# OFFICE OF CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| NDA: 22185, S-18, SDN136 | Submission Date(s): 10/31/2013, 12/12/2013 |
| Brand Name | Taclonex Topical Suspension, 0.005%/0.064% |
| Generic Name | Calcipotriene and Betamethasone Dipropionate Topical Suspension, 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 |
| Submission Type; Code | Efficacy supplement |
| Formulation; Strength(s) | Suspension, 0.005%/0.064% |
| Indication | Topical treatment of plaque psoriasis of the scalp and body in adult patients 18 years and older and topical treatment of plaque psoriasis of the scalp in adolescent patients aged 12 to 17 years |

## Table of Contents

# 1 Executive Summary

Taclonex Topical Suspension is a combination topical product with two active ingredients of Calcipotriene 0.005% and Betamethasone Dipropionate 0.064% in a suspension formulation. Taclonex Topical Suspension was approved on 5/9/2008 for the topical treatment of moderate to severe psoriasis vulgaris of the scalp in adults aged 18 years and above. In the approval letter, it stated that a deferred pediatric study is required to be conducted as a postmarketing study as follows:

> 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.

This submission is to fulfill the post-marketing requirement of the pediatric study for the original NDA approval dated 5/9/2008. In this submission, the applicant has submitted clinical reports from two clinical trials: MBL 0412 INT (efficacy and safety) and MBL 0801 (effect on hypothalamic pituitary adrenal (HPA) axis and calcium metabolism). Trial MBL 0801 is reviewed by clinical pharmacology and Trial 0412INT is reviewed by the clinical reviewer.

## 1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 has reviewed the results regarding HPA axis suppression of trial MBL 0801 and finds NDA 022185/S-018 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 5/9/2008.

## 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 two clinical trials MBL 0412 INT and MBL 0801. Both trials were 8-week, multi-center, prospective, non-controlled, open-labeled, single-group, phase 2 trials in adolescent subjects (aged 12 to 17 years, inclusive) with psoriasis vulgaris on the scalp using Taclonex Topical Suspension once daily. Trial MBL 0412 INT was a safety and efficacy trial, and is reviewed by the medical officer. Trial MBL 0801 was to evaluate the effect on HPA axis and calcium metabolism, and is reviewed by this reviewer.

***Method*** – A total of 31 subjects 12 to 17 years of age with clinical signs of or earlier diagnosed with psoriasis vulgaris on trunk and/or limbs were enrolled. At Visit 1, enrolled subjects had a clinical diagnosis of scalp psoriasis which is:

1.) Amenable to topical treatment with a maximum of 60 g of study medication per week, and
2.) of an extent of more than or equal to 20% of the scalp area, and
3.) of at least moderate severity according to the investigator's global assessment

All subjects were instructed to apply Taclonex topical suspension to psoriasis on the scalp once daily for up to 8 weeks. The approved maximum weekly dose for adults is 100 g, and the maximum weekly dosage for adolescents of this trial was reduced to 60 g. ACTH (Adrenocorticotropic Hormone) challenge test was performed at screening, Visit 3 (Day 28), and Visit 5 (Day 56).

***Results*** – A total of 31 subjects were treated and 29 subjects completed the trial. One subject (CRF 1016) left the trial at Visit 3 (Day 28) due to signs of adrenal suppression (serum cortisol concentration ≤18 mcg/dl at 30 minutes after the ACTH-challenge) and one subject (CRF 1076) was withdrawn at Visit 2 (Day 14) when it was discovered that the inclusion criterion regarding the HPA axis function was not fulfilled. Three subjects (CRFs 1023, 1111, and 1079) had cleared scalp psoriasis after 4-weeks treatment and left the trial at Visit 3 (Day 28).

The mean weekly amount used during the entire treatment period was 24.5 g/week (median 13.7; range 0.7-59.9 g/week), and the mean weekly amount used was similar in Weeks 1 through 4 and Weeks 5 through 8. The mean of the total amount used during the entire treatment period was 203 g (median 109; range 6-496 g), and was similar in Weeks 1 through 4 (100.2 g) and Weeks 5 through 8 (104.6g).

ACTH-Challenge Test

One subject (CRF 1016), had serum cortisol concentration ≤18 mcg/dl at 30 minutes after ACTH challenge at Week 4 with a level of 16.8 mcg/dL. The subject had normal ACTH-challenge test at follow-up 4 weeks after end of treatment. One subject (CRF 1018) had serum cortisol concentration ≤18 mcg/dl at 60 minutes after ACTH challenge at Week 4 with a level of 13.7 mcg/dL. This was not considered adrenal suppression as the 30 minute value showed normal response. No subject showed signs of adrenal suppression (serum cortisol concentration ≤18 mcg/dl) at both 30 and 60 minutes after ACTH challenge at Week 4 nor at Week 8.

Effect on Calcium Metabolism

The changes in albumin-corrected serum calcium, 24-hour urinary calcium, and urinary calcium: creatinine ratio from Baseline to Week 4, Week 8, and end of treatment were evaluated. No subject had high albumin-corrected serum calcium. For the 24-hour urinary calcium excretion evaluation one subject (CRF 1002) had high 24-hour urinary calcium excretion at Week 4 with a level of 8.2 mmol/24 hr (reference range 2.5-7.5) and level was normalized at later visits. For the evaluation of urinary calcium:creatinine ratio one subject (CRF 1048) had a low value at Week 4 with a level of 0.25 mmol/g (reference range 0.3-6.1) and level was normalized at later visits.

***Conclusions*** – The rate of HPA axis suppression and effects on calcium metabolism are low (3%) with Taclonex topical suspension applied to adolescents with plaque psoriasis of the scalp involving at least 20% of the scalp area.

**Clinical Pharmacology Briefing:**
An optional intra-division level Clinical Pharmacology briefing was held on June 3, 2014 with the following in attendance: Dennis Bashaw, Melinda McCord, 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 5.1 and 12 of the label. Additions are noted as double underline and deletions are noted as ~~strikethrough~~.

### 5.1 Hypercalcemia and Hypercalciuria
Hypercalcemia and hypercalciuria have been observed with use of Taclonex® Topical Suspension. If hypercalcemia or hypercalciuria develop, discontinue treatment until parameters of calcium metabolism have normalized. The incidence of hypercalcemia and hypercalciuria following Taclonex® Topical Suspension treatment of more than 8 weeks has not been evaluated. [See Clinical Pharmacology (12.2)]

### 5.2 (b) (4) Effects on Endocrine System
(b) (4) Taclonex® Topical Suspension 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 of (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.

In a trial evaluating the effects of Taclonex® Topical Suspension and Taclonex® Ointment on the HPA axis, (b) (4) 32 adult subjects were treated with both Taclonex® Topical Suspension on the scalp and Taclonex® Ointment on the body.~~,~~ A~~a~~drenal suppression was identified in 5 of 32 subjects (16%) after 4 weeks of treatment and in 2 of 11 subjects (18%) who continued treatment for 8 weeks. In another trial of 43 subjects treated with Taclonex® Topical Suspension on body (including the scalp in 36 out of 43 subjects) adrenal suppression was identified in 3 out of 43 subjects (7%) after 4 weeks of treatment and in none of the 36 subjects who continued treatment for 8 weeks. [*See Clinical Pharmacology (12.2)*]

In a trial evaluating the effects of Taclonex® Topical Suspension on the HPA axis, 31 subjects aged 12 to 17 years were treated with Taclonex® Topical Suspension on the

scalp. Adrenal suppression was identified in 1 of 30 evaluable subjects (3.3%) after 4 weeks of treatment. [See Clinical Pharmacology (12.2)]

(b) (4)

If HPA axis suppression is documented, (b) (4) gradually withdraw the drug, reduce the frequency of application, or substitute a less potent corticosteroid. (b) (4)

Cushing's syndrome and hyperglycemia may also occur due to the systemic effects of the topical corticosteroid. These complications are rare and generally occur after prolonged exposure to excessively large doses, especially of high-potency topical corticosteroids.

Pediatric patients may be more susceptible to systemic toxicity (b) (4) due to their larger skin surface to body mass ratios. (b) (4) [*See Use in Specific Populations (8.4) and Clinical Pharmacology (12.2)]*

(b) (4)

**8.4 Pediatric Use**

~~The safety and effectiveness of Taclonex® Topical Suspension for plaque psoriasis of the scalp have been established in the age group 12 to 17 years.~~ (b) (4)

[redacted] Two prospective, non-controlled, open-label, single group trials ([redacted] N=109) were conducted in [redacted] pediatric subjects (aged 12 to 17 years) with scalp psoriasis, including assessment of HPA axis suppression in 30 subjects. [See Warnings and Precautions (5.2), [redacted] (6.1) and Clinical Pharmacology (12.2)]

[redacted]

Safety and effectiveness of the use of Taclonex® Topical Suspension in pediatric patients under the age of 12 years have not been established.

Because of a higher ratio of skin surface area to body mass [redacted]. [See Warnings and Precautions (5.2)]

[redacted]

### *12.2 Pharmacodynamics*

*Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression:*
HPA axis suppression was evaluated in [redacted] three trials (Trial A, B and C) following the application of Taclonex® Topical Suspension. 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 as indicated by a 30-minute post-stimulation cortisol level ≤18 mcg/dL 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 as indicated by a 30-minute post-stimulation cortisol level ≤18 mcg/dL was observed in 3 out of 43 subjects (7%) 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 [redacted] subjects 12 to 17 years old (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 as indicated by a 30-minute post-stimulation cortisol level ≤18 mcg/dL was observed in 1 of 30 evaluable subjects (3%) after 4 weeks of treatment and in no subjects who continued treatment for 8 weeks.

*Effects on Calcium Metabolism*
In Trial A described above, the effects of once daily application of Taclonex® Topical Suspension on the scalp in combination with Taclonex® Ointment on the body for 4 to 8 weeks on calcium metabolism were also examined. Following once daily application of Taclonex® Topical Suspension on the scalp in combination with Taclonex® Ointment on the body, 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, the effects on calcium metabolism of once daily application of Taclonex® Topical Suspension to 15-30% of the body surface area (including the scalp) for 4 to 8 weeks were also examined. 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 addition, calcium metabolism was evaluated in a total of 109 adolescent subjects aged 12 to 17 years with plaque psoriasis of the scalp involving at least 10% of the scalp area undergoing once daily application of Taclonex® Topical Suspension to the scalp for up to 8 weeks [redacted] (b) (4) No cases of hypercalcemia and no clinically relevant changes in urinary calcium were reported.

*Reviewer's note: The Clinical team will consider the clinical significance of the high 24-hr urinary calcium of one patient at Week 4.*

## 4 Detailed Findings for Trial MBL 0801:

**Title:** Effect of Calcipotriol plus Betamethasone Dipropionate Topical Suspension on the HPA Axis and Calcium Metabolism in adolescent Subjects (Aged 12 to 17 Years) with Scalp Psoriasis

*Reviewer's note: Calcipotriol is the same as calcipotriene.*

**Trial Initiation/Completion Dates:**
4/12/2010 (first enrollment) - 8/8/2012 (last completed)

**Objectives:**

- Primary objective
  The primary objective was to evaluate the safety of once daily use of calcipotriol (50 mcg/g) + betamethasone (0.5 mg/g) (as dipropionate) gel in adolescent subjects (aged 12 to 17 years) with scalp psoriasis.

- Secondary objective
  The secondary objective was to evaluate the efficacy of once daily use of calcipotriol (50 mcg/g) plus betamethasone (0.5 mg/g) (as dipropionate) gel in adolescent subjects (aged 12 to 17 years) with scalp psoriasis.

**Trial Design:**
This trial was an open-label trial evaluating the safety and efficacy of once daily use of the Taclonex topical suspension containing calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate) in adolescent subjects (aged 12 to 17 years) with scalp psoriasis. A total of 31 subjects 12 to 17 years of age with clinical signs of or earlier diagnosed with psoriasis vulgaris on trunk and/or limbs were enrolled, and 29 subjects completed the trial. At Visit 1, enrolled subjects had a clinical diagnosis of scalp psoriasis which is:

1.) Amenable to topical treatment with a maximum of 60 g of study medication per week, and
2.) of an extent of more than or equal to 20% of the scalp area
3.) of at least moderate severity according to the investigator's global assessment

Subjects should have a normal HPA axis function at Visit 1. Normal HPA axis function was defined as both serum cortisol concentration above 5 mcg/dl before adrenocorticotropic hormone (ACTH) challenge and serum cortisol concentration above 18 mcg/dl 30 minutes after ACTH challenge.

All subjects were instructed to apply Taclonex topical suspension to psoriasis on the scalp once daily for up to 8 weeks. The approved maximum weekly dose for adults is 100 g, and the maximum weekly dosage for adolescents of this trial was reduced to 60 g. ACTH challenge test was performed at screening, Visit 3 (Day 28), and Visit 5 (Day 56). If the result of the ACTH-challenge test at Visit 3 or Visit 5 showed a serum cortisol concentration ≤18 mcg/dl at 30 minutes after the ACTH-challenge, the subject was withdrawn and an additional ACTH-challenge test is required 28 days later (Visit FU2).

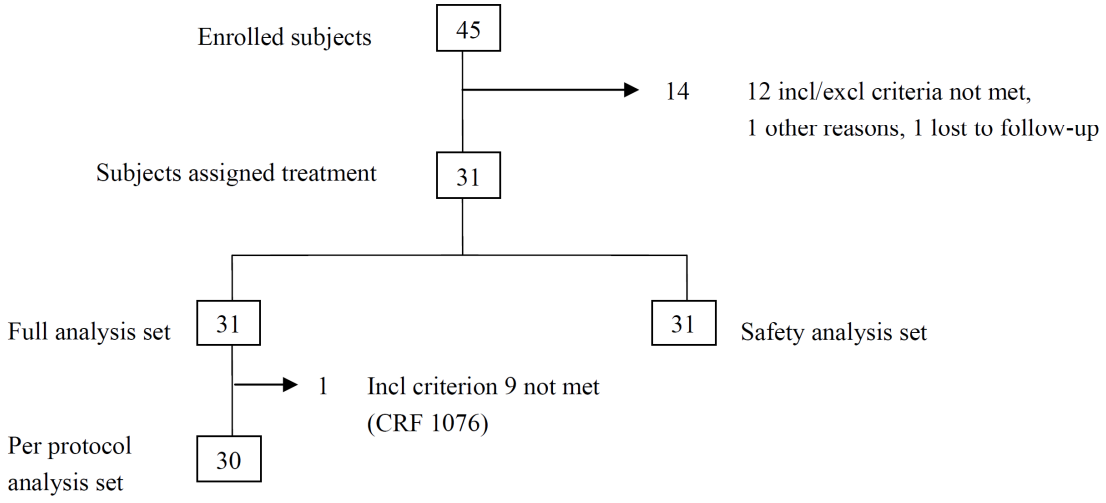
If the results of the ACTH-challenge test at Visit FU2 continued to show a serum cortisol concentration ≤18mcg/dl at 30 minutes after ACTH-challenge, further ACTH-challenge tests were to be performed, but not more often than at 4-weekly intervals, until the adrenal suppression resolves.

*Reviewer's comments:*
*Regarding the protocol design, the sponsor has amended the protocol to reflect the Agency's comments sent in the advice letter (dated 12/1/2009 in DARRTS). The design of this protocol is regarded as acceptable.*

**Results**
A total of 31 subjects were treated and 29 subjects completed the trial. One subject (CRF 1016) left the trial at Visit 3 due to signs of adrenal suppression (serum cortisol concentration ≤18 mcg/dl) at 30 minutes after the ACTH-challenge and one subject (CRF 1076) was withdrawn at Visit 2 when it was discovered that the inclusion criterion regarding the HPA axis function was not fulfilled. Three subjects (CRFs 1023, 1111, and 1079) had cleared scalp psoriasis after 4-weeks treatment and left the trial at Visit 3.

There are three analysis sets which are defined below:
Full Analysis Set: all subjects who applied study drug. (n=31)
Safety Analysis Set: all subjects who applied any study drug and for whom the presence or confirmed absence of adverse events is available. (n=31)
Per Protocol Analysis Set: This was defined for the analysis of the ACTH-challenge test and was based on the Full Analysis Set, excluding the subjects who did not:
• apply any study drug
• meet the inclusion criterion concerning adrenal function at Baseline
• provide any results for the ACTH-challenge test after applied study drug.
N=30 because one subject (CRF 1076) did not meet the inclusion criterion concerning evidence of adrenal function at baseline (inclusion criterion number 9) and was therefore excluded.

Schematic presentation of analysis sets:




## Demographics

| Baseline characteristics | Safety Analysis Set (n=31) Number of subjects | % | Per Protocol Analysis Set (n=30) Number of subjects | % |
|---|---|---|---|---|
| **Sex** | | | | |
| Male | 12 | 38.7 | 11 | 36.7 |
| Female | 19 | 61.3 | 19 | 63.3 |
| Total | 31 | 100.0 | 30 | 100.0 |
| **Ethnicity** | | | | |
| Hispanic or Latino | 9 | 29.0 | 9 | 30.0 |
| Not Hispanic or Latino | 22 | 71.0 | 21 | 70.0 |
| Total | 31 | 100.0 | 30 | 100.0 |
| **Race** | | | | |
| White | 28 | 90.3 | 27 | 90.0 |
| Black or African American | 1 | 3.2 | 1 | 3.3 |
| Asian | 1 | 3.2 | 1 | 3.3 |
| Other | 1 | 3.2 | 1 | 3.3 |
| Total | 31 | 100.0 | 30 | 100.0 |
| **Skin type** | | | | |
| I | 3 | 9.7 | 3 | 10.0 |
| II | 12 | 38.7 | 11 | 36.7 |
| III | 6 | 19.4 | 6 | 20.0 |
| IV | 8 | 25.8 | 8 | 26.7 |
| V | 2 | 6.5 | 2 | 6.7 |
| Total | 31 | 100.0 | 30 | 100.0 |

31OCT12:13:38:06 MBL 0801 INT t4_basecat.doc

1) Other = Caldenian

Age: safety analysis set and per protocol analysis set

| Centre<br>Age (years) | Safety Analysis Set<br>(n=31) | Per Protocol Analysis Set<br>(n=30) |
|---|---|---|
| **All Centres** | | |
| Mean | 14.8 | 14.9 |
| SD | 1.7 | 1.7 |
| Median | 15.0 | 15.0 |
| Minimum | 12 | 12 |
| Maximum | 17 | 17 |
| Number | 31 | 30 |

*Reviewer's comments: There were an adequate number of subjects at the lower limit of age in the safety analysis set (n=31), with 3 subjects aged 12 years and 6 subjects aged 13 years.*

ACTH-Challenge Test

One subject (CRF 1016, age 17), had serum cortisol concentration ≤18 mcg/dl at 30 minutes after ACTH challenge at Week 4 with a level of 16.8 mcg/dL. The subject had normal ACTH-challenge test at follow-up 4 weeks after end of treatment. One subject (CRF 1018) had serum cortisol concentration ≤18 mcg/dl at 60 minutes after ACTH challenge at Week 4 with a level of 13.7 mcg/dL. This is not considered adrenal suppression as the 30 minute value showed normal response with a level of 21.2 mcg/dL. This subject also had normal response at Week 8 at both 30 and 60 minutes after ACTH challenge test. No subject showed signs of adrenal suppression (serum cortisol concentration ≤18 mcg/dl) at both 30 and 60 minutes after ACTH challenge at Week 4 nor at Week 8. Table 1 below shows the serum cortisol concentration for subjects who had level ≤18 mcg/dL (CRF 1016 and CRF 1018) at either 30 minutes or 60 minutes after ACTH challenge test. Table 3 below shows the serum cortisol concentration at 30 minutes after ACTH challenge at baseline, Week 4 and Week 8 (per protocol analysis set).

**Table 1: Individual data for subjects with serum cortisol concentration ≤ 18 mcg/dL at either 30 minutes or 60 minutes after ACTH challenge**

| CRF number | Visit | Sample time | Serum cortisol concentration (mcg/dL) | Change in serum cortisol concentration from time 0 (mcg/dL) | Extent of scalp psoriasis (%) | Amount of IP used visit 1 to 3 (g) | Amount of IP used visit 3 to 5 (g) |
|---|---|---|---|---|---|---|---|
| **LEO 80185** | | | | | | | |
| 1016 | Baseline | 0 min | 12.4 | | 75 | 110.14 | |
| | | 30 min | 19.8 | 7.4 | | | |
| | | 60 min | 20.4 | 8.0 | | | |
| | Week 4 (Visit 3) | 0 min | 3.4 | | | | |
| | | 30 min | 16.8 | 13.4 | | | |
| | | 60 min | 18.5 | 15.1 | | | |
| | Follow-up | 0 min | 5.6 | | | | |
| | | 30 min | 20.9 | 15.3 | | | |
| | | 60 min | 22.8 | 17.2 | | | |
| 1018 | Baseline | 0 min | 11.8 | | 60 | 82.89 | 32 |
| | | 30 min | 20.4 | 8.6 | | | |
| | | 60 min | 22.8 | 11.0 | | | |
| | Week 4 (Visit 3) | 0 min | 24.8 | | | | |
| | | 30 min | 21.2 | -3.6 | | | |
| | | 60 min | 13.7 | -11.1 | | | |
| | Week 8 (Visit 5) | 0 min | 20.0 | | | | |
| | | 30 min | 27.5 | 7.5 | | | |
| | | 60 min | 28.1 | 8.1 | | | |

20NOV12:13:19:35 MBL 0801 INT t18_cortlpp.doc

The mean extent of psoriasis on the scalp was 60.4% of the scalp area (median 62.0; range 20-100% of the scalp area) and the mean total extent of psoriasis on the scalp, face, and body was 5.2% of BSA (median 5.0; range 1-13% of BSA). The investigator's assessment of extent of psoriasis is shown in Table 2.

**Table 2: Investigator's assessment of extent of psoriasis (safety analysis set and per protocol analysis set)**

| Investigator's assessment of extent | Safety Analysis Set (n=31) | Per Protocol Analysis Set (n=30) |
|---|---|---|
| **Total body surface area (%)** | | |
| Mean | 5.2 | 5.2 |
| SD | 3.5 | 3.5 |
| Median | 5.0 | 4.5 |
| Minimum | 1 | 1 |
| Maximum | 13 | 13 |
| Number | 31 | 30 |
| **Scalp (%)** | | |
| Mean | 60.4 | 61.1 |
| SD | 28.2 | 28.4 |
| Median | 62.0 | 62.0 |
| Minimum | 20 | 20 |
| Maximum | 100 | 100 |
| Number | 31 | 30 |

22NOV12:13:21:31 MBL 0801 INT t8_bdoccalp.doc

**Table 3: Serum cortisol concentration at 30 minutes after ACTH challenge at baseline, Week 4 and Week 8: per protocol analysis set**

| Serum Cortisol Concentration (mcg/dL) | LEO 80185 (n=30) |
|---|---|
| **30 min after ACTH challenge test** | |
| **Baseline** | |
| Mean | 24.57 |
| SD | 3.58 |
| Median | 24.50 |
| Minimum | 19.4 |
| Maximum | 31.8 |
| Number | 30 |
| **Week 4** | |
| Mean | 23.73 |
| SD | 3.70 |
| Median | 22.75 |
| Minimum | 16.8 |
| Maximum | 32.5 |
| Number | 30 |
| **Week 8** | |
| Mean | 24.21 |
| SD | 3.41 |
| Median | 24.30 |
| Minimum | 18.4 |
| Maximum | 31.1 |
| Number | 26 |

**Table 4: Average weekly amount of Taclonex topical suspension used (safety analysis set)**

| Visit interval<br>Average weekly amount[1] (g) | LEO 80185<br>(n=31) |
|---|---|
| **Visit 1 to Visit 3 (4 weeks)** | |
| Mean | 25.4 |
| SD | 20.4 |
| Median | 20.0 |
| Minimum | 0.7 |
| Maximum | 57.4 |
| Number[2] | 28 |
| **Visit 3 to Visit 5 (4 weeks)** | |
| Mean | 24.2 |
| SD | 20.9 |
| Median | 17.7 |
| Minimum | 0.7 |
| Maximum | 62.6 |
| Number[2] | 24 |
| **Visit 1 to End of Treatment** | |
| Mean | 24.5 |
| SD | 21.1 |
| Median | 13.7 |
| Minimum | 0.7 |
| Maximum | 59.9 |
| Number[2] | 24 |

19NOV12:13:25:25 MBL 0801 INT t68_avgamt.doc

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

*Reviewer's comments:*
*The dose of taclonex topical suspension used in Subject 1016 was as follows:*
*Visit 1-2/Average weekly use: 94 g/47 g*
*Visit 2-3/Average weekly use: 16 g/8 g*
*Visit 3-Unscheduled: 4 g*
*Visit 1-3/Average weekly use: 110 g/27.5 g*

*The sponsor stated that the mean weekly amount used during the entire treatment period for all subjects was 24.5 g/week (median 13.7; range 0.7-59.9 g/week) as shown in Table 4, and was similar in Weeks 1 through 4 and Weeks 5 through 8. By looking at the dose data of taclonex topical suspension for each individual, it appears that the amount of medication used differ a lot from each individual to individual. The dose of taclonex topical suspension of Subject CRF 1016 was higher than the median dose (27.5g/week compared to 13.7 g/week); however, there were other subjects who had even higher dose but with normal serum cortisol concentration at 30 minutes after ACTH challenge. Therefore, there was no direct link between the dose of taclonex topical suspension used and the subjects who developed HPA axis suppression after 4 weeks of treatment.*

*For subject CRF 1018, the serum cortisol concentration was 21.2mcg/dL at 30 minutes after ACTH challenge at Week 4, but dropped to 13.7 mcg/dL at 60 minutes. At Week 8, the serum cortisol concentration was 27.5 mcg/dL at 30 minutes after ACTH challenge and 28.1 mcg/dL at 60 minutes. Subject CRF1018 is not considered as HPA axis suppressed because the pre-set criteria of HPA axis suppression was 30 minutes after ACTH challenge. However, it is likely that the low level at 60 minutes post ACTH challenge was an anomaly because both the pre-challenge serum cortisol concentration (24.8 mcg/dL) and the concentration after 30 minutes of ACTH challenge (21.2 mcg/dL) were above the 18 mcg/dL threshold.*

Effect on Calcium Metabolism

The change in albumin-corrected serum calcium from Baseline to Week 4, Week 8, and end of treatment was evaluated. No subject had high albumin-corrected serum calcium at Week 4, Week 8, and end of treatment. The change in albumin-corrected serum calcium and the level categorized as low, normal or high from baseline to Week 4, Week 8 and end of treatment (safety analysis set) is shown in Table 5 and Table 6.

**Table 5: Change in albumin-corrected serum calcium from baseline to Week 4, Week 8 and end of treatment: safety analysis set**

| Visit<br>Albumin-corrected serum calcium (mmol/l) | LEO 80185<br>(n=31) |
|---|---|
| **Baseline** | |
| Mean | 2.262 |
| SD | 0.090 |
| Median | 2.250 |
| Minimum | 2.13 |
| Maximum | 2.43 |
| Number | 31 |
| **Change at Week 4 (Visit 3)** | |
| Mean | -0.028 |
| SD | 0.087 |
| Median | -0.025 |
| Minimum | -0.23 |
| Maximum | 0.13 |
| Number | 30 |
| Lower 95% confidence limit (mean) | -0.060 |
| Upper 95% confidence limit (mean) | 0.005 |
| **Change at Week 8 (Visit 5)** | |
| Mean | 0.002 |
| SD | 0.087 |
| Median | 0.025 |
| Minimum | -0.15 |
| Maximum | 0.13 |
| Number | 26 |
| Lower 95% confidence limit (mean) | -0.033 |
| Upper 95% confidence limit (mean) | 0.037 |
| **Change at End of Treatment** | |
| Mean | -0.007 |
| SD | 0.090 |
| Median | 0.013 |
| Minimum | -0.15 |
| Maximum | 0.13 |
| Number | 30 |
| Lower 95% confidence limit (mean) | -0.040 |
| Upper 95% confidence limit (mean) | 0.027 |

09NOV12:11:09:23 MBL 0801 INT t20_chalb.doc

**Table 6: Albumin-corrected serum calcium categorized as low, normal or high at Week 4, Week 8 and end of treatment shown against baseline category: safety analysis set**

| Visit<br>Albumin-corrected serum calcium | Baseline category[1] | LEO 80185 (n=31)<br>End of period category[1]<br>Low | Normal | High |
|---|---|---|---|---|
| Week 4 (Visit 3) | Low | 1 | 1 | 0 |
| | Normal | 1 | 27 | 0 |
| Week 8 (Visit 5) | Low | 0 | 2 | 0 |
| | Normal | 2 | 22 | 0 |
| End of Treatment | Low | 0 | 2 | 0 |
| | Normal | 2 | 26 | 0 |

09NOV12:13:24:08 MBL 0801 INT t21_shalb.doc

For the 24-hour urinary calcium excretion evaluation at Baseline, Week 4, and Week 8, one subject (CRF 1002) had high 24-hour urinary calcium excretion at Week 4 with a level of 8.2 mmol/24 hr (reference range 2.5-7.5) and level was normalized at later visit (3.7 mmol/24 hr at Week 8). For this subject (CRF 1002), the 24-hour urinary calcium excretion at baseline was 4.15 mmol/24hr. The 24-hour urinary calcium excretion (mmol/24 hr) at baseline, Week 4 and Week 8 (safety analysis set) is shown in Table 7.

*Reviewer's comments:*
*Subject CRF 1002 had a normal level of 24-hour urinary calcium excretion at Baseline (4.15 mmol/24 hr), but had a high level of 8.2 mmol/24 hr at Week 4. The level was normalized at Week 8 with a value of 3.7 mmol/24 hr. This subject had normal albumin-corrected serum calcium at all three timepoints (2.250 mmol/L at baseline, 2.225 mmol/L at Week 4, and 2.200 mmol/L at Week 8). The dietary calcium intake of this subject remained similar at the 3 timepoints.*

**Table 7: 24-hour urinary calcium excretion (mmol/24 hr) at baseline, Week 4 and Week 8: safety analysis set. N=31.**

| 24-hour urinary calcium excretion (mmol/24hr) | |
|---|---|
| **Baseline** | |
| Mean | 3.03 |
| SD | 1.64 |
| Median | 2.68 |
| Minimum | 0.6 |
| Maximum | 6.7 |
| Number | 31 |
| **Week 4 (Visit 3)** | |
| Mean | 3.17 |
| SD | 1.97 |
| Median | 2.95 |
| Minimum | 0.3 |
| Maximum | 8.2 |
| Number | 28 |
| **Week 8 (Visit 5)** | |
| Mean | 3.12 |
| SD | 1.62 |
| Median | 3.36 |
| Minimum | 0.8 |
| Maximum | 6.0 |
| Number | 22 |

For the evaluation of urinary calcium:creatinine ratio at Baseline, Week 4, and Week 8, one subject (CRF 1048) had a low value at Week 4 with a level of 0.25 mmol/g (reference range 0.3-6.1). This subject's urinary calcium:creatinine ratio value was 1.15 mmol/g at baseline and 0.675 mmol/g at Week 8. It is noted that for this subject, the 24-hour urinary calcium was 0.775 mmol/24 hr at baseline, 0.325 mmol/24 hr at Week 4, and 0.95 mmol/24 hr at Week 8 (reference range 2.5-7.5). The 24-hour creatinine was 5.96 mmo/24 hr at baseline, 12.08 mmol/24 hr at Week 4, and 12.39 mmol/24 hr at Week 8 (reference range 9.194-20.774). The urinary calcium: creatinine ratio at baseline, Week 4 and Week 8 (safety analysis) is shown in Table 8.

*Reviewer's comment:*
*Subject CRF 1048 had low 24-hour urinary calcium levels at all three timepoints assessed (Baseline, Week 4, and Week 8).Therefore, the low urinary calcium:creatinine ratio at Week 4 was probably due to the low level of urinary calcium. The higher but still normal level of urinary calcium:creatinine ratio at baseline was probably due to the reason that both of the urinary calcium and creatinine was low.*

**Table 8: urinary calcium: creatinine ratio (mmol/g) at baseline, Week 4 and Week 8: safety analysis set. N=31.**

| Urinary calcium:creatinine ratio (mmol/g) | |
|---|---|
| **Baseline** | |
| Mean | 3.2048 |
| SD | 1.8723 |
| Median | 2.4500 |
| Minimum | 1.000 |
| Maximum | 8.475 |
| Number | 31 |
| **Week 4 (Visit 3)** | |
| Mean | 2.8804 |
| SD | 1.5094 |
| Median | 2.8625 |
| Minimum | 0.250 |
| Maximum | 6.700 |
| Number | 28 |
| **Week 8 (Visit 5)** | |
| Mean | 3.2068 |
| SD | 1.7820 |
| Median | 3.0375 |
| Minimum | 0.675 |
| Maximum | 7.275 |
| Number | 22 |

Amount of Taclonex topical suspension used

The mean weekly amount used during the entire treatment period was 24.5 g/week (median 13.7; range 0.7-59.9 g/week), and was similar in Weeks 1 through 4 and Weeks 5 through 8. The mean amount used during the entire treatment period was 203 g (median 109; range 6-496 g), and was similar in Weeks 1 through 4 and Weeks 5 through 8. The average weekly amount used (safety analysis set) is shown in Table 9.

**Table 9: Average weekly amount used: safety analysis set**

| Visit interval<br>Average weekly amount[1] (g) | LEO 80185<br>(n=31) |
|---|---|
| **Visit 1 to Visit 3 (4 weeks)** | |
| Mean | 25.4 |
| SD | 20.4 |
| Median | 20.0 |
| Minimum | 0.7 |
| Maximum | 57.4 |
| Number[2] | 28 |
| **Visit 3 to Visit 5 (4 weeks)** | |
| Mean | 24.2 |
| SD | 20.9 |
| Median | 17.7 |
| Minimum | 0.7 |
| Maximum | 62.6 |
| Number[2] | 24 |
| **Visit 1 to End of Treatment** | |
| Mean | 24.5 |
| SD | 21.1 |
| Median | 13.7 |
| Minimum | 0.7 |
| Maximum | 59.9 |
| Number[2] | 24 |

19NOV12:13:25:25 MBL 0801 INT t68_avgamt.doc

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

Bioanalytical Method:

- Serum Cortisol

The ADVIA Centaur® Cortisol assay was for the use 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

(b) (4)

(b) (4)

| | | | | | |
|---|---|---|---|---|---|
| | 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: | C514 | | | |
| | 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 |

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.

- 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: | (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 |


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

**Applicant's conclusion:**
One subject (3.3%) showed signs of possible adrenal suppression (serum cortisol concentration ≤18 mcg/dl) at 30 minutes after ACTH challenge at Week 4 (>18 mcg/dl at 60 minutes after ACTH challenge). Serum cortisol level was normalized at follow-up 4 weeks after end of treatment. No cases of hypercalcaemia were reported and there were no clinically relevant increases in urinary calcium or other parameters of calcium metabolism.

The mean weekly amount of taclonex topical suspension used during the entire treatment period was 24.5 g/week, which was similar in Weeks 1 through 4 and Weeks 5 through 8. In the adult 8-week pivotal trials in scalp psoriasis (Trials MBL 0405 INT and MBL 0406 INT) the mean weekly amount of taclonex topical suspension was 15-22 g/week. Therefore, the weekly dose was similar between the two adult trials and this adolescent trial for the indication of scalp psoriasis.

In terms of safety, 16 subjects (52%) reported 20 adverse events; none of them were SAEs and the majority (14/20) of the adverse event were mild and none of them lesional/perilesional. There was one possible related adverse event that led to withdrawal (the possible adrenal suppression).

*Reviewer's comments:*
*The sponsor's conclusion is generally acceptable. The Clinical team will evaluate whether the high 24-hour urinary calcium excretion of 8.2 mmol/24 hr at Week 4 in subject CRF 1002 is clinically relevant.*

---

**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
06/12/2014

DOANH C TRAN
06/12/2014

EDWARD D BASHAW
06/12/2014