CLINICAL REVIEW

Application Type	Supplement
Application Number(s)	NDA 22185/ S-18
Priority or Standard	Standard
Submit Date(s)	October 31, 2013
Received Date(s)	October 31, 2013
PDUFA Goal Date	August 31, 2014
Division / Office	DDDP/ ODE III
Reviewer Name(s)	Melinda McCord
Review Completion Date	July 7, 2014
Established Name	Calcipotriene and betamethasone dipropionate
Trade Name	Taclonex® Topical Suspension
Therapeutic Class	Psoriasis agent
Applicant	Leo Pharmaceuticals, Ltd
Formulation(s)	Topical suspension
Dosing Regimen	Once daily
Proposed Indication(s)	topical treatment of plaque psoriasis of the scalp and body in adult patients18 years and older and for the topical treatment of plaque psoriasis of the scalp in adolescent patients aged 12 to 17 years
Intended Population(s)	12 years of age and older

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends an approval action for this application to extend the current indication to include the treatment of psoriasis vulgaris on the scalp in patients age 12 years and older. This recommendation is contingent upon successful completion of labeling negotiations with the applicant.

The applicant submitted data from 2 trials to address the Post Marketing Requirement (PMR #1) under the Pediatric Research Equity Act (PREA) to conduct a trial in pediatric patients ages 12 to 17 years of Taclonex ® Topical Suspension for the treatment of scalp psoriasis (Approval Letter dated May 9, 2008). To support the extension of the indication to the topical treatment of plaque psoriasis of the scalp in pediatric patients age 12 to 17 years, the applicant conducted 2 open-label trials in this pediatric population. The data provided in this supplement is sufficient to establish safety of Taclonex ® Topical Suspension for the use in the pediatric population age 12 to 17 years. Taclonex® Topical Suspension is approved for the topical treatment of plaque psoriasis of the scalp and body in patients18 years and older. Because pathophysiology and response to treatment are similar, findings of efficacy for Taclonex® Topical Suspension in the pediatric population age 12 to 17 years could be extrapolated from the adult population.

1.2 Risk Benefit Assessment

Taclonex Scalp® (calcipotriene 0.005% and betamethasone dipropionate 0.064%) Topical Suspension1 was approved on May 9, 2008 for the treatment of moderate to severe psoriasis vulgaris of the scalp in adults 18 years and older. The initial assessment of efficacy in the adult population was based on two adequate and well-controlled Phase 3 trials. The initial assessment of safety in the adult population was based on two Phase 3 trials, a long-term safety trial and special safety studies [e.g. the evaluation of dermal safety and the effects of the product on hypothalamic-pituitary-adrenal axis (HPA axis) and calcium metabolism.]

The risk benefit assessment in the pediatric population age 12 to 17 years was based on the analysis of data from 2 uncontrolled clinical trials: MBL 0801 and MBL 0412. Trial MBL 0801 was designed to assess the safety of Taclonex® Topical Suspension by evaluating HPA axis function and calcium metabolism in 31 pediatric subjects age 12 to 17 years with plaque psoriasis of the scalp. Enrolled subjects had at least moderate scalp psoriasis on Investigator's Global Assessment of disease severity scale [IGA $\geq$3

1 Current Trade name is Taclonex ® Topical Suspension.

on a 6- point scale] and at least 20% involvement of the scalp area (maximal use conditions) and normal HPA axis function at Baseline Trial MBL 0412 was designed to assess the safety of Taclonex® Topical Suspension by evaluating calcium metabolism in 78 pediatric subjects age 12 to 17 years with plaque psoriasis of the scalp. Enrolled subjects had at least moderate scalp psoriasis [IGA $\geq$3 on a 6- point scale] and at least 10% involvement of the scalp area. All subjects applied Taclonex® Topical Suspension once daily to the scalp for up to 8 weeks.

There were no deaths or serious adverse events. There were 10 severe adverse events reported in 3 subjects under the following preferred terms: staphylococcal infection, headache, speech disorder, wheezing, dyspnea, toothache, pyrexia, oxygen saturation decreased, joint dislocation and tooth extraction. None of these severe adverse events were related to the use of Taclonex ® Topical Suspension.

A total of 6 subjects (5.5%) withdrew from Trial MBL 0412 or Trial MBL 0801. Three subjects reported a total of nine adverse events which were recorded as reasons for withdrawal. The only adverse reaction which resulted in withdrawal from the trial was the abnormal response to ACTH challenge. Of 30 subjects who completed ACTH challenge testing, one subject showed laboratory evidence of adrenal suppression at Week 4. Laboratory evidence of adrenal dysfunction was not accompanied by symptoms. The subject had normal adrenal function at Week 8 upon re-administration of ACTH challenge testing.

A total of 43 subjects (39.4%) reported 84 adverse events. Among the most common adverse events occurring in ≥1% of subjects in the Safety Analysis Set were upper respiratory tract infections (5.5%), headache (4.6%), pharyngitis (3.7%), cough(3.7%), oropharyngeal pain(3.7%), acne (2.8%) and urinary calcium decreased (2.8%). There were 8 adverse drug reactions (ADRs) in 6 subjects (5.5%) which were mild or moderate in intensity and reported by 1 subject each. The clinically relevant adverse reactions were: Hypothalamic-pituitary disorder, acne and application site pruritus. All of these adverse reactions are included in current labeling.

“Adverse events of clinical interest” were defined as adverse events related to exposure to topical corticosteroids, topical calcipotriene or accidental eye exposure. Seven subjects experienced events potentially related to exposure to betamethasone, the corticosteroid component of Taclonex® Topical Suspension: 3 cases of acne and one case each of dermatitis acneiform, hypothalamic-pituitary disorder, skin striae, and otitis externa. One subject reported an event of allergic conjunctivitis potentially related to ocular exposure to the study product (conjunctivitis allergic). There were no adverse events potentially related to calcipotriol absorption.

The 2 uncontrolled trials in this development program (Trials MBL 0801 and MBL 0412) were not designed to allow statistical conclusions related to efficacy. However, the proportion of subjects achieving controlled disease at Week 8 was 17/31 (54.8%) in

Trial MBL 0801 and 66/78 (84.6%) in Trial MBL 0412. These findings of treatment effect are comparable to the efficacy findings observed in the 2 Phase 3 trials in the adult population (70.0% and 67.2% achieving controlled disease at Week 8).

Trial MBL 0801 and Trial MBL 0412 were adequate to inform safety and support the short-term use of Taclonex ® Topical Suspension in the pediatric population age 12 to 17 years. Based on a similar pathophysiology and response to treatment, efficacy in the pediatric population ages 12 to 17 years could be extrapolated from findings of efficacy in the adult population. Therefore, the data submitted by the applicant supports the extension of the current indication to include the treatment of psoriasis vulgaris on the scalp in patients age 12 years and older and fulfills the post marketing requirement under PREA.

This reviewer recommends no additional risk management activities other than including the safety outcomes in product labeling.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

None recommended.

2 Introduction and Regulatory Background

2.1 Product Information

On October 31, 2013 the applicant, LEO Pharma, Inc., submitted a 505(b)(1) supplemental new drug application (sNDA) for Taclonex® (calcipotriene and betamethasone dipropionate) Topical Suspension, 0.005%/0.64%). The objective of the current sNDA is to provide additional data for Taclonex ® Topical Suspension (marketed as Daivobet® gel in Europe) to extend the current indication to include the treatment of psoriasis vulgaris on the scalp in patients age 12 years and older.

Taclonex® Topical Suspension contains a fixed combination of calcipotriene 50 mcg/g and betamethasone 0.5 mg/g (as dipropionate). Calcipotriene is the US Adopted Name (USAN) of calcipotriol (the International Non-proprietary Name.) Calcipotriene hydrate is a synthetic vitamin D3 analog and betamethasone dipropionate is a synthetic corticosteroid.

Taclonex® Topical Suspension is a viscous, nearly odorless, clear to slightly off-white suspension. A thin oily layer may form on the surface of the product upon standing which requires the product to be shaken before each use. Each gram of Taclonex® Topical Suspension contains 52.18 mcg of calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in a base of hydrogenated castor oil (b) (4) PPG (b) (4) stearyl ether (b) (4) and mineral oil.

The product is distributed in a 60 gram bottle or two 60 gram bottles co-packaged in a larger carton. The containers are white high-density polyethylene plastic multi-dose bottles with a hexagonal profile and screw thread. The bottle is equipped with a white (b) (4) plastic screw cap.

The current indication for Taclonex® Topical Suspension is "the topical treatment of plaque psoriasis of the scalp and body in patients18 years and older."

2.2 Tables of Currently Available Treatments for Proposed Indications

The FDA approved products specifically indicated for the treatment of scalp psoriasis include: Clobex 0.05% Shampoo and SORILUX™ (calcipotriene) foam, 0.005%. These topical products are listed in Table 1. There are no FDA approved products indicated for the treatment of scalp psoriasis in pediatric patients.

Table 1: FDA Approved Products for the Topical Treatment of Scalp Psoriasis

Product Name	Applicant	NDA #	Approval Date	Indication/ Age in Labeling
Clobex (clobetasol propionate) 0.05% Shampoo	Galderma Laboratories	021644	02/05/2004	treatment of moderate to severe forms of scalp psoriasis in subjects 18 years of age and older
SORILUX™ (calcipotriene) foam, 0.005%	Stiefel Laboratories, Inc	022563/S-002	09/27/2012	topical treatment of plaque psoriasis of the scalp and body in patients 18 years and older

Source: Reviewer's Table

Examples of FDA approved products which are indicated for the topical treatment of psoriasis are listed in **Error! Not a valid bookmark self-reference.**.

Table 2: FDA Approved Products for the Topical Treatment of Psoriasis

Product Name	Applicant	NDA #	Approval Date	Indication/ Age in Labeling
Taclonex (calcipotriene 0.005% and betamethasone dipropionate 0.064%) Topical Suspension	Leo Pharma	022185 S-10	10/23/2012	topical treatment of plaque psoriasis of the scalp and body in patients 18 years of age and older
Sorilux (calcipotriene) Foam 0.005%	Stiefel	22563 S-2	9/27/2012	topical treatment of plaque psoriasis of the scalp and body in patients 18 years of age and older
Vectical (calcitriol) Ointment	Galderma Laboratories	022087	1/23/2009	topical treatment of mild to moderate plaque psoriasis in adults 18 years and older.
Taclonex (calcipotriene 0.005% and betamethasone dipropionate 0.064%) Ointment	Leo Pharma	021852	1/9/2006	topical treatment of psoriasis vulgaris in adults 18 years of age and older
Clobex (clobetasol propionate) 0.05% Spray	Galderma Laboratories	021835	10/27/2005	topical treatment of moderate to severe plaque psoriasis affecting up to 20% body surface area (BSA) in patients 18 years of age or older
Clobex (clobetasol propionate) shampoo, 0.05%	Galderma Laboratories	021644	3/25/2004	treatment of moderate to severe forms of scalp psoriasis in subjects 18 years of age and older
Tazorac (tazarotene) Cream 0.05%, 0.1%	Allergan	021184	9/29/2000	topical treatment of patients with plaque psoriasis. ≥18 years *
Tazorac (tazarotene) Gel 0.05%,	Allergan	020600	6/13/1997	topical treatment of patients with stable plaque psoriasis of up to 20% body surface

0.1%				area involvement. ≥12 years **
Dovonex (calcipotriene) Cream 0.005%	Leo Pharma	020554	7/22/1996	treatment of plaque psoriasis ≥18 years ***

Source: Adapted from Table 1 from NDA 22-563
*The safety and efficacy of tazarotene cream have not been established in patients with psoriasis under the age of 18 years (Current labeling: Pediatric Use Section)
**The safety and efficacy of tazarotene gel have not been established in pediatric patients under the age of 12 years. (Current labeling: Pediatric Use Section)
***Safety and effectiveness (of Dovonex Cream 0.005%) in pediatric patients have not been specifically established. Because of a higher ratio of skin surface area to body mass, pediatric patients are at greater risk than adults of systemic adverse effects when they are treated with topical medication. (Current labeling: Pediatric Use Section)

2.3 Availability of Proposed Active Ingredients in the United States

Table 3: Availability of Proposed Active Ingredients in the United States

Generic Name and Dosage Form	Brand Name	Applicant	NDA/ANDA Number	FDA Approval Date
Calcipotriene foam, 0.005%	Sorilux	Stiefel Laboratories,Inc	22563	10/6/2010
Calcipotriene ointment, 0.005%	generic	Glenmark Generics	90633	3/24/2010
Calcipotriene cream, 0.005%	Dovonex & generics	Leo Pharma, Tolmar	20554, 200935	7/22/1996
Calcipotriene solution, 0.005%	generics	Fougera Pharms, Tolmar, G and W Labs Inc Pharma, Nycomed US	77029, 78305, 78468	3/3/1997
Calcipotriene 0.005% and Betamethasone 0.064% ointment,	Taclonex	Leo Pharma	21852	1/9/2006
Calcipotriene 0.005% and Betamethasone 0.064% solution	Taclonex Topical Suspension	Leo Pharma	22185	5/9/2008
Betamethasone dipropionate	Diprolene &	Merck, Sharp Dohme, Actavis,	18741, 74304, 75373, 76753	7/27/1983

0.05% ointment, augmented	generics	Fougera, Taro		
Betamethasone dipropionate 0.05% lotion, augmented	Diprolene & generics	Merck, Sharp Dohme, Fougera, Taro	19716, 77111,77477	8/1/1988
Betamethasone dipropionate 0.05% cream, augmented	Diprolene AF & generics	Merck, Sharp Dohme, Fougera, Glenmark, Perrigo, Taro, Tolmar	19555, 76215, 78930, 76592, 76543, 76603	4/27/1987
Betamethasone dipropionate 0.05% gel, augmented	generics	Taro, Fougera,	76508, 75276	12/2/2003

Sources: NDA 22563/S-2, Table 3. Updated from Drugs @FDA accessed 7/1/2014

2.4 Important Safety Issues with Consideration to Related Drugs

The adverse event profile for each of the active ingredients (calcipotriene hydrate and betamethasone dipropionate) is well characterized.

Adverse reactions associated with vitamin D analogues (e.g. calcipotriene) include both local and systemic effects. Per labeling, the most common local adverse reactions associated with calcipotriene containing products are: application site erythema, application site pain, skin irritation, burning, pruritus, rash, dermatitis, dry skin, peeling and worsening of psoriasis (Adverse Reaction Sections: SORILUX Foam, Dovonex Products). Systemic absorption of topical vitamin D analogues can produce hypercalcemia and hypercalciuria.

Topical corticosteroids may be associated with both local and systemic adverse reactions. Rare systemic adverse reactions reported with topical corticosteroids include: Cushing's syndrome, hyperglycemia, osteopathy, adrenocortical suppression, decreased growth rate, edema, hypocalcemia, hypertension, posterior subcapsular cataracts, and glaucoma. Children are at higher risk than adults for HPA axis suppression due to their greater body surface area to volume ratio. Common local adverse effects include atrophy, striae, rosacea, perioral dermatitis, acne, and purpura, and less frequent adverse effects include hypertrichosis, pigmentary alterations, delayed wound healing, exacerbation of skin infections, and contact sensitization reactions.

The adverse reactions observed with the fixed combination products (calcipotriene 0.005% and betamethasone dipropionate 0.064%) are similar to those reported for the

active ingredients. Per current labeling, the most common adverse reactions (≥1%) reported for Taclonex® Topical Suspension were folliculitis and burning sensation of skin and for Taclonex® Ointment were pruritus and scale rash.

Taclonex® Topical Suspension and other products containing calcipotriene and betamethasone dipropionate are pregnancy category C drug products.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On May, 9 2008 the Agency approved Taclonex Scalp® (calcipotriene 0.005% and betamethasone dipropionate 0.064%) Topical Suspension [2] for the topical treatment of moderate to severe psoriasis vulgaris of the scalp in adults aged 18 years and above. The Approval Letter (dated May 9, 2008) included a waiver of the pediatric study requirement for ages 0 months up to 12 years because there was evidence that the drug product was unsafe in this pediatric population. The following deferred pediatric study was required under the Pediatric Research Equity Act (PREA):

> "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."
> Final Report Submission: September 2012

On January 29, 2009 (SD-73), the applicant submitted the following 2 draft protocols (and additional questions) to IND 67835 to address the pediatric study requirement (100 subjects evaluated for changes in calcium metabolism and 30 subjects evaluated for HPA axis suppression):

> **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"
>
> > International, multi-center, prospective, non-controlled, single-group, 8-week trial in 70 pediatric subjects (aged 12 to 17 years) with psoriasis

2 The applicant requested a review of a new proprietary name "Taclonex® Topical Suspension" to reflect the use of the product on other sites of application beyond the scalp. (Letter dated April 7, 2011) On October 5, 2011 the Division of Medication Error Prevention and Analysis completed their review of the proposed proprietary name and concluded that it was conditionally acceptable pending approval of the safety and efficacy data supporting the use of this product on additional sites of application beyond the scalp. On December 11, 2011 the applicant submitted a Supplemental New Drug application (S-0010) which provided for revision of the prescribing information for Taclonex® Topical Suspension to include the additional indication for plaque psoriasis of the body.(Approval 10/17/12)

vulgaris of the scalp. The psoriasis vulgaris of the scalp must affect ≥10% of the scalp and be of at least moderate severity according to the IGA.
Safety: lab evaluation, adverse events.

2) MBL 0801 INT: "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"

US, multi-center, prospective, non-controlled, single-group, 8-week trial in 30 pediatric subjects (aged 12 to 17 years) with psoriasis vulgaris on the scalp. The psoriasis vulgaris of the scalp should involve ≥20% of the scalp and be of at least moderate severity according to the IGA.
Safety: HPA axis testing, lab evaluation, adverse events.

After amending the protocols to address Agency comments (Advice Letters dated December 1, 2009 and June 10, 2010), Trial MBL 0801 was initiated on April 12, 2010 (first subject visit) and completed on August 8, 2012 (last subject visit). Trial MBL 0412 was initiated on November 22, 2010 (first subject visit) and completed on October 15, 2012 (last subject visit).

On November 14, 2012 the Pediatric and Maternal Health Staff (PMHS), sent the applicant a Deferral Extension Notice per the Food and Drug Administration Safety and Innovation Act (FDASIA; signed July 12, 2012). In response to the Deferral Extension Notice, on January 5, 2013, the applicant submitted a request for a Deferral Extension for the submission of the final study report for the clinical study protocol MBL 0801 to March 1, 2013 and the study protocol MBL 0412 to May 6, 2013. Although the applicant submitted the final study report for Trial MBL 0801 on February 25, 2013, it was not submitted to NDA 22185 as a labeling or efficacy supplement.

In view of the requirement to submit the pediatric study reports as a supplement to permit the data to be included in labeling, the applicant requested another Deferral Extension for the submission of the final study reports of protocol MBL 0801 and protocol MBL 0412 to October 31, 2013 (Letter dated March 12, 2013).

2.6 Other Relevant Background Information

(b) (4)

(b) (4)

sNDA S-010

- On December 23, 2011 the applicant submitted a Supplemental New Drug application (S-010) which provided for revision of the prescribing information for Taclonex® Scalp Topical Suspension to include the additional indication for plaque psoriasis of the body. In addition, the applicant requested a review of a new proprietary name "Taclonex® Topical Suspension" to reflect the use of the product on other sites of application beyond the scalp. (Letter dated April 7, 2011) As the previous trials provided no information about systemic exposure under maximal use conditions and safety of Taclonex® Topical Suspension when applied to the body (in addition to the scalp) of pediatric patients age 12 to 17 years, the following required study was attached to the approval of the supplement (Approval Letter dated October 17, 2012):

  Conduct a trial in 100 evaluable pediatric patients with plaque psoriasis of the scalp and body ages 12 to 16 years, 11 months, to evaluate the safety and effect of Taclonex® (calcipotriene and betamethasone dipropionate) Topical Suspension, 0.005%/0.064% on calcium metabolism. Evaluate the hypothalamic-pituitary axis and pharmacokinetics of the two drug components, calcipotriene and betamethasone dipropionate, in a subset of at least 30 patients treated with Taclonex® Topical Suspension under maximal use conditions.

  Final Protocol Submission: 04/2013
  Trial Completion: 10/2015
  Final Report Submission: 10/2016

3 Ethics and Good Clinical Practices

The Division did not request that the Office of Scientific Investigations (OSI) conduct clinical inspections of investigational sites. The clinical team concluded that there were no irregularities in the data requiring OSI consultation.

3.1 Submission Quality and Integrity

The overall quality of the clinical information contained in this submission is adequate.

3.2 Compliance with Good Clinical Practices

The applicant certified that the trials in their development program were conducted In compliance with the requirements of the Code of Federal Regulations (21 CFR), Parts

50, 54, 56, 312, and 314, and the International Conference on Harmonization (ICH), and Guideline for Good Clinical Practice (E6).

3.3 Financial Disclosures

The applicant completed Form FDA 3454 to document financial conflicts of interest and arrangements of clinical investigators. The applicant certified that he has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

This submission contained no chemistry, microbiology, or pharmacology/toxicology data.

4.1 Chemistry Manufacturing and Controls

Not applicable. Refer to the CMC review of the original application by Zhengfang Ge, Ph.D. dated 2/7/2008.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Safety data supporting pediatric assessments in subjects age 12 to 17 years old is provided by multiple-dose toxicity studies that included peripubertal animals and were submitted with the original NDA. No nonclinical toxicology studies in a juvenile animal model were conducted to support clinical pediatric trials. See the Pharmacology/Toxicology Review by Norman See, Ph.D. dated 2/20/2008 for an evaluation of the preclinical data.

4.4 Clinical Pharmacology

In a review dated 6/12/2014, An-Chi Lu, M.S., Pharm.D. provided the following recommendation regarding Supplement 18:

> "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."

4.4.1 Mechanism of Action

The applicant proposed a minor change to the Mechanism of Action 12.1 section of labeling. The following text includes the labeling change (additions are noted as double underline and deletions are noted as ~~strikethrough~~):

> **12.1 Mechanism of Action**
> Taclonex® Topical Suspension combines the pharmacological effects of calcipotriene hydrate as a synthetic vitamin D_3 analog and betamethasone dipropionate as a synthetic corticosteroid. However, while their pharmacologic and clinical effects are known, the exact mechanisms of their actions in plaque psoriasis (b) (4) are unknown.

4.4.2 Pharmacodynamics

The systemic pharmacodynamics of the active ingredients of Taclonex® Topical Suspension, calcipotriene and betamethasone dipropionate, were indirectly assessed using surrogate markers (e.g. serum / urinary calcium, cortisol levels after ACTH challenge).

The applicant proposed the following additions to labeling (additions are noted as double underline and deletions are noted as strikethrough):

> **12.2 Pharmacodynamics**
> *Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression:*
>
> (b) (4)
>
> *Effects on Calcium Metabolism*

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 (b) (4)). No cases of hypercalcemia and no clinically relevant changes in urinary calcium were reported.

The recommended changes to section 12.2 of the labeling include the following (additions noted as double underline):

Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression

In Trial C, HPA axis suppression was evaluated in pediatric 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 (3.3%) after 4 weeks of treatment and in no subjects who continued treatment for 8 weeks.

Effects on Calcium Metabolism

In addition, calcium metabolism was evaluated in a total of 109 pediatric 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. No cases of hypercalcemia and no clinically relevant changes in urinary calcium were reported.

4.4.3 Pharmacokinetics

Pharmacokinetic assessments were not performed during the conduct of trial MBL 0801 or trial MBL 0412. The applicant proposed no changes to this section of the currently approved labeling. See Clinical Pharmacology Review by Abimbola Adebowale Ph.D. dated 3/19/2008 for an evaluation of the pharmacokinetic data in adults.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4: Summary of Trials MBL 0801 and MBL 0412 INT

Trial/ Dates*/ Sites	Trial Design/ # Subjects	Study Population	# Subjects/ Median age/ Sex	Study Product/ Dosing Regimen	Duration of Treatment
MBL 0801 4/12/2010-8/8/2012 5 sites in US	Open-label, single-group, non-controlled trial in adolescent subjects (aged 12 to 17 years)	Psoriasis (scalp) ≥ moderate ≥20% of scalp Present/previous psoriasis (body) Normal HPA Serum albumin corrected Ca+ below the upper reference limit	Dosed: 31 Completed: 29 15 years 12M/19F	calcipotriol 50 mcg/g + betamethasone 0.5 mg/g (dipropionate) topical suspension applied once daily	8 weeks (withdraw if clear after 4 weeks of treatment)
MBL 0412 INT 11/22/2010 10/12/2012 17 sites in CA,FR, UK	Open-label, single-group, non-controlled trial in adolescent subjects (aged 12 to 17 years)	Psoriasis (scalp) ≥ moderate ≥10% of scalp Typical scalp psoriasis or present/previous psoriasis (body) and atypical scalp psoriasis	Dosed: 78 Completed: 74 15 years 35M/43F	calcipotriol 50 mcg/g + betamethasone 0.5 mg/g (dipropionate) topical suspension applied once daily	8 weeks (withdraw if clear after 4 weeks of treatment)

Source: Adapted from Module 2.7.6 Synopses of Individual Studies, Table 1 page 3
*First visit of the first subject to last visit of the last subject
ACTH = adrenocorticotropic hormone; ADR = adverse drug reaction; CSR = Clinical Study Report; F = females; FSFV = first subject first visit; HPA = hypothalamic-pituitary-adrenal; IP = investigational product; LSLV = last subject last visit; M = males

5.2 Review Strategy

The review of safety was based on pooled data from two uncontrolled trials (MBL0801 and MBL0412) enrolling a total of 109 subjects age 12 to 17 years with at least moderate scalp psoriasis on the IGA (≥3 on a 6-point scale) and amenable to topical treatment with a maximum of 60 g of study medication per week. Trial MBL 0801 was designed to assess the safety of Taclonex® Topical Suspension by evaluating HPA axis function and calcium metabolism in 31 pediatric subjects with plaque psoriasis of the scalp. The entry criteria for subjects enrolled in Trial MBL 0801 included at least 20%

involvement of the scalp area (maximal use conditions) and clinical signs of psoriasis vulgaris on trunk and/or limbs, or earlier diagnosis of psoriasis vulgaris on trunk and/or limbs. Trial MBL 0412 was designed to assess the safety of Taclonex® Topical Suspension by evaluating calcium metabolism in 78 pediatric subjects with plaque psoriasis of the scalp. The entry criteria for subjects enrolled in Trial MBL 0412 included at least 10% involvement of the scalp area and clinical signs of psoriasis vulgaris on trunk and/or limbs, or earlier diagnosis of psoriasis vulgaris on trunk and/or limbs only when the scalp lesions were not typical. All subjects applied Taclonex® Topical Suspension once daily for 4 to 8 weeks. Subjects discontinued treatment at Week 4 if scalp psoriasis resolved.

The evaluation of treatment effect in these trials was a secondary objective and was supportive of the review conclusions related to the original application. For the original NDA approval action, the applicant established the efficacy of the combination product in the adult population with 2 adequate and well-controlled Phase 3 trials.

The other sources of safety data included a review of the worldwide medical literature and the120-Day Safety Update.

5.3 Discussion of Individual Studies/Clinical Trials

Trial MBL 0801 and Trial MBL 0412 were similar with regard to the study design, study population (as defined by the inclusion/exclusion criteria), methodology, and endpoints. In addition to the evaluation of systemic and local safety, subjects enrolled in Trial MBL 0801 were evaluated for hypothalamic-pituitary-adrenal axis (HPA axis) function. The differences in the study population, assessments and conduct are noted in the discussion.

1. MBL 0801

Title of Trial:
“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”

Investigators/Study Centers:
In Trial MBL 0801, 31 subjects were enrolled and assigned to treatment in 5 study centers in the United Sates. These study centers are listed in Table 5.

Table 5: Investigators and Study Centers for MBL 0801

Site No.	Principal Investigator	Site address	# Subjects enrolled/ assigned treatment
US086	Joel Schlessinger	Skin Specialists, PC 2802 Oak View Mall Drive Omaha, NE 68144	9/6
US093	James A. Solomon	Leavitt Medical Associates of Florida, INC. (DBA) Ameriderm Research 725 W. Granada Blvd Suite 44 Ormond Beach, Florida 32174	3/2
US096	Jeffrey K. Moore	Deaconess Clinic Downtown Research Institute 421 Chestnut Street Evansville, IN 47714	4/2
US097	Douglas N. Robins	Leavitt Medical Associates of Florida, INC (DBA) Ameriderm Research 4100 Southpoint Drive East, Suite 1 Jacksonville, FL 32216	1/0
US098	Jamie D. Weisman	Peachtree Dermatology Associates, PC The Borghese 3286 Northside Parkway, Suite 130 Atlanta, Georgia 30327	4/1
International Coordinating Investigator			
US081	Lawrence F. Eichenfield	Rady Children's Hospital San Diego 8010 Frost Street, Suite 602 San Diego, CA 92123	24/20

Source: Adapted from Section 5.3.5.2; Appendix 1.4: List of Investigators and CV for International Coordinating Investigator and Study report body MBL 0801
page 105, Table 1

Trial period:
Date of first enrollment: April 12, 2010.
Date of last completion: August 8, 2012

Objectives:
Primary objective

- 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

- 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.

Drug Development Phase: Phase 4 Post Marketing Commitment

Investigational Product: Taclonex® Topical Suspension

Study Population:
Male and female subjects of any race or ethnicity aged 12 to 17 years with clinical signs of psoriasis vulgaris on trunk and/or limbs, or previous diagnosis of psoriasis vulgaris on trunk and/or limbs and a clinical diagnosis of scalp psoriasis which is at least moderate in severity according to IGA and involves at least 20% of the scalp area. In total, 31 subjects were treated with at least 1 application of investigational product and 29 subjects completed the trial.

Main criteria for inclusion**:**

1) Clinical signs of psoriasis vulgaris on trunk and/or limbs, or earlier diagnosed with psoriasis vulgaris on trunk and/or limbs.
2) At SV2 and Visit 1, a clinical diagnosis of scalp psoriasis which is:
    a. amenable to topical treatment with a maximum of 60 g of study medication per week, and
    b. of an extent of more than or equal to 20% of the scalp area
    c. of at least moderate severity according to the investigator's global assessment.
3) Subjects with a normal HPA axis function at SV2 including serum cortisol concentration above 5 mcg/dl before ACTH challenge and serum cortisol concentration above 18 mcg/dl 30 minutes after ACTH challenge.
4) Serum albumin-corrected calcium below the upper reference limit at SV2.
5) Females of child-bearing potential must have a negative urine pregnancy test result and must agree to use a highly effective method of contraception during the study and/or the judgment of the investigator (abstinence is an acceptable method). The contraception should have started an adequate period of time before the pregnancy test, as judged by the (sub) investigator.

Main criteria for exclusion:

1) Current diagnosis of guttate, erythrodermic, exfoliative or pustular psoriasis.
2) Subjects with any of the following conditions present on the treatment area: viral (e.g. herpes or varicella) lesions of the skin, fungal and bacterial skin infections, parasitic infections, skin manifestations in relation to syphilis or tuberculosis, rosacea, perioral dermatitis, acne vulgaris, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne rosacea, ulcers and wounds Known or suspected: endocrine disorder (e.g. diabetes mellitus, Cushing's disease or

Addison's disease), cardiac condition or serious allergy, allergic asthma or serious allergic skin rash

3) Systemic treatment with:
    a. Corticosteroids (including inhaled and nasal steroids) within12 weeks prior to SV2 or during the study.
    b. Estrogen therapy (e.g. contraceptives) or any other medication known to affect cortisol levels or HPA axis integrity within 4 weeks prior to SV2 or during the study.
    c. Enzymatic inductors (e.g., barbiturates, phenytoin, rifampicin) within 4 weeks prior to SV2 or during the study.
    d. Systemic cytochrome P450 inhibitors (e.g., ketoconazole, itraconazole, metronidazole) within 4 weeks prior to SV2 or during the study. Topical ketoconazole 2 weeks prior to SV2.
    e. Hypoglycemic sulfonamides or antidepressants within 4 weeks prior to SV2 or during the study.
    f. Biological therapies (marketed or not marketed), with a possible effect on scalp psoriasis within the following time period prior to Visit 1 and during the study:
        1) Etanercept: within 4 weeks prior to Visit 1
        2) Adalimumab, alefacept, infliximab: within 2 months prior to Visit 1
        3) Ustekinumab: within 4 months prior to Visit 1
        4) Experimental products: within 4 weeks/5 half lives (whichever is longer) prior to Visit 1
    g. Therapies other than biologicals (e.g., retinoids, immunosuppressants, PUVA) within 4 weeks prior to Visit 1 (Day 0) or during the study.
    h. Systemic calcium, vitamin D supplements, antacids, diuretics, antiepileptics, diphosphonates or calcitonin within 4 weeks prior to SV2 or during the study.
4) UVB therapy within 2 weeks prior to Visit 1 or during the study.
5) Topical treatment with:
    - corticosteroids within 2 weeks prior to SV2 or during the study
    - topical cytochrome P450 inhibitors
    - Any product on the scalp (except for emollients and non-steroid medicated shampoos) within 2 weeks prior to Visit 1 or during the study.
6) Planned initiation of, or changes to, concomitant medication that could affect scalp psoriasis (e.g., betablockers, chloroquine, lithium, ACE inhibitors) during the study.
7) Not following nocturnal sleep patterns.

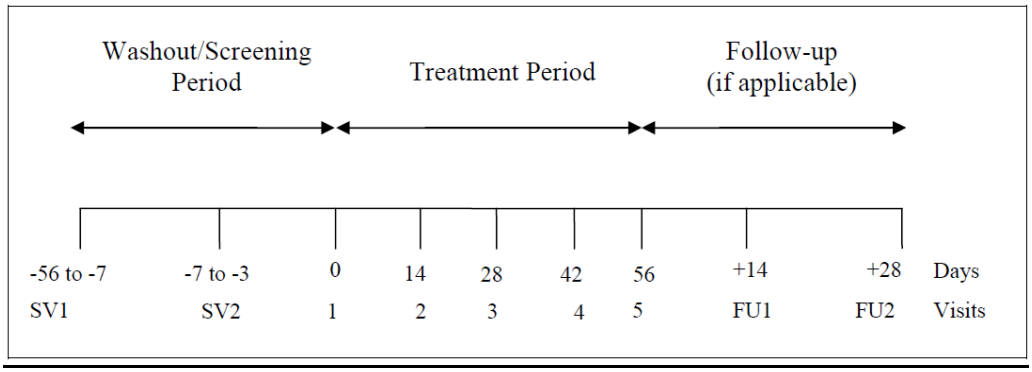
<u>Allowed Concomitant Medication – Treatment Period</u> (Visit 2 to 5):
Anti-psoriatic treatments allowed during the treatment period

- Scalp – No other treatment except non-medicated shampoo was allowed.

- Trunk/limbs/face – Any topical treatment except corticosteroids. The maximum amount of topical treatment containing Vitamin D analogs was limited to a total of 75 g per week. Bath oils and moisturizing soaps were allowed.

Trial Plan:
This trial was a national, multi-center, prospective, non-controlled, open-label, single-group, trial in pediatric subjects (aged 12 to 17 years) with scalp psoriasis. The subjects were treated with Taclonex® Topical Suspension once daily for up to 8 weeks. The trial consisted of 3 periods: a wash-out/screening period, a treatment period, and a follow-up period (if indicated due to an adverse event or findings of HPA suppression.) See Figure 1.

Figure 1: Trial Design



Source: NDA 22185, S 18, Section 5.3.5.2 Protocol MBL 0801, page 44

The duration of the wash-out/ screening period for each subject was determined by their use of the concomitant medications listed in the exclusion criteria (e.g. ≤ 8 weeks). The procedures and assessments conducted during the screening period are included in Table 12. Investigators instructed subjects to record dietary calcium intake and to collect a 24 hour urine collection.

The duration of the treatment period was up to 8 weeks. Subjects with a clear scalp at Week 4 left the trial while subjects with any signs of scalp psoriasis continued treatment for another 4 weeks. Subjects with a clear scalp at Visit 2 (Week 2) or Visit 4 (Week 6) discontinued treatment but remained in the trial. Investigators reinitiated treatment if the psoriasis recurred. Subject evaluations occurred on Days 0, 14, 28, 42 and 56.

During Visit 1, the investigator reviewed the inclusion/exclusion criteria to confirm eligibility, queried subjects regarding adverse events and concomitant medications, assessed the extent of psoriasis and disease severity according to Investigator's Global Assessment of Disease Severity (IGA). Subjects assessed their disease severity according Patient's Global Assessment of Disease Severity and the severity of their

baseline pruritus and received study medication. The schedule of evaluations of safety and treatment effect are summarized in Table 12.

Two follow-up visits were included in the protocol for subjects with adverse events or abnormal laboratory findings. Follow-up Visit 1 (Day 70) was scheduled for subjects with an ongoing adverse events that were related (or relationship not assessable) to the investigational product and for subjects with an albumin corrected serum calcium value above reference range at the last on-treatment visit. Abnormal laboratory values were reassessed. Follow-up Visit 2 (Day 84) was scheduled for subjects with a serum cortisol value ≤18 mcg/dl at 30 minutes after the ACTH challenge test at Visit 3 or Visit 5.

ACTH Challenge test

Study participants performed an ACTH-challenge test at SV2 and after 4 and 8 weeks of treatment (Visit 3 and Visit 5) with the topical suspension. The pre-treatment testing ensured that adrenal function was normal before starting study treatment. Following standard methodology, a blood sample was drawn at 8 AM and then 30 and 60 minutes after a 250 mcg intravenous dose of cortrosyn. Serum cortisol concentrations at 30 and 60 minutes after injection were measured in order to show the maximum cortisol level achieved. Subjects with a serum cortisol concentration ≤ 5 mcg/dl at SV2 prior to injection of cortrosyn or ≤18 mcg/dl at 30 minutes after injection of cortrosyn were excluded from participation in the trial. 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, then the testing was repeated in 28 days.

Assessment of Calcium Metabolism

Investigators evaluated calcium metabolism at SV2 and after 4 and 8 weeks of treatment (Day 28 and Day 56). The evaluation included measurements of serum calcium, albumin, phosphate, plasma parathyroid hormone (PTH) level and calculation of the albumin-corrected serum calcium concentration. In addition, subjects provided 24 hour urine collections for measurement of urinary volume, calcium-, phosphate-, hydroxyproline-, sodium- and creatinine excretion and calculation of the calcium: creatinine, phosphate: creatinine, hydroxyproline: creatinine and sodium: creatinine ratios.

Refer to Section 7 of this review for a discussion of the safety results.

Subject Treatment Instructions

Investigators provided subjects with the following instructions:

1. Shake the bottle before use
2. Gently apply the topical suspension to the affected areas of the scalp once daily during the treatment period (unless otherwise instructed.)
3. Avoid contact with eyes, lips and mucous membranes.
4. Do not apply to the face, trunk, legs or arms.
5. Wash hands after use.

6. Do not apply more than 1 bottle per week (60 g.)
7. Do not occlude the treatment site or apply the topical suspension within 2 hours before a study visit.
8. To aid in emptying the bottle, store it upside down.

Clinical Assessments

1) Treatment Effect

Psoriasis plaques that extended beyond the area defined by the hair line were not included in the assessments.

- Investigator's Global Assessment (IGA) of Disease Severity of the scalp: all visits from Screening Visit 2 to Visit 5. Refer to Table 6.

- Investigator's Assessment of Clinical Signs (redness, thickness and scaliness): all visits from Screening Visit 2 to Visit 5. For each sign, a single score reflects the average severity of all lesions of psoriasis on the scalp. The sum of the three scores (redness, thickness and scaliness) comprised the Total Sign Score of the scalp ranging from 0 to 12. Refer to Table 7.

- Investigator's Assessment of the Extent of Psoriasis Vulgaris: Screening Visit 2. Estimate extent of psoriasis as the percentage of total BSA which is involved with psoriasis using a flat palm and 5 fingers to represent 1% of the BSA.

- Investigator's Assessment of the Extent of Scalp Psoriasis: Screening Visit 1 to Visit 1. Estimate extent of psoriasis as a percentage of the total scalp area using a flat palm and 5 fingers to represent 25%.

- Patient's Global Assessment of Disease Severity: all visits from Screening Visit 2 to Visit 5. Categories to be explained by qualified staff. Completed prior to IGA. Refer to Table 8.

- Patient's Assessment of Itching by use of the 4-point scale at the time of evaluation and not in relation to the condition at a previous visit. The investigator will describe the categories and the subject will select one. Refer to Table 9.

Refer to Tables 7 to 10 below for the assessment scales.

Table 6: Investigator's Global Assessment of Disease Severity – 6-point Scale

Clear	Plaque thickening = no elevation or thickening of normal skin Scaling = no evidence of scaling Erythema = none (no residual red coloration but post-inflammatory hyperpigmentation may be present)
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
Mild	Plaque thickening = slight but definite elevation Scaling = fine scales partially or mostly covering lesions Erythema = light red coloration
Moderate	Plaque thickening = moderate elevation with rounded or sloped edges Scaling = most lesions at least partially covered Erythema = definite red coloration
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
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: Consolidated Clinical Study Report MBL 0801 Table 5

Table 7: Total Sign Score (TSS) – Redness, Thickness, and Scaliness

Redness	0 = none (no erythema) 1 = mild (faint erythema, pink to very light red) 2 = moderate (definite light red erythema) 3 = severe (dark red erythema) 4 = very severe (very dark red erythema)
Thickness	0 = none (no plaque elevation) 1 = mild (slight, barely perceptible elevation) 2 = moderate (definite elevation but not thick) 3 = severe (definite elevation, thick plaque with sharp edge) 4 = very severe (very thick plaque with sharp edge)
Scaliness	0 = none (no scaling) 1 = mild (sparse, fine-scale lesions, only partially covered) 2 = moderate (coarser scales, most of lesions covered) 3 = severe (entire lesion covered with coarse scales) 4 = very severe (very thick coarse scales, possibly fissured)

Source: Consolidated Clinical Study Report MBL 0801 Table 6

Table 8: Patient's Global Assessment of Disease Severity – 5-point Scale

Clear	No psoriasis symptoms at all
Very mild	Very slight psoriasis symptoms, does not interfere with daily life
Mild	Slight psoriasis symptoms, interferes with daily life only occasionally
Moderate	Definite psoriasis symptoms, interferes with daily life frequently
Severe	Intense psoriasis symptoms, interferes or restricts daily life very frequently

Source: Consolidated Clinical Study Report MBL 0801 Table 7

Table 9: Patient's Assessment of Itching – 4-point Scale

None	No itching
Mild	Slight itching, not really bothersome
Moderate	Definite itching, somewhat bothersome without loss of sleep
Severe	Intense itching that has caused pronounced discomfort; night rest interrupted. Scratch marks of the skin from scratching may be present.

Source: Consolidated Clinical Study Report MBL 0801 Table 8

2) Safety

- The safety laboratory evaluation is summarized in Table 10.

Table 10: Laboratory Assessments: SV2, Visit 3 and Visit 5

Biochemistry**	Hematology**	Urine	
		Urinalysis**24 hour urine collection	Spot urine collection
Cortisol	Hemoglobin	Calcium	Glucose
Urea	Hematocrit	Phosphate	Ketones
Creatinine	Red blood cell (RBC) count	Creatinine	Urine Pregnancy Testing*
Albumin	Mean corpuscular volume (MCV)	Hydroxyproline	
Sodium	White blood cell (WBC) count	Sodium	
Potassium	Differential count	Volume	
Chloride	Platelet count		
Phosphate			
Parathyroid hormone			

Source: Reviewer's summary
*urine pregnancy test: if applicable, at FU2
** Blood and urine samples should be collected at the end of treatment for subjects who are withdrawn from study prior to Visit 5 and FU1 if needed.

- Adverse Events (AEs): elicited by non-leading questions. Cutaneous adverse events reported by site and categorized as lesional/perilesion (≤ 2 cm from the border of treated lesions) or distant (> 2 cm from the border of treated lesions)(Classified by MedDRA version 14.1.)

- Reportable events: pregnancy followed until delivery/termination, overdose, worsening of psoriasis from baseline.

Other Assessments
At screening investigators recorded demographic data including Fitzpatrick Skin Type as summarized in Table 11.

Table 11: Fitzpatrick Skin Type

Skin Type	Skin Colour (unexposed skin)	History (to first 30 to 45 minutes of sun exposure after a winter season of no sun exposure)
I	White	Always burns easily; never tans
II	White	Always burns easily; tans minimally
III	White	Burns moderately; tans gradually (light brown)
IV	White	Burns minimally; always tans well (moderate brown)
V	Brown	Rarely burns; tans profusely (dark brown)
VI	Black	Never burns; deeply pigmented

Source: Consolidated Clinical Study Report MBL 0801 Table 4 page 35

Primary endpoints/response criteria
- Adverse drug reactions (ADRs).
- Subjects with serum cortisol concentration of ≤18 mcg/dl at 30 minutes after ACTH challenge at Week 4, and Week 8.
- Subjects with serum cortisol concentration of ≤18 mcg/dl at 30 and 60 minutes after ACTH-challenge at Week 4, and Week 8.
- Change in albumin-corrected serum calcium from Baseline (SV2) to Week 4, Week 8, and end of treatment.
- Change in 24-hour urinary calcium excretion from Baseline (SV2) to Week 4, Week 8, and end of treatment.
- Change in urinary calcium: creatinine ratio from Baseline (SV2) to Week 4, Week 8 and, end of treatment.

Secondary endpoints/response criteria

1) Safety
    - Adverse events (AEs)
    - Change in serum phosphate from Baseline (SV2) to Week 4 and Week 8
    - Change in 24-hour urinary phosphate excretion from Baseline (SV2) to Week 4 and Week 8
    - Change in urinary phosphate: creatinine ratio from Baseline (SV2) to Week 4 and Week 8
    - Change in 24-hour urinary hydroxyproline excretion from Baseline (SV2) to Week 4 and Week 8
    - Change in urinary hydroxyproline: creatinine ratio from Baseline (SV2) to Week 4 and Week 8
    - Change in plasma PTH from Baseline (SV2) to Week 4 and Week 8
    - Change in other laboratory parameters from Baseline (SV2) to Week 4 and Week 8
    - Reasons for withdrawal
    - Change in blood pressure and heart rate from Baseline (SV2) to Week 4 and Week 8

2) Treatment Effect
    - Proportion of subjects with controlled disease (i.e., clear or almost clear) according to the investigator's global assessment of disease severity at Weeks 2, 4, 8, and end of treatment.
    - Percentage change in Total Sign Score (TSS; sum of severity scores for each individual clinical sign, redness, thickness, and scaliness) from Baseline to Weeks 2, 4, 8, and end of treatment.
    - Proportion of subjects with success (Total Sign Score ≤1) at Weeks 2, 4, 8, and end of treatment.
    - Proportion of subjects with controlled disease (defined as clear or very mild) according to the patient's global assessment of disease severity at Weeks 2, 4, 8, and end of treatment.

Tertiary endpoint/response criterion:

- Patient's assessment of itching at Weeks 2, 4, 8, and end of treatment.

Table 12: Study Procedures- MBL 0801

Visit	Screening		Treatment					Follow-up	
	SV1	SV2[1]	1	2	3[1]	4	5[1,10]	FU1[2]	FU2[3]
Day	-56 to -7	-7 to -3	0	14 ± 2	28 ± 2	42 ± 2	56 ± 2	+14 ± 2	+ 28 ± 2
Screening/Baseline									
Informed consent	x								
Inclusion/exclusion criteria	x	x	x						
Demographics	x								
Physical examination	x								
Medical history	x								
Investigator assessment of extent of psoriasis		x	x						
Efficacy Assessments									
Investigator and patient assessment of psoriasis[9]		x	x	x	x	x	x		
Safety Assessments									
Adverse events		x	x	x	x	x	x	x	x
Vital signs		x			x		x		
Clinical Laboratory Tests[4]		x			x		x	x[5]	
ACTH challenge test[6]		x			x		x		x
Collection of 24-hour urine[7]		x			x		x		
Dietary calcium diary		x			x		x		
Pregnancy test[8] (urine)		x			x		x		x
IP									
Dispensing of IP			x	x	x	x			
Return of IP				x	x	x	x		
Compliance				x		x	x		
Concomitant medication	x	x	x	x	x	x	x	x	x

Source: Study MBL 0801 Report Body page 34

1. It was acceptable that the following assessments were done on the day prior to the ACTH challenge: vital signs, spot urine collection, pregnancy test, adverse events, concomitant medication, and assessments of psoriasis
2. Follow-up Visit 1 was only applicable for subjects who at the last on-treatment visit had ongoing adverse event(s) (serious or non-serious) classified as possibly/probably related/not assessable relationship to IMP or subjects with albumin corrected serum calcium above the reference range.
3. Follow-up Visit 2 was only applicable for subject who had serum cortisol is ≤18 mcg/dl at 30 minutes after the ACTH challenge test at Visit 3 or Visit 5.
4. Blood and urine samples were to be collected at the end of treatment for subjects who were withdrawn from the Trial prior to Visit 5.
5. If albumin corrected serum calcium was above the reference range at the last on-treatment visit, a follow-up test were to be performed.
6. ACTH challenge test were to be performed at 8.00 a.m. ± 30 minutes after vital signs, blood and urine samples.
7. It was acceptable that the 24-hour urine sample was collected up to three days prior to the visit.
8. For women of childbearing potential, only.
9. Comprises Patient's Global Assessment of Disease Severity of the scalp, Patient's Assessment of Itching of the scalp, Investigator's Assessment of Extent of Psoriasis, Investigator's Global Assessment of Disease Severity of the scalp, and Investigator's Assessment of Clinical Signs.

10. If a subject withdrew/was withdrawn prior to Visit 5, the tests scheduled for Visit 5 should be done at the end of treatment (blood/urine sampling for hematology/biochemistry/urinalysis/pregnancy test, physical examination, and measurement of vital signs), with the exception of the ACTH-challenge test and the 24- hour urine collection.

Withdrawal Criteria: per protocol

A. Subjects **may** withdraw for any of the following reasons:
   1. Subject completed treatment according to the Clinical Study Protocol.
   2. *Unacceptable treatment efficacy*: the investigator is free to withdraw the subject at any time for medical reasons.
   3. *Unacceptable adverse events*: any adverse event that the investigator or the subject considers unacceptable.
   4. *Exclusion criteria*: any exclusion criteria which emerge/become apparent during the subject's participation in the clinical trial.
   5. *Voluntary withdrawal*: subjects will be free to withdraw from the clinical trial at any time and for any reason.
   6. *Other reasons*: other reasons than stated above which requires the subject to (be) withdraw(n) should be specified.

B. Subjects **must** be withdrawn if they are found to have become pregnant or experience an allergic reaction to CORTROSYN.

Data Analysis

The Full Analysis Set, defined as all subjects who received Taclonex® Topical Suspension, was the primary analysis set for the evaluation of treatment effect. The Safety Analysis Set, defined as all subjects who applied any study product and for whom the presence or confirmed absence of adverse events was available, was the primary analysis set for safety. The Per Protocol Analysis Set was the primary analysis set for the ACTH-challenge test. The Per Protocol Analysis Set was defined as the Full Analysis Set excluding subjects who did not:

- apply any study medication
- meet the inclusion criterion concerning adrenal function at baseline
- provide any results for the ACTH-challenge test after receiving study treatment.

Categorical data were summarized using the number and percentage of subjects in each category. Continuous data were summarized using the mean, standard deviation (SD), median, minimum, and maximum values.

Key Amendments to Version 1.0 of the Protocol

- Subjects should discontinue treatment on individual lesions if/when a lesion has cleared
- 24 hour urine collection measurements included: Calcium: creatinine ratio, Phosphate: creatinine ratio, Hydroxyproline: creatinine ratio, Sodium: creatinine ratio
- Wash-out period was extended from 5 weeks to 8 weeks
- Abstinence was removed as an acceptable method of contraception

The efficacy trends from this open- label trial are discussed in Section 6 and the safety results are discussed in Section 7.

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2. MBL 0412

Title of Trial:
"Safety and Efficacy of Calcipotriol plus Betamethasone Dipropionate Gel in Adolescent Subjects (Aged 12 to 17 Years) with Scalp Psoriasis."

Investigators/Study Centers:
In Trial MBL 0412, 78 subjects were enrolled and assigned to treatment in 17 study centers in Canada, France and the United Kingdom which are listed in Table 13.

Table 13: Investigators and Study Centers for MBL 0412

Site Number	Principal Investigator	Site address	# Subjects enrolled/ assigned treatment
CA004	Jill Keddy-Grant	Winnipeg Clinic Dermatology Research, 425 St. Mary Avenue, Winnipeg MB R3C 0N2	15/10
CA006	Charles Lynde	Lynderm Research Inc., 5762 Highway #7 East, Suite 201, Markham ON L3P1A8	5/13
CA013	Kirk Barber	Kirk Barber Research, 1100 1 Street, SE, Suite 510, Calgary, AB T2G 1B1	2/1
CA0122	Lyn Guenther	The Guenther Dermatology Research Centre, 835 Richmond Street, London, ON N6A 3H7	3/3
CA0133	Peter Hull	Royal University Hospital, Division of Dermatology, 103 Hospital Dr. Room 5556, Saskatoon, SK S7N 0W8	1/0
CA0181	Mani Raman	The Centre for Dermatology and Cosmetic Surgery, 312 Highway #7 East, Richmond Hill, ON L4B 1A5 P: 905-889-2019	9/9
CA0189	Rodion Kunynetz	UltraNova Skincare, 104-125 Bell Farm Rd., Barrie, ON L4M 6L2	5/4
CA0212	Melinda Gooderham	Skin Centre for Dermatology, 743 Lansdowne St., W., Peterborough, ON K9J 1Z2	9/7
FR029	Jean-Philippe	C.H.U. de Nice	

	LACOUR	Hôpital de l'Archet II, Service de Dermatologie-Vénérologie, 151, Route Saint Antoine de Ginestière, 06202 Nice Cedex 03	3/3
FR133	Mireille RUER MULARD	Cabinet Médical, Le Bateau Blanc-Immeuble A, Chemin de Paradis1, 13500 Martigues	7/6
FR171	Gilles ROSTAIN	Cabinet Médical, 11, Rue Châteauneuf, 06000 Nice	2/1
FR232	Jean-Jacques GROB	Hôpital de la Timone Service de Dermatologie Vénérologie, 264, rue Saint Pierre, 13385 Marseille Cedex 5	2/1
FR458	Jean-Michel DEBARRE	Cabinet de Dermatologie, 11 rue Georges Clemenceau, 9300 Cholet	11/11
UK005	M Goodfield	Department of Dermatology, Chapel Allerton Hospital, Chapeltown Road, Leeds LS7 4SA	15/12
UK074	G Gupta	Monklands Hospital, Lanarkshire Acute Hospitals NHS Trust, Dermatology, Monkscourt Avenue, Airdrie, Lanarkshire, ML6 0JS	5/2
UK084	A Layton	Consultant Dermatologist, Department of Dermatology, Harrogate District Hospital, Lancaster Park Road, Harrogate, North Yorkshire HG2 7SX P: 01423 553 740	2/1
UK742	A Bewley	Whipps Cross University Hospital Dermatology, Whipps Cross Road, Leytonstone, London, E11 1NR	3/2
UK825	A Abdullah	City Hospital,Birmingham Skin Centre, Sandwell & West Birmingham Hospitals NHS Trust, Dudley Road, Winson Green Birmingham, B18 7QH	1/0
International Coordinating Investigator			
UK557	A Anstey	Royal Gwent Hospital, Department of Dermatology, Cardiff Road, Newport, NP20 2UB	2/2

Source: Adapted from Section 5.3.5.2; Appendix 1.4: List of Investigators and CV for International Coordinating Investigator and Study report body MBL 0412
page 106, Table 1

Trial Period:
Date of first enrollment: 22-Nov-2010
Date of last completion: 15-Oct-2012

Objectives:
Primary objective

- to evaluate the safety 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.

Secondary objective

- to evaluate the treatment effect 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

Drug Development Phase: Phase 4 Post Marketing Commitment

Investigational Product: Taclonex® Scalp Topical Suspension (Marketed as Daivobet®/Dovobet®/Xamiol® gel)

Study Population:
Male and female subjects of any race or ethnicity aged 12 to 17 years with clinical signs of psoriasis vulgaris on trunk and/or limbs, or previous diagnosis of psoriasis vulgaris on trunk and/or limbs. Subjects had a clinical diagnosis of scalp psoriasis which is at least moderate in severity according to IGA and involves at least 10% of the scalp area. In total, 78 subjects were treated with at least 1 application of investigational product and 74 subjects completed the trial.

Inclusion and Exclusion Criteria
The study population as defined by the inclusion / exclusion criteria was similar for both protocols (MBL 0412 and MBL 0801).

In Protocol MBL 0801 enrolled subjects must have normal HPA axis function at baseline and estrogen therapy or other drug products known to impact cortisol levels or HPA axis integrity were not permitted. Subjects exposed to systemic or topical corticosteroid were excluded from trial MBL 0801.

In Protocol MBL 0412, subjects exposed to the following were excluded:

- systemic corticosteroids
- very high potency topical corticosteroid applied to the trunk / limbs within 2 weeks prior to Visit 1 or during the study or
- potent or very potent (WHO groups III-IV) corticosteroids applied to face and/or genital/skin folds within 2 weeks prior to Visit 1 or during the study

In addition, subjects exposed to estrogen therapy, enzymatic inductors (e.g., barbiturates, phenytoin, rifampicin), systemic cytochrome P450 inhibitors (e.g., ketoconazole, itraconazole, metronidazole), topical ketoconazole, hypoglycemic sulfonamides or antidepressants are not excluded from trial MBL 0412.

Table 14: Comparison of Inclusion and Exclusion Criteria of MBL 0801 and MBL 0412

Main Inclusion Criteria	**MBL 0801**	**MBL 0412 INT**
Clinical diagnosis of scalp psoriasis amenable to topical treatment with a maximum of 60 g Daivobet® gel per week	x	x
Clinical signs of psoriasis vulgaris on trunk and/or limbs, or earlier diagnosed with psoriasis vulgaris on trunk and/or limbs	x	x[a]
Extent of scalp psoriasis	≥20% of the scalp area	≥10% of the scalp area
Investigator's Global Assessment (IGA) of disease severity on the scalp	at least moderate	at least moderate
Serum albumin-corrected calcium below the upper reference limit at SV2	x	x
Subjects with a normal HPA axis function at SV2 including serum cortisol concentration above 5 mcg/dL before ACTH challenge and serum cortisol concentration above 18 mcg/dL 30 minutes after ACTH challenge	x	
Main Exclusion Criteria		
Systemic treatment with corticosteroids within 12 weeks of SV2 or during the trial	x	
Topical treatment with corticosteroids within 2 weeks of SV2 or during the trial	x	
Oestrogen therapy or any other medication known to affect cortisol levels or HPA axis integrity within 4 weeks of SV2 or during the trial	x	
Topical treatment on the trunk and/or limbs with very potent (WHO group IV) corticosteroids within 2 weeks of start of treatment with Daivobet® gel or during the trial		x
Topical treatment on the face and/or genital/skin folds with potent or very potent (WHO groups III-IV) corticosteroids within 2 weeks of start of treatment with Daivobet® gel or during the trial		x
Systemic biological which may affect the disease within 4 weeks to 4 months of start of treatment with Daivobet® gel	x	x
Other systemic treatments which may affect the disease within 4 weeks of start of treatment with Daivobet® gel	x	x
UVB therapy within 2 weeks of start of treatment with Daivobet® gel or during the trial	x	x
Any topical treatment on the scalp (except for emollients and non-steroid medicated shampoos) within 2 weeks of start of treatment with Daivobet® gel or during the trial	x	x
Systemic calcium, vitamin D supplements, antacids, diuretics, antiepileptics, diphosphonates, or calcitonin within 4 weeks of SV2 or during the trial	x	x
Current diagnosis of guttate, erythrodermic, exfoliative, or pustular psoriasis	x	x
Other scalp conditions such as viral, fungal, bacterial, and atrophic skin, parasitic infections, skin manifestations in relation to syphilis or tuberculosis, rosacea, acne vulgaris, acne rosacea, striae atrophicae, fragility of skin veins, ichthyosis, ulcers, and wounds	x	x
Known or suspected severe renal insufficiency or severe hepatic disorders	x	x
Known or suspected disorders of calcium metabolism associated with hypercalcaemia	x	x

a Only required if the subject did not have psoriasis vulgaris lesions on the scalp of typical appearance as judged by the investigator
Source: NDA 22185/S-18 Summary of Clinical Efficacy Module 2.7.3, page 14

Refer to the inclusion/ exclusion criteria for MBL 0801.

Trial Plan:
This trial was an international, multi-center, prospective, non-controlled, open-label, single-group, 8-week trial in pediatric subjects (aged 12 to 17 years) with scalp psoriasis. The subjects were treated with calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate) topical suspension once daily for up to 8 weeks. The trial consisted of 3 periods: a wash-out/screening period, a treatment period, and a follow-up period (if indicated due to an adverse event or findings of HPA suppression.) See Figure 1 for an overview of the trial design for MBL 0412 INT.

The duration of the wash-out/ screening period for each subject was determined by the use of the concomitant medications listed in the exclusion criteria (e.g. ≤ 8 weeks). The procedures and assessments conducted during the screening period are included in Table 15. Investigators provided instructions regarding the documentation of dietary calcium intake and to collection of 24 hour urine specimens.

The duration of the treatment period was up to 8 weeks. Subjects with a clear scalp at Week 4 left the trial while subjects with any signs of scalp psoriasis continued treatment for another 4 weeks. Subjects with a clear scalp at Visit 2 (Week 2) or Visit 4 (Week 6) discontinued treatment but remained in the trial. Investigators reinitiated treatment if the psoriasis recurred. Subject evaluations occurred on Days 0, 14, 28, 42 and 56.

During Visit 1, the investigator reviewed the inclusion/exclusion criteria to confirm eligibility, queried subjects regarding adverse events and concomitant medications, assessed the extent of psoriasis and disease severity according to Investigator's Global Assessment of Disease Severity (IGA). Subjects assessed their disease severity according Patient's Global Assessment of Disease Severity and the severity of their baseline pruritus and received study medication. The schedule of assessments is summarized in Table 15.

Investigators conducted a follow-up visit 14 days after the last treatment visit for subjects with an ongoing adverse event that was related (or relationship not assessable) to the investigational product and for subjects with a albumin corrected serum calcium value above reference range. Abnormal laboratory values were reassessed.

Assessment of Calcium Metabolism: (same procedure as MBL 0801) Refer to summary of MBL 0801.

Subject Treatment Instructions: (same procedure as MBL 0801) Refer to summary of MBL 0801.

Concomitant medications not permitted during the trial (Visits 1-5)- includes those medication requiring a washout period (refer to exclusion criteria for MBL 0801) and the following:

- Initiation of, or changes to, concomitant medication that could affect scalp psoriasis (e.g. beta-blockers, lithium, chloroquine, ACE inhibitors).
- Excessive exposure of treated areas to either natural or artificial sunlight (including tanning booths, sunlamps, etc).

Allowed Concomitant Medication – Treatment Period (Visit 2 to 5):
Anti-psoriatic treatments allowed during the treatment period

- Scalp – No other treatment except non-medicated shampoo was allowed.
- Trunk/limbs – Any topical treatment except very potent (WHO group IV) corticosteroids. The maximum amount of topical treatment containing Vitamin D analogs was limited to a total of 75 g per week. Bath oils and moisturizing soaps were allowed.
- Face- Any topical treatment allowed except potent or very potent (WHO groups III-IV) corticosteroids. Bath oils and moisturizing soaps are allowed.

Clinical Assessments

1) Treatment Effect
   Psoriasis plaques that extended beyond the area defined by the hair line were not included in the assessments.
   - Investigator's Global Assessment (IGA) of Disease Severity of the scalp: all visits from Screening Visit 2 to Visit 5. Refer to Table 6.
   - Investigator's assessment of clinical signs (redness, thickness and scaliness): all visits from Screening Visit 2 to Visit 5. For each sign, a single score reflects the average severity of all lesions of psoriasis on the scalp. The sum of the three scores (redness, thickness and scaliness) will comprise the Total Sign Score of the scalp ranging from 0 to 12. Refer to Table 7.
   - Investigator's Assessment of the Extent of Psoriasis Vulgaris: Screening Visit 2. Estimate extent of psoriasis as the percentage of total BSA which is involved with psoriasis using a flat palm and 5 fingers to represent 1% of the BSA.
   - Investigator's Assessment of the Extent of Scalp Psoriasis: Screening Visit 1 to Visit 1. Estimate extent of psoriasis as a percentage of the total scalp area using a flat palm and 5 fingers to represent 25%.
   - Patient's Global Assessment of Disease Severity: all visits from Screening Visit 2 to Visit 5. Categories to be explained by qualified staff. Completed prior to IGA. Refer to Table 8.

- Patient's assessment of itching: all visits from Screening Visit 2 to Visit 5 using a 4-point scale at the time of evaluation and not in relation to the condition at a previous visit. The investigator will describe the categories and the subject will select one. Refer to Table 9.

2) Safety

- Safety laboratory evaluation is summarized in Table 10.
- Adverse Events (AEs): elicited by non-leading questions. Cutaneous adverse events reported by site and categorized as lesional/perilesion (≤ 2 cm from the border of treated lesions) or distant (> 2 cm from the border of treated lesions)(Classified by MedDRA version 14.1.)
- Reportable events: pregnancy followed until delivery/termination, overdose, worsening of psoriasis from baseline

Withdrawal Criteria: per protocol

A. Subjects **may** withdraw for any of the following reasons:
   1. Subject completed treatment according to the Clinical Study Protocol.
   2. *Unacceptable treatment efficacy*: the investigator is free to withdraw the subject at any time for medical reasons.
   3. *Unacceptable adverse events*: any adverse event that the investigator or the subject considers unacceptable.
   4. *Exclusion criteria*: any exclusion criteria which emerge/become apparent during the subject's participation in the clinical trial.
   5. *Voluntary withdrawal*: subjects will be free to withdraw from the clinical trial at any time and for any reason.
   6. *Other reasons*: other reasons than stated above which requires the subject to (be) withdraw(n) should be specified.

B. Subjects **must** be withdrawn if they are found to have become pregnant

Other Assessments

At screening investigators recorded demographic data including Fitzpatrick Skin Type as summarized in Table 11.

Table 15: Schedule of Trial Procedures

Visit	Screening		Treatment					Follow-up
	SV1[1]	SV2[1]	1	2	3	4	5[9]	FU[2]
Day	-56 to -7	-7 to -3	0	14 ± 2	28 ± 2	42 ± 2	56 ± 2	+ 14 ± 2
Screening/Baseline								
Informed consent	x							
Inclusion/exclusion criteria	x	x	x					
Demographics	x							
Physical examination	x							
Medical history	x							
Investigator assessment of extent of psoriasis		x	x					
Efficacy Assessments								
Investigator and patient assessment of psoriasis[8]		x	x x		x x x			
Safety Assessments								
Adverse events		x	x x		x x x			x
Vital signs		x			x		x	
Clinical Laboratory Tests[4]		x			x		x	x[3]
Instructions for 24-hour urine collection and dietary calcium diary	x			x		x		
Collection of 24-hour urine[5]		x		x			x	
Dietary calcium diary		x			x		x	
Pregnancy test[6,7] (urine)		x		x			x	
IP								
Dispensing of IP			x	x	x x			
Return of IP				x	x	x	x	
Compliance				x	x x x			
Concomitant medication	x	x	x x		x x x			x

Source: NDA 22185/ S-18 Clinical Study Report MBL-0412, Table 2, page 34
1. There should be at least 4 days between SV1 and SV2 in order for dietary information (diary) to be collected.
2. Follow-up (visit or contact) was only applicable for subjects who at the last on-treatment visit had ongoing adverse event(s) (serious or non-serious) classified as possibly/probably related/not assessable relationship to IP or subjects with an albumin-corrected serum calcium value above the reference range.
3. If albumin-corrected serum calcium was above the reference range at the last on-treatment visit, a follow-up test were to be performed.
4. Blood and urine samples were to be collected at the end of treatment for subjects who were withdrawn from the Trial prior to Visit 5.
5. It was acceptable that the 24-hour urine sample was collected up to three days prior to the visit.
6. For women of childbearing potential, only.
7. If the subject was withdrawn from the trial, a pregnancy test should be performed at the last on-treatment visit.
8. Comprises Patient's Global Assessment of disease severity of the scalp, patient's assessment of itching of the scalp, Investigator's Global Assessment (IGA) of disease severity, and Investigator's Assessment of Clinical Signs – Total Sign Score (TSS).

9. If a subject withdrew/was withdrawn prior to Visit 5, the tests scheduled for Visit 5 should be done at the end of treatment (blood/urine sampling for hematology/biochemistry/urinalysis/pregnancy test, physical examination, and measurement of vital signs), with the exception of the 24-hour urine collection.

Data Analysis

Primary endpoints/response criteria

- Adverse drug reactions (ADRs).
- Change in albumin-corrected serum calcium from Baseline (SV2) to Week 4, Week 8, and end of treatment.
- Change in 24-hour urinary calcium excretion from Baseline (SV2) to Week 4, Week 8, and end of treatment.
- Change in urinary calcium: creatinine ratio from Baseline (SV2) to Week 4, Week 8 and, end of treatment.

Secondary and Tertiary endpoints/response criteria

Same as above for protocol MBL 0801.

There was no formal sample size calculation as the Agency recommended that a total of 100 subjects was adequate to establish the safety and treatment effect of Taclonex® Topical suspension in the pediatric population age 12 to 17 years.

The Full Analysis Set, defined as all subjects who received Taclonex® Topical Suspension, was the primary analysis set forthe evaluation of treatment effect. The Safety Analysis Set, defined as all subjects who applied any study product and for whom the presence or confirmed absence of adverse events was available, was the primary analysis set for safety.

Protocol Amendments

There were 4 amendments to Protocol MBL-0412. The first 2 were implemented prior to enrollment and included the following provisions:

- Instructions for subjects to discontinue treatment on individual lesions when a lesion has cleared
- Addition of cortisol to the biochemistry assessment
- Addition of the following calculations from the 24-hour urine sample: calcium: creatinine, phosphate: creatinine, hydroxyproline: creatinine, and sodium: creatinine ratios

The second 2 amendments included the following provisions

- The number of study sites was increased (many sites were not used)
- Added “Clinical diagnosis of psoriasis vulgaris as evidenced by scalp psoriasis lesions of typical appearance” so that not all enrolled subjects had signs of psoriasis on the body

- Addition of the following analyses from the 24-hour urine sample: calcium, phosphate, creatinine, hydroxyproline, sodium, and volume.

6 Review of Efficacy

Efficacy Summary

The applicant conducted 2 open-label, multicenter trials (Trials MBL 0801 and MBL 0412) to assess the safety of Taclonex® Topical Suspension for the treatment of scalp psoriasis in the pediatric population age 12-17 years. Although the trials were uncontrolled, subjects were evaluated for treatment effect.

The evaluation of treatment effect in these trials was viewed as supportive of the review conclusions related to the original application. For the original NDA approval action, the applicant established the efficacy of the combination product in the adult population with 2 adequate and well-controlled Phase 3 trials demonstrating superiority of Taclonex® Topical Suspension to all comparators (e.g. vehicle and monads). Efficacy in the pediatric population was established by extrapolating the effectiveness results of adequate and well controlled studies in the adult population because the pathogenesis and response to treatment are essentially the same {21 CFR 201.57(f)(9)(iv).}

Trial MBL0801 and Trial MBL0412 enrolled a total of 109 subjects age 12 to 17 years with at least moderate scalp psoriasis on the IGA ($\geq$3 on a 6-point scale) and amenable to topical treatment with a maximum of 60 g of study medication per week. Trial MBL 0801 was designed to assess the safety of Taclonex® Topical Suspension by evaluating HPA axis function and calcium metabolism in 31 pediatric subjects with plaque psoriasis of the scalp. The entry criteria for subjects enrolled in Trial MBL 0801 included at least 20% involvement of the scalp area (maximal use conditions) and clinical signs of psoriasis vulgaris on trunk and/or limbs, or earlier diagnosis of psoriasis vulgaris on trunk and/or limbs. Trial MBL 0412 was designed to assess the safety of Taclonex® Topical Suspension by evaluating calcium metabolism in 78 pediatric subjects with plaque psoriasis of the scalp. The entry criteria for subjects enrolled in Trial MBL 0412 included at least 10% involvement of the scalp area and clinical signs of psoriasis vulgaris on trunk and/or limbs, or earlier diagnosis of psoriasis vulgaris on trunk and/or limbs only when the scalp lesions were not typical. All subjects applied Taclonex® Topical Suspension once daily for 4 to 8 weeks. Subjects without signs of psoriasis at Week 4 discontinued treatment.

The 2 uncontrolled trials in this development program (Trials MBL 0801 and MBL 0412) were not designed to allow statistical conclusions related to efficacy. Therefore, this data should not be included in the revised labeling. However, the proportion of subjects achieving controlled disease at Week 8 was 17/31 (54.8%) in Trial MBL 0801 and 66/78 (84.6%) in Trial MBL 0412. This treatment effect is comparable to the efficacy findings

observed in the 2 Phase 3 trials enrolling adult subjects (70.0% and 67.2% achieving controlled disease at Week 8).

6.1 Indication

The current indication for Taclonex® Topical Suspension is the topical treatment of plaque psoriasis of the scalp and body in patients18 years and older. The applicant proposed to extend the indication for Taclonex® Topical Suspension to the topical treatment of plaque psoriasis of the scalp and body in adult patients18 years and older and for the topical treatment of plaque psoriasis of the scalp in adolescent patients aged 12 to 17 years.

The following changes are recommended for section 1 of labeling. Additions are noted as double underline and deletions are noted as ~~strikethrough~~.

> 1 INDICATIONS AND USAGE
>
> Taclonex® Topical Suspension is indicated for the topical treatment of plaque psoriasis of the scalp and body in adult patients 18 years and older and for the topical treatment of plaque psoriasis of the scalp in pediatric patients 12 to 17 years and older.

6.1.1 Methods

The assessment of treatment effect was a secondary objective in the following 2 safety trials.

- MBL 0801:
  National, multi-center, uncontrolled 8- week trial enrolling 31 subjects aged 12 to 17 years with scalp psoriasis. The trial was designed to assess the effect of Taclonex® Topical Suspension on HPA axis function and calcium metabolism. The trial was conducted at 5 sites in the US. Enrolled subjects had a clinical diagnosis of scalp psoriasis which was at least moderate in severity according to IGA (IGA $\geq$3) and involved at least 20% of the scalp area. In addition, subjects had clinical signs of psoriasis vulgaris on the trunk and/or limbs, or a previous diagnosis of psoriasis vulgaris on the trunk and/or limbs.

- MBL 0412:
  International, multi-center, uncontrolled 8-week trial enrolling 78 subjects aged 12 to 17 years with scalp psoriasis. The trial was designed to assess the effect of Taclonex® Topical Suspension on safety including calcium metabolism. The trial was conducted at 17 sites in the United Kingdom, France and Canada. Enrolled

subjects had a clinical diagnosis of scalp psoriasis which is at least moderate in severity according to IGA (IGA ≥3) and involved at least 10% of the scalp area. In addition, subjects had a clinical signs of psoriasis vulgaris on trunk and/or limbs, or a previous diagnosis of psoriasis vulgaris on trunk and/or limbs.

6.1.2 Demographics

The demographic characteristics of the study population included in Trial MBL 0801 were comparable to Trial MBL 0412. In both trials, the majority of subjects were White and female with moderate disease at Baseline. However, because a primary objective of Trial MBL 0801 was to evaluate the effect of Taclonex® Topical Suspension on HPA axis function under maximal use conditions, a greater number of subjects enrolled in Trial MBL 0801 had "severe" or "very severe" disease at Baseline. See Table 16 for a comparative summary of the demographic information for both trials. Refer to Section 7.2.1 of this review for a discussion of the demographic information regarding the pooled data from Trials MBL 0801 and MBL 0412.

Table 16: Demographic Information from Trial MBL 0801 and MBL 0412

	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: Statistical Review and Evaluation, Matthew Guerra, Ph.D.

6.1.3 Subject Disposition

The majority of subjects who were enrolled in Trial MBL 0801 and MBL 0412 completed their trials. The number of subjects who discontinued each trial was comparable. One subject in each trial discontinued due to an adverse event. However, only one of these adverse events was related to exposure to the study product, signs of adrenal suppression experienced by one subject enrolled in Trial MBL 0801. Refer to Section 7.3.3 for the analysis of data regarding subject disposition.

Table 17: Disposition of Subjects in Trial MBL 0801 and MBL 0412

	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 Emerging During Study	1	2
Other	0	1

Source: Statistical Review and Evaluation, Matthew Guerra, Ph.D.

6.1.4 Analysis of Primary Endpoint(s)

All of the primary endpoints in Trials MBL 0801 and MBL 0412 involved the assessment of safety parameters. Refer to Section 7 of this review.

6.1.5 Analysis of Secondary Endpoints(s)

The key evaluation of treatment effect in both Trial MBL 0801 and Trial MBL 0412 was the proportion of subjects with controlled disease {an IGA score of 0 (clear) or 1 (almost clear)} at Weeks 2, 4, and 8.

Table 18: Percentage of Pediatric Subjects with Controlled Disease on the Scalp

	Trial MBL-0801 (N=31)		**Trial 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: Statistical Review and Evaluation, Matthew Guerra, Ph.D.

The proportion of subjects who achieved controlled disease in Trial MBL 0412 was greater than the proportion of subjects who achieved controlled disease in Trial MBL 0801. This observation may be related to greater disease severity among subjects

enrolled in Trial MBL-0801 compared with Trial MBL 0412. However, the analysis of this data is limited by the absence of a control group.

The findings in the pediatric population with scalp psoriasis in this development program are comparable to the findings in the adult population with scalp psoriasis in the original development program as summarized in **Error! Reference source not found.**.

Table 19: Percentage of Adult Subjects with Controlled Disease on the Scalp

Percentage of Patients with Clear or Almost Clear Disease According to the Investigator's Global Assessment of Disease Severity in Trials on the Scalp				
	Taclonex® Topical Suspension	**Betamethasone Dipropionate in vehicle**	**Calcipotriene in vehicle**	**Vehicle**
Trial One	(N = 494)	(N = 531)	(N = 256)	(N = 126)
Week 2	55.5%	46.1%	18.4%	9.5%
Week 8	70.0%	63.1%	36.7%	19.8%
Trial Two	(N = 512)	(N = 517)	(N = 251)	-
Week 2	47.1%	36.4%	12.7%	-
Week 8	67.2%	59.6%	41.0%	-

Source: Taclonex® Topical Suspension labeling Section 14 Clinical Studies

As the trials were not designed to allow statistical conclusions regarding treatment effect in the pediatric population age 12-to 17 years, this data is not recommended for inclusion in the revised labeling. The following changes are recommended for section 14 of labeling. Additions are noted as double underline and deletions are noted as ~~strikethrough~~.

Clinical Trials Conducted in Pediatric Subjects 12 to 17 years with Scalp Psoriasis

Two prospective, uncontrolled, trials (N=109) were conducted in pediatric subjects age 12 to 17 years. Subjects were treated once daily for up to 8 weeks with Taclonex® Topical Suspension. In trial one, 78 subjects with at least moderate scalp psoriasis at baseline and at least 10% scalp involvement were evaluated for safety. Seventy four percent (74%) of subjects had disease of moderate severity at baseline. In trial two, 31 subjects with at least moderate scalp psoriasis at baseline and at least 20% scalp involvement were evaluated for safety including HPA axis suppression. Sixty eight percent (68%) of subjects had disease of moderate severity at baseline. Calcium metabolism was evaluated in all subjects (N=109).

Although an evaluation of treatment effect was not the primary objective of these trials, disease severity is relevant for the assessment of safety. See Table 20 for a comparison of Baseline disease severity according to IGA and changes in treatment effect [Proportion of subjects who achieved controlled disease, Percentage change in Total Sign Score (TSS), Proportion of subjects with success (Total Sign Score ≤1), and

Proportion of subjects with controlled disease (defined as clear or very mild) according to the patient's global assessment of disease severity.)]

Table 20: Overview of Treatment Effect from Trials MBL 0801 and MBL 0412 INT

N (FAS)	Baseline IGA	Treatment Effect Response Criteria (FAS)	Week 2	Week 4	Week 8	End of Treatment
MBL 0801						
N= 31	Moderate: 67.7% Severe: 25.8% Very Severe: 6.5%	Controlled disease by IGA (%)	32.3	43.3	53.8	54.8
		Change in TSS (%)	-48.0	-48.8	-57.2	-59.2
		Subjects with success (TSS≤1)(%)	22.6	16.7	34.6	38.7
		Controlled disease by Patient's Global (%)	45.2	50.0	57.7	58.1
MBL 0412						
N=78	Moderate: 74.4% Severe: 20.5 % Very Severe: 5.1%	Controlled disease by IGA (%)	47.4	75.6	80.3	84.6
		Change in TSS (%)	-62.7	-72.1	-76.6	-80.4
		Subjects with success (TSS≤1) (%)	20.5	39.7	55.7	62.8
		Controlled disease by Patient's Global (%)	56.4	70.5	83.6	87.2

Source: Module 2.7.3 Appendix 4 Page 4 (Applicant's analysis)
FAS = Full Analysis Set; IGA = Investigator's Global Assessment of disease severity; TSS = Total Sign Score
a. Treatment effect was secondary response criteria.
b. Controlled disease is defined as subjects with disease severity classified as clear or almost clear by the IGA after the treatment period.
c. Controlled disease is defined as subjects with disease severity classified as clear or very mild by the Patient's Global Assessment of disease severity after the treatment period

It should be noted that Table 20 includes only observed cases at Week 2, 4 and 8. The methodology for handling missing data at the end of treatment was the last observation carried forward (LOCF).

6.1.6 Other Endpoints

Tertiary endpoints in Trials MBL 0801 and MBL 0412 included the Patient's Assessment of Itching at Weeks 2, 4, 8, and end of treatment. The severity of itching was evaluated using a 4-point scale.

The results of the Patient's Assessment of Itching were not included in labeling and are not discussed in this review. It should be noted that the applicant did not include a Patient Report Outcome dossier with the submission to support the validity of the assessment tool.

6.1.7 Subpopulations

Given the limitations of the database (small sample size and limited enrollment of non-White subjects) and the study design (e.g. open-label), no analysis of treatment effect by age, race or sex was performed by Agency reviewers.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant established the safe and effective dosing regimen (concentration, duration of application and dosing interval) with data submitted to support approval of the original application for the treatment of moderate to severe psoriasis vulgaris of the scalp in adults 18 years and older. The applicant did not investigate alternative dosing regimens for pediatric subjects age 12 to 17 years. Subjects in all age groups applied Taclonex® (calcipotriene and betamethasone dipropionate) Topical Suspension, 0.005%/0.064%, once daily for up to 8 weeks.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy and the development of tolerance were not assessed in this development program in the pediatric population age 12 to 17 years.

6.1.10 Additional Efficacy Issues/Analyses

There were no additional issues or analyses regarding treatment effect.

7 Review of Safety

Safety Summary

The applicant submitted data from 2 uncontrolled, multicenter trials of similar design (Trials MBL 0801 and MBL 0412) to support the safety of Taclonex® Topical Suspension for the treatment of scalp psoriasis in the pediatric population age 12-17 years.

Trials MBL0801 and Trial MBL0412 enrolled a total of 109 subjects age 12 to 17 years with at least moderate scalp psoriasis on the Investigator Global Assessment scale (IGA ≥3 on a 6-point scale) and amenable to topical treatment with a maximum of 60 g of study medication per week. Trial MBL 0801 was designed to assess the safety of Taclonex® Topical Suspension by evaluating HPA axis function and calcium metabolism in 31 pediatric subjects with plaque psoriasis of the scalp. The entry criteria for subjects enrolled in Trial MBL 0801 included at least 20% involvement of the scalp area (maximal use conditions) and clinical signs of psoriasis vulgaris on trunk and/or limbs, or earlier diagnosis of psoriasis vulgaris on trunk and/or limbs. Trial MBL 0412 was designed to assess the safety of Taclonex® Topical Suspension by evaluating calcium metabolism in 78 pediatric subjects with plaque psoriasis of the scalp. The entry criteria for subjects enrolled in Trial MBL 0412 included at least 10% involvement of the scalp area and clinical signs of psoriasis vulgaris on trunk and/or limbs, or earlier diagnosis of psoriasis vulgaris on trunk and/or limbs only when the scalp lesions were not typical. All subjects applied Taclonex® Topical Suspension once daily for 4 to 8 weeks. Subjects without signs of psoriasis at Week 4 discontinued treatment.

Pediatric subjects enrolled in Trial MBL 0801 and Trial MBL 0412 applied a maximum weekly dose of 60 grams of Taclonex® Topical Suspension. The labeled maximum adult dose of 100 grams was adjusted based on the expected body surface area (BSA) of pediatric subjects compared with adult subjects using data from Trial MCB 0501 INT. The mean duration of treatment was 7.2 weeks (range 0.1-11.0 weeks).The mean amount of the drug product used per week was 32.3 grams (range 0.7-68.6 grams/week.) The mean weekly amount used was similar for the first 4-week period (30.9 g/week) and the second 4-week period (33.2 g/week).Exposure to Taclonex® Topical Suspension in the pediatric population was comparable to similar trials in the adult population with scalp psoriasis. Therefore, the overall exposure to the study product was adequate to characterize the safety profile in the intended pediatric population.

The safety evaluation was conducted on the “Safety Analysis Set”, defined as all subjects who applied any study product and for whom the presence or confirmed absence of adverse events was available. The safety evaluation included adverse events elicited by open ended questioning (summarized by severity, frequency and relationship to the study drug), vital signs, laboratory testing (e.g. chemistry, hematology and urinalysis), concomitant medication query, dietary calcium diary and pregnancy testing. Cutaneous adverse events were categorized as lesional/perilesional to the application site or distant (> 2 cm from the application site).

There were no deaths, non-fatal serious adverse events (SAEs) or pregnancies among subjects in “Safety Analysis Set”. There were 10 severe adverse events reported in 3 subjects under the following preferred terms: staphylococcal infection, headache, speech disorder, wheezing, dyspnea, toothache, pyrexia, oxygen saturation decreased,

joint dislocation and tooth extraction. It is unlikely that these severe adverse events were related to the use of Taclonex ® Topical Suspension.

A total of 6 subjects (5.5%) withdrew from Trial MBL 0412 or Trial MBL 0801. Three subjects reported a total of nine adverse events which were recorded as reasons for withdrawal. These included: hypothalamic-pituitary disorder, speech disorder, dyspnea, wheezing, pyrexia, blood parathyroid hormone increased, oxygen saturation decreased, urine calcium decreased and urine phosphorous increased. The only adverse event which was related to the study product was the abnormal response to ACTH challenge (hypothalamic-pituitary disorder). Among the 3 subjects who experienced adverse events, 2 subjects were categorized as withdrawing due to “unacceptable adverse events” and the third as withdrawing due to “emerging exclusion criteria” resulting from treatment of the adverse events. Two additional subjects withdrew from the trial due “emerging exclusion criteria” (initiation of methotrexate and abnormal HPA axis function at baseline). Investigators withdrew another subject when she failed to attend the final visit (Visit 5).

A total of 43 (39.4%) subjects reported 84 adverse events. Among the most common adverse events occurring in ≥1% of subjects in the “Safety Analysis Set” were upper respiratory tract infections (5.5%), headache (4.6%), pharyngitis (3.7%), cough(3.7%), oropharyngeal pain(3.7%), acne (2.8%) and urinary calcium decreased (2.8%). All other adverse events were reported by 1 to 2 subjects each. There were 8 ADRs in 6 subjects (5.5%) which were mild or moderate in intensity and reported by 1 subject each. The clinically relevant adverse reactions which were consistent with the mechanism of action of the product were: Hypothalamic-pituitary disorder, acne and application site pruritus. Two other subjects experienced acne which was assessed as not related by investigators. (This conclusion could not be confirmed by an evaluation of the case report forms.) All of these adverse reactions are included in current labeling.

“Adverse events of clinical interest” were defined as adverse events related to exposure to topical corticosteroids, topical calcipotriene or accidental eye exposure. “Adverse events of clinical interest” were reported in 8 subjects. Seven subjects experienced events potentially related to exposure to betamethasone, the corticosteroid component of Taclonex® Topical Suspension: 3 cases of acne and one case each of dermatitis acneiform, hypothalamic-pituitary disorder, skin striae, and otitis externa. One subject reported one event of allergic conjunctivitis potentially related to ocular exposure to the study product (conjunctivitis allergic). There were no adverse events potentially related to calcipotriol absorption.

Dermal safety studies were not included in the evaluation of the safety of Taclonex® Topical Suspension for the treatment of scalp psoriasis in the pediatric population age 12-17 years. The applicant conducted dermal safety studies to support approval of the original NDA. Local safety findings in the pediatric population were consistent with local

safety findings in adults. Refer to the Clinical Review of the original NDA by Brenda Carr dated 4/23/2008.

The applicant did not evaluate the long term safety of Taclonex® Topical Suspension in the pediatric population age 12 to 17 years. The applicant conducted two 52- week trials (MBL 0407 and MBL 0502) to evaluate long term safety in the adult population using Taclonex® Topical Suspension on the scalp. Trial MBL 0502 US also included Taclonex® Ointment on the body. Refer to the Clinical Review of the original NDA by Brenda Carr dated 4/23/2008.

Trial MBL 0801 and Trial MBL 0412 were adequate to inform safety and support the short-term use of Taclonex ® Topical Suspension in the pediatric population age 12 to 17 years. Safety findings in the pediatric population are similar to safety findings in the adult population. The adverse reactions which were identified in the pediatric population were already included in current labeling. The data submitted by the applicant supports the extension of the current indication to include the treatment of psoriasis vulgaris on the scalp in patients age 12 years and older and fulfills the post marketing requirement under PREA.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Under the Pediatric Research Equity Act (PREA), the applicant was required to assess the effect of their drug product on calcium metabolism in 100 evaluable subjects and the effect on the hypothalamic-pituitary axis (HPA) in a subset of 30 subjects age 12-17 years with scalp psoriasis. To address this requirement, the applicant conducted two uncontrolled trials (MBL0801 and MBL0412) enrolling a total of 109 subjects age 12 to 17 years with at least moderate scalp psoriasis on the Investigator Global Assessment scale (IGA $\geq$3 on a 6-point scale) and amenable to topical treatment with a maximum of 60 g of study medication per week. Trial MBL 0801 was designed to assess the safety of Taclonex® Topical Suspension by evaluating HPA axis function and calcium metabolism in 31 pediatric subjects with plaque psoriasis of the scalp. The entry criteria for subjects enrolled in Trial MBL 0801 included at least 20% involvement of the scalp area (maximal use conditions) and clinical signs of psoriasis vulgaris on trunk and/or limbs, or earlier diagnosis of psoriasis vulgaris on trunk and/or limbs. Trial MBL 0412 was designed to assess the safety of Taclonex® Topical Suspension by evaluating calcium metabolism in 78 pediatric subjects with plaque psoriasis of the scalp. The entry criteria for subjects enrolled in Trial MBL 0412 included at least 10% involvement of the scalp area and clinical signs of psoriasis vulgaris on trunk and/or limbs, or earlier diagnosis of psoriasis vulgaris on trunk and/or limbs only when the scalp lesions were not typical. All subjects applied Taclonex® Topical Suspension once daily for 4 to 8 weeks. Subjects without signs of psoriasis at Week 4 discontinued treatment.

The safety evaluation was conducted on the “Safety Analysis Set”, defined as all subjects who applied any study product and for whom the presence or confirmed absence of adverse events was available. The safety evaluation included adverse events elicited by open ended questioning (summarized by severity, frequency and relationship to the study drug), vital signs, laboratory testing (e.g. chemistry, hematology and urinalysis), concomitant medication query, dietary calcium diary and pregnancy testing. Cutaneous adverse events were categorized as lesional/perilesional to the application site or distant (> 2 cm from the application site).Based on data collected in the adult population, adverse events of clinical interest were identified to evaluate in the pediatric population. These adverse events were included in current labeling and related to local and systemic effects of corticosteroids (e.g. hypothalamic-pituitary disorder, striae, acne and acneiform eruptions), effects from potential ocular exposure (due to suspension dosage form) and effects on calcium metabolism.

7.1.2 Categorization of Adverse Events

In this safety analysis, all adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.1. Adverse events were presented by system organ class and preferred term.

The assignment of verbatim terms to system organ classes and preferred terms appears to be acceptable.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Safety Analysis Set included all subjects who applied Taclonex® Topical Suspension and for whom the presence or confirmed absence of adverse events was available. A total of 109 subjects enrolled in Trial MBL 0801 and Trial MBL 0412 provided safety data and 103 subjects (94.5%) completed the trials according to the protocols.

The applicant tabulated the number and percentage of subjects experiencing each type of adverse event (AE) (according to MedDRA preferred term within SOC) regardless of the number of times each AE was reported by each subject. The intensity of an AE was recorded as the worst intensity reported by the subject. The applicant defines adverse drug reactions (ADR) as AEs for which the investigator had not described the causal relationship to trial medication as ‘not related.’

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall Exposure

The overall exposure of pediatric subjects age 12-17 years to Taclonex® Topical Suspension in the Safety Analysis Set (Trial MBL 0801 and Trial MBL 0412) was analyzed by duration of treatment and extent of exposure to the drug product. The mean duration of treatment was 7.2 weeks (range 0.1-11.0 weeks). The mean total amount of the drug product used was 257.8 grams (range 5.7-519.7 g). The mean amount used during the first 4- week period (123.7 g) was similar to the mean amount used during the second 4-week period (130.0 g). The mean amount of the drug product used per week was 32.3 grams (range 0.7-68.6 grams/week.) The mean weekly amount used was similar for the first 4-week period (30.9 g/week) and the second 4-week period (33.2 g/week).

Compared with pediatric subjects, the mean duration of exposure in adult subjects with scalp psoriasis enrolled in 8 week controlled trials of similar design was 7.3 weeks in the Taclonex® Topical Suspension arm. The mean total amount of Taclonex® Topical Suspension used by adults was134 grams.

The maximum weekly dose of Taclonex® Topical Suspension allowed for pediatric subjects enrolled in Trial MBL 0801 and Trial MBL 0412 was 60 g. In contrast, the maximum weekly dose approved for adults age 18 years and older was 100 gram (Taclonex® Topical Suspension labeling, Dosage and Administration). The maximum dose was adjusted based on the expected body surface area (BSA) of pediatric subjects age 12 to 17 years compared with adult subjects using data from Trial MCB 0501 INT.

A total of 21 subjects used more than 60 grams per week for 2 or more weeks. Investigators distributed two 60 gram bottles to each subject at study visits 2-4 (Week 2, 4, 6). Subjects were able to exceed the maximum dose by returning for their visits early when their bottles of study product were empty. There was no difference in the adverse event profile of subjects who applied less than 40 grams of Taclonex® Topical Suspension compared with subjects who applied more than 40 grams of Taclonex® Topical Suspension. See Section 7.5.1 of this review for a discussion of adverse events related to weekly dose.

Table 21: Duration and Extent of Exposure to Treatment: Safety Analysis Set

Duration (weeks)	Taclonex® Topical Suspension N=109
Mean (SD)	7.2 (1.9)
Min/Max	0.1/11.0
Extent of Exposure (subject treatment weeks)	781

Source: Modified from Module 2.7.4 Summary of Clinical Safety, Table 2

Table 22: Amount of Taclonex® Topical Suspension Used: Safety Analysis Set

Visit interval Amount used (g)	Taclonex® Topical Suspension N=109
Visit 1-3 (4 weeks)	
Mean (SD)	123.7 (74.8)
Median	122.8
Min/Max	3.2/271.5
Number	100
Visit 3-5	
Mean (SD)	130.0 (80.9)
Median	174.7
Min/Max	2.1/264.9
Number	77
Visit 1-end of treatment	
Mean (SD)	257.8 (154.4)
Median	330.8
Min/Max	5.7/519.7
Number	75

Source: Modified from Module 2.7.4 Summary of Clinical Safety, Table 3

Table 23: Average Weekly Amount of Taclonex® Topical Suspension Used: Safety Analysis Set

Visit interval Average weekly amount used (g)	Taclonex® Topical Suspension N=109
Visit 1-3 (4 weeks)	
Mean (SD)	30.9 (18.8)
Median	31.9
Min/Max	0.7/67.9
Number	100
Visit 3-5	
Mean (SD)	33.2 (21.6)
Median	41.6
Min/Max	0.7/87.3

Number	77
Visit 1-end of treatment	
Mean (SD)	32.3 (19.5)
Median	40.1
Min/Max	0.7/68.6
Number	75

Source: Modified from Module 2.7.4 Summary of Clinical Safety, Table 4

Table 24: Average Weekly Amount of Taclonex® Topical Suspension Used in Defined Usage Categories: Safety Analysis Set

Visit interval Average weekly amount used (g)	Taclonex® Topical Suspension N=109	
	Number of Subjects	Percent
Visit 1-3 (4 weeks)		
< 20 g/week	34	34.0
20 to < 40 g/week	22	22.0
40 to < 60 g/week	43	43.0
≥ 60	1	1.0
Total	100	100.0
Visit 3-5		
< 20 g/week	26	33.8
20 to < 40 g/week	11	14.3
40 to < 60 g/week	34	44.2
≥ 60	6	7.8
Total	77	100.0
Visit 1-end of treatment		
< 20 g/week	26	34.7
20 to < 40 g/week	11	14.7
40 to < 60 g/week	37	49.3
≥ 60	1	1.3
Total	75	100.0

Source: Modified from Module 2.7.4 Summary of Clinical Safety, Table 5

The following changes are recommended for section 6 of labeling. Additions are noted as double underline and deletions are noted as strikethrough.

(b) (4) P~~p~~atients 18 years and older should not (b) (4) use more than 100 g per week. Patients aged 12 to 17 years should not use more than 60 g per week.

Demographics of Target Population

The baseline demographic information regarding subjects enrolled in Trial MBL 0801 and Trial MBL 0412 was pooled and presented in Table 25 and Table 26. The majority

of the subjects in the safety population were White, female, not Hispanic/Latino, with a mean age of 14.6 years. The mean BMI was 23.7 kg/m², the mean duration of psoriasis vulgaris on the scalp was 5.6 years. The majority of subjects had Fitzpatrick skin types II-IV (85.3%).

It should be noted that the racial distribution of subjects in this study population does not reflect the racial distribution in the general population (e.g.72.4% White, 12.6 % Black, and 4.8% Asian as of the 2010 Census)[3] or the racial distribution of patients with psoriasis (prevalence in White patients is 2.5% and in Black patients is 1.3%).4

Table 25: Demographics for Safety Analysis Set (Trial MBL 0801 and Trial MBL 0412)

Baseline Characteristics	Taclonex® Topical Suspension N=109	
	Number of Subjects	Percent
Sex		
Male	47	43.1
Female	62	56.9
Age group		
12<14 years	53	48.6
15<17 years	56	51.4
Ethnicity		
Hispanic/Latino	14	12.8
Other	95	87.2
Race		
White	98	89.9
Black	2	1.8
Asian	4	3.7
Other	5	4.6
Skin type		
I	10	9.2
II	37	33.9
III	35	32.1
IV	21	19.3
V	4	3.7
VI	2	1.8

Source: Modified from Module 2.7.4 Summary of Clinical Safety, Table 6

3 Humes, KR, Jones NA, Ramirez RR: 2010 Census Briefs -Overview of Race and Hispanic Origin: 2010. Issued March 2011 by U.S. Census Bureau.

4 Gelfand JM et al. The prevalence of psoriasis in African Americans: results from a population-based study. J Am Acad Dermatol.2005 Jan; 52(1):23-6.

Table 26: Baseline Characteristics of Subjects in the Safety Analysis Set (Trial MBL 0801 and Trial MBL 0412)

Baseline Characteristics	Taclonex® Topical Suspension N=109
Age (years)	
Mean (SD)	14.6 (1.7)
Median	15.0
Min/Max	12/17
BMI (kg/m2)	
Mean (SD)	23.66 (6.51)
Median	21.97
Min/Max	14.7/47.1
Height (cm)	
Mean (SD)	164.51 (11.16)
Median	165.00
Min/Max	123.0/188.0
Weight	
Mean (SD)	64.66 (21.27)
Median	61.70
Min/Max	29.0/147.5
Duration of Scalp Psoriasis (years)	
Mean (SD)	5.6 (4.2)
Median	5.0
Min/Max	0/17

Source: Modified from Module 2.7.4 Summary of Clinical Safety, Table 7

7.2.2 Explorations for Dose Response

The applicant did not conduct an evaluation of dose response in this development program.

7.2.3 Special Animal and/or In Vitro Testing

Special animal and/or in vitro testing was not included in the current submission.

7.2.4 Routine Clinical Testing

The routine clinical testing was designed to assess safety including effects on HPA axis function and calcium metabolism following daily application of Taclonex® Topical Suspension in pediatric subjects for up to 8 weeks.

7.2.5 Metabolic, Clearance, and Interaction Workup

The applicant did not perform an analysis of metabolic parameters or drug clearance for this submission.

An evaluation of potential drug interactions was not included in this submission. Current approved labeling does not contain data regarding drug interactions.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Taclonex® Topical Suspension is a combination product containing a corticosteroid and a vitamin D analog. The primary systemic safety assessment for topical corticosteroids is ACTH challenge testing to evaluate HPA suppression as discussed in Section 7.4.5 of this review.

Hypercalcemia is a known adverse event observed with vitamin D analogs. The applicant assessed the effect of Taclonex® Topical Suspension on calcium metabolism in all subjects in Trial MBL 0801 and Trial MBL 0412. Investigators evaluated calcium metabolism at Screening Visit 2 and after 4 and 8 weeks of treatment (Day 28 and Day 56). The evaluation included measurements of serum calcium, albumin, phosphate, plasma parathyroid hormone (PTH) level and calculation of the albumin-corrected serum calcium concentration. In addition, subjects provided urine collections for measurement of urinary volume, calcium-, phosphate-, hydroxyproline-, sodium- and creatinine excretion and calculation of the calcium: creatinine, phosphate: creatinine, hydroxyproline: creatinine and sodium: creatinine ratios. The results of the evaluation of the effect of Taclonex® Topical Suspension on calcium metabolism are discussed in Section 7.4.2.

The safety evaluation which was conducted by the applicant to assess the potential adverse events associated with exposure to corticosteroids and vitamin D analogs in the pediatric population age 12 to 17 years was acceptable.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during Trial MBL 0412 or Trial MBL 0801.

7.3.2 Nonfatal Serious Adverse Events

No nonfatal serious adverse events occurred during Trial MBL 0412 or Trial MBL 0801.

7.3.3 Dropouts and/or Discontinuations

The majority of the subjects in the Safety Analysis Set (94.5%, 103/109 subjects) completed the trials per protocol at Week 4 (if the scalp was clear) or at Week 8. A total of 6 subjects withdrew from Trial MBL 0412 or Trial MBL 0801). Per applicant, 2 subjects withdrew from the trials due to unacceptable adverse events (AEs), 3 subjects withdrew due to emerging exclusion criteria and 1 withdrew due to other reasons.

Table 27: Reasons for Withdrawal from Trial MBL 0412 or Trial MBL 0801.

Reason for Withdrawal	Taclonex® Topical Suspension N=109	
	Number of Subjects	Percent
Number subjects completing the trial	103	94.5
Withdrawals		
Unacceptable adverse event	2	1.8
Emerging exclusion criteria	3	2.8
Other reason	1	0.9
Total Number of withdrawn subjects	6	5.5

Source: Modified from Module 2.7.4 Summary of Clinical Safety, Table 1

Three subjects reported a total of nine adverse events which were recorded as reasons for withdrawal. These included: hypothalamic-pituitary disorder, speech disorder, dyspnea, wheezing, pyrexia, blood parathyroid hormone increased, oxygen saturation decreased, urine calcium decreased and urine phosphorous increased. Among the 3 subjects, 2 subjects were categorized as withdrawing due to “unacceptable adverse events” and the third as withdrawing due to “emerging exclusion criteria” resulting from treatment of the adverse events. Only 1 subject withdrew due to an adverse reaction (narrative #1 below.) The narratives of these 3 subjects with adverse events are as follows:

1. A 17-year old white male (CRF 1016) with a 5 year history of moderate scalp psoriasis on IGA withdrew from Trial MBL 0801 due to signs of adrenal suppression. At baseline the subject had 75% involvement of his scalp with psoriasis and 4 % involvement of the total body surface area with psoriasis. No concomitant medications were documented. He applied a total of 114 grams of Taclonex® Topical Suspension over 4.6 weeks. The results of the ACTH challenge at Week 4 indicated a cortisol concentration ≤ 18 mcg/dl at 30 minutes (16.8 mcg/dl) and > 18 mcg/dl at 60 minutes (18.5 mcg/dl). On repeat ACTH challenge at Week 8,,l the subject had normal adrenal function at both timepoints (20.9 mcg/dl at 30 minutes and 22.8 at 60 minutes). This adverse event was related to the study product.

2. A 14-year old white female (CRF 1222) with a 13 year history of moderate scalp psoriasis on IGA withdrew from Trial MBL 0412 due to abnormal laboratory parameters. At baseline the subject had 25% involvement of her scalp and of the total body surface area with psoriasis. She applied a total of 100 grams of Taclonex® Topical Suspension over 6 weeks. She treated the plaque psoriasis on her body with diflucortolone valerate (concentration not provided) during the trial. Laboratory evaluation at Visit 3 showed increased PTH {73 ng/L , normal range 9-52 ng/L}, decreased urine calcium {1.2 mmol/24 hour, normal range 2.5-7.5 mmol/24 hour}, and decreased urine phosphate {11.9 mmol/24 hour, normal ranger 12.9-42.0} . Vital signs were normal. Urine calcium was below the reference range at screening (SV2 2.3 mmol/24 hour.)The etiology of the abnormal laboratory parameters was not documented on the case report form. These adverse events were assessed as not related and the status of the adverse event reported as resolved after 17 days.

3. A 17 year old white female (CRF 1091) with a 4 year history of moderate scalp psoriasis on IGA who experienced pyrexia, oxygen saturation decreased, speech disorder, dyspnea, and wheezing withdrew from Trial MBL 0412. At baseline the subject had 10% involvement of her scalp with psoriasis and 4 % involvement of the total body surface area with psoriasis. She applied the study treatment for 4.9 weeks but did not return all bottles of Taclonex Topical Suspension. Because she required treatment with prednisolone for 6 days and Ventolin, the cause of her withdrawal was classified as “emerging exclusion criteria” (#5 use of systemic corticosteroids). These adverse events were assessed as severe and not related. The status of the adverse event was reported as resolved after 10 days.

Three subjects withdrew from the trial due emerging exclusion criteria (See narrative 3 above).The narratives of the other 2 subjects who withdrew due to emerging exclusion criteria are as follows:

4. A 16 year old white male (CRF 1424) with a 2 year history of moderate scalp psoriasis was withdrawn from the Trial MBL 0412 when he initiated methotrexate for his psoriasis. Other concomitant medications included: Diprolene Ointment for the treatment of psoriasis on his trunk and extremities and Protopic 0.1% ointment for the treatment of psoriasis in his groin. At baseline the subject had 75% involvement of his scalp with psoriasis and 8 % involvement of the total body surface area with psoriasis. At Visit 2 on Day 14 his scalp was assessed as “clear” and he discontinued the Taclonex® Topical suspension. By Visit 3 on Day 28 the psoriasis recurred and his scalp was assessed as “almost clear”.

5. A 12 year old white male (CRF 1076) with a 1 year history of moderate scalp psoriasis and environmental allergies was withdrawn when investigators identified that he had an exclusionary ACTH lab value at enrollment which indicated potential HPA axis suppression. At Follow-up Visit 2, ACTH challenge

testing was repeated. Concomitant medications are not included on the case report form. At baseline the subject had 38% involvement of his scalp with psoriasis and 5 % involvement of the total body surface area with psoriasis. No concomitant medications were documented. This adverse event was assessed as mild and not related. The status of the adverse event was reported as resolved.

A 13 year old Asian female (CRF 1181) with a 6 year history of moderate scalp psoriasis and hearing loss did not attend the scheduled Visit 5 and was withdrawn for "other reason". At baseline the subject had 30% involvement of her scalp and 10 % involvement of her body with psoriasis.

7.3.4 Significant Adverse Events

In the category of significant adverse events, the applicant included serious adverse events (SAEs), pregnancies (not recorded as SAEs), adverse events of clinical interest and adverse events that were clinically significant or led to a substantial intervention (e.g. discontinuation of study product).

There were no deaths, SAEs or pregnancies reported during Trial MBL 0412 or Trial MBL 0801.
Adverse events of clinical interest were adverse events known to be related to exposure to corticosteroids or calcipotriol. These included the following:

1. Events potentially related to corticosteroid use: skin atrophy, skin striae, telangiectasia, tachyphylaxis or rebound (including lesional/perilesional or treatment related psoriasis), skin hypopigmentation, hypertrichosis, acne, rosacea, dermatitis, suppression of the HPA axis, pustular psoriasis, and lesional/perilesional or treatment related skin infections (folliculitis, rash pustular, herpes simplex, otitis externa, ear infection, eye infection, furuncle), ocular hypertension, intraocular pressure increased, glaucoma, hypertension, diabetes mellitus, increased blood glucose
2. Events potentially related to calcipotriol absorption: hypercalcemia, blood calcium increased and urine calcium increased
3. Events potentially due to contamination of the eyes with the drug product: AEs coded to the eye disorder primary SOC.

Adverse events of clinical interest were reported in 8 subjects. Seven subjects experienced events potentially related to exposure to betamethasone, the corticosteroid component of Taclonex® Topical Suspension: 3 cases of acne and one case each of dermatitis acneiform, hypothalamic-pituitary disorder, skin striae, and otitis externa. One subject reported one event of allergic conjunctivitis potentially related to ocular exposure to the study product (conjunctivitis allergic). There were no adverse events potentially related to calcipotriol absorption.

Adverse events that were clinically significant included those that resulted in discontinuation from the trial (See Section 7.3.3) and severe AEs. There were10 adverse events categorized as severe which included the following preferred terms: staphylococcal infection, headache, speech disorder, wheezing, dyspnea, toothache, pyrexia, oxygen saturation decreased, joint dislocation and tooth extraction. The following are narratives for the 3 subjects who experienced severe adverse events:

1. A 17-year old white female (CRF 1344) with a 2 year history of moderate scalp psoriasis on IGA experienced headache, fatigue, pharyngitis and (pharyngeal) staphylococcal infection. She was enrolled in MBL 0412 and evaluated at a study site in France. At baseline the subject had 75% involvement of her scalp and 3% involvement of the total body surface area with psoriasis. She was treated with aerius, spedifen, colludol, gerimax and bristophen. The subject recovered and completed the study according to the protocol.

2. A 16 year old, white male (CRF 1345) with a 7 year history of moderate scalp psoriasis on IGA experienced a toothache and molar tooth extraction. He was enrolled in Trial MBL 0412. He improved with amoxicillin, lamaline, spifen, dafalgan and eludril. At baseline the subject had 75% involvement of his scalp and 3 % involvement of the total body surface area with psoriasis. He was also noted to have moderate striae on his back, buttocks and legs. The subject completed the study according to the protocol.

3. A 13 year old white male (CRF 1027) with a 4 year history of severe scalp psoriasis on ISGA experienced a dislocated wrist which was treated with Vicodin. He was enrolled in Trial MBL 0801. At baseline the subject had 100% involvement of his scalp and 6 % involvement of the total body surface area with psoriasis. The subject recovered and completed the study according to the protocol.

These severe adverse events were related to the use of Taclonex ® Topical Suspension.

7.3.5 Submission Specific Primary Safety Concerns

There were no new specific safety concerns regarding the pediatric population which were identified or addressed in this submission. The safety profile of Taclonex ® Topical Suspension for the treatment of scalp psoriasis in the pediatric population age 12 to 17 years is similar to the safety profile in the adult population. Common adverse reactions (≥1%) included in current labeling are folliculitis and burning sensation of the skin. In Trial MBL 0801 and Trial MBL 0412, a total of 8 adverse drug reactions (ADRs) were reported in 6 subjects (5.5%). The clinically relevant adverse reactions which were consistent with the mechanism of action of the product were: Hypothalamic-pituitary

disorder, acne and application site pruritus. These adverse reactions are included in current labeling. HPA axis suppression and the effects on calcium metabolism are the primary systemic safety concerns with the use of Taclonex ® Topical Suspension in the pediatric population and are addressed in this review in Section 7.2.6 and Section 7.4.2, respectively.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Investigators collected data regarding adverse events in both clinical trials by posing non-leading questions and recording their own observations regarding changes in subject status. In addition, investigators categorized cutaneous events as lesional/perilesional (located less than or equal to 2 cm from the border of the treated lesion) or distant from the treatment site. Investigators documented the location of the cutaneous adverse event (face, scalp, or trunk/limbs) and the intensity of an adverse event as the most severe intensity rating.

In the safety population, 43 (39.4%) subjects reported 84 adverse events. Among the subjects reporting adverse events, 6 subjects (5.5%) reported 8 adverse events which were categorized as adverse drug reactions.

As summarized in Table 28, among the most common adverse events occurring in ≥1% of subjects in the safety population were upper respiratory tract infections (5.5%), headache (4.6%), pharyngitis (3.7%), cough(3.7%), oropharyngeal pain(3.7%), acne (2.8%) and urinary calcium decreased (2.8%). All other adverse events were reported by 1 to 2 subjects each.

Table 28: Adverse Events Occurring in ≥1% of Subjects by MedDRA Primary System Organ Class and Preferred Term

MedDRA System Organ Class MedDRA Preferred Term	Taclonex® Topical Suspension N=109	
	Number of subjects	Percentage
Infections and Infestations		
Upper Respiratory Tract Infection	6	5.5
Pharyngitis	4	3.7
Gastroenteritis	2	1.8
Nasopharyngitis	2	1.8
Immune system disorders		
Seasonal allergy	2	1.8

Nervous System Disorders		
Headache	5	4.6
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	4	3.7
Oropharyngeal pain	4	3.7
Wheezing	2	1.8
Gastrointestinal Disorders		
Abdominal pain	2	1.8
Diarrhea	2	1.8
Skin and Subcutaneous Disorders		
Acne	3	2.8
Psoriasis	2	1.8
General Disorders /Site Administration Conditions		
Pyrexia	2	1.8
Investigations		
Urine calcium decreased	3	2.8
Blood parathyroid hormone increased	2	1.8

Source: Table 14, Module 2.7.4 Summary of Clinical Safety-Pooled data

Adverse drug reactions (ADRs) were defined as adverse events for which the investigator had not described the causal relationship to study product as 'not related'. There were 8 ADRs in 6 subjects (5.5%) which were mild or moderate in intensity and reported by 1 subject each. The clinically relevant adverse reactions which were consistent with the mechanism of action of the product were: Hypothalamic-pituitary disorder, acne and application site pruritus. These adverse reactions are included in current labeling.

Narratives are provided in this review (Section 7.3.3) for the subjects who experienced adverse reactions that resulted in discontinuation from the trials.

It should be noted that 3 subjects in the pooled data set experienced the adverse event of acne. However, only 1 subject who experienced a "flare" of baseline acne was assessed as reporting an adverse reaction possibly related to exposure to the study product. Interpretation of these findings is compromised by the absence of a vehicle arm. Review of the case report forms for subjects with acne does not support a relationship to exposure to the study product.

Table 29: Adverse Drug Reactions by MedDRA Primary System Organ Class and Preferred Term

MedDRA System Organ Class MedDRA Preferred Term	Taclonex® Topical Suspension N=109	
	Number of subjects	Percentage

Endocrine Disorders		
Hypothalamic-pituitary disorder	1	0.9
Nervous System Disorders		
Headache	1	0.9
Skin and Subcutaneous Disorders		
Acne	1	0.9
Dermatitis acneiform	1	0.9
General Disorders /Site Administration Conditions		
Application site pruritus	1	0.9
Investigations		
Urine calcium decreased	1	0.9
Blood parathyroid hormone increased	1	0.9
Urine calcium decreased	1	0.9
Total Number of Drug Reactions	8	
Total Number of Subjects	6	5.5

Source: Table 17, Module 2.7.4 Summary of Clinical Safety-Pooled data

Application site pruritus and alopecia were classified as lesional/perilesional adverse events. Only application site pruritus was also assessed by investigators as related to the study product. Alopecia may be observed in the setting of inflammatory disease of the scalp and may be difficult to attribute to the treatment rather than the primary process.

Table 30: Lesional/Perilesional Adverse Events on the Scalp by MedDRA Primary System Organ Class and Preferred Term

MedDRA System Organ Class MedDRA Preferred Term	Taclonex® Topical Suspension N=109	
	Number of subjects	Percentage
Skin and Subcutaneous Disorders		
Alopecia	1	0.9
General Disorders /Site Administration Conditions		
Application site pruritus	1	0.9
Total Number of Events	2	
Total Number of Subjects	2	1.8

Source: Table 19, Module 2.7.4 Summary of Clinical Safety-Pooled data

The following changes are recommended for section 6 of labeling. Additions are noted as <u>double underline</u> and deletions are noted as ~~strikethrough~~.

<u>Clinical Trials Conducted in Pediatric Subjects 12 to 17 years with Scalp Psoriasis</u>

In two uncontrolled, prospective clinical trials, a total of 109 subjects age 12-17 years with plaque psoriasis of the scalp were treated with Taclonex® Topical Suspension once daily for up to 8 weeks. The median weekly dose was 40 g. Adverse reactions included acne, acneiform dermatitis and application site pruritus (0.9% each).

7.4.2 Laboratory Findings

The following laboratory testing was performed as part of the safety evaluation of pediatric subjects in Trial MBL 0801 and Trial 0412:

Biochemistry: serum calcium, albumin, albumin-corrected serum calcium, potassium, chloride, creatinine, blood urea nitrogen, serum phosphate, cortisol, and plasma PTH.

Urinalysis (24-hour urine): calcium, total calcium excretion, calcium: creatinine ratio, phosphate, total phosphate excretion, phosphate: creatinine ratio, total hydroxyproline excretion, hydroxyproline: creatinine ratio, creatinine, creatinine excretion, sodium, total sodium excretion, sodium: creatinine ratio and volume. Urinalysis (spot urine): glucose and ketones.

Hematology: hemoglobin, hematocrit, RBC count/erythrocytes, MCV, WBC count/leukocytes including differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelet count.

HPA axis evaluation
In Trial MBL 0801 ACTH challenge testing was performed to evaluate the effect Taclonex® Topical Suspension used once daily for up to 8 weeks on the HPA axis. One subject (CRF 1016) showed evidence of adrenal suppression (serum cortisol concentration ≤18 mcg/dL) 30 minutes after ACTH challenge testing at Week 4. No associated symptoms were reported. Investigators discontinued another subject (CRF 1076) from Trial MBL 0801 at Week 2 when review of baseline data indicated that he failed to meet the entry criteria with regard to normal HPA axis functioning. See Section 7.3.3 of this review for narratives of these subjects and the Clinical Pharmacology Review by An-Chi Lu, Ph.D. dated 6/12/2014.

Calcium metabolism
The key parameters that should be evaluated in pediatric subjects receiving vitamin D analogs include calcium, phosphorus, alkaline phosphatase, parathyroid hormone (PTH) and urinary calcium/creatinine ratio (Ali Mohamadi, MD, Division of Metabolism and Endocrinology Products, IND 71198 Consultation dated 1/20/2012). An evaluation of calcium metabolism was performed at Screening Visit 2 (SV2) and after 4 and 8 weeks of treatment (Day 28 and Day 56) in Trial MBL 0801 and Trial MBL 0412. Alkaline phosphatase was not evaluated in these trials. No meaningful changes in

calcium metabolism were detected in the pediatric population age 12 to 17 years under the conditions of these trials. However, it should be noted that hypervitaminosis D, which results in elevated serum calcium levels, does not tend to occur until after several months of excessive absorption of vitamin D.

The following is a summary of the key findings in the evaluation of the effect of Taclonex® Topical Suspension on calcium metabolism:

Albumin-corrected serum calcium:
None of the subjects had high albumin- corrected serum calcium at Week 4, Week 8, or the end of treatment. A similar number of subjects shifted between the normal and low category and the low and normal category in albumin- corrected serum calcium. The mean albumin-corrected serum calcium was 2.26 mmol/L at Baseline. There were small changes in the mean of -0.018, -0.001 and -0.002 mmol/L at Week 4, Week 8, and end of treatment, respectively.

24-hour Urinary Calcium
The mean 24-hour urinary calcium excretion was 2.46 mmol/24 hr at Baseline with mean changes of 0.05, 0.04, and 0.01 mmol/24 hr at Week 4, Week 8, and end of treatment.

One 13-year old female subject (CRF 1002) with a normal level of 24-hour urinary calcium excretion at Baseline (4.15 mmol/24 hour) experienced a minor increase at Week 4 (8.2 mmol/24 hour). Her level returned to the normal range at Week 8 (3.7 mmol/24 hour). She had a 2 year history of scalp psoriasis and her past medical history was remarkable for acne and psoriasis on the body. Concomitant medications included Motrin as needed. Baseline evaluation of disease severity indicated moderate scalp psoriasis involving 57% of the total scalp area and 5% of the total body surface area. The total number of servings of dietary calcium that were recorded for four days prior to the assessment of the 24-hour urinary calcium excretion at Week 4 ranged from 1 to 3. At Week 4, her vital signs were normal with no documented symptoms. Based on the available data, this abnormal laboratory value is not clinically significant.

It should be noted that investigators conducted an assessment of 24-hour urinary calcium excretion in study MBL 0404FR to support the original NDA submission (Review by Brenda Carr dated 4/23/2008) and in study LEO 80185-G24 to support the extension of the indication to plaque psoriasis of the body (Review by Patricia Brown dated 9/10/2012). In each study 2 subjects had increases in the 24-hour urinary calcium excretion.

One subject (CRF 1048) had low 24-hour urinary calcium excretion at all timepoints. A similar number of subjects shifted between the normal and low category and the low and normal category in 24-hour urinary calcium excretion.

Urinary Calcium: Creatinine Ratio:
The mean urinary calcium: creatinine ratio was 2.68 mmol/g at Baseline with mean changes of -0.245, -0.003, and -0.058 mmol/g at Week 4, Week 8, and end of treatment. The majority of subjects had a urinary calcium: creatinine ratio in the normal range. One subject with a high value at Baseline had a normal value at Week 4 and Week 8. In addition, one subject (CRF 1048) had a low urinary calcium: creatinine ratio at Week 4 (0.25 mmol /g with a reference range of 0.3-6.1) and low -normal levels at Baseline (1.12 mmol/g) and Week 8 (0.675 mmol/g).

Parathyroid Hormone:
The mean plasma PTH was 35.4 ng/L at Baseline with mean changes of 0.0 and -2.7ng/L at Weeks 4 and 8 respectively. Three subjects with normal values at baseline had low plasma PTH at Week 4 and Week 8, but the changes were small. A similar number of subjects shifted between the normal and high category and the high and normal category in plasma PTH.

Serum Phosphate:
The majority of subjects had serum phosphate values within the normal range throughout the trial. None of the subjects had a low serum phosphate at baseline. One subject who had a normal value at baseline had low serum phosphate at Week 4 and one subject who had a normal value at baseline had a low serum phosphate at Week 8. A similar number of subjects shifted between the normal and high category and the high and normal category in serum phosphate. The mean serum phosphate was 1.39 mmol/L at baseline. There were small mean changes of -0.005 and 0.014 mmol/L at Weeks 4 and 8, respectively.

Hematology
The majority of subjects had values for hemoglobin, hematocrit, platelet count and differential within the normal range.

7.4.3 Vital Signs

Vital signs including blood pressure and heart rate were assessed at Baseline, Week 4 and Week 8 as part of the safety evaluation of Taclonex ® Topical Suspension in the pediatric population age 12-17 years. Changes from Baseline to the end of treatment were small and not clinically relevant. No clinically relevant changes in blood pressure or heart rate were found by clinical reviewers in their assessments of the data collected in the adult population (Review by Brenda Carr dated 4/23/2008 and review by Patricia Brown dated 9/10/2012).

7.4.4 Electrocardiograms (ECGs)

The applicant did not conduct cardiac safety monitoring in Trial MBL 0801 and Trial MBL 0412.

To support approval of Taclonex® Topical Suspension for the treatment of scalp psoriasis in adults, applicant collected ECGs as part of the safety monitoring during Trial MBL 0404 FR. Mean changes seen in QT and QTc were not assessed as clinically significant. Both calcipotriene and betamethasone were evaluated for cardiovascular effects in nonclinical studies. No effects were seen on cardiac parameters including ECGs following oral dosing to conscious telemetered dogs or in repeated dose toxicology studies in minipigs. See the Pharmacology/Toxicology Review by Norman See, Ph.D. dated 2/20/2008 for an evaluation of the preclinical data.

7.4.5 Special Safety Studies/Clinical Trials

The applicant conducted one special safety study (MBL 0801) to assess the effect of Taclonex® Topical Suspension on the HPA axis function and calcium metabolism in the pediatric population age 12-17 years. The primary systemic safety assessment was the response to the ACTH-challenge testing. ACTH-challenge testing was performed at baseline and the final visit (either Week 4 or 8) to evaluate HPA axis suppression. An abnormal HPA response was defined as a 30-minute post-stimulation serum cortisol level < 18 micrograms/dL at the end of treatment. Subjects with an abnormal ACTH-challenge test result were withdrawn from the trial and followed until the result of repeated testing was normal.

A total of 31 subjects enrolled in Trial MBL 0801 and applied treatment. Twenty nine subjects completed the trial. Investigators withdrew one subject (CRF 1076) from the trial at Visit 2 (Day 14) when review of baseline laboratory data indicated that the subject did not meet the inclusion criterion regarding the HPA axis function.

Another subject (CRF 1016) withdrew from 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).The subject was a 17-year old white male (CRF 1016) with a 5 year history of moderate scalp psoriasis. He applied a total of 114 grams of Taclonex® Topical Suspension over 4.6 weeks. After ACTH challenge at Week 4, his cortisol concentration was16.8 mcg/dl at 30 minutes and 18.5 mcg/dl at 60 minutes. Following repeat ACTH challenge at Week 8, the subject had normal adrenal function at both timepoints (20.9 mcg/dl at 30 minutes and 22.8 at 60 minutes). (Refer to Section 7.3.3 of this review and the Clinical Pharmacology review by An-Chi Lu, M.S., Pharm.D. for additional details regarding this case). I concur with the clinical pharmacology reviewer that this case demonstrates a clinically relevant effect on adrenal function despite the normal response at the 60 minute timepoint.

Per current labeling, the applicant conducted two trials to assess the effect of Taclonex® Topical Suspension on HPA Axis function in the adult population (MBL 0404 FR and LEO 80185-G24). In Trial MBL 0404 FR, 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 LEO 80185-G24, 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.

The results of the assessment of the effect of Taclonex® Topical Suspension on calcium metabolism in the pediatric population age 12-17 years are discussed in Section 7.4.2.

Data regarding systemic safety from Trial MBL 0801 supports the conclusion that the safety profile in the pediatric population is similar to the safety profile in the adult population.

Refer to Section 5.3 of this review for a discussion of the study design of Trial MBL 0801 and the Clinical Pharmacology Review by An-Chi Lu, Ph.D. dated 6/12/2014.

The following are the recommended additions to revised labeling in section 5.2: (Additions are noted as double underline and deletions are noted as ~~strikethrough~~).

5.2 (b) (4) Effects on Endocrine System
In a trial evaluating the effects of Taclonex® Topical Suspension on the HPA axis, 310 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.

7.4.6 Immunogenicity

Immunogenicity was not anticipated in this drug class or evaluated.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The data does not support a correlation between adverse events and dose. However, the small sample size and limited number of adverse events precludes a definitive conclusion. A summary of adverse events by exposure is provided in Table 31. Adverse events observed in subjects applying < 40 grams per week of Taclonex® Topical Suspension are compared with adverse events observed in subjects applying ≥ 40 grams per week of Taclonex® Topical Suspension.

Table 31: Adverse Events by Exposure

System Organ Class Preferred Term	Taclonex® Topical Suspension Usage (n=109)			
	< 40 grams per week (n=37)		≥ 40 grams per week (n=38)	
	# Subjects	%	# Subjects	%
Infections and infestations				
Upper respiratory infection	2	5.4	3	7.9
Gastroenteritis	1	2.7	1	2.6
Nasopharyngitis	2	5.4	0	0.0
pharyngitis	0	0.0	2	5.3
Gastroenteritis viral	1	2.7	0	0.0
Otitis externa	0	0.0	1	2.6
Staphylococcal infection	0	0.0	1	2.6
Urinary tract infection	0	0.0	1	2.6
Immune system disorder				
Seasonal allergy	1	2.7	1	2.6
Nervous system disorder				
Headache	3	8.1	2	5.3
Sinus headache	1	2.7	0	0.0
Eye disorder				
Conjunctivitis allergic	1	2.7	0	0.0
Cardiac disorder				
Cardiac flutter	1	2.7	0	0.0
Respiratory, thoracic & mediastinal disorders				
Oropharyngeal pain	2	5.4	2	5.3
Cough	2	5.4	0	0.0
Asthma	0	0.0	1	2.6
Nasal congestion	0	0.0	1	2.6
Wheezing	1	2.7	0	0.0
Gastrointestinal disorder				
Abdominal pain	2	5.4	0	0.0

Diarrhea	1	2.7	1	2.6
Nausea	1	2.7	0	0.0
Toothache	0	0.0	1	2.6
Vomiting	0	0.0	1	2.6
Skin & subcutaneous tissue disorders				
Acne	1	2.7	1	2.6
Psoriasis	0	0.0	2	5.3
Dermatitis acneiform	1	2.7	0	0.0
Skin striae	0	0.0	1	2.6
Musculoskeletal & connective tissue disorders				
Arthritis	0	0.0	1	2.6
Jaw disorders	0	0.0	1	2.6
Myalgia	1	2.7	0	0.0
Tendonitis	1	2.7	0	0.0
General disorders & administration site disorders				
Application site pruritus	1	2.7	0	0.0
Fatigue	0	0.0	1	2.6
Malaise	1	2.7	0	0.0
Pain	1	2.7	0	0.0
Pyrexia	0	0.0	1	2.6
Investigations				
Blood calcium decreased	1	2.7	0	0.0
Blood parathyroid hormone increased	1	2.7	0	0.0
Urine calcium decreased	1	2.7	0	0.0
Injury, poisoning& procedural complications				
Joint dislocation	1	2.7	0	0.0
Ligament sprain	0	0.0	1	2.6
Skeletal injury	0	0.0	1	2.6
Surgical & medical procedures				
Tooth extraction	0	0,0	1	2.6
Total number of adverse events	33		30	
Total number of subjects	19	51.4	14	36.8

Source: Modified from NDA 22185 Module 2.7.4 Table 15

Among the 109 subjects in the safety analysis set, 21 subjects used more than 60 gram per week for 2 or more weeks (mean usage 52.4 grams per week based on complete data from 15 subjects). One subject used more than 60 grams every week during the entire treatment period (68.6 grams per week for 7.6 weeks.) See Section 7.2.1 of this review.

Eight of 21 subjects reported 17 adverse events. Investigators assessed that none of these adverse events were related to the study product except for one adverse event of acne. Seventeen of the subjects using greater than 60 grams per week of Taclonex® Topical Suspension were enrolled in MBL 0412 and 4 of these subjects were enrolled in MBL 0801. A total of 7 subjects among the 17 enrolled in MBL 0412 reported 15 adverse events. Investigators assessed that all adverse events except one (acne) were not related to the study product. One subject among the 4 subjects enrolled in Trial MBL 0801 who used more than 60 g/week for two or more weeks reported 2 adverse events. Both of the adverse events were assessed as not related.

7.5.2 Time Dependency for Adverse Events

The applicant did not design these trials to evaluate time dependency of adverse events.

7.5.3 Drug-Demographic Interactions

The applicant conducted safety analyses based on the following subgroups: race (white, black/African American, Asian and other), age (12-14 years and 15-17 years), sex (male and female), and baseline disease severity (discussed in Section 7.5.4 of this review.)

The analysis of safety based on race was limited by the small numbers of non-white subjects. Race was established for each subject by self- reporting. Among the 109 subjects in the safety analysis set 89.9% of the subjects (98 subjects) were white, 1.8% of the subjects (2 subjects) were black/ African American, 3.7% of the subjects (4 subjects) were Asian, and 4.6% of the subjects (5 subjects) were “other”. In addition, 3 non-White subjects experienced only 3 adverse events compared 40 white subjects who experienced 81 adverse events. Thus, no meaningful conclusions result from an analysis of safety with regard to race.

Comparisons of adverse event data based on age group and sex are provided in Table 32 and Table 33. Adverse events are summarized by age group (12-14 years and 15-17 years) and listed by System Organ Class and Preferred Term in Table 32. For both age groups, the percentage of subjects experiencing at least one adverse event was similar: 41.5% in subjects age 12-14 years and 37.5% in subjects age 15-17 years. The distribution of adverse events is similar in both groups. However, older subjects reported a greater percentage of upper respiratory infections while younger subjects reported a greater percentage of cough.

Table 32: Adverse Events by Age Group by MedDRA Primary System Organ Class and Preferred Term

System Organ Class Preferred Term	Age Group (n=109)	
	12-14 years (n=53)	15-17 years (n=56)

	# Subjects	%	# Subjects	%
Infections and infestations				
Upper respiratory infection	1	1.9	5	8.9
Pharyngitis	2	3.8	2	3.6
Gastroenteritis	2	3.8	0	0.0
Nasopharyngitis	1	1.9	1	1.8
Gastroenteritis viral	1	1.9	0	0.0
Hand-foot-mouth disease	0	0	1	1.8
Otitis externa	1	1.9	0	0
Staphylococcal infection	0	0.0	1	1.8
Urinary tract infection	0	0.0	1	1.8
Immune system disorder				
Seasonal allergy	1	1.9	1	1.8
Endocrine disorders				
Hypothalamic-pituitary disorders	0	0.0	1	1.8
Psychiatric disorder				
Anxiety	1	1.9	0	0.0
Nervous system disorder				
Headache	3	5.7	2	3.6
Nystagmus	1	1.9	0	0.0
Sinus headache	1	1.9	0	0.0
Speech disorder	0	0.0	1	1.8
Eye disorder				
Conjunctivitis allergic	1	1.9	0	0.0
Cardiac disorder				
Cardiac flutter	0	0.0	1	1.8
Respiratory, thoracic & mediastinal disorders				
Cough	3	5.7	1	1.8
Oropharyngeal pain	2	3.8	2	3.6
Wheezing	1	1.9	1	1.8
Asthma	1	1.9	0	0.0
Dypnea	0	0	1	1.8
Nasal congestion	0	0	1	1.8
Gastrointestinal disorder				
Abdominal pain	2	3.8	0	0.0
Diarrhea	1	1.9	1	1.8
Nausea	1	1.9	0	0.0
Toothache	0	0.0	1	1.8
Vomiting	1	1.9	0	0.0
Skin & subcutaneous tissue disorders				
Acne	2	3.8	1	1.8
Psoriasis	1	1.9	1	1.8
Alopecia	1	1.9	0	0.0

Dermatitis acneiform	0	0.0	1	1.8
Skin striae	0	0.0	1	1.8
Musculoskeletal & connective tissue disorders				
Arthritis	1	1.9	0	0.0
Jaw disorders	1	1.9	0	0.0
Myalgia	1	1.9	0	0.0
Tendonitis	1	1.9	0	0.0
General disorders & administration site disorders				
Pyrexia	1	1.9	1	1.8
Application site pruritus	1	1.9	0	0.0
Asthenia	1	1.9	0	0.0
Fatigue	0	0.0	1	1.8
Malaise	1	1.9	0	0.0
Pain	0	0.0	1	1.8
Investigations				
Urine calcium decreased	2	3.8	1	1.8
Blood parathyroid hormone increased	2	3.8	0	0.0
Blood calcium decreased	1	1.9	0	0.0
Oxygen saturation decreased	0	0.0	1	1.8
Urine phosphorus decreased	1	1.9	0	0.0
Injury, poisoning& procedural complications				
Joint dislocation	1	1.9	0	0.0
Ligament sprain	1	1.9	0	0.0
Skeletal injury	1	1.9	0	0.0
Surgical & medical procedures				
Tooth extraction	0	0,0	1	1.8
Total number of adverse events	49		35	
Total number of subjects	22	41.5	21	37.5

Source: Modified from NDA 22185, Module 2.7.4, Table 27

Adverse events are summarized by sex and listed by System Organ Class and Preferred Term in Table 33. For both groups, the percentage of subjects experiencing at least one adverse event was similar: 36.2% of males experienced at least one adverse event compared with 41.9% of females. The distribution of adverse events is similar in both groups.

Table 33: Adverse Events by Sex by MedDRA Primary System Organ Class and Preferred Term

System Organ Class	Sex

Preferred Term	Males (n=47)		Females (n=62)	
	# Subjects	%	# Subjects	%
Infections and infestations				
Upper respiratory infection	5	10.6	1	1.6
Pharyngitis	2	4.3	2	3.2
Gastroenteritis	1	3.8	1	1.6
Nasopharyngitis	1	1.9	1	1.6
Gastroenteritis viral	0	1.9	1	1.6
Hand-foot-mouth disease	0	0	1	1.6
Otitis externa	1	1.9	0	0
Staphylococcal infection	0	0.0	1	1.6
Urinary tract infection	1	0.0	0	0
Immune system disorder				
Seasonal allergy	1	1.9	1	1.6
Endocrine disorders				
Hypothalamic-pituitary disorders	1	0.0	0	0
Psychiatric disorder				
Anxiety	0	1.9	1	1.6
Nervous system disorder				
Headache	2	4.3	3	4.8
Nystagmus	1	2.1	0	0.0
Sinus headache	0	0.0	1	1.6
Speech disorder	0	0.0	1	1.6
Eye disorder				
Conjunctivitis allergic	0	0.0	1	1.6
Cardiac disorder				
Cardiac flutter	0	0.0	1	1.6
Respiratory, thoracic & mediastinal disorders				
Cough	3	6.4	1	1.6
Oropharyngeal pain	0	0.0	4	6.5
Wheezing	0	2.1	1	1.6
Asthma	0	0.0	1	1.6
Dypnea	0	0.0	1	1.6
Nasal congestion	0	0.0	1	1.6
Gastrointestinal disorder				
Abdominal pain	0	0.0	2	3.2
Diarrhea	1	2.1	1	1.6
Nausea	0	0.0	1	1.6
Toothache	1	2.1	0	0.0
Vomiting	0	0.0	1	1.6
Skin & subcutaneous tissue disorders				
Acne	1	2.1	2	3.2
Psoriasis	1	2.1	1	1.6

Alopecia	0	0.0	1	1.6
Dermatitis acneiform	0	0.0	1	1.6
Skin striae	1	2.1	0	0.0
Musculoskeletal & connective tissue disorders				
Arthritis	1	2.1	0	0.0
Jaw disorders	0	0.0	1	1.6
Myalgia	0	0.0	1	1.6
Tendonitis	0	0.0	1	1.6
General disorders & administration site disorders				
Pyrexia	0	0.0	2	3.2
Application site pruritus	0	0.0	1	1.6
Asthenia	1	2.1	0	0.0
Fatigue	0	0.0	1	1.6
Malaise	0	0.0	1	1.6
Pain	0	0.0	1	1.6
Investigations				
Urine calcium decreased	2	4.3	1	1.6
Blood parathyroid hormone increased	1	2.1	1	1.6
Blood calcium decreased	1	2.1	0	0.0
Oxygen saturation decreased	0	0.0	1	1.6
Urine phosphorus decreased	0	0.0	1	1.6
Injury, poisoning& procedural complications				
Joint dislocation	1	2.1	0	0.0
Ligament sprain	0	0.0	1	1.6
Skeletal injury	0	0.0	1	1.6
Surgical & medical procedures				
Tooth extraction	1	2.1	0	0.0
Total number of adverse events	33		51	
Total number of subjects	17	36.2	26	41.9

Source: NDA 22185, Module 2.7.4, Table 28

There were no clinically significant differences in the distribution of adverse events related to the demographic factors that were evaluated.

7.5.4 Drug-Disease Interactions

The study population included subjects with a clinical diagnosis of scalp psoriasis which was at least moderate in severity according to IGA (i.e. at least 3 on a 6 point scale.) The majority of subjects had moderate disease at Baseline (moderate: 79/109; severe: 24/109 and very severe 6/109). The percentage of subjects who reported at least one

adverse event was similar across treatment groups: moderate 38.0%, severe 45.8% and very severe 33.3%. However, among subjects with very severe scalp disease, no adverse event was reported by more than one subject. Therefore, due to the limited numbers of subjects in the severe and very severe groups, identification of trends in adverse events by baseline disease severity is not meaningful. Refer to Table 34 for the distribution of adverse events by baseline disease severity.

Table 34: Adverse Events by Baseline IGA

System Organ Class Preferred Term	Baseline IGA n=109					
	Moderate n=79		Severe n=24		Very Severe n=6	
	# Subjects	%	# Subjects	%	# Subjects	%
Infections and infestations						
Upper respiratory infection	2	2.5	4	16.7	0	0.0
Pharyngitis	4	5.1	0	0.0	0	0.0
Gastroenteritis	2	2.5	0	0.0	0	0.0
Nasopharyngitis	2	2.5	0	0.0	0	0.0
Gastroenteritis viral	0	0.0	1	4.2	0	0.0
Hand-foot-mouth disease	1	1.3	0	0.0	0	0.0
Otitis externa	1	1.3	0	0.0	0	0.0
Staphylococcal infection	1	1.3	0	0.0	0	0.0
Urinary tract infection	1	1.3	0	0.0	0	0.0
Immune system disorder						
Seasonal allergy	1	1.3	1	4.2	0	0.0
Endocrine disorders						
Hypothalamic-pituitary disorders	1	1.3	0	0.0	0	0.0
Psychiatric disorder						
Anxiety	1	1.3	0	0.0	0	0.0
Nervous system disorder						
Headache	3	3.8	2	8.3	0	0.0
Nystagmus	1	1.3	0	0.0	0	0.0
Sinus headache	0	0.0	1	4.2	0	0.0
Speech disorder	1	1.3	0	0.0	0	0.0
Eye disorder						
Conjunctivitis allergic	0	0.0	1	4.2	0	0.0
Cardiac disorder						
Cardiac flutter	1	1.3	0	0.0	0	0.0
Respiratory, thoracic & mediastinal disorders						
Cough	3	3.8	1	4.2	0	0.0
Oropharyngeal pain	3	3.8	0	0.0	1	16.7

Wheezing	2	2.5	0.0	0.0	0.0	0
Asthma	0	0.0	0	0.0	1	16.7
Dypnea	1	1.3	0	0.0	0	0.0
Nasal congestion	1	1.3	0	0.0	0	0.0
Gastrointestinal disorder						
Abdominal pain	1	1.3	0	0.0	1	16.7
Diarrhea	2	2.5	0	0.0	0	0.0
Nausea	1	1.3	0	0.0	0	0.0
Toothache	1	1.3	0	0.0	0	0.0
Vomiting	1	1.3	0	0.0	0	0.0
Skin & subcutaneous tissue disorders						
Acne	3	3.8	0	0.0	0	0.0
Psoriasis	1	1.3	0	0.0	1	16.7
Alopecia	0	0.0	1	4.2	0	0.0
Dermatitis acneiform	1	1.3	0	0.0	0	0.0
Skin striae	1	1.3	0	0.0	0	0.0
Musculoskeletal & connective tissue disorders						
Arthritis	1	1.3	0	0.0	0	0.0
Jaw disorders	1	1.3	0	0.0	0	0.0
Myalgia	1	1.3	0	0.0	0	0.0
Tendonitis	1	1.3	0	0.0	0	0.0
General disorders & administration site disorders						
Pyrexia	2	2.5	0	0.0	0	0.0
Application site pruritus	0	0.0	1	4.2	0	0.0
Asthenia	1	1.3	0	0.0	0	0.0
Fatigue	1	1.3	0	0.0	0	0.0
Malaise	1	1.3	0	0.0	0	0.0
Pain	0	0.0	1	4.2	0	0.0
Investigations						
Urine calcium decreased	3	3.8	0	0.0	0	0.0
Blood parathyroid hormone increased	2	2.5	0	0.0	0	0.0
Blood calcium decreased	1	1.3	0	0.0	0	0.0
Oxygen saturation decreased	1	1.3	0	0.0	0	0.0
Urine phosphorus decreased	1	1.3	0	0.0	0	0.0
Injury, poisoning& procedural complications						
Joint dislocation	0	0.0	1	4.2	0	0.0
Ligament sprain	1	1.3	0	0.0	0	0.0
Skeletal injury	0	0.0	1	4.2	0	0.0
Surgical & medical procedures						

Tooth extraction	1	1.3	0	0.0	0	0.0
Total number of adverse events	64		16		4	
Total number of subjects	30	38.0	11	45.8	2	33.3

Source: Modified from NDA 22185 Module 2.7.4 Table 29

7.5.5 Drug-Drug Interactions

The applicant did not conduct an assessment of drug-drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The applicant did not evaluate human carcinogenicity as part of the evaluation of Taclonex® Topical Suspension in the pediatric population age 12 to 17 years. The trials were uncontrolled and the duration was insufficient to provide meaningful data.

Nonclinical data regarding carcinogenicity in rats and mice is included in Section 13.1 of labeling. Recommended labeling for the recently submitted data (Supplement 20) from the oral carcinogenicity study with calcipotriene in rats is as follows (Additions are noted as double underline and deletions are noted as ~~strikethrough~~).

> 13.1 Carcinogenesis, mutagenesis, impairment of fertility
> When calcipotriene was applied topically to mice for up to 24 months at dosages of 3, 10, and 30 mcg/kg/day (corresponding to 9, 30, and 90 mcg/m^2/day), no significant changes in tumor incidence were observed when compared to control.
>
> In a study in which albino hairless mice were exposed to both ultra-violet radiation (UVR) and topically applied calcipotriene, a reduction in the time required for UVR to induce the formation of skin tumors was observed (statistically significant in males only), suggesting that calcipotriene may enhance the effect of UVR to induce skin tumors.
>
> A 104-week oral carcinogenicity study was conducted with calcipotriene in male and female rats at doses of 1, 5 and 15 mcg/kg/day (corresponding to dosages of approximately 6, 30, and 90 mcg/m^2/day). Beginning week 71, the dosage for high-dose animals of both genders was reduced to 10 mcg/kg/day (corresponding to a dosage of approximately 60 mcg/m^2/day). A treatment-related increase in benign C-cell adenomas was observed in the thyroid of females that received 15 mcg/kg/day. A treatment-related increase in benign pheochromocytomas was observed in the adrenal glands of males that received 15 mcg/kg/day. No other

statistically significant differences in tumor incidence were observed when compared to control. The relevance of these findings to patients is unknown.

When betamethasone dipropionate was applied topically to CD-1 mice for up to 24 months at dosages approximating 1.3, 4.2, and 8.5 mcg/kg/day in females, and 1.3, 4.2, and 12.9 mcg/kg/day in males (corresponding to dosages of up to approximately 26 mcg/m^2/day and 39 mcg/m^2/day, in females and males, respectively), no significant changes in tumor incidence were observed when compared to control.

When betamethasone dipropionate was administered via oral gavage to male and female Sprague Dawley rats for up to 24 months at dosages of 20, 60, and 200 mcg/kg/day (corresponding to dosages of approximately (b) (4) 120, 360, and 1200 mcg/m^2/day), no significant changes in tumor incidence were observed when compared to control.

7.6.2 Human Reproduction and Pregnancy Data

There were no reports of pregnancies during the conduct of Trial MBL 0801 or Trial MBL 0412. Post marketing data includes one report of a 17- year- old pregnant patient who was exposed to Taclonex Topical Suspension. No adverse events were reported in association with the exposure but the outcome of the pregnancy is unknown.

The post marketing database included 3 cases of lactating pediatric patients who were exposed to Taclonex® Topical Suspension. There were no associated adverse events reported for either the mother or the infant.

The applicant conducted no studies in pregnant women as part of this clinical development program. Taclonex® Topical Suspension is a Pregnancy Category C in current labeling.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Pediatric Review Committee met on June 4, 2014 to discuss the data submitted by the applicant to fulfill the Postmarketing Requirement (PMR) under PREA attached to the original approval of Taclonex Topical Suspension (dated May 9, 2008). The Division presented recommendations to PeRC regarding the adequacy of the data submitted by the applicant to support the extension of the indication to include the treatment of scalp psoriasis in the pediatric population age 12 to 17 years. PeRC concurred with the Division that the assessment was adequate and that the findings in the pediatric population were similar to the findings in the adult population. The Division recommended that the PREA PMR for the topical treatment of scalp psoriasis in pediatric patients age 12 to 17 was fulfilled.

The following are the recommended additions to the revised labeling in section 8.4: (Additions are noted as double underline and deletions are noted as ~~strikethrough~~).

> Safety and effectiveness of the use of Taclonex® Topical Suspension in pediatric patients under the age of 12 years have not been (b) (4) established.
>
> The safety and effectiveness of Taclonex® Topical Suspension for the treatment of plaque psoriasis of the scalp have been established in the age group 12 to 17 years. Two prospective, uncontrolled, trials (N=109) were conducted in pediatric subjects (aged 12 to 17 years) with scalp psoriasis, including assessment of HPA axis suppression in 30 subjects.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose
The applicant stated that “no data are available regarding overdose in the adolescent population”. However, a total of 21 subjects in the safety population applied more than 60 grams/week for 2 or more weeks during the trials. (Per protocol, the maximal weekly exposure was 60 grams). Refer to Section 7.2.1.

Drug Abuse Potential
No reports of drug abuse are included in this submission. The applicant stated that “no data are available regarding drug abuse in the adolescent population”.

Withdrawal and Rebound
The applicant did not evaluate the potential for withdrawal or rebound in adolescents who use Taclonex® Topical Suspension. The applicant stated that “no data are available regarding withdrawal or rebound in the adolescent population”.

7.7 Additional Submissions / Safety Issues

The applicant submitted a 120-Day Safety Update in accordance with 21 CFR 314.50(d)(5)(vi)(b). This submission included all the safety data in the global safety database received by the applicant regarding the use of Taclonex® Topical Suspension in the pediatric population (age 0-17 years) from July 1, 2013 to February 28, 2014. Taclonex® Topical Suspension is currently approved for the topical treatment of plaque psoriasis of the scalp and body in patients 18 years and older. Thus, all cases of exposure to the product in the pediatric population represent off-label use. Nine patients reported 19 adverse events including 1 serious adverse event. The majority of cases (5/9) involved the pediatric population age 12-17 years.

The case categorized as serious involved a 15-year-old female subject who applied Taclonex® Topical Suspension on the scalp for an unknown indication. The subject developed a hematuria and a urinary tract infection which her physician attributed to sexual activity. The outcome was unknown. The physician assessed the adverse event as not related.

In 7 of 9 cases involving off-label use, there were no additional adverse events. The application site was the scalp in 4 of 9 cases, the body in 2 of 9 cases and unidentified in 3 of 9 cases. The adverse events are summarized in Table 35.

Table 35: Adverse Events from the Worldwide Safety Database

SOC	Adverse event (PT)	No. of events
General disorders and administration site conditions	Drug ineffective	1
	No adverse event	3
Infections and infestations	Urinary tract infection	1
Injury, poisoning and procedural complications	Drug administered at inappropriate site	1
	Inappropriate schedule of drug administration	1
Renal and urinary disorders	Haematuria	1
Skin and subcutaneous tissue disorders	Psoriasis	1
Surgical and medical procedures	Off label use	9
Vascular disorders	Haemorrhage	1
Total		**19**

Source: 120-Day Safety Update Report dated 3/14/2014 page 3

No new safety issues were identified in the submission. This data supports the conclusion that the safety profile is similar in the pediatric population age 12 to 17 years and the adult population.

8 Postmarket Experience

In this sNDA submission, the applicant included a summary of safety information in the pediatric population compiled from worldwide sources. There were no deaths and no serious adverse events.

The applicant received 58 spontaneous case reports representing 83 adverse events in pediatric patients treated with Taclonex® Topical Suspension between May 2008 (when marketing was initiated) and June 2013. All 58 case reports included non-serious adverse events. Of the cases reported; 24 concerned pediatric patients age 12-17 years, 27 concerned pediatric patients age 12 years and younger and 7 concerned pediatric patients of unspecified age. A total of 55 cases included the event of “off- label

use" and 3 case concerned exposures of female pediatric patients who were breast feeding (not considered off- label use.) In 34 of the cases, no adverse event other than off- label use was reported. Among the remaining 28 adverse events, local reactions were the most common. The site of the adverse event was on the scalp in 24 cases and on a non-scalp location in 8 cases. The remaining cases did not include the site of involvement. The six case reports involving pediatric patients in the United States were included in the periodic adverse event reports. Table 36 includes a summary of the adverse events reported in pediatric subjects world-wide.

Table 36: Adverse events reported post-marketing world-wide in the pediatric population

Adverse event (PT)	**No. of events**
Off label use	55
Medication residue (greasy hair)	4
Exposure during breast-feeding	3
Drug ineffective	3
Drug administered at inappropriate site	2
Inappropriate schedule of drug administration	2
Erythema	2
Eye irritation	1
Application site atrophy	1
Application site bruise	1
Application site irritation	1
Application site pain	1
Condition aggravated	1
Drug ineffective for unapproved indication	1
Headache	1
Drug dispensing error	1
Exposure during pregnancy	1
Alopecia	1
Skin hypopigmentation	1
Total	**83**

Source: NDA 22185, Module 5.3.6 Reports of Post-Marketing Experience, page 3

Most of these adverse events are addressed in current labeling for Taclonex® Topical Suspension. Although application site bruising is not included in labeling it is related to application site atrophy and telangiectasia. Reduction in the thickness of the epidermis

which results from chronic corticosteroid exposure increases the risk that minor injury will result in bruising.

The adverse event of alopecia is not included in current labeling. Alopecia was reported by one 12 year old female subject who was enrolled in Trial MBL 0412 (assessed as not related) and 1 pediatric subject in the world wide safety database. In addition, alopecia was reported by 15 subjects (6 in the study product arm and 9 in the calcipotriene comparator arm) in the original development program to support approval of Taclonex® Topical Suspension for the topical treatment of moderate to severe psoriasis vulgaris of the scalp in adults aged 18 years and above. Alopecia has multiple causes and may be observed in association with many inflammatory scalp diseases (e.g. psoriasis, eczema, tinea capitis, seborrheic dermatitis etc.). Thus, reports of alopecia among subjects with moderate to severe scalp psoriasis would be anticipated in the adult and pediatric population.

9 Appendices

9.1 Literature Review/References

Literature references are included as footnotes within the review document.

9.2 Labeling Recommendations

The applicant submitted labeling which was reviewed and modified to be consistent with current thinking regarding the content and format of labeling for corticosteroid products. The following sections of the revised draft labeling include significant changes:

1 INDICATIONS AND USAGE (See Section 6.1 of this review)
2 DOSAGE AND ADMINISTRATION (See Section 7.2.1 of this review)
5 WARNINGS AND PRECAUTIONS (See Section 7.4.5 of this review)
6 ADVERSE REACTIONS (See Section 7.4.1 of this review)
8 USE IN SPECIFIC POPULATIONS (See Section 7.6.3 of this review)
12 CLINICAL PHARMACOLOGY (See Section 4.4.2 of this review)
14 CLINICAL STUDIES (See Section 6.1.5 of this review)

9.3 Advisory Committee Meeting

The Agency conducted no Advisory Committee Meetings regarding this sNDA application.

9.4 Financial Disclosure

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 22185

Submission Date(s): 10/31/2013

Applicant: LEO Pharmaceuticals

Product: Taclonex® Topical Suspension

Reviewer: Melinda McCord

Date of Review: 7/3/2014

Covered Clinical Study: MBL0412, MBL0801

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: The sponsor provided data from 22 study sites and provided the names of the investigators.		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information

		from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The applicant completed FDA Form 3454 and certified that they have not entered into any financial arrangements with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). Attachment A provides a list of investigators who have completed the financial disclosure forms and certified that they have no financial interests/arrangements with the applicant. The applicant adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators.*

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/s/

MELINDA L MCCORD
07/07/2014

GORDANA DIGLISIC
07/07/2014