	Total	107	100.0%	31	100.0%
Race	Asian	6	5.6%	1	3.2%
	Black or African American	2	1.9%	1	3.2%
	Other	2	1.9%	0	0.0%
	White	97	90.7%	29	93.5%
	Total	107	100.0%	31	100.0%
Country	Canada	6	5.6%	0	0.0%
	France	5	4.7%	0	0.0%
	Germany	20	18.7%	0	0.0%
	Great Britain	8	7.5%	0	0.0%
	Poland	14	13.1%	0	0.0%
	Romania	42	39.3%	22	71.0%
	United States	12	11.2%	9	29.0%

	Total	107	100.0%	31	100.0%
Skin classification	TYPEI	2	1.9%	0	0%
	TYPEII	47	43.9%	12	38.7%
	TYPEIII	34	31.8%	13	41.9%
	TYPEIV	20	18.7%	5	16.1%
	TYPEV	2	1.9%	0	0.0%
	TYPEVI	2	1.9%	1	3.2%
	Total	107	100.0%	31	100.0%

Reviewer's table based on the ADSL.xpt. The content for the variables presented were consistent with Panel 17 and Panel 18, CSR for LP0076-1017. The geographic region (country) and distribution of age were added by the reviewer.

Baseline disease characteristics are presented in Table 2 and Table 3. For the safety analysis set, majority (81%) of the subjects had moderate body psoriasis assessed by Investigator's global assessment (IGA). Mean BSA involved on body and scalp was 14.9%. For subjects in PP analysis set, 29 subjects had moderate and 2 subjects had severe severity in their body psoriasis and the mean (range) BSA involved on body and scalp was 18.4% (10-29%). It is noted that all subjects had scalp psoriasis with mean (range) involved BSA of 55.1% (10-100%) for Safety analysis set and 62% (20-100%) for PP analysis set. Treatment conditions in PP analysis set appear to constitute the maximal use of the study product.

Table 2. Investigator's global assessment of disease severity on the body at baseline

	Safety Analysis Set		Per Protocol Analysis Set	
Investigator's global assessment	No. of subjects	%	No. of subjects	%
Mild	14	13.1%	0	0.0%
Moderate	87	81.3%	29	93.5%
Severe	6	5.6%	2	6.5%
Total	107	100.0%	31	100.0%

Reviewer's table based on the ADSL.xpt. Contents are same as Panel 20, CSR for LP0076-1017.

Table 3. Investigator's assessment of extent of psoriasis at baseline

	Safety Analysis Set		Per Protocol Analysis Set	
Extent of BSA involvement (%)	n	Mean (SD) (min, max)	n	Mean (SD) (min, max)
Body	80	13.3 (10.3) (3, 68)	23	18.0 (4.7) (10, 26)
Scalp	107	55.1 (29.5) (10, 100)	31	62.4 (26.4) (20, 100)
Body and Scalp	107	14.9 (8.3) (4, 68)	31	18.4 (5.4) (10, 29)

Table adapted from Panel 19, CSR for LP0076-1017

Study Drug Exposure and Compliance

LEO 80185 was to be applied once daily to scalp and body psoriasis lesions. The applicant noted that 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 (Day 14) or Visit 4 (Day 42), 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.

For PP analysis set, the applicant reported that 25 subjects (81%) had not missed any drug applications and 6 subjects (19%) had missed ≤10% of applications. The mean amount of the study product used during the first 4 weeks of treatment period was 157 g and ranged from 18.7 g to 266.2 g. The mean daily dose is estimated to be approximately 5.6 g.

Pharmacokinetics

PK samples were collected from 32 subjects at pre-dose on Day 14, and at pre-dose prior to the ACTH-challenge test, and post dose 1, 3, and 5 hours after ACTH-challenge test on Day 28. The applicant noted one subject had only one sample taken and was not included in HPA axis assessment (PP analysis set). PK samples were analyzed using a validated bioanalytical assay for 4 analytes: calcipotriol, betamethasone dipropionate (BDP), and the metabolites MC1080 and betamethasone 17-propionate (B17P).

Most PK concentrations were below lower limit of quantification (LLOQ) where LLOQ was 30.0 pg/mL for BDP and B17P, 50.0 pg/mL for calcipotriol, and 20.0 pg/mL for MC1080. BDP was quantified in five PK samples from four subjects (13%) and B17P was quantified in 12 PK samples from 5 subjects (16%). Quantifiable concentrations are listed in Table 4. Neither calcipotriol nor its metabolite MC1080 were quantifiable in any of the samples. No subjects had both quantifiable B17P and BDP. The applicant reported that AUC_{all} was only calculable for 2 subjects for B17P and the values were 188 and 462 pg*h/mL.

Table 4. List of Quantifiable Plasma Concentrations of Drug Components

Subject ID	Analytes	Concentration (pg/mL)	Time	Day
(b) (6)	B17P	42.5	Trough	14
	B17P	78.5	Trough	29
	B17P	34.1	1 h	29
	B17P	41	3 h	29
(b) (6)	B17P	126	Trough	30
	B17P	73.5	1 h	30
	B17P	66.1	3 h	30
	B17P	56.9	5 h	30

(b) (6)	B17P	33.4	Trough	15
	BDP	41.4	1 h	29
	B17P	43	Predose	19
	B17P	30.1	Predose	28
	B17P	35.5	3 h	28
	BDP	47.3	Predose	30
	BDP	49.9	1 h	29
	BDP	104	Predose	29
	BDP	75.4	1 h	29

Reviewer's table based on PC.xpt.

HPA axis suppression

The applicant assessed the effect on the HPA axis using an ACTH-challenge test at Screen Visit, Visit 3 (Day 28), and Visit 5 (Day 56) in 31 subjects assigned to HPA axis assessment group. The applicant noted that two separate commercial solutions for injection containing cosyntropin products, CORTROSYN® and Synacthen® were used for the respective US and European sites. The primary response endpoint was adrenal suppression as indicated by serum cortisol concentration ≤18 mcg/dL at 30 minutes after ACTH-challenge at Weeks 4 and 8. The applicant also evaluated cortisol suppression 60 minutes after ACTH-challenge at Weeks 4 and 8 as the secondary response endpoint, which is considered exploratory.

Following once daily application of LEO 80185, a total of 5 subjects (16.1%) had a serum cortisol ≤18 mcg/dL 30 minutes after the ACTH stimulation test; specifically, 4 subjects (12.9%) had HPA axis suppression at Week 4 and 2 subjects (6.5%) at Week 8, including 1 subject had a decrease at both periods (Weeks 4 and 8). The list of the subjects who showered abnormal HPA axis suppression is presented in Table 5. The applicant reported that one subject who showed sign of suppression at Week 4 was withdrawn from the trial. It is also noted that one subject in the list (table 5) had an abnormal HPA axis suppression at Baseline.

Among 5 subjects how had abnormal HPA axis suppression either at Week 4 or Week 8, HPA axis suppression was recovered in three subjects (Table 5). No data was found that allows determining whether HPA axis suppression returned to normal in the two patients (b) (6) Based on submitted data, it could not be determined whether the HPA axis suppression was reversible in this study population.

Table 5: List of the individuals with abnormal HPA axis suppression

ID		Cortisol levels after 30 min ACTH challenge		Follow-up (following the last test abnormal)
(b) (6)	Baseline	25.9	Normal	NA
	Week 4	15	Abnormal	

	Week 8	13.2	Abnormal	
(b) (6)	Baseline	24.2	Normal	NA
	Week 4	8.6	Abnormal	
	Week 8	NR	NR	
	Baseline	10	Abnormal	Recovered at Week 8
	Week 4	12.7	Abnormal	
	Week 8	21.5	Normal	
	Baseline	18.6	Normal	Recovered at follow-up visit (2 months after the abnormal result at Week 4
	Week 4	17.4	Abnormal	
	Week 8	NR	NR (withdrew)	
	Baseline	20.3	Normal	Recovered at follow-up visit (1 month after the abnormal result at Week 8)
	Week 4	22	Normal	
	Week 8	17.8	Abnormal	

Table was adapted from Table 3-4, CSR for LP0076-1017 and Listing 8-4

Five subjects who did not fulfill the inclusion criteria were still included in the applicant's analysis. This reviewer evaluated the HPA axis suppression rate by excluding those subjects. The comparison was presented in Table 6. Recalculated HPA axis suppression rate (%) were similar to those in the applicant's report.

Table 6. HPA axis suppression evaluation

	No. of Subjects evaluated for HPA axis suppression	Week 4	Week 8
Applicant's calculation	31[a]	4 (12.9%)[c]	2 (6.5%)[c]
Reviewer's calculation	26[b]	3 (11.5%)[d]	2 (8.3%)[d]

[a] number of subjects who were assigned to 'HPA axis group'.
[b] number of subjects excluding the subjects who did not meet the inclusion criteria.
[c] Percentage values (%) were calculated based on total number of PP analysis set
[d] Percentage values (%) were calculated based on the number of evaluated subjects for the respective visits.

Reviewing the subject level data revealed that all 5 subjects with abnormal HPA axis suppression after application of LEO 80185 were from Romania. None of subjects from the U.S. had an abnormal HPA axis suppression. The applicant did not provide explanation for the discrepancy between two geographic regions. Considering the composition of study subjects (9 US subjects and 22 Romanian) and overall low HPA axis suppression rate, this reviewer opines that there are not sufficient data to conclude that the geographic region has significant impact on HPA axis suppression rate at this time.

PK samples from 3 of the 5 subjects with evidence of suppression had quantifiable analytes; B17P was detectable in 2 subjects and BDP was detected in 1 subject.

Effect on Calcium Metabolism

The applicant examined the effect of once daily application of LEO 80185 gel containing vitamin D analogue on calcium metabolism by measuring serum calcium concentrations and urinary excretion of calcium. These assessments were performed in subjects included in Safety analysis set (N=107) as parts of clinical laboratory tests which were performed at baseline, Visit 3 (Week 4), and Visit 5 (Week 8).

The applicant calculated albumin-corrected serum calcium levels (in mmol/L) using observed serum calcium levels, and albumin levels and reported the change in albumin-corrected serum calcium from baseline to Week 4, Week 8, and end of treatment as the response variable. The mean levels (SD) of albumin-corrected serum calcium levels were 2.246 (0.085) mmol/L at baseline and 2.245 (0.113) mmol/L at the end of treatment. The highest value observed was 2.52 mmol/L throughout the study (Table 7). Mean change from baseline for albumin corrected calcium levels were -0.012 (0.131), -0.008 (0.125), and -0.003 (0.121) at Week 4, Week 8, and end of treatment, respectively (Table 8). Overall, the albumin-corrected serum calcium levels seemed to remain similar throughout the treatment period.

Table 7. Albumin-Corrected Serum Calcium (mmol/L) by Visit

Visit	N	Mean	SD	min	Max
Baseline	107	2.246	0.085	2.05	2.47
Visit 3 (Week 4)	101	2.235	0.133	1.61	2.47
Visit 5 (Week 8)	88	2.234	0.115	1.72	2.52
End of Treatment	102	2.245	0.113	1.72	2.52

Reviewer's table based on ADLB.xpt. The content is similar with Table 3-6, CSR for LP0076-1017

Table 8. Change in Albumin-Corrected Serum Calcium from Baseline

Visit Albumin-corrected serum calcium (mmol/l)	LEO 80185 (n=107)
Calcium corrected (mmol/L)	
Baseline	
Mean	2.246
SD	0.085
Median	2.240
Minimum	2.05
Maximum	2.47
Number	107
Lower 95% confidence limit (mean)	2.229
Upper 95% confidence limit (mean)	2.262
Change at Week 4	
Mean	-0.012
SD	0.131
Median	0.000
Minimum	-0.67
Maximum	0.23
Number	100
Lower 95% confidence limit (mean)	-0.038
Upper 95% confidence limit (mean)	0.014
Change at Week 8	
Mean	-0.008
SD	0.125
Median	0.000
Minimum	-0.48
Maximum	0.28
Number	87
Lower 95% confidence limit (mean)	-0.034
Upper 95% confidence limit (mean)	0.019
Change at End of Treatment	
Mean	-0.003
SD	0.121
Median	0.000
Minimum	-0.48
Maximum	0.28
Number	102
Lower 95% confidence limit (mean)	-0.027
Upper 95% confidence limit (mean)	0.021

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Source: panel 38, CSR for LP0076-1017

The applicant reported change in 24-hour urinary calcium excretion from baseline to Week 4, Week 8, and end of treatment as the response variable for urinary calcium excretion. The mean levels of 24-hour urinary calcium excretion by each visit are presented in Table 9. The mean changes from baseline were -0.49, 0.04, and 0.069 mmol/24hr at Week 4, Week 8, and end of treatment, respectively (Table 10). There were no cases of hypercalcemia and hypercalciuria based on the applicant's reference range [2.1 - 2.58 mmol/L] for serum calcium and [2.5 - 7.5 mmol/day] for urine calcium excretion rate. No apparent changes were noted neither for serum calcium levels, or urine calcium excretion following treatment with LEO 80185 gel.

Table 9. 24-hour Urinary Calcium Excretion (mmol/24hr) by Visit

Visit	N	Mean	SD	min	Max
Baseline	98	2.471	1.551	0.2	7.4
Visit 3 (Week 4)	92	2.045	1.335	0	6.4

Visit 5 (Week 8)	79	2.569	1.216	0.6	6.4
End of Treatment	92	2.538	1.259	0.6	6.4

Reviewer's table based on ADLB.xpt. The contents are same as Table 3-9, CSR for LP0076-1017.

Table 10. Change in 24-hour urinary calcium excretion (mmol/24hr) from baseline

Visit 24-hour urinary calcium excretion (mmol/24hr)	LEO 80185 (n=107)
Calcium excretion rate (mmol/day)	
Baseline	
Mean	2.471
SD	1.551
Median	2.125
Minimum	0.20
Maximum	7.40
Number	98
Lower 95% confidence limit (mean)	2.160
Upper 95% confidence limit (mean)	2.782
Out of the limit for quantification (subjects)	8
Change at Week 4 (Visit 3)	
Mean	-0.493
SD	1.669
Median	-0.400
Minimum	-7.40
Maximum	3.50
Number	85
Lower 95% confidence limit (mean)	-0.853
Upper 95% confidence limit (mean)	-0.133
Out of the limit for quantification (subjects)	10
Change at Week 8 (Visit 5)	
Mean	0.040
SD	1.638
Median	-0.050
Minimum	-4.90
Maximum	4.80
Number	72
Lower 95% confidence limit (mean)	-0.345
Upper 95% confidence limit (mean)	0.425
Out of the limit for quantification (subjects)	10
Change at End of Treatment	
Mean	0.069
SD	1.593
Median	0.000
Minimum	-4.90
Maximum	4.80
Number	85
Lower 95% confidence limit (mean)	-0.275
Upper 95% confidence limit (mean)	0.412
Out of the limit for quantification (subjects)	12

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Source: panel 39, CSR for LP0076-1017

In the Table 10, the applicant reported the number of subjects whose 24-hour urinary calcium excretion rate was "out of the limit for quantification". This reviewer further evaluated the original dataset and confirmed that there was a total of 28 cases where the 24 hour-urine calcium excretion rates were not able to be calculated. It was revealed that the values were not calculable because the urine calcium concentrations

were out of limit of quantification range [0.5 – 7.5 mmol/L]: 24 cases had the urine calcium levels < 0.5 mmol/L, and 4 cases had urine calcium levels > 7.5 mmol/L. Especially for those with urine calcium above upper limit of quantification, it was unable to determine whether the 24-hour urine calcium excretion rates are within or above the reference range. These cases were further discussed with Dr. Melinda McCord, the medical reviewer. Dr. McCord noted that urine calcium excretion can be affected by other factors (i.e. age, sex, muscle mass, diet, fluid consumption) and urine calcium data in this study was not collected in a manner accounting for those factors. In aforementioned cases, the effects on the calcium metabolism is not interpretable.

Safety
For further detail refer to clinical review authored by Dr. Melinda McCord. Briefly, 38 subjects (35.5%) in the Safety population (n=107) reported a total of 62 treatment emergent adverse events (TEAEs) of which 8 AEs were considered possibly or probably related by the applicant. There was a serious adverse event (SAE) which was suicide attempt. The applicant noted that this SAE was considered *unrelated*. There was a one subject withdrew due to cortisol suppression at week 4 (see the section "HPA axis suppression"). Eight of TEAEs were adverse drug reaction. The most common AEs were nasopharyngitis and headache.

3.3. Bioanalytical Methods

PK samples
Human plasma PK samples from Study LP0076-1017 were quantified using adequately validated method. LC/MS/MS was used to determine plasma concentrations of betamethasone dipropionate, betamethasone 17-propionate, calcipotriol, and MC1080. It is noted that the applicant used the same analytical method that had been used in the previous submission (supplement 10) under the same NDA. With this submission (supplement 27), the applicant submitted an additional partial validation report to support long term stability of the plasma samples.

The applicant noted that all plasma samples were kept frozen at approximately -80°C until analyzed and frozen stability has been proven for 1435 days at -80°C and all samples were analyzed within the validated 4 cycles of freeze/thaw at -80°C. Bioanalysis report indicated that 25 samples were stored at -70°C upon receipt at the analysis facility for 28 days, then moved to -80°C storage. This deviation does not appear to impact on the quality of the samples as frozen stability has been established at -20°C for 218 days.

The linearity ranges for each analyte were adequate as none of the plasma concentrations exceeded the upper limit of the quantifiable concentration range. The applicant reported that > 10 % (23 out of 160 samples) were analyzed for incurred sample repeat analysis (ISR) and greater than two thirds of ISR samples for BDP, and B17P met the criteria of assay reproducibility, which was the percent difference must be

within 20% of the mean of the original and repeated values. As calcipotriol and MC1080 were not quantifiable in any PK samples, ISR is not applicable.

Table 11. Summary of Bioanalytical Methods and Validation Report for PK samples

Method Validation Report	Validation of a bioanalytical method for the determination of betamethasone dipropionate, betamethasone 17-propionate, calcipotriol, and MC1080 in Human K2 EDTA Plasma by LC/MS/MS
Bioanalytical Report	The Determination of Betamethasone Dipropionate, Betamethasone 17-Propionate, Calcipotriol, and MC1080 in Human Plasma by LC/MS/MS
Method	LC/MS/MS
Relevant Clinical Trial	LP0076-1017
Matrix	Human plasma
Analytes	betamethasone dipropionate (BDP), betamethasone-d_{10} dipropionate, Internal Standards betamethasone 17-propionate (B17P), betamethasone 17-Propionate-d_5, Internal Standard calcipotriol, calcipotriol-d_4, Internal Standard MC1080, MC1080-d_4, Internal Standard
Linearity	30.0 to 400 pg/mL for BDP 30.0 to 500 pg/mL for B17D 50.0 to 250 pg/mL for calcipotriol 20.0 to 400 pg/mL for MC1080
LLOQ	30.0 pg/mL for BDP 30.0 pg/mL for B17D 50.0 pg/mL for calcipotriol 20.0 pg/mL for MC1080
Precision (% CV)	≤ 6.51% for BDP ≤ 5.72% for B17P ≤ 5.78% for calcipotriol ≤ 11.0% for MC1080.
Accuracy (% Bias)	-3.44% to -1.00% for BDP -2.75% to -1.50% for B17P -4.00% to -2.67% for calcipotriol 0.625% to 5.45% for MC1080
Matrix Stability	
Freeze-thaw Stability	4 cycles at -80°C
Bench-top Stability	2 hours at room temperature
Long Term Stability	1435 days at -80°C 218 days at -20°C

Incurred sample reanalysis (ISR)	Twenty-three (23) human plasma samples were reanalyzed ISR purposes. Following number of samples were within ± 20% of the mean result for each analyte • BDP: 20 of 23 (87.0%) • B17P: 22 of 23 (95.7%)

Serum Cortisol, and Serum and Urine Calcium

Human serum and urine samples from Study LP0076-1017 were analyzed for quantification of serum cortisol, serum calcium or urine calcium using commercial analyzers. The samples were analyzed at two locations: the US location for laboratory samples from North American sites and the UK location for the samples from the European sites. The applicant noted that the analyzers (Table 12) had been validated by ACM and submitted the series of validation reports for these analyzers. The applicant noted that all the samples that provided the reported results were analyzed within their respective analyte stability. The validation reports appear to support reliability of the resulting data submitted with this submission.

Table 12. Analyzers used for serum cortisol, serum calcium, and urine calcium

	Cortisol	Calcium	
Analyzer	ADVIA Centaur or ADVIA Centaur XP	ADVIA 1800 Siemens chemistry platform	
Matrix	Serum	Serum/Plasma	Urine
Conversion formula	1 ug/dL = 27.59 nmol/L	1 mg/dL * 4 = mmol/L	
Linearity Range	0.2 - 75 ug/dL (5.5 - 2069 nmol/L)	1.0 - 15.0 mg/dL (0.25 - 3.75 mmol/L)	1.0 - 30.0 mg/dL (0.25 - 7.50 mmol/L)
Stability	10 days at Ambient	14 days Ambient 21 days refrigerated	

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/s/

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