U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	sNDA 022185 / S-018
Drug Name:	Taclonex® (calcipotriene and betamethsone dipropionate) Topical Suspension, 0.005%/0.064%
Indication(s):	Treatment of psoriasis (b) (4) on the scalp
Applicant:	LEO Pharma Inc.
Date(s):	Letter Date: 10/31/2013
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Review Priority:	Standard
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Keywords: psoriasis, combination product, pediatric subjects

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1 INTRODUCTION

1.1 Overview

Taclonex Scalp® (calcipotriene and betamethasone dipropionate) Topical Suspension, 0.005%/0.064% (NDA 22-185) was approved by the Division of Dermatology and Dental Products on May 9, 2008 for the topical treatment of moderate to severe psoriasis vulgaris of the scalp in patients 18 years and older. On October 17, 2012, the Agency approved a supplemental application to include the additional indication for plaque psoriasis of the body in patients 18 years and older, and the proprietary name became Taclonex® Topical Suspension.

In the approval letter dated May 9, 2008, the Agency waived the pediatric study requirement for ages 0 months to up to 12 years because there is evidence strongly suggesting that the drug product would be unsafe in this pediatric age group. In addition, the Agency deferred the pediatric study for ages 12 to 17 years because the product was ready for approval for use in adults. In the letter, the Agency listed the following required post-marketing study:

> "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."

On January 29, 2009, the sponsor submitted the following 2 draft protocols with questions to IND 67835 to address the pediatric study requirement:

1. MBL-0412 INT: "Safety and efficacy of calcipotriene plus betamethasone dipropionate (topical solution) in pediatric subjects (aged 12 to 17 years) with scalp psoriasis"
2. MBL-0801: "Effect of calcipotriene plus betamethasone dipropionate topical suspension on the HPA axis and calcium metabolism in pediatric subjects (aged 12 to 17 years) with scalp psoriasis"

On December 1, 2009 the Agency provided responses to the questions submitted by the sponsor. The Agency provided additional comments to the December 1, 2009 correspondence in an advice letter on March 2, 2010.

On March 3, 2010, the sponsor submitted an amended protocol for MBL-0801. According to the sponsor, the amended protocol was submitted before the March 2, 2010 letter was received; therefore, it did not address the Agency's comments. On June 10, 2010, the Agency provided comments regarding the protocol submitted on March 3, 2010. On August 19, 2010 the sponsor submitted a final amended protocol for MBL-0801, which was revised to address Agency comments.

1.2 Clinical Studies Overview

The applicant submitted data from two open-label studies (MBL-0801 and MBL-0412 INT). An overview of the studies is presented in Table 1.

Table 1: Clinical Study Overview

Study	Location	Study Population	Treatment Arms	Number of Subjects	Dates
MBL-0801	US (5 sites)	Age 12-17 years, IGA ≥ 3 (moderate), ≥ 20% of scalp involvement	Taclonex® Topical Suspension	31	5/12/2010 – 8/8/2012
MBL-0412 INT	Canada (7 sites), France (5 sites), & UK (5 sites)	Age 12-17 years, IGA ≥ 3 (moderate), ≥ 10% of scalp involvement	Taclonex® Topical Suspension	78	11/22/2010 – 10/15/2012

1.3 Data Sources

This reviewer evaluated the sponsor's clinical study reports, datasets, clinical summaries, and proposed labeling. This submission was submitted in eCTD format and was and entirely electronic. The datasets in this review are achieved at the following location: \\cdsesub1\evsprod\NDA022185\0114\m5\datasets\.

2 STATISTICAL EVALUATION

2.1 Data and Analysis Quality

The databases for the study required minimal data management prior to performing analyses and no request for additional datasets were made to the sponsor.

2.2 Study Design

Study MBL-0801 was a multicenter, prospective, non-controlled, open-label, single-group, 8-week, Phase 2 study in pediatric subjects (aged 12 to 17 years) with scalp psoriasis. The primary objective of this study was to evaluate the safety of once daily use of Taclonex® Topical Suspension. In particular, it was designed to evaluate the effect of Taclonex® Topical Suspension on the hypothalamic-pituitary-adrenal (HPA) axis and calcium metabolism. The secondary objective was to evaluate the efficacy of Taclonex® Topical Suspension. For enrollment subjects must have met the following key inclusion criteria:

- Aged 12 to 17 years
- A clinical diagnosis of scalp psoriasis which is:
    - More than or equal to 20% of the scalp area
    - Have an Investigator's Global Assessment (IGA) score of at least 3 (moderate)

Study MBL-0412 INT was a multicenter, prospective, non-controlled, open-label, single-group, 8-week, Phase 2 study in pediatric subjects (aged 12 to 17 years) with scalp psoriasis. The primary objective of this study was to evaluate the safety of once daily use of Taclonex® Topical

Suspension. The secondary objective was to evaluate the efficacy of Taclonex® Topical Suspension. For enrollment subjects must have met the following key inclusion criteria:

- Aged 12 to 17 years
- A clinical diagnosis of scalp psoriasis which is:
    - More than or equal to 10% of the scalp area
    - Have an Investigator's Global Assessment (IGA) score of at least 3 (moderate)

Study MBL-0801 enrolled 31 subjects from 5 sites in the US. Study MBL-0412 INT enrolled 78 subjects from 17 centers (7 in Canada, 5 sites in France, and 5 sites in UK). In both studies, subjects applied study product once daily for up to 8 weeks. Subjects that achieved an IGA score of 0 (clear) after 4 weeks of treatment were allowed to stop treatment at the investigator's discretion. Subjects were evaluated at 9 scheduled visits: screening visit #1, screening visit #2, baseline (Week 0), Weeks 2, 4, 6, 8 (end of treatment), 10, and 12.

Table 2: Investigator's Global Assessment (IGA) scale

Scale	Grade	Description
0	Clear	Plaque thickening = no elevation or thickening over normal skin Scaling = no evidence of scaling Erythema = none or hyperpigmentation or residual red coloration
1	Almost Clear	Plaque thickening = none or possible thickening but difficult to ascertain whether there is a slight elevation above normal skin level Scaling = none or residual surface dryness and scaling Erythema = light pink coloration
2	Mild	Plaque thickening = slight but definite elevation Scaling = fine scales partially or mostly covering lesions Erythema = light red coloration
3	Moderate	Plaque thickening = moderate elevation with rounded or sloped edges Scaling = most lesions at least partially covered Erythema = definite red coloration
4	Severe	Plaque thickening = marked elevation typically with hard or sharp edges Scaling = non-tenacious scale predominates, covering most or all of the lesions Erythema = very bright red coloration
5	Very Severe	Plaque thickening = very marked elevation typically with hard or sharp edges Scaling = thick tenacious scale covers most or all of the lesions Erythema = extreme red coloration; deep red coloration

Source: Sponsor's Protocols, Module 5.3.5.2.mbl-0412-int and Module 5.3.5.2.mbl-0801

2.3 Statistical Methodologies

The safety population was defined as all subjects who apply any study medication and for whom the presence or confirmed absence of adverse events is available. The primary population for the evaluation of efficacy was the full analysis set (FAS), defined as all subjects who applied any study product.

The protocol specified that the proportion of subjects with "controlled disease" (an IGA score of 0 or 1) will be presented for each visit (Weeks 2, 4, and 8). In addition, the protocol specified

that a 95% confidence interval based on the binomial distribution will be presented for the proportions. The statistical analysis plan (SAP) specified that missing data will be imputed using the last observation carried forward (LOCF) approach.

2.4 Patient Disposition, Demographic and Baseline Characteristics

The disposition of subjects is presented in Table 3. The rate of discontinuation was similar between the two studies. The demographics were generally similar between the two studies and are summarized in Table 4. The proportion of subjects with a baseline IGA score of 3 (moderate) in Study MBL-0801 was slightly smaller than the proportion in Study MBL-0412 INT (i.e., 64.7% vs. 74.4%).

Table 3: Disposition of Subjects (FAS)

	Study MBL-0801 (N=31)	**Study MBL-0412 INT (N=78)**
Completed	29 (93.5%)	74 (94.9%)
Discontinued	2 (6.5%)	4 (5.1%)
Unacceptable Adverse Event	1	1
Exclusion Criteria During Study	1	2
Other	0	1

Source: Reviewer's Analysis

Table 4: Demographics and Baseline Disease Severity (FAS)

	Study MBL-0801 (N=31)	**Study MBL-0412 INT (N=78)**	**Combined (N=109)**
Age (year)			
12	3 (9.7%)	12 (15.4%)	15 (13.8%)
13	6 (19.4%)	12 (15.4%)	18 (16.5%)
14	6 (19.4%)	14 (17.9%)	20 (18.4%)
15	3 (9.7%)	11 (14.1%)	14 (12.8%)
16	6 (19.4%)	17 (21.8%)	23 (21.1%)
17	7 (22.6%)	12 (15.4%)	19 (17.4%)
Mean (SD)	14.8 (1.7)	14.6 (1.7)	14.6 (1.7)
Median	15	15	15
Gender			
Male	12 (38.7%)	35 (44.9%)	47 (43.1%)
Female	19 (61.3%)	43 (55.1%)	62 (56.9%)
Race			
White	28 (90.3%)	70 (89.7%)	98 (89.9%)
Black or African American	1 (3.2%)	1 (1.3%)	2 (1.8%)
Asian	1 (3.2%)	3 (3.8%)	7 (3.7%)
Other	1 (3.2%)	4 (5.1%)	5 (4.6%)
Baseline IGA			
3 - Moderate	28 (67.7%)	58 (74.4%)	79 (72.5%)
4 - Severe	8 (25.8%)	16 (20.5%)	24 (22.0%)
5 - Very Severe	2 (6.5%)	4 (5.1%)	6 (5.5%)

Source: Reviewer's Analysis
SD: Standard Deviation

2.5 Evaluation of Efficacy

The evaluation of efficacy was a secondary objective in both studies. Table 5 displays the proportion of subjects with controlled disease (an IGA score of 0 or 1) at Weeks 2, 4, and 8. The rates were much higher in Study MBL-0412 INT than in Study MBL-0801; however, as both studies did not contain a vehicle arm and were conducted in an open-label manner, it makes interpretation of these findings difficult. It should be noted that on average the amount of product used in Study MBL-0412 INT was higher than the amount used in Study MBL-0801, see Table 6 in Section 2.6.

Table 5: Controlled Disease[(1)] Rates (FAS, LOCF)

	Study MBL-0801 (N=31)		Study MBL-0412 INT (N=78)	
	Controlled Disease	**95% CI**	**Controlled Disease**	**95% CI**
Week 2	10 (32.3%)	(15.8%, 48.7%)	37 (47.4%)	(36.4%, 58.5%)
Week 4	13 (41.9%)	(24.6%, 59.3%)	59 (75.6%)	(66.1%, 85.2%)
Week 8	17 (54.8%)	(37.3%, 72.4%)	66 (84.6%)	(76.6%, 92.6%)

Source: Reviewer's Analysis
(1) Controlled Disease is defined as achieving an IGA of 0 (Clear) or 1 (Almost Clear)

2.6 Evaluation of Safety

Table 6 presents the extent of exposure in both studies. Treatment duration was similar in both studies. The average weekly amount used in Study MBL-0412 INT was higher in comparison to Study MBL-0801. In the US, the approved maximum weekly dose in adults is 100 grams. In these two studies, the maximum weekly dosage was specified to be 60 grams. In Study MBL-0801, 4 subjects used more than 60 grams per week for two or more weeks during the study (note that visits were scheduled every two weeks). In Study MBL-0412 INT, 17 subjects used more than 60 grams per week for two or more weeks during the study.

An overview of adverse events (AEs) is presented in Table 7. In Study MBL-0801, 16 subjects (51.6%) reported 20 AEs. In Study MBL-0412 INT, 27 subjects (34.6%) reported 64 AEs. None of the AEs reported in both studies were serious. Table 8 displays all AEs reported in both studies. Table 9 displays the adverse reactions in both studies.

Table 6: Extent of Exposure (Safety Population)

	Study MBL-0801 (N=31)	Study MBL-0412 INT (N=78)	Combined (N=109)
Duration (Weeks)			
Mean (SD)	7.5 (2.0)	7.1 (1.9)	7.2 (1.9)
Median	8.0	7.9	8.0
Range	0.4 - 11.0	0.1 - 9.3	0.1 - 11.0
Amount Used (g)			
N[(1)]	24	51	75
Mean (SD)	202.6 (172.6)	283.7 (139.4)	257.8 (154.4)
Median	109.2	345.4	330.8
Range	5.7 - 496.0	25.9 - 519.7	5.7 - 519.7
Average Weekly Amount (g)			
N[(1)]	24	51	75
Mean (SD)	24.5 (21.1)	36.0 (17.7)	32.3 (19.5)
Median	13.7	41.7	40.1
Range	0.7 - 59.9	3.5 - 68.6	0.7 - 68.6
Missed Applications			
None	17 (54.8%)	25 (32.1%)	42 (38.5%)
≤ 10% missed	9 (29.0%)	21 (26.9%)	30 (27.5%)
>10% to ≤ 20% missed	2 (6.5%)	8 (10.3%)	10 (9.2%)
>20% to ≤ 30% missed	1 (3.2%)	8 (10.3%)	9 (8.3%)
>30% to ≤ 40% missed	0	3 (3.8%)	3 (2.8%)
>40% to ≤ 50% missed	0	2 (2.6%)	2 (1.8%)
>50% missed	2 (6.5%)	11 (14.1%)	13 (11.9%)

Source: Reviewer's Analysis
(1) Subjects who returned dispensed bottles.

Table 7: Overview of Adverse Events Reported (Safety Population)

	Study MBL-0801 (N=31)	Study MBL-0412 INT (N=78)	Combined (N=109)
Subjects Reporting at Least 1 AE	16 (51.6%)	27 (34.6%)	43 (39.4%)
AEs Reported[(1)]	20	64	84
AEs Intensity			
Mild	14	33	47
Moderate	5	22	27
Severe	1	9	10
Serious AEs	0	0	0
Subjects Discontinued due to AEs	1 (3.2%)	2 (2.6%)	3 (2.8%)
Adverse Drug Reactions	1	7	8

Source: Reviewer's Analysis
(1) Different adverse events with the same preferred term involving the same subject was counted as one.

Table 8: Adverse Events by MedDRA Preferred Term (Safety Population)

Preferred Term	Study MBL-0801 (N=31)	Study MBL-0412 INT (N=78)	Combined (N=109)
Upper respiratory tract infection	2 (6.5%)	4 (5.1%)	6 (5.5%)
Headache	1 (3.2%)	4 (5.1%)	5 (4.6%)
Cough	3 (9.7%)	1 (1.3%)	4 (3.7%)
Oropharyngeal pain	3 (9.7%)	1 (1.3%)	4 (3.7%)
Pharyngitis	0	4 (5.1%)	4 (3.7%)
Acne	1 (3.2%)	2 (2.6%)	3 (2.8%)
Urine calcium decreased	0	3 (3.8%)	3 (2.8%)
Abdominal pain	1 (3.2%)	1 (1.3%)	2 (1.8%)
Blood parathyroid hormone increased	0	2 (2.6%)	2 (1.8%)
Diarrhoea	0	2 (2.6%)	2 (1.8%)
Gastroenteritis	0	2 (2.6%)	2 (1.8%)
Nasopharyngitis	2 (6.5%)	0	2 (1.8%)
Psoriasis	0	2 (2.6%)	2 (1.8%)
Pyrexia	0	2 (2.6%)	2 (1.8%)
Seasonal allergy	0	2 (2.6%)	2 (1.8%)
Wheezing	1 (3.2%)	1 (1.3%)	2 (1.8%)
Alopecia	0	1 (1.3%)	1 (0.9%)
Anxiety	1 (3.2%)	0	1 (0.9%)
Application site pruritus	0	1 (1.3%)	1 (0.9%)
Arthritis	0	1 (1.3%)	1 (0.9%)
Asthenia	0	1 (1.3%)	1 (0.9%)
Asthma	0	1 (1.3%)	1 (0.9%)
Blood calcium decreased	0	1 (1.3%)	1 (0.9%)
Cardiac flutter	0	1 (1.3%)	1 (0.9%)
Conjunctivitis allergic	0	1 (1.3%)	1 (0.9%)
Dermatitis acneiform	0	1 (1.3%)	1 (0.9%)
Dyspnoea	0	1 (1.3%)	1 (0.9%)
Fatigue	0	1 (1.3%)	1 (0.9%)
Gastroenteritis viral	0	1 (1.3%)	1 (0.9%)
Hand-foot-and-mouth disease	1 (3.2%)	0	1 (0.9%)
Hypothalamo-pituitary disorder	1 (3.2%)	0	1 (0.9%)
Jaw disorder	0	1 (1.3%)	1 (0.9%)
Joint dislocation	1 (3.2%)	0	1 (0.9%)
Ligament sprain	0	1 (1.3%)	1 (0.9%)
Malaise	0	1 (1.3%)	1 (0.9%)
Myalgia	0	1 (1.3%)	1 (0.9%)
Nasal congestion	1 (3.2%)	0	1 (0.9%)
Nausea	0	1 (1.3%)	1 (0.9%)
Nystagmus	0	1 (1.3%)	1 (0.9%)
Otitis externa	0	1 (1.3%)	1 (0.9%)
Oxygen saturation decreased	0	1 (1.3%)	1 (0.9%)
Pain	1 (3.2%)	0	1 (0.9%)
Sinus headache	0	1 (1.3%)	1 (0.9%)
Skeletal injury	0	1 (1.3%)	1 (0.9%)
Skin striae	0	1 (1.3%)	1 (0.9%)
Speech disorder	0	1 (1.3%)	1 (0.9%)
Staphylococcal infection	0	1 (1.3%)	1 (0.9%)
Tendonitis	0	1 (1.3%)	1 (0.9%)
Tooth extraction	0	1 (1.3%)	1 (0.9%)

Toothache	0	1 (1.3%)	1 (0.9%)
Urinary tract infection	0	1 (1.3%)	1 (0.9%)
Urine phosphorus decreased	0	1 (1.3%)	1 (0.9%)
Vomiting	0	1 (1.3%)	1 (0.9%)

Source: pg. 82 of Study Report for Study MBL-0801 and pg. 80-81 of Study Report for Study MBL-0412 INT

Table 9: Adverse Reactions Events by MedDRA Preferred Term (Safety Population)

Preferred Term	Study MBL-0801 (N=31)	Study MBL-0412 INT (N=78)	Combined (N=109)
Hypothalamo-pituitary disorder	1 (3.2%)	0	1 (0.9%)
Headache	0	1 (1.3%)	1 (0.9%)
Acne	0	1 (1.3%)	1 (0.9%)
Dermatitis acneiform	0	1 (1.3%)	1 (0.9%)
Application site pruritus	0	1 (1.3%)	1 (0.9%)
Blood calcium decreased	0	1 (1.3%)	1 (0.9%)
Blood parathyroid hormone increased	0	1 (1.3%)	1 (0.9%)
Urine calcium decreased	0	1 (1.3%)	1 (0.9%)

Source: pg. 83 of Study Report for Study MBL-0801 and pg. 83 of Study Report for Study MBL-0412 INT

3 SUMMARY AND CONCLUSIONS

3.1 Collective Evidence and Conclusions

The applicant submitted data from two 8-week, multicenter, prospective, non-controlled, open-label, Phase 2 trials in pediatric subjects (aged 12 to 17 years) with psoriasis vulgaris on the scalp. The primary objective in both studies was to evaluate the safety of once daily use of Taclonex® Topical Suspension. The secondary objective in both studies was to evaluate efficacy. Approximately 55% and 85% of subjects achieved controlled disease (IGA score of 0 or 1) at Week 8 in Studies MBL-0801 and MBL-0412, respectively.

3.2 Labeling Recommendations

(b) (4)

SIGNATURES/DISTRIBUTION LIST

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