OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21852/S015	Submission Date(s): 2/27/2014
Brand Name	Taclonex ® Ointment, 0.005%/0.064%.
Generic Name	Calcipotriene and betamethasone dipropionate ointment, 0.005%/0.064%.
Primary Reviewer	An-Chi Lu, M.S., Pharm.D.
Team Leader	Doanh Tran, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Dermatology and Dental Products
Sponsor	LEO Pharma Inc.
Submission Type	Efficacy supplement
Formulation; Strength(s)	Ointment; 0.005%/0.064%
Indication	Topical treatment of psoriasis vulgaris in patients 12 years and older

Table of Contents

1 EXECUTIVE SUMMARY 2

1.1 Recommendation 2

1.2 Phase IV Commitments/Requirements 2

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings 2

2 QUESTION-BASED REVIEW 3

3 DETAILED LABELING RECOMMENDATIONS 3

4 DETAILED FINDINGS FOR TRIAL MCB 0501 INT: 8

1 Executive Summary

Taclonex ® Ointment is a combination topical product with two active ingredients of calcipotriene and betamethasone dipropionate ointment, 0.005%/0.064%. Taclonex ® Ointment was approved on January 9, 2006 for the topical treatment of psoriasis vulgaris in patients 18 years and older. Both active ingredients have been approved individually for marketing in the United States.

At the time of approval, the Agency waived the pediatric trial requirement for ages 0 to 11 years and deferred pediatric trials for ages 12 to 17 years. The Post Marketing Requirement (PMR) as required under the Pediatric Research Equity Act (PREA) was described in the approval letter dated 1/9/2006 as follows:

Deferred pediatric study under PREA for the treatment of psoriasis vulgaris in pediatric patients ages 12 to 17.

To fulfill the Post Marketing Requirement, a clinical trial report has been submitted for review under this supplement.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 has reviewed the results of Trial MCB 0501 INT and finds NDA 21852/S015 acceptable pending agreement on recommended labeling changes.

This efficacy supplement is considered acceptable to fulfill the post marketing requirement stated in the approval letter dated 1/9/2006.

1.2 Phase IV Commitments/Requirements

Not Applicable

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Background - To fulfill the post marketing requirement, the sponsor conducted one clinical trial MCB 0501 INT. This was a national, multi-center, prospective, non-controlled, single-group, 4 week trial.

Method – A total of 33 subjects aged 12 to 17 years with an extent of psoriasis on the trunk and/or limbs of 5-30% of the body surface area (BSA) and a disease severity of at least moderate according to the investigator's global assessment (IGA) were enrolled. All subjects were applied with Taclonex ointment once daily to psoriasis on the trunk/limbs in the evening for 4 weeks. A maximum weekly dosage was decided to be 60 g (60% of the maximum weekly adult dosage of 100g). The adrenocorticotropic hormone (ACTH) challenge test was performed at Screening Visit 2 (about 3 to 14 days before treatment starts) and Visit 3 (28 days after treatment starts).

Results – All 33 subjects were included in the full and safety analysis sets. There was one subject (CRF 1002) who did not provide data for the ACTH-challenge test following the start of treatment at Week 4, so a total of 32 subjects were included in the per protocol analysis set.

The baseline extent of psoriasis on arms, trunk and legs ranged between 5% and 30% of the BSA with the mean around 14%. The mean weekly amount used during the entire treatment period for all subjects was 29.6 g/week (median 29.4; range 8.1-55.8 g/week). The weekly amount used was similar in Weeks 1 through 2 and Weeks 3 through 4.

ACTH-Challenge Test
None of the subjects had a serum cortisol concentration of ≤18 mcg/dL at either 30 or 60 minutes following ACTH challenge. After 30 minutes, the mean serum cortisol concentration at baseline was 24.68 mcg/dL (range 18.5 to 30.6 mcg/dL), and 24.74 mcg/dL (range 19.2 to 32.1 mcg/dL) at Week 4.

Effect on Calcium Metabolism
The changes in albumin-corrected serum calcium and urinary calcium: creatinine ratio from Baseline to Week 4 were evaluated. There were no clinically significant mean changes in albumin corrected serum calcium or urinary calcium:creatinine ratio from baseline to week 4, and no subject had albumin corrected serum calcium above the reference range at week 4. One subject had an increase in urinary calcium: creatinine ratio, and the clinical reviewer assessed it as not clinically significant as the subject reported no associated symptoms and there were no other related abnormal lab parameters.

Conclusions – With Taclonex ointment applied to 32 pediatric subjects aged 12 to 17 years with an extent of psoriasis on the trunk and/or limbs of 5-30% of the BSA and a disease severity of at least moderate, there was no subject who had HPA axis suppression. There was one subject who had an increase in urinary calcium:creatinine ratio, but it was deemed not clinically significant.

Clinical Pharmacology Briefing:
An optional intra-division level Clinical Pharmacology briefing was conducted on 9/25/2014 with the following in attendance: Edward D Bashaw, Hae-Young Ahn, Doanh Tran, Chinmay Shukla, and An-Chi Lu.

2 Question-Based Review
Not Applicable

3 Detailed Labeling Recommendations
The following changes are recommended for sections 5, 8 and 12 of the label. Additions are noted as double underline and deletions are noted as ~~strikethrough~~.

5.1 Effects on Calcium Metabolism
Hypercalcemia and hypercalciuria have been (b) (4) with use of Taclonex®. If hypercalcemia or hypercalciuria develop, treatment should be discontinued until

parameters of calcium metabolism have normalized. In the trials that included assessment of the effects of Taclonex® Ointment on calcium metabolism, such testing was done after 4 weeks of treatment. The effects of Taclonex® Ointment on calcium metabolism following treatment durations of longer than 4 weeks have not been evaluated.

5.2 Effects on Endocrine System

(b) (4) Taclonex® Ointment can (b) (4) cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal (b) (4) treatment. Factors that predispose a patient to HPA axis suppression include the use of high-potency steroids , large treatment surface areas, prolonged use , use of occlusive dressings, altered skin barrier, liver failure, and young age. Evaluation for HPA axis suppression may be done by using the adrenocorticotropic hormone (ACTH) stimulation test.

(b) (4)

In a trial evaluating the effects of Taclonex® Topical Suspension and Taclonex® Ointment on the HPA axis (b) (4) 32 adult subjects (b) (4) were treated with Taclonex® Scalp Topical Suspension on the scalp and Taclonex® Ointment on the body~~,~~. ~~a~~Adrenal suppression was identified in 5 of 32 subjects (~~15.6~~16%) after 4 weeks of treatment [*see Clinical Pharmacology: Pharmacodynamics (12.2)*]. The effects of Taclonex® Ointment on the HPA axis following treatment durations of longer than 4 weeks have not been adequately studied.

(b) (4)

If HPA axis suppression is documented, gradually withdraw the drug, reduce the frequency of application, or substitute with a less potent corticosteroid.

Cushing's syndrome~~,~~ and hyperglycemia, (b) (4) may also (b) (4) occur due to systemic (b) (4) effects of topical corticosteroids.

Use of more than one corticosteroid-containing product at the same time may increase the total systemic corticosteroid exposure.

Pediatric patients may be more susceptible to systemic toxicity (b) (4) due to their larger skin surface to body mass ratios [*see Use in Specific Populations (8.4)*].

8.4 Pediatric Use

Safety and effectiveness of the use of Taclonex® Ointment in pediatric patients under the age of 12 years have not been established. (b) (4)

The safety and effectiveness of Taclonex® Ointment for the treatment of plaque psoriasis have been established in the age group 12 to 17 years. In a prospective, uncontrolled trial, 33 pediatric subjects aged 12-17 years with plaque psoriasis on the body were treated with Taclonex® Ointment for 4 weeks up to a maximum of 56 g per week. Subjects were assessed for HPA axis suppression and effects on calcium metabolism .

Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of systemic toxicity when treated with topical drugs. They are, therefore, also at greater risk of HPA axis suppression and adrenal insufficiency upon the use of topical corticosteroids. [See Warnings and Precautions (5.2)]

Rare systemic toxicities such as Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients, especially those with prolonged exposure to large doses of high potency topical corticosteroids.

(b) (4)

12.2 Pharmacodynamics

Vasoconstriction:
In a vasoconstrictor trial in healthy subjects, the skin blanching response of Taclonex® Ointment was consistent with that of a potent corticosteroid when compared with other topical corticosteroids. However, similar blanching scores do not necessarily imply therapeutic equivalence.

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® Ointment. In Trial A, Taclonex® Ointment was applied once daily for 4 weeks to adult subjects (N = 12) with (b) (4) to study its effects on the hypothalamic-pituitary-adrenal (HPA) axis. Of eleven subjects tested, none demonstrated adrenal suppression as indicated by a 30-minute post-stimulation cortisol level ≤ 18 mcg/dL.

In Trial B, (b) (4) Taclonex® Ointment was evaluated in adult subjects (N = 19), one subject (b) (4) demonstrated adrenal suppression.

In Trial C, 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 Scalp® Topical Suspension on the scalp in combination with Taclonex® Ointment on the body. Adrenal suppression as indicated by a 30-minutes post-stimulation cortisol level less than or equal to 18 mcg/dL was observed in 5 of 32 subjects (15.6%) after 4 weeks of treatment as per the recommended duration of use (*see Dosage and Administration (2.1)*).

In Trial D, HPA axis suppression was evaluated in subjects 12 to 17 years (N=32) with plaque psoriasis of the body involving 5-30% of the body surface area. Treatment consisted of once daily application of Taclonex® Ointment to the affected areas (Mean weekly dose was 29.6 g; range 8.1-55.8 g/week) for up to 4 weeks. Adrenal suppression as indicated by a 30-minute post-stimulation cortisol level <18 mcg/dL was observed in none of 32 evaluable subjects after 4 weeks of treatment.

Effects on Calcium Metabolism
In (b) (4) Trial C described above, the effects of once daily application of Taclonex® Ointment on the body in combination with Taclonex Scalp® Topical Suspension on the scalp on calcium metabolism were also examined. Elevated urinary calcium levels outside the normal range were observed in 1 of 35 subjects (2.9%) after 4 weeks of treatment.

In Trial D, calcium metabolism was evaluated in a total of 33 subjects aged 12 to 17 years with plaque psoriasis involving 5-30% of the body surface area undergoing once daily application of Taclonex® Ointment for up to 4 weeks. No cases of hypercalcemia and no clinically relevant changes in urinary calcium were reported. However, one

subject had a normal urinary calcium:creatinine ratio at baseline (3.75 mmol/g), which increased above the normal range at week 4 (16 mmol/g). There were no relevant changes in albumin-corrected serum calcium or other markers of calcium metabolism for this subject. The clinical significance of this finding is unknown.

12.3 Pharmacokinetics

Absorption

In Trial C, ~~T~~the systemic effect of Taclonex® Ointment in extensive psoriasis was investigated in the trial described above. In this trial, the serum levels of calcipotriene and betamethasone dipropionate and their major metabolites were measured after 4 weeks (maximum recommended duration of treatment) and also after 8 weeks of once daily application of Taclonex® Ointment on the body in combination with Taclonex Scalp® Topical Suspension on the scalp. Both 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 five 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 seven 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.

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 alpha,beta-unsaturated ketone analogue of calcipotriene), which is metabolized further to MC1080 (a saturated ketone analogue). 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 6beta-hydroxy derivatives of those compounds by hydrolysis. Betamethasone 17-propionate (B17P) is the primary metabolite.

4 Detailed Findings for Trial MCB 0501 INT:

Title: A Phase 2 Study Evaluating the Safety and Efficacy of 4 Weeks of Once Daily Use of Taclonex Ointment, Containing Calcipotriene 50 mcg/g plus Betamethasone 0.5 mg/g (as dipropionate), in the Treatment of Psoriasis Vulgaris on the Trunk and/or Limbs in Adolescent Patients (aged 12 to 17 years)

Trial Initiation/Completion Dates:
7/15/2009-12/5/2011

Objectives:
The primary objective was to evaluate the safety of Taclonex ointment in the treatment of psoriasis vulgaris on the trunk and/or limbs in adolescent patients (aged 12 to 17 years). The secondary objective was to evaluate the efficacy of Taclonex ointment in the treatment of psoriasis vulgaris on the trunk and/or limbs in adolescent patients (aged 12 to 17 years).

Trial Design:
This was a national, multi-center, prospective, non-controlled, single-group, 4 week trial. A total of 33 subjects aged 12 to 17 years with an extent of psoriasis on the trunk and/or limbs of 5-30% of the BSA and a disease severity of at least moderate according to the investigator's global assessment (IGA) were enrolled. All subjects were applied with Taclonex ointment once daily to psoriasis on the trunk/limbs in the evening for 4 weeks. A maximum weekly dosage was decided to be 60 g (60% of the maximum weekly adult dosage of 100g). This trial consisted three successive individual phases:

- Washout/Screening Phase

This phase lasted for 3 days to 6 weeks depending on the prior use of excluded treatments.

- Treatment Phase

This phase lasted for 4 weeks.

- Follow-up Phase

This phase lasted for up to 4 weeks depending on whether the subject had adrenal suppression or ongoing adverse drug reactions at the end of treatment.

At weeks 0, 2, and 4 in the treatment phase, the investigator and subject each made a global assessment of disease severity. The investigator also assessed the extent and severity of clinical signs of psoriasis by body region. The ACTH-challenge test was performed at Screening Visit 2 (about 3 to 14 days before treatment starts) and Visit 3 (28 days after treatment starts). If the result at Visit 3 showed a serum cortisol concentration ≤ 18 mcg/dL at 30 minutes after the ACTH-challenge, a further ACTH-challenge test was required 28 days later at Follow-up Visit 2. If the results at Follow-up Visit 2 continued to show a serum cortisol concentration ≤ 18 mcg/dL at 30 minutes after the ACTH-challenge, further ACTH-challenge tests were to be performed, but not more often than at 4-weekly intervals, until the adrenal suppression resolved.

To perform the ACTH-challenge test, 2.5 mL of venous blood was drawn at 08:00 a.m. ±30 minutes, and then 250 mcg Cortrosyn™ was injected intravenously over a 2-minute

period. Two further 2.5 mL samples of venous blood were drawn 30 and 60 minutes after the injection.

Test Product: Taclonex ointment-Calcipotriene 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate) manufactured by LEO Pharma A/S. **Batch numbers/ expiry dates:** 08089661/ 02.2010; 092787101/ 09.2011; 110547101/ 02.2013
Non-investigational medicinal product: Cortrosyn™ (cosyntropin) for injection manufactured by Amphastar Pharmaceuticals.

Safety Evaluation
Primary response criteria related to the effect of the study medication on adrenal function and calcium metabolism were:

- Adverse drug reactions (ADRs).
- Serum cortisol concentration of ≤18 mcg/dL at 30 minutes after ACTH-challenge at end of treatment
- Serum cortisol concentration of ≤18 mcg/dL at 30 and 60 minutes after ACTH-challenge at end of treatment
- Change in albumin-corrected serum calcium from baseline to end of treatment
- Change in urinary calcium: creatinine ratio from baseline to end of treatment.

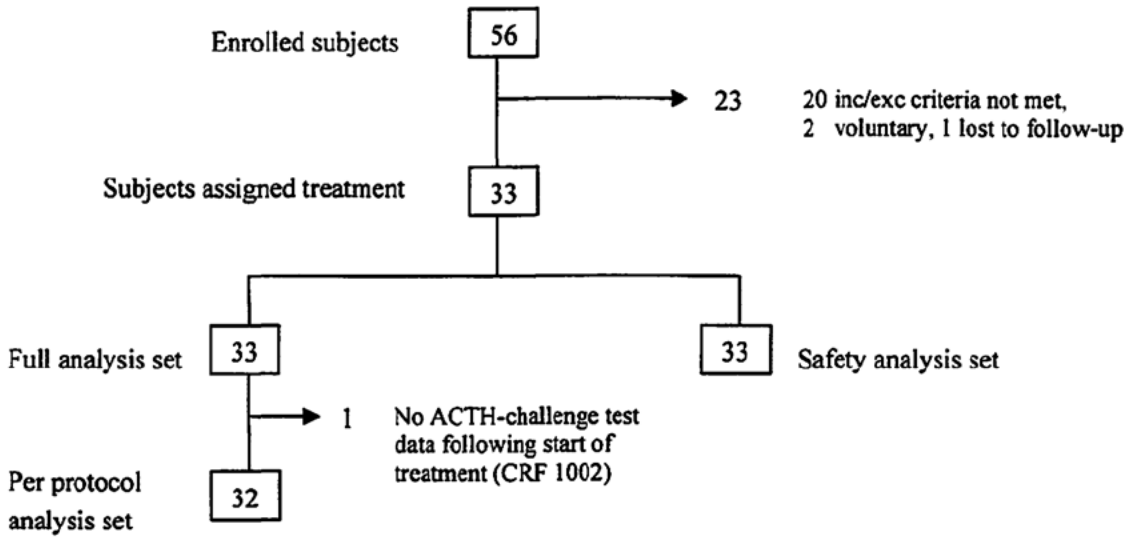
The albumin-corrected serum calcium in mmol/L was calculated by using the formula: Serum calcium (total) in mmol/L + (0.02 x [40-serum albumin in g/L])

Efficacy Evaluation

- "Controlled disease" (clear or almost clear) by the investigator's global assessment of disease severity at week 4.
- Controlled disease (clear or very mild) by the patient's global assessment of disease severity at week 4.
- The absolute and percentage change in psoriasis area and severity index (PASI) from baseline to week 4.
- PASI 75 (at least 75% reduction in PASI) and PASI 50 (at least 50% reduction in PASI) at week 4.

Results:
All 33 subjects were included in the full and safety analysis sets. There was one subject (CRF 1002) who did not provide data for the ACTH-challenge test following the start of treatment at Week 4, so a total of 32 subjects were included in the per protocol analysis set.

Schematic presentation of analysis sets:



Demographic Characteristics:

Sex	Safety Analysis Set (n=33) Number of subjects	%	Per Protocol Analysis Set (n=32) Number of subjects	%
Male	16	48.5	15	46.9
Female	17	51.5	17	53.1
Total	33	100.0	32	100.0
29FEB12:15:19:27 MCB 0501 INT t4_sex.doc				
Hispanic or Latino	11	33.3	10	31.3
Not Hispanic or Latino	22	66.7	22	68.8
Total	33	100.0	32	100.0
29FEB12:15:16:02 MCB 0501 INT t5_ethnic.doc				
White	22	66.7	21	65.6
Black or African American	4	12.1	4	12.5
Asian	5	15.2	5	15.6
Other	2	6.1	2	6.3
Total	33	100.0	32	100.0
06MAR12:10:20:43 MCB 0501 INT t6_race.doc				

1) Other: Subject 1156 Middle Eastern, subject 1161 Filipino

Baseline Characteristics

Duration of psoriasis (Years)	Safety Analysis Set (n=33)	Per Protocol Analysis Set (n=32)
Mean	4.5	4.6
SD	3.5	3.5
Median	3.0	3.5
Minimum	0	0
Maximum	11	11
Number	33	32

29FEB12:15:11:12 MCB 0501 INT t7_duration.doc

Body Surface Area (%)	Safety Analysis Set (n=33)	Per Protocol Analysis Set (n=32)
Mean	14.2	13.8
SD	8.3	8.0
Median	11.0	10.5
Minimum	5	5
Maximum	30	30
Number	33	32

01MAR12:15:30:21 MCB 0501 INT t8_invass.doc

Modified PASI	Safety Analysis Set (n=33)	Per Protocol Analysis Set (n=32)
Mean	8.1	8.1
SD	4.1	4.1
Median	6.7	6.7
Minimum	3	3
Maximum	18	18
Number	33	32

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	Safety Analysis Set (n=33)		Per Protocol Analysis Set (n=32)	
Investigator's global assessment	Number of subjects	%	Number of subjects	%
Moderate	30	90.9	29	90.6
Severe	3	9.1	3	9.4
Total	33	100.0	32	100.0

01MAR12:15:30:40 MCB 0501 INT t10_invga.doc

	Safety Analysis Set (n=33)		Per Protocol Analysis Set (n=32)	
Patient's global assessment	Number of subjects	%	Number of subjects	%
Very Mild	2	6.1	1	3.1
Mild	3	9.1	3	9.4
Moderate	28	84.8	28	87.5
Total	33	100.0	32	100.0

01MAR12:15:31:10 MCB 0501 INT t11_patga.doc

Reviewer's Comments:
The baseline extent of psoriasis on arms, trunk and legs ranged between 5% and 30% of the BSA with the mean around 14%. This was in accordance with the trial inclusion criteria.

Age: safety analysis set and per protocol analysis set

Centre Age (years)	Safety Analysis Set (n=33)	Per Protocol Analysis Set (n=32)
All Centres		
Mean	14.6	14.7
SD	1.6	1.6
Median	15.0	15.0
Minimum	12	12
Maximum	17	17
Number	33	32

Reviewer's comments:
There were an adequate number of subjects at the lower limit of age in the safety analysis set (n=33), with 5 subjects aged 12 years and 5 subjects aged 13 years.

ACTH-Challenge Test

None of the subjects had a serum cortisol concentration of ≤18 mcg/dL at either 30 or 60 minutes following ACTH challenge. After 30 minutes, the mean serum cortisol concentration at baseline was 24.68 mcg/dL (range 18.5 to 30.6 mcg/dL), and 24.74 mcg/dL (range 19.2 to 32.1 mcg/dL) at Week 4. After 60 minutes, the mean serum cortisol concentration at baseline was 28.05 mcg/dL (range 21.4 to 36.2 mcg/dL) compared to 27.65 mcg/dL (range 21.5 to 34.8 mcg/dL) at Week 4. Table 1 below shows the serum cortisol concentration at 30 minutes after ACTH challenge at baseline and Week 4 (per protocol analysis set).

The mean baseline extent of psoriasis on arms, trunk and legs was 14.2% and 13.8% of the BSA for the safety and per protocol analysis sets, respectively, and ranged between 5% and 30% of the BSA. The investigator's assessment of extent of psoriasis is shown in Table 2.

Table 1: Serum cortisol concentration at 30 minutes after ACTH challenge at baseline and Week 4: per protocol analysis set

Serum Cortisol Concentration (mcg/dL)	TACLONEX ointment (n=32)
30 min after ACTH challenge test	
Baseline	
Mean	24.68
SD	3.31
Median	24.90
Minimum	18.5
Maximum	30.6
Number	32
Week 4	
Mean	24.74
SD	3.53
Median	23.90
Minimum	19.2
Maximum	32.1
Number	32

Figure 1: Box Plot Representation of Cortisol Level 30 minutes after ACTH Challenge Test at Baseline and Week 4: per protocol analysis set

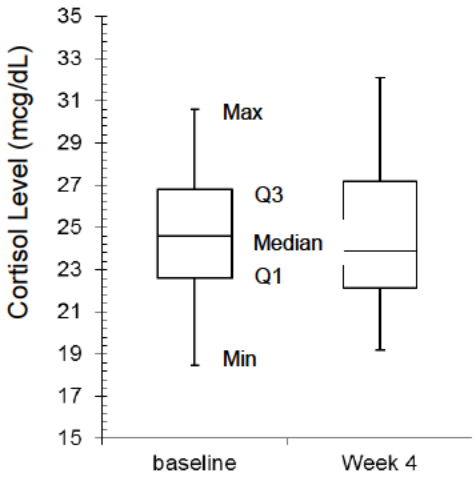

Table 2: Investigator's assessment of extent of psoriasis on arms, trunk and legs: safety analysis set and per protocol analysis set

Body Surface Area (%)	Safety Analysis Set (n=33)	Per Protocol Analysis Set (n=32)
Mean	14.2	13.8
SD	8.3	8.0
Median	11.0	10.5
Minimum	5	5
Maximum	30	30
Number	33	32

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Table 3: Average weekly amount of study medication used: safety analysis set

Visit interval Average weekly amount[1] (g)	TACLONEX ointment (n=33)
Visit 1 to Visit 2 (2 weeks)	
Mean	28.8
SD	17.6
Median	27.6
Minimum	4.4
Maximum	54.2
Number[2]	30
Visit 2 to Visit 3 (2 weeks)	
Mean	28.5
SD	18.5
Median	27.7
Minimum	3.7
Maximum	66.1
Number[2]	32
Visit 1 to End of Treatment	
Mean	29.6
SD	17.0
Median	29.4
Minimum	8.1
Maximum	55.8
Number[2]	29

13MAR12:10:26:32 MCB 0501 INT t35_avgamt.doc

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

Reviewer's Comments:

The mean weekly amount used during the entire treatment period for all subjects was 29.6 g/week (median 29.4; range 8.1-55.8 g/week) as shown in Table 3. The weekly amount used was similar in Weeks 1 through 2 and Weeks 3 through 4.

Effect on Calcium Metabolism

At baseline, the mean albumin-corrected serum calcium was 2.27 mmol/L (range 2.13 to 2.48 mmol/L). The mean change in albumin-corrected serum calcium from baseline to week 4 was 0.005 mmol/L (range -0.3 to 0.13, 95% CI:-0.0285 to 0.0395). A total of 29

subjects had normal albumin-corrected serum calcium values both at baseline and week 4, and 3 had low albumin-corrected serum calcium at week 4. The change in albumin-corrected serum calcium from baseline to Week 4 is shown in
Table 4.

Table 4: Change in albumin-corrected serum calcium from baseline to Week 4 (safety analysis set):

Visit Albumin-Corrected Serum Calcium (mmol/L)	TACLONEX ointment (n=33)
Baseline	
Mean	2.268
SD	0.084
Median	2.250
Minimum	2.13
Maximum	2.48
Number	33
Change at Week 4	
Mean	0.005
SD	0.094
Median	0.025
Minimum	-0.30
Maximum	0.13
Number	32
Statistical analysis	
95% CI (mean)	-0.0285 to 0.0395

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Figure 2: Boxplot Representation of Albumin-Corrected Serum Calcium (mmol/L) at Baseline and Week 4.

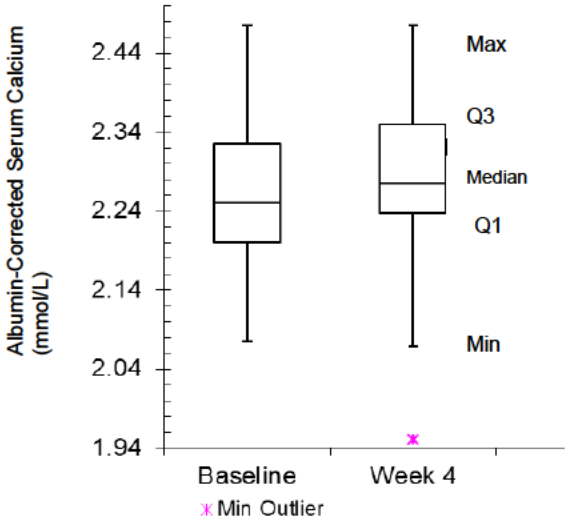

Table 5: Albumin-corrected serum calcium categorized as low, normal or high at Week 4 shown against baseline category: safety analysis set

		TACLONEX ointment (n=33)		
		End of treatment category[1]		
Laboratory parameter	Baseline category[1]	Low	Normal	High
Albumin-corrected serum calcium	Normal	3	29	0

12MAR12:17:23:07 MCB 0501 INT t19 shalb.doc

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

Reviewer's comments:
Subject CRF1002 did not have any laboratory results at Visit 3 (Week 4), therefore in Table 5 the total number of subjects was 3+29=32, which was the per-protocol analysis set. The three subjects who had low albumin-corrected serum calcium appear to have the level close to the lower limit of normal value (2.15 mmol/L), with subject CRF1156 had a value of 2.05 mmol/L, CRF 1351 had a value of 1.95 mmol/L, and CRF1401 had a value of 2.1 mmol/L.

For the effects on urinary calcium: creatinine ratio, at baseline, the mean ratio was 2.38 mmol/g (range 0.50 to 5.00 mmol/g). The mean change in urinary calcium:creatinine ratio from baseline to week 4 was 0.717 mmol/g (range -3.5 to 12.25, 95% CI: -0.357 to 1.791). A total of 29 subjects had normal urinary calcium: creatinine ratio both at baseline and week 4. One subject (CRF 1311) had a normal urinary calcium:creatinine ratio of 3.75 mmol/g at baseline (Screening Visit 2), and increased to 16 mmol/g at week 4 (Visit 3). This subject was a 13- year old boy with psoriasis vulgaris involving 7 % of the BSA who used 219.81 g of ointment over the 4-week trial period. There were no relevant changes in albumin-corrected serum calcium or other markers of calcium metabolism for this subject. The change in urinary calcium:creatinine ratio from baseline to week 4 for the safety analysis set is shown in Table 6. Urinary calcium:creatinine ratio categorized as low, normal or high (i.e. below, within or above the laboratory reference range, respectively) at week 4 against baseline category is shown in Table 7.

Table 6: Change in urinary calcium:creatinine ratio from baseline to Week 4 (safety analysis set)

Visit Urinary calcium:creatinine ratio (mmol/g)	TACLONEX ointment (n=33)
Baseline	
Mean	2.383
SD	1.300
Median	1.875
Minimum	0.50
Maximum	5.00
Number	32
Change at Week 4	
Mean	0.717
SD	2.877
Median	-0.125
Minimum	-3.50
Maximum	12.25
Number	30
Statistical analysis	
95% CI (mean)	-0.357 to 1.791

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Figure 3: Boxplot Representation of Urinary Calcium:Creatinine Ratio at Baseline, Week 4, and Change at Week 4

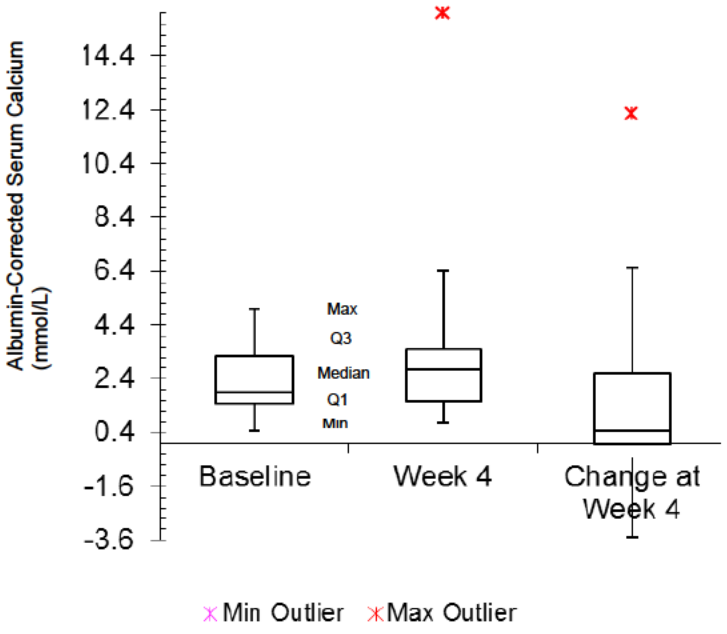

Table 7: Urinary calcium:creatinine ratio categorized as low, normal or high at Week 4 shown against baseline category (safety analysis set)

		TACLONEX ointment (n=33)		
		End of treatment category[1]		
Laboratory parameter	Baseline category[1]	Low	Normal	High
Urinary calcium:creatinine ratio	Normal	0	29	1
	Unknown	0	1	0

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

Reviewer's comments:
For the 33 subjects in the safety data set, the sponsor counted 29 subjects had normal values, 1 subject had high value, and 1 subject was unknown. This reviewer reviewed the raw data, and confirmed that there was only 1 subject who had urinary calcium ratio above normal.

For Subject CRF1311 who had a high urninary calcium:creatinine ratio on Week 4, the total amount of 219.81 g of ointment used over the 4-week trial period was higher than the average amount used in this trial. This subject had normal albumin-corrected serum calcium of 2.4 mmol/L at Week 4, and the serum cortisol concentration after 30 minutes of ACTH challenge was normal with a value of 20 mcg/dL. The clinical reviewer, Dr. Melinda McCord, assessed this finding as not clinically significant, in that the subject reported no associated symptoms and there were no other related abnormal lab parameters.

Bioanalytical Method:

- Serum Cortisol

The ADVIA Centaur® Cortisol assay was used to test serum cortisol. In short, this is a competitive immunoassay using direct chemiluminescent technology. Cortisol in the patient sample competes with acridinium ester-labeled cortisol in the Lite Reagent for binding to polyclonal rabbit anti-cortisol antibody in the Solid Phase. The polyclonal rabbit anti-cortisol antibody is bound to monoclonal mouse anti-rabbit antibody, which is covalently coupled to paramagnetic particles in the Solid Phase.

- Serum and Urinary Calcium

The ADVIA 1800 calcium assay was run for serum and urinary calcium testing. This is a colorimetric assay measured spectrophotometrically by the analyzer at 545 nm. Calcium ions in the patient's sample (either serum or urine) form a violet complex with 0-cresolphthalein complexone in an alkaline medium. The absorbance measurement of the patient sample is then compared to a calibration curve stored on the analyzer and a

calcium concentration can be calculated. The calcium assay minimally undergoes a two point calibration weekly (water blank and chemistry calibrator) and also a daily water blank prior to QC being performed.

Validations:

- Serum Cortisol

Prepared for:	(b) (4)	Prepared by:	(b) (4)
Contact:		Verification Date:	

New Method	Comparison Method
ADVIA Centaur XP (S/N IRL90370840)	**ADVIA Centaur (S/N N/A)**
Cortisol (ug/dL)	**Cortisol (ug/dL)**
Traceability:	Traceability:
Reference Range: 3.09 - 22.40	Reference Range: 3.09 - 22.40
Analytical Range: 0.20 - 75.00	Analytical Range: 0.20 - 75.00
Reagent Lot: 227	
Calibrator Lot: CE14	
MCM Lot: 23224	

Correlation

Number of Samples:	36	Correlation Coefficient (r):	0.998
New Method Mean:	13.79	Average Bias (%):	- 3.0
Comparison Method Mean:	14.22	Average Difference:	- 0.43
Slope:	0.975	Standard Error (Sy.x):	0.904
Y Intercept:	- 0.077	T-test:	0.010

Sensitivity

Number of Replicates:	6
Calculated Sensitivity:	0.09
Test Claim Sensitivity:	0.20
Acceptable Limit:	0.40

Within Run Precision

Control	Level	N	Assayed Mean	SD	%CV	Verification Limit Within Run	Comment
9833411	1	10	4.38	0.24	5.47	6.55 %CV	Within Acceptable Limits
9833412	2	10	16.08	0.53	3.27	6.20 %CV	Within Acceptable Limits
9833413	3	10	29.28	0.69	2.37	6.20 %CV	Within Acceptable Limits

Accuracy

Control	Level	N	Assayed Mean	Published Control Range	Comment
9833411	1	10	4.38	3.01 - 6.03	Within Acceptable Limits
9833412	2	10	16.08	11.20 - 21.20	Within Acceptable Limits
9833413	3	10	29.28	19.90 - 37.30	Within Acceptable Limits

Reviewer's comments:
QC samples were conducted at the same time frame as the trial bioanalysis was conducted. The QC results appear reasonable.

Long term stability of cortisol:

Ambient	3 days
Refrigerated	3 days
Frozen	8 months
Ultra Cold	8 months

All serum cortisol samples were collected and shipped at ambient temperature, and were analyzed within 72 hours from the date/time of collection except for one subject (1001).

For Subject 1001 at screening visit 2, serum sample was analyzed approximately 100 hours after sample was collected.

- Serum and Urinary Calcium

Prepared for:	(b) (4)	Prepared by:	(b) (4)
Contact:		Verification Date:	

New Method	Comparison Method
ADVIA 1800 (S/N CA12340046)	**ADVIA 1800 (S/N CA12340022)**
CA_c (mg/dL)	**CA_c (mg/dL)**
Traceability: NIST atomic Absorption ref method w/	Traceability: NIST atomic Absorption ref method w/
Reference Range: 8.300 - 10.600	Reference Range: 8.300 - 10.600
Analytical Range: 1.000 - 15.000	Analytical Range: 1.000 - 15.000
Reagent 1: 091	
Reagent 2: 092	

Correlation

Number of Samples:	36	New Method Mean:	9.256
Range of Observations:	4.400 to 16.600	Comparison Method Mean:	8.953
Correlation Coefficient (r):	0.996	Average Difference:	+ 0.30
Linear Slope:	1.000	Average Difference (%):	+ 3.4
Linear Intercept:	+ 0.306	Standard Error (Sy.x):	0.189

Prepared for:		Prepared by:	
Contact:		Verification Date:	

New Method	Comparison Method
ADVIA 1800 (S/N CA12340046)	**ADVIA 1800 (S/N CA12340022)**
CA_c (mg/dL)	**CA_c (mg/dL)**
Traceability: NIST atomic Absorption ref method w/	Traceability: NIST atomic Absorption ref method w/
Reference Range: 8.300 - 10.600	Reference Range: 8.300 - 10.600
Analytical Range: 1.000 - 15.000	Analytical Range: 1.000 - 15.000
Reagent 1: 091	
Reagent 2: 092	

Correlation

Number of Samples:	36	New Method Mean:	9.256
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Correlation Coefficient (r):	0.996	Average Difference:	+ 0.30
Linear Slope:	1.000	Average Difference (%):	+ 3.4
Linear Intercept:	+ 0.306	Standard Error (Sy.x):	0.189

Both of the serum cortisol and serum/urinary calcium validations are acceptable.

Applicant's conclusion:

A total of 33 subjects between 12 and 17 years of age with psoriasis vulgaris were treated with taclonex ointment for 4 weeks, and 32 subjects provided data for the ACTH-challenge test at week 4. There was no subject had a serum cortisol concentration of ≤18 mcg/dL at either 30 or 60 minutes following ACTH challenge at week 4. There were no clinically significant mean changes in albumin corrected serum calcium or urinary calcium:creatinine ratio from baseline to week 4, and no subject had albumin corrected serum calcium above the reference range at week 4. One subject had an increase in urinary calcium: creatinine ratio and a relationship to study treatment cannot be excluded.

A total of 11 subjects (33%) reported to experience adverse events with 2 subjects had one adverse drug event each (headache and pruritus). There were no serious adverse events or withdrawals due to adverse events in this trial. There was one event of pruritus

(deemed to be possibly related to treatment by the sponsor) and two rash popular (deems not related to treatment by the sponsor) as lesional/perilesional adverse events.

The mean amount of Taclonex ointment used per week was 29.6 g (range 8.1 to 55.8 g).

Reviewer's comments:
The one subject who has an increase in urinary calcium: creatinine ratio is regarded as not clinically significant by the clinical reviewer. Otherwise, the sponsor's conclusion is acceptable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AN-CHI LU
09/26/2014

DOANH C TRAN
09/26/2014

EDWARD D BASHAW
10/05/2014