

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213422Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA 213422 Multidisciplinary Review and Evaluation
WYNZORA (calcipotriene/betamethasone dipropionate) Cream, 0.005%/0.064%

NDA/BLA Multidisciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	213422
Priority or Standard	Standard
Submit Date(s)	September 20, 2019
Received Date(s)	September 20, 2019
PDUFA Goal Date	July 20, 2020
Division/Office	Division of Dermatology and Dentistry
Review Completion Date	July 17, 2020
Established/Proper Name	calcipotriene and betamethasone dipropionate
(Proposed) Trade Name	WYNZORA
Pharmacologic Class	Vitamin D analog/Corticosteroid
Code Name	MC2-01
Applicant	MC2 Therapeutics Ltd (part of MC2 Therapeutics)
Dosage Form	Cream
Applicant proposed Dosing Regimen	Apply to affected areas once daily for up to 8 weeks. Therapy should be discontinued when control is achieved.
Applicant Proposed Indication(s)/Population(s)	For the topical treatment of plaque psoriasis in patients 18 years of age and older
Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication	For the topical treatment of plaque psoriasis
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the topical treatment of plaque psoriasis in patients 18 years of age and older.
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	
Recommended Dosing Regimen	Apply to affected areas once daily for up to 8 weeks. Rub in gently to ensure that the plaques are saturated with the cream. Discontinue therapy when control is achieved.

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DDD, Division of Dermatology and Dentistry; DB III, Division of Biometrics III; DPT-II, Division of Pharm/Tox for Immunology and Inflammation; DIIP, Division of Inflammation and Immune Pharmacology

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OPQ, Office of Pharmaceutical Quality
OPDP, Office of Prescription Drug Promotion
OSI, Office of Scientific Investigations
OSE, Office of Surveillance and Epidemiology
DEPI, Division of Epidemiology
DMEPA, Division of Medication Error Prevention and Analysis

Signatures

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Nonclinical Reviewer	Carmen Booker	OII/DPT-II	Sections: 5, 14.3	Select one: ☒ Authored ☐ Approved
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Clinical Reviewer	Kevin Clark	OII/DDD	Sections: 1, 2, 3, 4.1, 4.3, 4.4, 8.2, 8.3.2, 9, 10, 11, 12, 13, 14.2, 14.5	Select one: ☒ Authored ☐ Approved
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Clinical Team Leader	Gordana Diglisic	OII/DDD	Sections: 1, 2, 3, 4.1, 4.3, 4.4, 8.2, 8.3.2, 9, 10, 11, 12, 13, 14.2, 14.5	Select one: ☐ Authored ☒ Approved

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WYNZORA (calcipotriene/betamethasone dipropionate) Cream, 0.005%/0.064%

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
	Signature: <i>{See appended electronic signature page}</i>			
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Glossary

ACTH	adrenocorticotrophic hormone
AE	adverse event
AET	analytical evaluation threshold
AR	adverse reaction
AUC _{0-7h}	area under the concentration-time curve from 0 to 7 hr
AUC _{last}	area under the concentration-time curve from time zero to the time of the last measurable concentration
BA	bioavailability
B17P	betamethasone 17-propionate
BDP	betamethasone dipropionate
BLA	biologics license application
BSA	body surface area
CAL	calcipotriene
CCS	container closure system
CFR	Code of Federal Regulations
CI	confidence interval
C _{max}	maximum concentration
DHOT	Division of Hematology Oncology Toxicology
DMEPA	Division of Medication Error Prevention and Analysis
DMF	drug master file
ECG	electrocardiogram
FDA	U.S. Food and Drug Administration
HPA	hypothalamic–pituitary–adrenal
IL	interleukin
IND	Investigational New Drug
ITT	intent-to-treat
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LLOQ	lower limit of quantification
mPASI	modified Psoriasis Area and Severity Index
MUsT	maximal-usage trial
NDA	new drug application
NRS	numerical rating scale
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion (OPDP)
PASI	Psoriasis Area and Severity Index
pg/mL	picogram per milliliter
PGA	Physician's Global Assessment
PI	prescribing information
PK	pharmacokinetic
PP	per protocol
PPI	patient package insert (also known as Patient Information)

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PPT	psoriasis plaque test
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PTCS	Psoriasis Treatment Convenience Scale
SAE	serious adverse event
SAP	statistical analysis plan
SCT	safety concern threshold
SOC	system organ class
TEAE	treatment-emergent adverse event
TK	thymidine kinase
TQT	thorough QT/QTc
URI	upper respiratory infection
URTI	upper respiratory tract infection

1 Executive Summary

1.1. Product Introduction

The Applicant is seeking approval for WYNZORA (calcipotriene/betamethasone dipropionate) Cream, 0.005%/0.064% (hereafter referred to as CAL/BDP Cream) under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The listed drugs (LDs) are Taclonex (calcipotriene/betamethasone dipropionate) Topical Suspension, 0.005%/0.064% (New Drug Application (NDA) 22185), which is currently indicated for the topical treatment of plaque psoriasis of the scalp and body in patients 12 years and older, and Taclonex (calcipotriene/betamethasone dipropionate) Ointment, 0.005%/0.064% (NDA 21852), which is indicated for the topical treatment of plaque psoriasis in patients 12 years of age and older.

The Applicant established a clinical bridge between CAL/BDP Cream and Taclonex Ointment, and proposes to rely on the Agency's finding of safety for nonclinical toxicology (reproductive toxicity, carcinogenesis, mutagenesis, and impairment of fertility) for the LD. In addition, the Applicant established a clinical bridge between CAL/BDP Cream and Taclonex Topical Suspension by demonstrating noninferiority to the LD. The Applicant addressed the fixed-combination rule (21 CFR 300.50) by means of reliance on Taclonex Topical Suspension.

The active ingredients are calcipotriene (CAL), 0.005%, and betamethasone dipropionate (BDP), 0.064%, in a fixed-dose combination. CAL is a vitamin D analog and BDP is a corticosteroid. This fixed-dose combination is marketed in the United States in a variety of dosage forms, including ointment, topical suspension, and topical foam. The proposed indication is topical treatment of plaque psoriasis in patients 18 years of age and older. The proposed dosing regimen is application to affected areas once daily for up to 8 weeks.

The Agency concluded that the proposed proprietary name, WYNZORA, was acceptable from both a promotional and safety perspective under NDA 213422 (proprietary name review by Dr. Madhuri R. Patel, Division of Medication Error Prevention and Analysis dated June 18, 2020).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from an adequate and well-controlled Phase 3 trial (MC2-01-C2), which provided evidence of the effectiveness of CAL/BDP Cream for the topical treatment of plaque psoriasis in the target population. The trial assessed the primary endpoint of "treatment success" at Week 8. Treatment success was defined as a Physician's Global Assessment (PGA) score of 0 ("clear") or 1 ("almost clear") and a minimum two-point decrease from Baseline (i.e., PGA score of 0 or 1 if moderate disease at Baseline or PGA score of 0 if mild disease at Baseline).

CAL/BDP Cream was superior to vehicle cream ($p < 0.001$) and noninferior to Taclonex Topical Suspension, 0.005%/0.064% (difference [95% confidence interval (CI)]: 14.6% [7.6%, 21.6%]) for the primary endpoint of treatment success at Week 8. The Applicant has demonstrated that

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CAL/BDP Cream is effective for its intended use in the target population and has met the evidentiary standard required by 21 CFR 314.126(a)(b) to support approval.

APPEARS THIS WAY ON ORIGINAL

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The Applicant, MC2 Therapeutics, Ltd. submitted NDA 213422 for WYNZORA (calcipotriene/betamethasone dipropionate) Cream, 0.005%/0.064% (hereafter referred to as CAL/BDP Cream). The proposed indication is topical treatment of plaque psoriasis in patients 18 years of age and older. CAL/BDP Cream is a cream formulation of CAL, a vitamin D analog, and BDP, a corticosteroid. The listed drugs (LDs) are Taclonex (calcipotriene/betamethasone dipropionate) Topical Suspension, 0.005%/0.064% (NDA 22185), which is currently indicated for the topical treatment of plaque psoriasis of the scalp and body in patients 12 years and older, and Taclonex (calcipotriene/betamethasone dipropionate) Ointment, 0.005%/0.064% (NDA 21852), which is indicated for the topical treatment of plaque psoriasis in patients 12 years of age and older.

The Applicant established a clinical bridge between CAL/BDP Cream and Taclonex Ointment and proposes to rely on the Agency's finding of safety for nonclinical toxicology (reproductive toxicity, carcinogenesis, mutagenesis, and impairment of fertility) for the LD. In addition, the Applicant established a clinical bridge between CAL/BDP Cream and Taclonex Topical Suspension by demonstrating noninferiority to the LD. The Applicant addressed the fixed-combination rule (21 CFR 300.50) through reliance on Taclonex Topical Suspension.

In a Phase 3 randomized, multicenter, investigator-blinded, vehicle and active-comparator controlled, parallel-group trial conducted in 794 subjects ≥ 18 years of age with mild to moderate psoriasis on the body, CAL/BDP Cream was superior to vehicle ($p < 0.001$) and noninferior to CAL/BDP topical suspension, 0.005%/0.064% (difference [95% confidence interval]: 14.6% [7.6%, 21.6%]) for the primary endpoint of "treatment success" at Week 8. Treatment success was defined as a Physician's Global Assessment (PGA) score of 0 ("clear") or 1 ("almost clear") with at least a two-grade reduction from baseline.

The safety profile for CAL/BDP Cream was adequately characterized during the drug development program. Two deaths occurred during the development program; neither was related to treatment with CAL/BDP Cream. Serious adverse events (SAEs) occurred in 2.3% of subjects treated with CAL/BDP Cream, 2.7% of subjects treated with Taclonex Topical Suspension, and 3.5% of subjects treated with vehicle cream. Investigators considered none of the SAEs to be related to treatment with any of the study products. The most common adverse reactions (ARs) were upper respiratory infection (URI), headache, and application site irritation. URI was reported in 6.7% of subjects treated with CAL/BDP Cream, 5.3% of subjects treated with Taclonex Topical Suspension, and 5.2% of subjects treated with vehicle; headache was reported by 1.5% of subjects treated with CAL/BDP Cream, 1.2% of subjects treated with Taclonex Topical Suspension, and 0% of subjects treated with vehicle; application site irritation was reported in 0.9% of subjects treated with CAL/BDP Cream, 0% of subjects treated with Taclonex Topical Suspension, and 0% of subjects treated with vehicle. Active assessments of local tolerability in the Phase 3 trial revealed the following results at Week 8 in subjects treated with CAL/BDP Cream (all levels of severity combined): erythema (19.8%), scaling (19.2%), burning or pain (5.1%), edema (4.2%), atrophy (3.2%), erosion/ulceration (1.9%),

and vesicles (0.6%). Local tolerability findings occurred at a similar or greater frequency in the vehicle group. Most of the local tolerability findings were mild or moderate in severity.

The Applicant also evaluated the potential of CAL/BDP Cream to cause hypothalamic–pituitary–adrenal (HPA) axis suppression and the effect of CAL/BDP Cream on calcium metabolism. Following once daily application of CAL/BDP Cream in a Phase 2 trial conducted under conditions of maximal use, 23% and 12% of subjects showed HPA axis suppression at Week 4 and Week 8, respectively. This will be included in Section 5.2 (Warnings and Precautions) of the product labeling. Once daily application of CAL/BDP Cream did not appear to cause significant changes in calcium metabolism based on the results from the Phase 2 and 3 trials. However, the risk of hypercalcemia and hypercalciuria will be conveyed in Section 5.1 (Warnings and Precautions) of the product labeling.

In summary, psoriasis is a chronic disease that may be associated with substantial impairment of quality of life. CAL/BDP Cream provides a new dosage form of a well-known fixed combination for the topical treatment of psoriasis. The available evidence of safety and efficacy supports the approval of WYNZORA (calcipotriene/betamethasone dipropionate) Cream, 0.005%/0.064% for the topical treatment of plaque psoriasis in patients 18 years of age and older. In view of a favorable overall benefit/risk assessment, the review team recommends approval of this product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Psoriasis is a common, chronic, inflammatory multisystem disorder that primarily affects the skin and joints and is associated with substantial impairment of quality of life. The prevalence of psoriasis in the United States is approximately 2 to 3%, and an estimated 20% of patients with psoriasis have moderate-to-severe disease.	Plaque psoriasis can be a serious disease because of its chronicity and impact on quality of life.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	Mild disease is commonly treated with topical corticosteroids or synthetic vitamin D products, but systemic treatments may be needed for more widespread disease. Systemic agents include adalimumab, etanercept, infliximab (tumor necrosis factor antagonists), secukinumab, ixekizumab (interleukin [IL]-17 antagonists), brodalumab (an IL-17 receptor antagonist), and ustekinumab (an IL-12/-23 antagonist), and the IL-23p19 antagonists guselkumab, tildrakizumab, and risankizumab. Other approved systemic psoriasis therapies include acitretin, methotrexate, cyclosporine, and apremilast. Phototherapy, either ultraviolet (UV) A light combined with psoralen methoxsalen or UV-B light therapy (narrow or broadband) may also be an appropriate first-line or adjunctive treatment for patients with moderate-to-severe psoriasis. U.S. Food and Drug Administration (FDA) approved topical drugs for the treatment of psoriasis include synthetic vitamin D3 derivatives, retinoids, corticosteroids, and fixed combinations of these moieties. Topical products come in a variety of formulations. The currently marketed dosage forms of the fixed combination of calcipotriene/betamethasone are ointment, topical suspension, and topical foam.	There are a number of FDA-approved products with an acceptable risk-benefit profile for the topical treatment of plaque psoriasis in adults. None of these treatments provides a permanent cure. For topical drug products, patients have preferences for various vehicles or dosage forms. The currently available dosage forms of the fixed combination of calcipotriene (CAL) and betamethasone dipropionate (BDP) include ointment, topical suspension, and topical foam. Approval of this application would add to the treatment armamentarium for plaque psoriasis by providing a new dosage form of the fixed combination of combination of CAL and BDP.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Data from an adequate and well-controlled trial provide substantial evidence of the effectiveness of CAL/BDP Cream for the topical treatment of plaque psoriasis. The trial was conducted in 794 subjects ≥18 years of age with mild-to-moderate psoriasis on the body, CAL/BDP Cream was superior to vehicle cream ($p < 0.001$) and noninferior to calcipotriene/betamethasone dipropionate topical suspension, 0.005%/0.064% (difference [95% confidence interval]: 14.6% [7.6%, 21.6%]) for the primary endpoint of “treatment success” at Week 8. Treatment success was defined as a PGA score of 0 (“clear”) or 1 (“almost clear”) with at least a 2-grade reduction from Baseline. Review of the safety data from the clinical trials identified no new safety signal with CAL/BDP Cream, which was well tolerated in all evaluated subgroups.	CAL/BDP Cream provides an effective and safe treatment option for the topical treatment of plaque psoriasis in patients 18 years of age and older.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	The primary safety database (Phase 3 trial MC2-01-C2) included 342 subjects who were treated with CAL/BDP Cream. Two deaths occurred during the development program; neither was related to treatment with CAL/BDP Cream. There were no SAEs related to treatment with CAL/BDP Cream. The most common ARs were URI, headache, and application site irritation. URI was reported in 6.7% of subjects treated with CAL/BDP Cream, 5.3% of subjects treated with Taclonex Topical Suspension, and 5.2% of subjects treated with vehicle cream; headache was reported by 1.5% of subjects treated with CAL/BDP Cream, 1.2% of subjects treated with Taclonex Topical Suspension, and 0% of subjects treated with vehicle cream; application site irritation was reported in 0.9% of subjects treated with CAL/BDP Cream, 0% of subjects treated with Taclonex Topical Suspension, and 0% of subjects treated with vehicle cream. Active assessments of local tolerability in the Phase 3 trial revealed the following results at Week 8 in subjects treated with CAL/BDP Cream (all levels of severity combined): erythema (19.8%), scaling (19.2%), burning or pain (5.1%), edema (4.2%), atrophy (3.2%), erosion/ulceration (1.9%), and vesicles (0.6%). Local tolerability findings occurred at a similar or greater frequency in the vehicle group. Most of the local tolerability findings were mild or moderate in severity. Following once daily application of CAL/BDP Cream in a Phase 2 maximal-usage trial (MUSt), 23% and 12% of subjects showed HPA axis suppression at Week 4 and Week 8, respectively. Once daily application of CAL/BDP Cream did not appear to cause significant changes in calcium metabolism based on the results from the Phases 2 and 3 trials. Labeling: Prescription labeling adequately addresses the known risks associated with the moiety and those identified during product development. No issues require further assessment with a postmarketing requirement or postmarketing commitment. A risk evaluation and mitigation strategy is not recommended.	The risks associated with use of CAL/BDP Cream appear favorable. Local reactions that occurred were mostly mild or moderate in severity. Prescription labeling, patient labeling, and routine pharmacovigilance are adequate to manage the risks of the product.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable
X	Clinical outcome assessment (COA) data, such as	
X	Patient-reported outcome (PRO)	8.1.1, 8.1.5, 8.2.6
☐	Observer-reported outcome (ObsRO)	
X	Clinician-reported outcome (ClinRO)	8.1.1, 8.1.4, 8.1.5
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify):	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
X	Patient-focused drug development or other stakeholder meeting summary reports	2.1
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify):	
☐	Patient experience data were not submitted as part of this application.	

2 Therapeutic Context

2.1. Analysis of Condition

Psoriasis is a common, chronic, immune-mediated skin disorder. The characteristic lesion is a sharply demarcated erythematous plaque with micaceous scale, and the plaques may be localized or widespread in distribution (Feldman 2015). Psoriasis is a complex autoimmune inflammatory disease that occurs in genetically susceptible individuals. The pathophysiology of psoriasis involves the activation of innate immune cells in the skin, which produce proinflammatory cytokines that trigger and perpetuate the inflammatory cascade (Blauvelt and Ehst 2015).

In the United States and Canada, prevalences as high as 4.6% and 4.7% have been reported, respectively (Blauvelt and Ehst 2015). It is estimated that approximately 7.5 million people in the United States have psoriasis. Approximately 80% of those affected by psoriasis have mild-to-moderate disease, and 20% have moderate-to-severe psoriasis affecting more than 5% of the body surface area (BSA). The most common form of psoriasis is plaque psoriasis, affecting about 80% to 90% of patients with psoriasis (Menter et al. 2008).

Psoriasis can first appear at any age, from infancy to the eighth decade of life. Two peaks in age of onset have been reported: one at 20 to 30 years of age and a second peak at 50 to 60 years. In approximately 75% of patients, the onset is before the age of 40 years, and in 35% to 50%, it is before the age of 20 years. The age of onset is earlier in women than in men (Blauvelt and Ehst 2015).

The natural history of psoriasis is chronic with intermittent remissions. Plaque psoriasis is the most common presentation; other forms include guttate, pustular, erythrodermic, and inverse psoriasis. Psoriasis may affect fingernails and toenails, most frequently in association with psoriatic arthritis. A diagnosis of psoriasis can be made by history taking and physical examination in the vast majority of cases. The differential diagnosis of psoriasis may include seborrheic dermatitis, lichen simplex chronicus, atopic dermatitis, and nummular eczema. Occasionally, a skin biopsy is performed to rule out other conditions (Blauvelt and Ehst 2015).

The presentation of psoriasis in the pediatric population can be different from that in adults. Psoriasis in infants often presents with involvement of the diaper area. Infants with diaper-area involvement typically develop symmetrical, well-demarcated erythematous patches with little scale. Maceration may be present. Unlike irritant diaper dermatitis, the inguinal folds are usually involved. Affected infants may also have psoriatic plaques in other body areas. These plaques are often smaller and thinner than the psoriatic plaques in adult patients. In children, scalp involvement is a common and often initial presentation of chronic plaque psoriasis. In addition, children with chronic plaque psoriasis are more likely to have facial involvement than are adults (Blauvelt and Ehst 2015).

A number of comorbid systemic conditions occur more frequently in patients with psoriasis. Examples of these conditions include cardiovascular disease, malignancy, diabetes, hypertension, metabolic syndrome, inflammatory bowel disease, serious infections, and autoimmune disorders. Psychiatric comorbidities associated with psoriasis include depression and suicidal ideation; neurotic, stress-related, or somatoform disorders; and personality and behavioral disorders (Korman 2017).

The impact of psoriasis on the daily lives of patients was among the topics discussed at a Patient-Focused Drug Development Meeting for psoriasis held by the Agency on March 17, 2016. Patients who attended the meeting described severe physical, social, and emotional effects, including depression, anxiety, limitations on activities, embarrassment, stigma, and social discrimination. Patients shared their experiences with currently available therapies, and they described varying degrees of success in managing symptoms with these therapies.

Patients stressed the need to enhance the treatment armamentarium, given current challenges with variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding the long-term effects of available treatments.

Psoriasis is a chronic, debilitating disease with significant impacts on the lives of affected patients. At the Patient-Focused Drug Development meeting, patients discussed current challenges with variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding long-term effects of available treatments. Therefore, development of additional safe and effective therapies continues to be an important goal. This is especially true for certain subgroups of patients with psoriasis, such as children and pregnant women.

2.2. Analysis of Current Treatment Options

The proposed indication is the topical treatment of plaque psoriasis in patients eighteen (18) years of age and older. Several examples of products available for the topical treatment of plaque psoriasis are listed in Table 1.

Table 1. Summary of Treatments Relevant to Proposed Indication of Plaque Psoriasis

Product Class	Example Product/Year Approved	Relevant Indication¹	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues
Corticosteroid	Olux E (clobetasol propionate) Foam/2007.	CSRD (one trial in mild-to-moderate plaque-type psoriasis).	Apply thin layer twice daily; treatment should be limited to 2 consecutive weeks and patients should not use more than 50 g per week.	In a randomized study of subjects 12 years of age and older with mild to moderate plaque psoriasis, 253 subjects were treated with Olux-E Foam and 123 subjects were treated with vehicle foam. 41 of 253 subjects (16%) treated with Olux-E Foam compared to 5 of 123 (4%) treated with vehicle foam achieved treatment success. Treatment success was defined by an Investigator's Static Global Assessment score of clear (0) or almost clear (1) with at least a 2-grade improvement from baseline, scores of none or faint/minimal (0 or 1) for erythema and scaling, and a score of none (0) for plaque thickness.	Use in pediatric patients under 12 years of age is not recommended because of a numerically high rate of HPA axis suppression.
Synthetic Vitamin D3 Derivative	Dovonex (calcipotriene) Cream/1996	Plaque psoriasis	Apply thin layer twice daily.	Adequate and well-controlled trials have demonstrated improvement usually beginning after 2 weeks of therapy. This improvement continued with approximately 50% of patients showing at least marked improvement in the signs and symptoms of psoriasis after 8 weeks of therapy, but only approximately 4% showed complete clearance.	Reversible elevation of serum calcium has occurred.

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Product Class	Example Product/Year Approved	Relevant Indication ¹	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues
Synthetic Vitamin D3 Derivative/Corticosteroid Combination Product	Taclonex (calcipotriene and betamethasone dipropionate) Ointment P2006.	Plaque psoriasis in patients 12 years of age and older.	Use once daily for up to 4 weeks.	1603 subjects with mild to very severe plaque psoriasis on the trunk and limbs were treated once daily for 4 weeks. Subjects were randomized to one of four treatment arms: Taclonex Ointment, calcipotriene hydrate 50 µg/g in the same vehicle, betamethasone dipropionate 0.64 mg/g in the same vehicle, and vehicle alone. Treatment effect was 48%, 16.5%, 23.3% and 7.6%, respectively. Efficacy was assessed as the proportion of subjects with absent or very mild disease according to the Investigator's Global Assessment of Disease Severity at end of treatment (4 weeks).	Hypercalcemia and hypercalciuria and HPA axis suppression have been observed. Patients aged 12 to 17 years should not use more than 60 g per week. Treatment of more than 30% of body surface area is not recommended.
Retinoid	Tazorac (tazarotene) Cream, 0.05%, 0.1%/2000	Plaque psoriasis	Apply thin film once daily.	Improvements in plaque elevation, scaling, and erythema were generally significantly greater with tazarotene 0.05% and 0.1% than with vehicle. The number of patients with none, minimal, or mild overall disease was significantly greater with tazarotene 0.05% and 0.1% vs. vehicle.	Retinoids may cause fetal harm when administered to a pregnant woman.

Sources: Table 2 from the Unireview for NDA 210566; Reviewer's table by Dr. Amy Weitach

¹ Some corticosteroids are indicated for the "treatment (or relief) of inflammatory and pruritic manifestations of moderate-to-severe corticosteroid-responsive dermatoses (CSRSD)," which is inclusive of the psoriasis indication.

Abbreviations: CSRSD, corticosteroid-responsive dermatoses; HPA, hypothalamic–pituitary–adrenal

Patients with more widespread, chronic, or advanced disease may require systemic treatments. Examples of approved systemic therapies for the treatment of moderate-to-severe plaque psoriasis are presented in Table 2.

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Table 2. Summary of Treatment Armamentarium for Moderate-to-Severe Plaque Psoriasis

FDA-Approved Treatment	Product(s) Name/Year Approved	Relevant Indication	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Antimetabolite/ Immuno-suppressant	Methotrexate 1972	Severe, recalcitrant, disabling, psoriasis not adequately responsive to other forms of therapy; but only when diagnosis established by biopsy and/or dermatologic consultation. Must rule out undiagnosed concomitant disease affecting immune responses	Starting dose schedules: 1. Weekly single oral, IM or IV dose: 10 to 25 mg per week until adequate response is achieved 2. Divided oral dose: 2.5 mg at 12 hr intervals for three doses 30 mg/week should not ordinarily be exceeded	No efficacy information for psoriasis in label	BW: potentially fatal toxic reactions including bone marrow suppression, aplastic anemia, and gastrointestinal toxicity with concomitant NSAID tx; hepatotoxicity, pulmonary toxicity, kidney toxicity, opportunistic infections, malignant lymphoma, tumor lysis syndrome, severe skin toxicity, fetal death and anomalies "should not be used in pregnant women with psoriasis"	Major AE derm dosing: ↑Liver enzymes stomatitis, diarrhea, nausea and vomiting, lymphoproliferative disorders Recommend periodic liver biopsy if tx long-term Pregnancy: X
Tumor Necrosis Factor Inhibitor	Infliximab (Remicade) 2006	Chronic severe (extensive or disabling) plaque psoriasis, candidates for phototherapy or systemic therapy and when other systemic therapies are medically less appropriate	5 mg/kg IV at 0, 2 and 6 weeks, then every 8 weeks	From label: 3 R, DB, PC trials PASI 75 at week 10 1. Infix (5 mg/kg)-80% vs. 3% placebo 2. Infix (5 mg/kg)-75% vs. 2% placebo 3. Infix (5 mg/kg)-88% vs. Infix (3 mg/kg) 72% vs. 6% placebo	BW: risk of serious infection (bacterial sepsis, TB, invasive fungal and opportunistic), malignancies including hepatosplenic T-cell lymphomas (adolescents and young adults) Warnings: Hepatitis B reactivation, heart failure, hepatotoxicity, cytopenias, hypersensitivity events, malignancy	Pregnancy: B

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FDA-Approved Treatment	Product(s) Name/Year Approved	Relevant Indication	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Tumor Necrosis Factor Inhibitor	Adalimumab (Humira) 2008	Moderate to severe chronic plaque psoriasis, candidates for phototherapy or systemic therapy	80 mg via SC initial dose, followed by 40 mg SC every other week starting 1 week after initial dose	From label: 2 R, DB, PC trials PASI 75 at Week 16 1. Ada-71% vs. 7% placebo 2. Ada-78% vs. 19% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), malignancy including hepatosplenic T-cell lymphoma Warnings: hypersensitivity reactions, hepatitis B reactivation, demyelinating disease, cytopenias, heart failure, Lupus-like syndrome	Pregnancy: B
Tumor Necrosis Factor Inhibitor	Etanercept (Enbrel) 2004; 2016	Chronic moderate to severe psoriasis, candidates for phototherapy or systemic therapy; 11/2016–approved for patients 4 years of age and older	50 mg SC twice weekly for 3 months, followed by 50 mg once weekly; <63 kg (138 lb)-0.8 mg/kg SC weekly.	From label: 2 R, DB, PC trials PASI 75 at 3 months 1. Etan-47% vs. 4% placebo 2. Etan-46% vs. 3% placebo	BW: risk of serious infection (bacterial sepsis, TB, invasive fungal and opportunistic), lymphomas, other malignancies Warnings: demyelinating disease, worsen CHF, pancytopenia, malignancy, hepatitis B reactivation	Pregnancy: B
IL-12 and IL-23 Blocker	Ustekinumab (Stelara) 2009	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy	Patients weighing <100 kg: 45 mg SC initially and 4 weeks later, followed by 45 mg SC every 12 weeks; patients weighing >100 kg: 90 mg SC initially and 4 weeks later, followed by 90 mg SC every 12 weeks	From label: 2 R, DB, PC trials PASI 75 at Week 12 1. Uste (90 mg)-66% vs. uste (45 mg)-67% vs. 3% placebo 2. Uste (90 mg)-76% vs. uste (45 mg)-67% vs. 4% placebo	W&Ps: infections (serious bacterial, fungal and viral), theoretical risk for serious infections, malignancy, reversible posterior leukoencephalopathy syndrome, pretreatment eval for TB	Pregnancy: B

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FDA-Approved Treatment	Product(s) Name/Year Approved	Relevant Indication	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
IL-17A Blocker	Secukinumab (Cosentyx) 2015	Moderate-to-severe psoriasis, candidates for phototherapy or systemic therapy	300 mg SC at weeks 0, 1, 2, 3 and 4 followed by 300 mg SC every 4 weeks. For some patients, a dose of 150 mg may be acceptable	From label: 4 R, DB, PC trials PASI 75 at Week 12 1. Sec (300 mg)-82% vs. sec (150 mg)-71% vs. 4% placebo 2. Sec (300 mg)-76% vs. sec (150 mg)-67% vs. 5% placebo 3. Sec (300 mg)-75% vs. sec (150 mg)-69% vs. 0% placebo 4. Sec (300 mg)-87% vs. sec (150 mg)-70% vs. 3% placebo	W&Ps: infections (serious bacterial, fungal and viral), theoretical risk for serious infections, Crohn's disease, hypersensitivity reactions, pretreatment eval for TB	Pregnancy: B
IL-17A Blocker	Ixekizumab (Taltz) 2016	Moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy	160 mg (two 80 mg injections) SC at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks	From label: 3 R, DB, PC trials PASI75 at Week 12 1. Ixe (80 mg q2wk) 89% vs. 4% placebo 2. Ixe (80 mg q2wk) 90% vs. 2% placebo 3. Ixe (160 mg × 1, then 80 mg q2wk) 87% vs. 7% placebo	W&Ps: infections (upper respiratory tract, oral candidiasis, conjunctivitis and tinea infections; inflammatory bowel disease (Crohn's disease and ulcerative colitis); hypersensitivity reactions; pretreatment eval for TB	
IL-17 Receptor A Antagonist	Brodalumab (Siliq) 2017	Moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and who have failed to respond or have lost response to other systemic therapies	210 mg by SC injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks	From label: 3 R, DB, PC trials PASI 75 and sPGA of 0 (clear) or 1 (almost clear) at Week 12 1. Bro (210 mg q2wk) PASI 75 83% vs. 3% placebo; sPGA 0 or 1 bro 76% vs. 1% placebo 2. Bro (210 mg q2wk) PASI 75 86% vs. 8% placebo; sPGA 0 or 1 bro 79% vs. 4% placebo; PASI 100 bro 44% vs. uste 22% 3. Bro (210 mg q2wk) PASI 75 85% vs. 6% placebo; sPGA 0 or 1 bro 80% vs. 4% placebo; PASI 100 bro 37% vs. uste 19%	BW for suicidal ideation and behavior W&Ps: Suicidal ideation and behavior; infections (serious infections and fungal infections); Crohn's disease; pretreatment eval for TB; avoid live vaccines	REMS requires prescribers and pharmacies to be certified; patients must sign a patient-prescriber agreement form

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FDA-Approved Treatment	Product(s) Name/Year Approved	Relevant Indication	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
IL-23 Blocker	Guselkumab (Tremfya) 2017	Moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy	100 mg by SC injection at week 0, week 4, and every 8 weeks thereafter	From label: 3 R, DB, PC, AC trials; 1 & 2: PASI 90 and sPGA of 0 ("cleared") or 1 ("minimal") at Week 16 1. Gus (100 mg weeks 0 & 4 then q8wk) PASI 90 73% vs. 3% placebo; IGA 0 or 1 85% vs. 7% placebo 2. Gus (100 mg Weeks 0 & 4 then q8wk) PASI 90 70% vs. 2% placebo; IGA 0 or 1 84% vs. 8% placebo 3. Subjects began tx with uste; at wk16 subjects with IGA ≥2 R to gus or continued uste; endpoint at Week 28 IGA 0 or 1 with ≥2 grade improvement; gus 31% vs. 14% uste	W&Ps: infections (upper respiratory tract infections, gastroenteritis, tinea infections, and herpes simplex infections); pretreatment eval for TB; avoid live vaccines	

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FDA-Approved Treatment	Product(s) Name/Year Approved	Relevant Indication	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
T-Cell Inhibitor/ Immuno-suppressant	Cyclosporine 1997	Adult, nonimmuno-compromised patients with severe recalcitrant disabling psoriasis who have failed at least one systemic therapy	Starting dose: 2.5 mg/kg/day, taken twice daily, dosage ↑ by 0.5 mg/kg/day at 2-week intervals, to a maximum of 4.0 mg/kg/day	From label: PASI 75 - 51% at 8 weeks, 79% at 16 weeks	BW: Should only be used by MDs experienced in management of systemic immunosuppressive Rx, ↑ susceptibility to infections and development of neoplasia including lymphoma, also hypertension, nephrotoxicity which ↑ with ↑ doses. In psoriasis patients with history of PUVA, UV-B, coal tar or radiation Rx-↑ risk of skin malignancies Warnings: Hepatotoxicity, hyperkalemia, thrombotic microangiopathy, progressive multifocal leukoencephalopathy, malignancies, serious infection, neurotoxicity	Pregnancy category: C

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FDA-Approved Treatment	Product(s) Name/Year Approved	Relevant Indication	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Retinoid	Acitretin (Soriatane) 1996	Severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments	Starting dose: 25 to 50 mg orally (PO) per day, maintenance doses of 25 to 50 mg per day may be given dependent upon an individual patient's response to initial Rx	From label: 2 DB, PC trials- Mean change in PGA at 8 weeks A. Acitretin (50 mg)-2 vs. -0.29 on placebo B. Acitretin (50 mg)-1.57 vs. Acitretin (25 mg)-1.06 vs. -0.06 on placebo (no multiplicity adjustment for trial B)	BW: pregnancy must be prevented during Rx and for 3 years following because of teratogenicity, no ethanol ingestion by FOCBP because of metabolism to etretinate and ↑ 1/2life, REMS (Do Your P.A.R.T.) participation required for FOCBP-see Drugs @FDA for details. Patients cannot donate blood for 3 years post-Rx; see label for data on pregnancies in partners of male patients on acitretin	W&P: hepatotoxicity, skeletal abnormalities, lipids ↑, cardiovascular risk ↑, ophthalmologic effects, pancreatitis, capillary leak syndrome, pseudotumor cerebri, exfoliative dermatitis, depression Pregnancy category: X
Phosphodiesterase 4 (PDE4) Inhibitor	Apremilast (Otezla) 2014	Moderate-to-severe psoriasis, candidates for phototherapy or systemic therapy	To reduce risk of gastrointestinal symptoms, titrate to recommended dose of 30 mg per oral twice daily	From label: 2 R, DB, PC trials PASI 75 at 16 weeks 1. Aprem 33% vs. 5% in placebo 2. Aprem 28.8% vs. 5.8% in placebo	W&Ps: depression, weight decrease, drug interactions with strong P450 enzyme inducers (rifampin, phenobarbital, carbamazepine phenytoin)	Diarrhea, nausea, URI, headache Pregnancy category: C

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FDA-Approved Treatment	Product(s) Name/Year Approved	Relevant Indication	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Phototherapy	PUVA-8-MOP (methoxsalen) + UV-A therapy	Severe, recalcitrant, disabling psoriasis not responsive to other forms of therapy	20-70 mg per oral (based on weight) taken 2-4 hr before exposure to UV-A light	No efficacy information for psoriasis in the label	BW: should only be used by MDs who have special competence in psoriasis management. Warnings: serious skin burning, ocular damage, aging of the skin, skin cancer (including melanoma)	Nausea, erythema, pruritus, must avoid all exposure to sunlight (even through windows) of eyes and skin for 24 hr after ingestion Pregnancy category: C

Source: Reviewer's table from the Unireview of BLA 761067

Abbreviations: AC, active comparator; ada, adalimumab; aprem, apremilast; bro, brodalumab; BW, boxed warning; DB, double-blind; etan, etanercept; gus, guselkumab; inflix, infliximab; Ixe, ixekizumab; NSAID, nonsteroidal anti-inflammatory drug; PASI, Psoriasis Area Severity Index; PC, placebo-controlled; R, randomized; sec, secukinumab; uste, ustekinumab; W&Ps, warnings and precautions; FDA, U.S. Food and Drug Administration; sPGA, static Physician's Global Assessment; REMS, risk evaluation and mitigation strategy; IM, intramuscular; IV, intravenous; MD, Doctor of Medicine; AE, adverse event; UV, ultraviolet; CHF, congestive heart failure; SC, subcutaneous injection; FOCBP, females of childbearing potential; IGA, Investigator's Global Assessment; IL, interleukin; TB, tuberculosis; URI, upper respiratory infection; tx, treatment; q8wk, every 8 weeks

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

CAL is a vitamin D analog and BDP is a corticosteroid. The fixed-combination of CAL/BDP 0.005%/0.064% was first approved on January 9, 2006, in an ointment dosage form and is currently approved for the topical treatment of plaque psoriasis in patients 12 years of age and older (Taclonex Ointment, NDA 21852). A topical suspension dosage form was approved on May 9, 2008, and is currently approved for the topical treatment of plaque psoriasis of the scalp and body in patients 12 years of age and older (Taclonex Topical Suspension, NDA 22185). In addition, a topical foam was approved on October 16, 2015, and is currently approved for the topical treatment of plaque psoriasis in patients 12 years of age and older (Enstilar Topical Foam, NDA 207589). CAL/BDP Cream represents a new dosage form of this fixed-combination product and is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed CAL/BDP Cream under investigational new drug (IND) application 127152 using the 505(b)(2) regulatory pathway. The Applicant selected Taclonex (calcipotriene/betamethasone dipropionate) Ointment, 0.005%/0.064% (NDA 21852) and Taclonex (calcipotriene/betamethasone dipropionate) Topical Suspension, 0.005%/0.064% (NDA 22185) as the LDs and proposed to rely on the Agency's previous findings of safety/effectiveness for the LDs. Specifically, the Applicant selected Taclonex Ointment as the comparator for the maximal-use pharmacokinetic (PK) trial MC2-01-C3 in order to establish a clinical bridge to the nonclinical safety (reproductive toxicity, carcinogenesis, mutagenesis, and impairment of fertility) of Taclonex Ointment. The Applicant also established a clinical bridge to the LD by demonstrating noninferiority to Taclonex Topical Suspension in a Phase 3 trial (MC2-01-C2). The Applicant addressed the fixed-combination rule (21 CFR 300.50) through reliance on Taclonex Topical Suspension.

The Applicant interacted with the Agency during the following meetings: pre-IND (October 7, 2015), a post-Special Protocol Assessment (SPA) nonagreement meeting (August 17, 2016), a guidance meeting with written responses sent on December 19, 2017, and a pre-NDA meeting on February 27, 2019. Key points from these meetings are discussed below.

The Agency held a pre-IND meeting with the Applicant on October 7, 2015. The purpose of the meeting was to discuss the development program for CAL/BDP Cream. The Agency provided advice regarding the information the Applicant would need to provide to establish a clinical bridge to rely on the Agency's previous findings of nonclinical and clinical systemic safety as well as effectiveness for the LDs. In addition, the Agency advised the Applicant to conduct a PK trial under conditions of maximal use to evaluate the systemic exposure of CAL/BDP Cream, the potential of CAL/BDP Cream to cause hypothalamic–pituitary–adrenal (HPA) axis suppression,

and its effect on calcium metabolism. The Applicant was also advised to conduct an evaluation of systemic exposure and HPA axis suppression under maximal-usage trial (MUsT) conditions in the pediatric population, and to conduct this trial prior to performing Phase 3 trials to identify the appropriate target population for further development. The Agency also provided advice regarding the evaluation of local and systemic safety, dermal safety studies, evaluation of the pro-arrhythmic potential of the product, the potential for drug interactions, and the need to conduct a vasoconstrictor assay.

On March 22, 2016, the Applicant submitted a request for special protocol assessment (SPA) for clinical protocol MC2-01-C2 entitled "A Randomized, Multicenter, Investigator-Blind, Parallel-Group Trial to Evaluate the Efficacy and Safety of MC2-01 Cream Compared to MC2-01 Vehicle Cream and Calcipotriene/Betamethasone Dipropionate Gel in Subjects with Mild-to-Moderate Psoriasis Vulgaris." On May 5, 2016, the Agency sent an SPA Nonagreement Letter. The nonagreements included the proposed noninferiority margin, the proposed evaluation of local and systemic safety, and the proposed active comparator. The Agency agreed that the general design of the protocol, the proposed study population, the proposed dosing regimen, and the proposed definition of the intent-to-treat (ITT) population were acceptable.

After receipt of the SPA Nonagreement Letter, the Applicant requested a Post-SPA Non-Agreement meeting, which was held on August 17, 2016.

(b) (4)

[REDACTED]

[REDACTED]. The Agency further informed the Applicant that that if they plan to rely on the Agency's finding of efficacy and safety for Taclonex Topical Suspension as an LD using the 505(b)(2) regulatory pathway, then the LD must be an approved product in the US and studies must be conducted using products approved in the US. During the meeting, the Agency reached agreement with the Applicant regarding the proposed noninferiority margin, the proposed safety monitoring, and choice of Taclonex Topical Suspension as an LD.

On April 21, 2017 (SDN 7), the Applicant submitted protocols MC2-01-C3 and MC2-01-C2. Protocol MC2-01-C3 was a Phase 2 MUsT to be conducted in adult subjects with psoriasis vulgaris.

Protocol MC2-01-C2 was for a Phase 3 trial to be conducted in adult subjects with mild-to-moderate psoriasis vulgaris. In the Study-May-Proceed letter of July 6, 2017, the Agency provided advice regarding the proposed Physician's Global Assessment scale and the proposed statistical analyses. Specifically, the Agency advised the Applicant that if the single proposed Phase 3 trial failed to demonstrate noninferiority of CAL/BDP Cream to the LD, then a second Phase 3 trial or robust statistical findings from a single trial would be needed. In this event, the Applicant would also need to address 21 CFR 300.50 for fixed-combination prescription drugs for humans (i.e., by conducting a study of factorial design). For both protocols, the Applicant

was also advised to include measurement of the 25-OH vitamin D level in the evaluation of the effect of their product on calcium metabolism.

The Study-May-Proceed letter also provided advice regarding the Applicant's proposed Psoriasis Treatment Convenience Scale (PTCS), which is a patient-reported outcome (PRO). Specifically, the Agency stated that "However, based on face validity, the concept of treatment convenience might be limited in providing meaningful information on the clinical benefit of calcipotriene/betamethasone, as it is primarily measuring product's cosmetic characteristics (e.g., ease of application, product greasiness). Efficacy endpoints should measure clinically meaningful outcomes, i.e., how a patient feels, functions, or survives." (b) (4)

Written responses from a guidance meeting were sent to the Applicant on December 19, 2017. Regarding the MUSt, the Agency again advised the Applicant that to establish a clinical bridge using the relative bioavailability (BA) approach, there should be adequate quantifiable systemic concentrations under maximal-use conditions to determine the PK parameters for both CAL and BDP in a sufficient number of subjects. The Agency also advised that the BSA treated in the Phase 2 MUSt be at least 20%. Regarding the Phase 3 trial, the Agency advised the Applicant that for assessing the efficacy on itch associated with psoriasis, the recommended endpoint is the proportion of subjects achieving at least a 4-point improvement from Baseline to a prespecified timepoint (e.g., Week 8) on an 11-point numerical rating scale (NRS). The Agency also reiterated that if the Phase 3 trial failed to demonstrate noninferiority, a second Phase 3 trial may be required, in which the fixed-combination policy would need to be addressed.

In the written responses, the Agency also stated that the proposed provocative dermal safety studies (combined cumulative irritation potential and repeat insult patch test study) were not required. The Applicant addressed dermal safety by conducting active assessments of local safety during Phase 2 and Phase 3 trials. The Agency also reiterated the need to conduct a single-point vasoconstrictor trial to provide information on potency classification of the product. Furthermore, the Agency advised the Applicant to evaluate urinary calcium excretion in the Phase 2 MUSt with 24 hr urine collections; for the Phase 3 trial, screening based on the first morning spot urine calcium to creatinine ratio would be sufficient. Subjects in the Phase 3 trial whose spot urine calcium to creatinine ratio showed evidence of hypercalciuria would need further evaluation with 24 hr urine collection.

The Agency and the Applicant met for a pre-NDA meeting on February 27, 2019. The Agency provided general guidance regarding the data requirements to support filing, as well as the content and format of the submission. Specifically, the Agency agreed that pooling of safety data from the Phase 2 MUSt and the pivotal Phase 3 trial would not be meaningful because of differences in trial design. The Agency also agreed that an Integrated Summary of Efficacy and Integrated Summary of Safety would not be required; instead, the Applicant was instructed to provide detailed safety and efficacy summaries and a risk-benefit discussion in Module 2 (Sections 2.7.4 and 2.7.5). (b) (4)

(b) (4)

On December 12, 2018 (SDN 35), the Applicant submitted a thorough QT/QTc (TQT) trial waiver request. On January 15, 2019 (SDN 40), the Applicant submitted a request that they not be required to conduct phototoxicity and photoallergenicity studies. After review of the submissions, the Agency granted the waiver requests in an Advice Letter dated June 19, 2019. However, the Applicant initiated the phototoxicity and photoallergenicity trials prior to receipt of the Advice Letter. These trials are discussed in Section 8.2.8 of this review.

(b) (4)

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

The overall quality of the clinical information contained in this submission was adequate. The sites were selected for inspection by the Office of Scientific Investigations based on the number of enrolled subjects, site efficacy, protocol deviations, and prior inspectional history. The findings of the clinical inspection summary (review by Jenn Sellers, MD, PhD, dated May 19, 2020) are summarized in Table 3.

Table 3. Site Inspection Results

Site Number, Name, and Address	Protocol ID	Number of Subjects	Classification
Lloyd Godwin, MD Site #44 4 Corporate Dr. Suite 386 Shelton, CT 06484	MC2-01-C2	17	NAI

Source: Reviewer's table

Abbreviation: ID, identification; MD, Doctor of Medicine; NAI, no action indicated

The clinical site of Dr. Brent Boyce (Site 30, Michigan) also was initially selected for inspection. However, because of travel restrictions related to the coronavirus disease-2019 (COVID-19) pandemic, the need for this inspection was reevaluated. Following discussion between the Office of Scientific Investigations and the Division of Dermatology and Dentistry, the decision was made that assessment of the application could proceed without inspection of Dr. Boyce's site.

The review team concluded that the conduct of the trials appears to be adequate and that the data generated appear to be acceptable to support the use of this product for the proposed indication. Refer to the Clinical Inspection Summary by Jenn Sellers, MD, PhD, for further information regarding the findings of the Clinical Site Inspections.

4.2. Product Quality

MC2 Therapeutics Ltd. has submitted this (505)(b)(2) NDA for a fixed-dose combination drug product, WYNZORA (calcipotriene/betamethasone dipropionate) Cream, 0.005%/0.064% (hereafter referred to as CAL/BDP Cream). This drug product is intended for topical administration for the treatment of plaque psoriasis in patients 18 years of age or older. It is to be topically applied once daily to affected areas of skin for up to 8 weeks.

Taclonex Ointment (NDA 21852) and Taclonex Topical Suspension (NDA 22185) are used as the LDs. Taclonex Ointment and Taclonex Topical Suspension are fixed-dose combinations of the two active ingredients in WYNZORA and at the same strengths.

- The Applicant of this 505(b)(2) NDA has provided sufficient chemistry, manufacturing, and controls information to assure the identity, purity, strength, and quality of the drug substances, CAL and BDP, and the fixed-dose combination drug product, WYNZORA (calcipotriene/betamethasone dipropionate) Cream, 0.0005%/0.064% intended for topical administration.
- Labels/labeling issues have been satisfactorily addressed.
- The Office of Process and Facility has made an overall Acceptable recommendation regarding the facilities involved in this NDA.
- The claim for categorical exclusion of the environmental assessment has been granted.

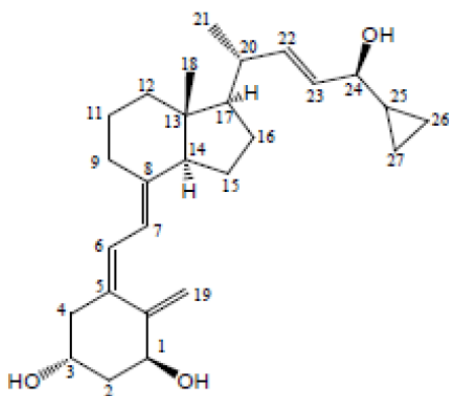
Therefore, from the Office of Pharmaceutical Quality perspective, this NDA is recommended for approval, with an expiration dating period of 24 months.

4.2.1. Drug Substances

Calcipotriene

The active ingredient, calcipotriene, is a synthetic analog of vitamin D3 and has immunomodulatory effects comparable to those of natural vitamin D. Calcipotriene is a compendial drug substance, and multiple brand name and generic drug products containing this active ingredient are currently marketed in the United States. It is a white to almost white powder. It is insoluble in water, freely soluble in ethanol, and slightly soluble in methylene chloride. Calcipotriene has the chemical name of (5Z,7E,22E,24S)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1 α ,3 β ,24-triol, a molecular weight of 412.6, and a molecular formula of C₂₇H₄₀O₃. Its molecular structure is shown in Figure 1.

Figure 1. Molecular Structure of Calcipotriene

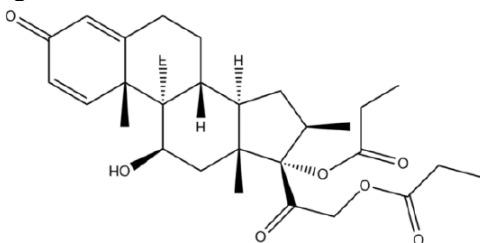


Anhydrous calcipotriene for this application is manufactured in compliance with the requirements of current good manufacturing practices (cGMP) by (b) (4). It is tested and released against a specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its assigned retest period of (b) (4), and it complies with the current United States Pharmacopeia monograph requirements. Detailed information regarding the manufacture of anhydrous calcipotriene by (b) (4) is provided in drug master file (DMF) (b) (4). This DMF has been reviewed and found to be adequate.

Betamethasone Propionate

Betamethasone dipropionate is a synthetic corticosteroid with anti-inflammatory, antipruritic, vasoconstrictive, and immunosuppressive properties. Betamethasone dipropionate is a compendial drug substance, and multiple brand name and generic drug products containing this active ingredient are currently marketed in the United States. It is a white to almost white crystalline powder. It is insoluble in water, freely soluble in acetone and methylene chloride, and sparingly soluble in alcohol. Betamethasone dipropionate has the chemical name of 9 α -fluoro-11 β ,17,21-trihydroxy-16 β -methylpregna-1,4-diene-3,20-dione-17,21-dipropionate, a molecular weight of 504.6, and a molecular formula of C₂₈H₃₇FO₇. Its molecular structure is shown in Figure 2.

Figure 2. Molecular Structure of Betamethasone Dipropionate



Betamethasone dipropionate for this application is manufactured in compliance with cGMP requirements by (b) (4). It is tested and released against a specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its assigned retest period of (b) (4), and it complies with the current United States

Pharmacopeia monograph requirements. Detailed information reading the manufacture of betamethasone dipropionate by (b) (4) is provided in DMF (b) (4). This DMF has been reviewed and found to be adequate.

4.2.2. Drug Product

WYNZORA (calcipotriene/betamethasone dipropionate) Cream, 0.005%/0.064% has been developed for the treatment of plaque psoriasis in patients 18 years of age or older.

Each gram of WYNZORA Cream contains 50 µg of calcipotriene and 0.644 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) as the active ingredients; and isopropyl myristate, mineral oil, medium-chain triglyceride, isopropyl alcohol, polyoxyl lauryl ether, poloxamer (407), polyoxyl 40 hydrogenated castor oil, carbomer interpolpolymer type A, butylated hydroxyanisole, trolamine, dibasic sodium phosphate, monobasic sodium phosphate, DL-A-tocopherol, and purified water as inactive ingredients. All of the inactive ingredients used in the composition of the drug product are compendial material, with the exception of carbomer interpolpolymer type A. Sufficient information supporting the use of carbomer interpolpolymer type A has been provided.

WYNZORA Cream is manufactured by (b) (4) for MC2 Therapeutics Ltd. in compliance with cGMP requirements and is packaged as 60 g in aluminum tubes. The drug product is tested and released against a specification that includes testing and acceptance criteria for all physical and chemical attributes essential for assuring the identity, strength, purity, and quality of the drug product at release and throughout its proposed shelf-life of 24 months. The applicant has provided sufficient stability data to support the expiration dating period of 24 months.

4.3. Clinical Microbiology

This section is not applicable.

4.4. Devices and Companion Diagnostic Issues

This section is not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant is proposing a new topical dosage form, WYNZORA Cream, of calcipotriene (0.005%, CAL) and betamethasone-17,21-dipropionate (0.064%, BDP). Limited pharmacology and/or toxicology studies have been conducted by the Applicant. The nonclinical safety profile is also being demonstrated based on the U.S. Food and Drug Administration's (FDA's) previous

findings of safety for the LDs, Taclonex (calcipotriene/betamethasone dipropionate) Ointment, 0.005%/0.064% (NDA 21852) and Taclonex (calcipotriene/betamethasone dipropionate) Topical Suspension, 0.005%/0.064% (NDA 22185). The Applicant has generated a clinical bridge to the LD, Taclonex Ointment, by conducting a clinical comparative BA pharmacokinetic study. The Applicant has generated a clinical bridge to the LD, Taclonex Topical Suspension, by carrying out a noninferiority Phase 3 clinical trial.

There are no nonclinical safety issues; therefore, this NDA is approvable from a pharmacology/toxicology perspective.

5.2. Referenced New Drug Applications, Biologics License Applications, Drug Master Files

NDA 21852 (Taclonex® Ointment), NDA 22185 (Taclonex® Topical Suspension), DMF (b) (4), DMF (b) (4), DMF (b) (4), and DMF (b) (4).

5.3. Pharmacology

CAL is a synthetic analog of 1,25-dihydroxyvitamin D3. CAL inhibits cell proliferation, stimulates cell differentiation and regulates inflammatory responses, especially in Th 17 cells. Vitamin D analogs also maintain calcium and phosphate homeostasis by facilitating calcium mobilization from the intestines and bone and regulating calcium excretion. BDP is a synthetic fluorinated corticosteroid. It binds to cytoplasmic glucocorticoid receptors and inhibits the expression of genes whose products are involved in the regulation of inflammation.

5.4. Absorption, Distribution, Metabolism, Excretion/PK

BDP is metabolized primarily to betamethasone 17-propionate (B17P), with a small amount of betamethasone 21-propionate formed. CAL is metabolized to two major metabolites (MC1046, the α , β -unsaturated ketone analog of CAL and MC1080, a saturated ketone analog). MC1046 is metabolized into MC1080, the major metabolite in plasma. MC1080 is slowly metabolized to calcitroic acid. No concerns with respect to PK drug interactions have been identified.

5.5. Toxicology

5.5.1. General Toxicology

Two pivotal Good Laboratory Practice (GLP) dermal repeat-dose toxicity studies were conducted in minipigs. The 8-week dermal minipig study was previously reviewed and is summarized here in. An 8-week study with daily topical dosing and coverage of and exposure to CAL/BDP Cream with porous gauze dressing for 6 hr was conducted. A 13-week study with intermittent topical CAL/BDP Cream administration using coverage with porous gauze dressing for 1 hr and 20 hr exposures was also carried out.

In the 8-week repeat-dose dermal toxicity study, two groups of minipigs (three/sex/group) were treated with either CAL/BDP Cream (25/320 µg/kg, CAL/BDP) or Daivobet Ointment (25/320 µg/kg, CAL/BDP) once daily for 6 hr. Treatment-related microscopic inflammatory changes were observed in the treated skin of all animals. Very low systemic exposure levels were observed, and no systemic toxicological effects were detected. Very few samples had quantifiable plasma concentrations of the parent compounds BDP and CAL. No sample had a quantifiable plasma concentration of the metabolite, 24-onecalcipotriol (MC1046). Exposure to the metabolite, B17P was shown for all animals in both treatment groups. On Day 8, the maximum concentration (C_{max}) and the area under the concentration-time curve from time zero to the time of the last measurable concentration (AUC_{last}) for B17P in male minipigs were 21.3 pg/mL and 344 hr*pg/mL, respectively. On Day 8, the C_{max} and AUC_{last} for B17P in female minipigs were 30.9 pg/mL and 282 hr*pg/mL, respectively. On Day 56, the C_{max} and AUC_{last} for B17P in male minipigs were 63.3 pg/mL and 1047 hr*pg/mL, respectively. On Day 56, the C_{max} and AUC_{last} for B17P in female minipigs were 85.3 pg/mL and 1491 hr*pg/mL, respectively. Very slight to well-defined erythema was observed after 2 to 3 weeks of treatment. No recovery group was included in this study.

The Applicant conducted a 13-week toxicity study in minipigs (study 78296); however, this study was terminated prematurely. Eighteen minipigs were placed in three treatment groups—vehicle, 1.8 g/kg/day CAL/BDP Cream (0.05 mg/g CAL, 0.64 mg/g BDP), and 1.8 g/kg/day stressed CAL/BDP Cream. Stressed CAL/BDP Cream was exposed to accelerated storage conditions at 40°C for 9 months prior to the study beginning. Formulations were applied to approximately 10% of the total skin surface area. Dosing was terminated on Day 17 because animals in both of the CAL/BDP Cream groups showed signs of subdued behavior, decreased activity, muscle trembling, shivering, reduced appetite, teeth grinding, and signs of pain. Avoidance behavior was also displayed when the animals were touched at the application sites. No toxicokinetic analysis was conducted because of the early termination of the study.

A 13-Week Dermal Toxicity Study in Minipigs with Toxicokinetics/78412

The protocol for study 78412 is outlined in Table 4.

- Dosing was variable from Days 26 to 42 for the CAL/BDP Cream (25/320 µg/kg, CAL/BDP) group because the animals in that group developed moderate-to-severe erythema accompanied by weight loss and clinical signs of pain.
- Hypercalcemia, decreased phosphorus, neutrophilia, lymphopenia, eosinopenia, polyuria, and decreased urine specific gravity were also seen in the animals in the CAL/BDP Cream (25/320 µg/kg, CAL/BDP) group prior to Day 26.
- On Days 23 and 25, an increased neutrophil count and calcium level, decreased lymphocyte and eosinophil counts, and a decreased phosphorus level were observed in the CAL/BDP Cream dose groups.

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes

NDA 213422 Multidisciplinary Review and Evaluation
WYNZORA (calcipotriene/betamethasone dipropionate) Cream, 0.005%/0.064%

Table 4. Protocol for Study 78412

Methods	
Dose and frequency of dosing	0.5 g/kg/day of vehicle or CAL/BDP Cream, (0.05 mg/g CAL, 0.64 mg/g BDP), normal and stressed. Daily dosing (according to schedule) to 10% of total skin surface area. All groups except the sham control were treated for 20 hr per day. See the dosing schedule in Table 5.
Route of administration	Dermal
Formulation/vehicle	Clinical vehicle cream
Species/strain	Gottingen Minipig
Number/sex/group	3/sex/group
Age	5 to 7 months
Satellite groups/unique design	The stressed CAL/BDP Cream group was included to qualify active ingredient impurities (b) (4). An altered dosing schedule was developed because the cream was not tolerated for more than 5 consecutive days of treatment.
Deviation from study protocol affecting interpretation of results	No

Source: Study 78412

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene

Table 5. Study Design, Study 78412

Group	Treatment	Dose ^a	Dose concentration	Nos of animals		Dosing period	Dosing schedule
		(g/kg/dosing day)	(mg/g)	♂	♀		
1	Sham	No dose	No dose	3	3	Day 1-42 Day 43-49 ^c From Day 50	5 days dosing 2 days off dose 2 days off dose 3 days dosing 2 days off dosing 2 days dosing 1 day off dose 2 days dosing 2 days off dose
2	Vehicle	0.5	0	3	3	Day 1-42 Day 43-49 ^c From Day 50	5 days dosing 2 days off dose 2 days off dose 3 days dosing 2 days off dosing 2 days dosing 1 day off dose 2 days dosing 2 days off dose
3	MC2-01 "normal"	0.5	0.05 mg/g CAL, 0.64 mg/g BDP	3	3	Day 1-25 Day 26-42 Day 43-49 ^c From 50	5 days dosing 2 days off dose ^b Off dose 2 days off dose 3 days dosing 2 days off dosing ^b 2 days dosing 1 day off dose 2 days dosing 2 days off dose ^b
4	MC2-01 "stressed"	0.5	0.05 mg/g CAL, 0.64 mg/g BDP	3	3	Day 1-25 Day 26-42 Day 43-49 ^c From 50	5 days dosing 2 days off dose ^b Off dose 2 days off dose 3 days dosing 2 days off dosing ^b 2 days dosing 1 day off dose 2 days dosing 2 days off dose ^b

^a 0.50 g/kg corresponds to 0.56 mL/kg. ^c 3 days of consecutive dosing prior to blood sampling for TK.

^b Individuals were in addition taken off dose as necessary in the period Day 18-93 due to clinical signs.

Source: Study 78412

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; TK, thymidine kinase

Based on the results observed of the 13-week dermal toxicity study in minipigs (study 78296) and the moderate-to-severe treatment effects observed early in this study, the modified dosing paradigm appears to be reasonable.

Observations and Results: Changes From the Control

Parameter	Major Findings
Mortality	None
Clinical signs	Skin reactions (moderate-to-severe erythema, slight edema, nodules, spotting and scaly skin) on neck, shoulder, abdomen, back, flank, hind part and legs; reduced appetite; pain; underweight; subdued behavior; decreased activity; trembling and effects on body temperature.
Body weight	Decreased body weight (animals in CAL/BDP Cream groups rebounded toward the end of the study, when dosing was less frequent)
Ophthalmoscopy	No changes
Electrocardiogram	No changes
Hematology	Day 23/25: Increased neutrophil counts and decreased lymphocyte and eosinophil counts in both CAL/BDP Cream groups (resolved by Day 92)
Clinical chemistry	Increased calcium and decreased phosphorus levels in both CAL/BDP Cream groups (resolved by Day 92)
Urinalysis	Day 25: Decreased urine specific gravity
Gross pathology	Crust, scaly skin, nodules, and red or brown foci were noted on the skin of animals in both CAL/BDP Cream groups
Organ weights	Females: Decreased adrenal gland weights in both CAL/BDP Cream groups; increased kidney and liver weights in both CAL/BDP Cream groups
Histopathology Adequate battery: Yes	Increased incidence of crust, epidermal hyperplasia, and hyperkeratosis in vehicle and CAL/BDP Cream groups as compared to sham control. Epidermal hyperplasia and hyperkeratosis had an increased incidence in CAL/BDP Cream groups when compared to vehicle control. Minimal-to-mild cortical atrophy of the adrenal gland was observed in CAL/BDP Cream groups. In the kidneys, mineralization of glomeruli/tubules/interstitium was observed in CAL/BDP Cream groups. Minimal-to-mild acinar mineralization was observed in CAL/BDP Cream groups.

5.5.2. Genetic Toxicology

The genotoxicity information contained in the LD (Taclonex Topical Suspension) labeling is provided below. That information will also be conveyed in Section 13.1 of the WYNZORA Cream labeling.

Calcipotriene did not elicit a genotoxic effect in the Ames mutagenicity assay, the mouse lymphoma thymidine kinase (TK) locus assay, the human lymphocyte chromosome aberration test, or the mouse micronucleus test. Betamethasone dipropionate did not elicit a genotoxic effect in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, or in the rat micronucleus test.

5.5.3. Carcinogenicity

The carcinogenicity information contained in the LD (Taclonex Topical Suspension) labeling is provided below. That information will also be conveyed in Section 13.1 of the WYNZORA Cream labeling.

When calcipotriene was applied topically to mice for up to 24 months at dosages of 3, 10, and 30 µg/kg/day (9, 30, and 90 µg/m²/day, respectively), no significant change in tumor incidence compared to the control was observed.

A 104-week oral carcinogenicity study of calcipotriene was conducted in male and female rats at doses of 1, 5 and 15 µg/kg/day (6, 30, and 90 µg/m²/day, respectively). Beginning at Week 71, the dosage for high-dose animals of both genders was reduced to 10 µg/kg/day (60 µg/m²/day). A treatment-related increase in the incidence of benign C-cell adenoma was observed in the thyroid of females that received 15 µg/kg/day. A treatment-related increase in the incidence of benign pheochromocytoma was observed in the adrenal glands of males that received 15 µg/kg/day. No other statistically significant difference in tumor incidence compared to the control was observed. The clinical 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 µg/kg/day in females, and 1.3, 4.2, and 12.9 µg/kg/day in males (up to 26 µg/m²/day and 39 µg/m²/day, in females and males, respectively), no significant change in tumor incidence compared to the control was observed.

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 µg/kg/day (120, 360, and 1200 µg/m²/day, respectively), no significant change in tumor incidence compared to the control was observed.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

The fertility and early embryonic development information contained in the LD (Taclonex Topical Suspension) labeling is provided below. That information will also be conveyed in Section 13.1 of the WYNZORA Cream labeling.

Studies in rats with oral doses of up to 54 µg/kg/day (324 µg/m²/day) of calcipotriene indicated no impairment of fertility or general reproductive performance. Studies in male rats at oral doses of up to 200 µg/kg/day (1200 µg/m²/day), and in female rats at oral doses of up to 1000 µg/kg/day (6000 µg/m²/day), of betamethasone dipropionate indicated no impairment of fertility.

Embryo-Fetal Development

The embryo-fetal development information contained in the LD (Taclonex Topical Suspension) labeling is provided below. That information will also be conveyed in Section 8.1 of the WYNZORA Cream labeling.

Embryo-fetal development studies involving oral administration of calcipotriene were performed in rats and rabbits. Pregnant rats received dosages of 0, 6, 18, or 54 µg/kg/day

(0, 36, 108, and 324 $\mu\text{g}/\text{m}^2/\text{day}$, respectively) on days 6 to 15 of gestation (the period of organogenesis). There was no apparent effect on maternal survival, behavior, or body weight gain, litter parameters, and the incidence of major malformations in fetuses. Fetuses from dams dosed at 54 $\mu\text{g}/\text{kg}/\text{day}$ exhibited a significantly increased incidence of minor skeletal abnormalities, including enlarged fontanelles and extra ribs.

Pregnant rabbits were dosed daily with calcipotriene at exposures of 0, 4, 12, or 36 $\mu\text{g}/\text{kg}/\text{day}$ (0, 48, 144, and 432 $\mu\text{g}/\text{m}^2/\text{day}$, respectively) on days 6 to 18 of gestation (the period of organogenesis). The mean maternal body weight gain was reduced in animals dosed at 12 or 36 $\mu\text{g}/\text{kg}/\text{day}$. The incidence of fetal death was increased in the group dosed at 36 $\mu\text{g}/\text{kg}/\text{day}$; reduced fetal weight was also observed in this group. The incidence of major malformations of fetuses was not affected. An increase in the incidence of minor skeletal abnormalities—including incomplete ossification of sternebrae, pubic bones, and forelimb phalanges—was observed in the group dosed at 36 $\mu\text{g}/\text{kg}/\text{day}$.

Embryo-fetal development studies with betamethasone dipropionate were performed via subcutaneous injection in mice and rabbits. Pregnant mice were administered doses of 0, 156, 625, or 2500 $\mu\text{g}/\text{kg}/\text{day}$ (0, 468, 1875, and 7500 $\mu\text{g}/\text{m}^2/\text{day}$, respectively) on days 7 to 13 of gestation (the period of organogenesis). Betamethasone dipropionate induced fetal toxicity, including fetal death, reduced fetal weight, malformations (increased incidence of cleft palate and crooked or short tail), and minor skeletal abnormalities (delayed ossification of vertebra and sternebrae). Fetal toxicity was observed at the lowest level of exposure evaluated (i.e., 156 $\mu\text{g}/\text{kg}/\text{day}$).

Pregnant rabbits were injected subcutaneously with dosages of 0, 0.625, 2.5, and 10 $\mu\text{g}/\text{kg}/\text{day}$ (0, 7.5, 30, and 120 $\mu\text{g}/\text{m}^2/\text{day}$, respectively) on days 6 to 18 of gestation (the period of organogenesis). Betamethasone dipropionate induced fetal toxicity, including fetal death, reduced fetal weight, external malformations (including malformed ears, cleft palate, umbilical hernia, kinked tail, club foot, and club hand), and skeletal malformations (including absence of phalanges on the first digit and cranial dysplasia) at dosages of ≥ 2.5 $\mu\text{g}/\text{kg}/\text{day}$.

Prenatal and Postnatal Development

The prenatal and postnatal development information contained in the LD (Taclonex Topical Suspension) labeling is provided below. That information will also be conveyed in Section 8.1 of the WYNZORA Cream labeling.

Calcipotriene was evaluated for effects on peri- and post-natal development when orally administered to pregnant rats at dosages of 0, 6, 18 or 54 $\mu\text{g}/\text{kg}/\text{day}$ (0, 36, 108, and 324 $\mu\text{g}/\text{m}^2/\text{day}$, respectively) from gestation day 15 to postpartum day 20. No remarkable effect on any parameter—including survival, behavior, body weight, litter parameters, or ability to nurse or rear pups—was observed.

Betamethasone dipropionate was evaluated for effects on peri- and post-natal development when orally administered to pregnant rats at dosages of 0, 100, 300, and 1000 µg/kg/day (0, 600, 1800, and 6000 µg/m²/day, respectively) from gestation day 6 to postpartum day 20. The mean maternal body weight was significantly reduced on gestation day 20 in animals dosed at 300 and 1000 µg/kg/day. The mean duration of gestation was slightly, but statistically significantly, increased at 100, 300, and 1000 µg/kg/day. The mean percentage of pups that survived to day 4 decreased with increasing dosage. On lactation day 5, the percentage of pups with a reflex to right themselves when placed on their back was significantly reduced at 1000 µg/kg/day. No effect on the ability of pups to learn was observed, and the ability of the offspring of treated rats to reproduce was not affected.

5.5.5. Other Toxicology Studies

Assessment of Extractables and Leachables Risk Assessment for Container Closure System

An extractables and leachables risk assessment was performed for the WYNZORA Cream container closure system (CCS). The risk assessment concluded that the primary packaging components of the WYNZORA Cream CCS are compliant with the FDA indirect food additive regulations (21 CFR 174-186). Based on the regulations for the CCS components of the WYNZORA Cream, the Applicant believes the leachables risk to be low. Despite the apparent low leachables risk, the Applicant conducted simulated-use studies to evaluate the compatibility of the CCS with WYNZORA Cream.

The simulated-use study was performed with isopropanol/methyl tert-butyl ether/water (40:40:20 [v:v:v]) as a surrogate solvent system. The tubes were filled with a solvent, capped with the closure after piercing the blind seal, and stored at 40°C. Sample extracts were evaluated at the following times: 0 (initial time point), 10, 20, and 30 days. The sample extracts were analyzed for volatile organic extractables by means of a combination of headspace gas chromatography with mass spectrometry (MS). Semivolatile organic extractables were examined by direct-injection gas chromatography with MS, nonvolatile organic extractables by ultrahigh-pressure liquid chromatography with a photodiode array and quadrupole-time-of-flight MS detection, and inorganic extractables by inductively coupled plasma MS. Based on the maximum daily dose of 15 g, the analytical evaluation threshold (AET) for the 60 g tube of WYNZORA Cream was determined to be (b) (4) µg/tube.

To determine the AET for the extraction study, a safety concern threshold (SCT) of 1.5 µg/day was selected. This value is derived from the threshold of toxicological concern in the assessment of acceptable limits of mutagenic impurities in drug substances and drug products. Below this SCT, it is believed that extractables and leachables would have negligible safety concerns in terms of carcinogenic, genetic toxicity, and noncarcinogenic effects. The calculated AET was based on the SCT, the tube having 60 g of drug product in the CCS, and the daily dose of 15 g/day. Therefore, AET = (b) (4) /CCS. The results of the simulated-use study and toxicological risk evaluation are summarized in Table 6.

Table 6. Summary of Results for Inorganic, Volatile, Semivolatile, and Nonvolatile Organic Extractables

Extracts	Observations	Toxicological risk evaluation
Volatile organic extractables	No volatile organic extractables were observed above the AET.	No toxicological risk evaluation was applicable
Semi-volatile organic extractables	There were 2 semi-volatile organic extractables observed above the AET in the 10-day CCS extract and there were 3 semi-volatile organic extractables observed above the AET in the 20- and 30-day CCS extracts. These extractables were identified as (b) (4). The highest observed extractable was (b) (4) which was observed at an approximate concentration of (b) (4) µg/tube in 10-, 20- and 30-day CCS extracts respectively.	Three of the extractants quantified are greater than the AET and belong to the (b) (4) group having similar toxicological profiles. All are classified as low to practically non-toxic via the oral and dermal routes of exposure. The very low-level exposure is unlikely to cause adverse effects.
Inorganic extractables	No inorganic extractables were observed above the AET.	None of the aluminum or metal impurities were found over the AET (b) (4)
Non-volatile organic extractables	There were no non-volatile organic extractables observed above the AET in Time 0 CCS extract. 10 non-volatile organic extractables were observed above the AET in the 10-day CCS extract, 12 non-volatile organic extractables were observed above the AET in the 20-day CCS extracts, and 14 non-volatile organic extractables were observed above the AET in the 30-day CCS extracts. The highest observed extractable was not identified: it was observed at an approximate concentration of (b) (4) µg/tube in 10-, 20- and 30-day CCS extracts, respectively.	In the non-volatile extractants, eight of the 13 extractants quantified are greater than the AET. None of the identified compounds were a health concerns when evaluated by the available oral or dermal comparison values. The remaining five compounds were evaluated as unknown (b) (4). These were evaluated similarly to other (b) (4) which lack genotoxic potential. Using the (b) (4) the total amount of the (b) (4) did not exceed the TTC for this class of materials and therefore not expected to be a concern.

Source: Module 3.2.P.5.6

Abbreviations: AET, analytical evaluation threshold; CCS, container closure system; TTC, threshold of toxicological concern; (b) (4)

The Applicant's toxicological assessment of the CCS extractables and leachables is acceptable. No extractable/leachable of toxicologic concern has been identified for this CCS.

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant has developed CAL/BDP Cream, a topical cream formulation containing a fixed dose of CAL and BDP, 0.005%/0.064%, for the topical treatment of plaque psoriasis in patients 18 years of age and older. CAL is a vitamin D analog with immunomodulatory effects and BDP is a synthetic fluorinated corticosteroid with anti-inflammatory, antipruritic, vasoconstrictive, and immunosuppressive properties.

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The Applicant is following a 505(b)(2) regulatory pathway and has identified two LDs:

- Taclonex Ointment (CAL/BDP, 0.005%/0.064%), approved for the topical treatment of plaque psoriasis in patients 12 years of age and older
- Taclonex Topical Suspension (CAL/BDP, 0.005%/0.064%), approved for the topical treatment of plaque psoriasis of the scalp and body in patients 12 years of age and older

The clinical pharmacology program in this NDA included the following:

- Maximal-use PK bridging study to Taclonex Ointment (study MC2-01-C3)
- HPA axis suppression evaluation of CAL/BDP Cream (study MC2-01-C3)
- Effect on calcium metabolism (studies MC2-01-C3 and MC2-01-C2 [Phase 3 trial])
- Vasoconstriction study to support a potency classification (study MC2-01-C4)

The key review findings, together with specific recommendations and comments, are summarized in Table 7.

Table 7. Summary of Clinical Pharmacology Review

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Efficacy was not evaluated as a part of the clinical pharmacology program. See Section 8.1 for efficacy studies and their results.
General dosing instructions	The proposed dosing regimen of once daily application to the affected areas for up to 8 weeks (not to exceed 100 g per week) is acceptable.
PK	The PK of CAL, BDP, and their main metabolites, MC1080 and betamethasone 17-propionate (B17P), following once daily application of CAL/BDP Cream and Taclonex Ointment were evaluated in adult subjects with psoriasis vulgaris to support establishment of a clinical bridge.
Clinical bridge between CAL/BDP Cream and listed drug (Taclonex Ointment)	The overall data support establishment of a clinical bridge between CAL/BDP Cream and Taclonex Ointment.
Evaluation of HPA axis suppression	The HPA axis suppression potential of CAL/BDP Cream was evaluated following once daily application for up to 8 weeks. Approximately 23% and 12% of subjects showed HPA axis suppression at Week 4 and Week 8, respectively.
Effect on calcium metabolism	The effect on calcium metabolism following administration of CAL/BDP Cream and the two listed drugs, Taclonex Ointment and Taclonex Suspension, was evaluated. There were a few instances of an elevated calcium level, but they did not have an apparent correlation to the systemic exposure of CAL resulting from the application of CAL/BDP Cream.
Potency classification	To support potency classification of CAL/BDP Cream, a single-point vasoconstriction study in healthy adult subjects was conducted. CAL/BDP Cream was compared to five reference products with varying potencies. The study results demonstrated that the skin-blanching response of CAL/BDP Cream is consistent with a mid-potency topical corticosteroid.

Source: Reviewer's summary

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; HPA, hypothalamic–pituitary–adrenal; PK, pharmacokinetic

6.1.1. Recommendations

From a clinical pharmacology standpoint, this NDA is acceptable.

6.1.2. Postmarketing Requirement(s) and Commitments(s)

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

The exact mechanism of action of CAL and BDP for the treatment of plaque psoriasis is unknown.

PK Parameters

The systemic concentrations of CAL, BDP, MC1080, and B17P were generally low following once daily application of CAL/BDP Cream. In most samples, the concentrations of the four analytes were below or close to the lower limit of quantification (LLOQ). Table 8 and Table 9 summarize the PK parameters of the four analytes following once daily application of CAL/BDP Cream or Taclonex Ointment.

Table 8. PK Parameters of Vitamin D Components Following Once Daily Application of CAL/BDP Cream or Taclonex Ointment

Week 4	Vitamin D Component					
	CAL Mean (SD)			MC1080 Mean (SD)		
	Above LLOQ	C _{max} (pg/mL)	AUC _{0-7h} (pg*h/mL)	Above LLOQ	C _{max} (pg/mL)	AUC _{0-7h} (pg*h/mL)
CAL/BDP Cream	1/27	30.3 (1.4)	229.0 (14.7)	3/27	30.0 (3.5)	223.7 (16.3)
Taclonex Ointment	0/27	30.0 (0.0)	216.4 (5.1)	2/27	29.2 (0.3)	209.9 (5.0)

Source: Reviewer's analysis

Concentrations below the LLOQ were replaced with the LLOQ value for calculations.

LLOQ, 30 pg/mL for CAL and 29.1 pg/mL for MC1080

Abbreviations: AUC_{0-7h}, area under the concentration-time curve from 0 to 7 hr; BDP, betamethasone dipropionate; CAL, calcipotriene; C_{max}, maximum concentration; LLOQ, lower limit of quantification

Table 9. PK Parameters of Glucocorticoid Components Following Once Daily Application of CAL/BDP Cream or Taclonex Ointment

Week 4	Glucocorticoid Component					
	BDP Mean (SD)			B17P Mean (SD)		
	Above LLOQ	C _{max} (pg/mL)	AUC _{0-7h} (pg*h/mL)	Above LLOQ	C _{max} (pg/mL)	AUC _{0-7h} (pg*h/mL)
CAL/BDP Cream	3/27	22.4 (8.7)	160.3 (36.4)	13/27	95.9 (233.9)	419.1 (646.3)
Taclonex Ointment	3/27	29.0 (38.4)	158.0 (64.3)	14/27	60.1 (79.2)	337.9 (448.5)

Source: Reviewer's analysis

Concentrations below the LLOQ were replaced with the LLOQ value for calculations.

LLOQ, 20 pg/mL for BDP and B17P

Abbreviations: AUC_{0-7h}, area under the concentration-time curve from 0 to 7 hr; BDP, betamethasone dipropionate; CAL, calcipotriene; C_{max}, maximum concentration; LLOQ, lower limit of quantification; B17P, betamethasone 17-propionate

Relative Bioavailability

The overall data suggest that there was no meaningful difference in the relative BA of CAL, MC1080, BDP and B17P at Week 4 following once daily administration of CAL/BDP Cream and Taclonex Ointment.

HPA Axis Suppression

Following once daily application of CAL/BDP Cream, 23% and 12% of subjects showed HPA axis suppression at Week 4 and Week 8, respectively.

Effect on Calcium Metabolism

Once daily application of CAL/BDP Cream did not cause significant changes in calcium metabolism based on the results of studies MC2-01-C3 and MC2-01-C2.

Potency Classification

The results of study MC2-01-C4 support a mid-potency classification of CAL/BDP Cream.

Bioanalytical Method

Two liquid chromatography-tandem mass spectrometric methods (LC-MS/MS) were used for quantification of CAL, MC1080, BDP, and B17P in human plasma samples collected in study MC2-01-C3. The bioanalytical methods were adequately validated, and the assays are considered sensitive as per current standards. See Section 14.4.1 for additional details.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant's proposed dosing regimen is to apply CAL/BDP Cream to affected areas once daily for up to 8 weeks and not to use more than 100 g per week. This dosing regimen is supported by systemic safety data from the maximal-use study (MC2-01-C3), as well as efficacy and safety data from a Phase 3 study (MC2-01-C2).

Therapeutic Individualization

Therapeutic individualization was not evaluated in this NDA.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

PK Assessment

The PK characteristics of CAL, BDP, MC1080, and B17P following once daily application of CAL/BDP Cream were assessed under maximal-use conditions in study MC2-01-C3. This was a randomized, open-label, parallel-group, multicenter study in adult subjects with plaque psoriasis, and was designed to evaluate the systemic safety and PK of topically applied CAL/BDP Cream in comparison to Taclonex Ointment.

Subjects eligible for the study were males and females at least 18 years of age with a clinical diagnosis of plaque psoriasis of at least moderate severity and with involvement of at least 20% of the BSA on the trunk, limbs, and/or scalp.

A total of 63 subjects was randomized—32 subjects to the CAL/BDP Cream group and 31 to the Taclonex Ointment group. Among them, subjects who received the planned application of treatment at the Week 4 or Week 8 visit and had at least one postapplication blood sample available for PK assessment at the corresponding visit were included in the PK population. There were 27 subjects in each treatment group at Week 4 and 19 subjects in the CAL/BDP Cream group at Week 8. The excluded subjects and the reasons for their exclusion are listed in Table 10. The demographics and baseline characteristics of the PK population are summarized in Table 11.

Table 10. Subjects Excluded From PK Population

	CAL/BDP Cream Treatment Group	Taclonex Ointment Treatment Group
Excluded from Week-4 analysis	Subj. (b) (6) was voluntarily withdrawn. Subj. (b) (6) was discontinued from the study (unknown reason). Subj. (b) (6), and (b) (6) were discontinued from the study because of HPA axis suppression on Day 0.	Subj. (b) (6) and (b) (6) were voluntarily withdrawn. Subj. (b) (6) did not have PK samples taken because of collapsed veins. Subj. (b) (6) did not have PK samples analyzed because of sample mishandling.
Excluded from Week-8 analysis	Subj. (b) (6) were discontinued from the study because of HPA axis suppression at Week 4.	N/A; treatment duration for the Taclonex Ointment group was 4 weeks.

Source: Clinical study report of MC2-01-C3 and listing 16.2.1.2

Abbreviations: PK, pharmacokinetic; BDP, betamethasone dipropionate; CAL, calcipotriene; HPA, hypothalamic–pituitary–adrenal

Subjects who had HPA axis suppression at Week 4 were discontinued from the treatment according to the study protocol; this is reasonable.

Table 11. Summary of Demographics and Baseline Characteristics of PK Population

	CAL/BDP Cream (n=27)	Taclonex Ointment (n=27)
Age (years)		
Mean (SD)	52.0 (14.6)	49.6 (15.7)
Minimum, maximum	22, 78	19, 79
Sex, n (%)		
Male	15 (55.6)	20 (74.1)
Female	12 (44.4)	7 (25.9)
Race, n (%)		
White	24 (88.9)	25 (92.6)
Black or African American	2 (7.4)	2 (7.4)
Ethnicity, n (%)		
American Indian or Alaska Native	1 (3.7)	0 (0)
Hispanic or Latino	21 (77.8)	22 (81.5)
Not Hispanic or Latino	6 (22.2)	5 (18.5)
Baseline PGA, n (%)		
3 – Moderate	25 (92.6)	27 (100.0)
4 – Severe	2 (7.4)	0 (0)
Baseline total BSA (%)		
Mean (SD)	24.5 (4.6)	25.4 (8.1)
Minimum, maximum ¹	20, 44	20, 62
Scalp involvement, n (%)		
Yes	20 (74.1)	22 (81.5)
No	7 (25.9)	5 (18.5)

Source: Adapted from Table 14.1.2.3 in the clinical study report of MC2-01-C3

¹ Three subjects (one in the CAL/BDP Cream group and two in the Taclonex Ointment group) were enrolled with a total BSA exceeding the maximum of 30% specified in the protocol.

Abbreviations: BDP, betamethasone dipropionate; BSA, body surface area; CAL, calcipotriene; PGA, physician's global assessment; PK, pharmacokinetic

PK samples were collected to quantify the systemic concentrations of CAL, MC1080, BDP, and B17P at the following time points:

- Baseline (Day 0)
- Week 2: Predose
- Week 4: Predose and at 0.5, 1, 2, 3, 5, and 7 hr postdose
- Week 8 (CAL/BDP Cream group only): Predose and at 0.5, 1, 2, 3, 5, and 7 hr postdose

Systemic exposures of CAL, MC1080, BDP, and B17P following once daily application of CAL/BDP Cream and Taclonex Ointment were generally low. In most samples, the concentrations of these four analytes were below or close to the LLOQ, despite the reasonably sensitive bioanalytical methods employed. The mean C_{max} and area under the concentration-time curve from 0 to 7 hr (AUC_{0-7h}) following once daily application of CAL/BDP Cream and Taclonex Ointment are summarized in Table 12 to Table 15. The relative BA of BDP and B17P in the two treatment groups is listed in Table 16.

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Table 12. Mean C_{max} and AUC_{0-7h} of CAL Following Once Daily Application of CAL/BDP Cream and Taclonex Ointment

	CAL at Week 4, Mean (SD)			CAL at Week 8, Mean (SD)		
	Above LLOQ	C_{max} (pg/mL)	AUC_{0-7h} (pg*h/mL)	Above LLOQ	C_{max} (pg/mL)	AUC_{0-7h} (pg*h/mL)
CAL/BDP Cream	1/27	30.3 (1.4)	229.0 (14.7)	0/19	30.0 (0.0)	222.58 (8.9)
Taclonex Ointment	0/27	30.0 (0.0)	216.4 (5.1)	N/A	N/A	N/A

Source: Reviewer's analysis

Concentrations below the LLOQ (30 pg/mL) were replaced with the LLOQ value for calculations.

Abbreviations: AUC_{0-7h} , area under the concentration-time curve from 0 to 7 hr; BDP, betamethasone dipropionate; CAL, calcipotriene; C_{max} , maximum concentration; LLOQ, lower limit of quantification; N/A, not applicable

Table 13. Mean C_{max} and AUC_{0-7h} of MC1080 Following Once Daily Application of CAL/BDP Cream and Taclonex Ointment

	MC1080 at Week 4, Mean (SD)			MC1080 at Week 8, Mean (SD)		
	Above LLOQ	C_{max} (pg/mL)	AUC_{0-7h} (pg*h/mL)	Above LLOQ	C_{max} (pg/mL)	AUC_{0-7h} (pg*h/mL)
CAL/BDP Cream	3/27	30.0 (3.5)	223.7 (16.3)	0/19	29.1 (0.0)	215.9 (8.7)
Taclonex Ointment	2/27	29.2 (0.3)	209.9 (5.0)	N/A	N/A	N/A

Source: Reviewer's analysis

Concentrations below LLOQ (29.1 pg/mL) were replaced with the LLOQ value for calculations.

Abbreviations: AUC_{0-7h} , area under the concentration-time curve from 0 to 7 hr; BDP, betamethasone dipropionate; CAL, calcipotriene; C_{max} , maximum concentration; LLOQ, lower limit of quantification

Table 14. Mean C_{max} and AUC_{0-7h} of BDP Following Once Daily Application of CAL/BDP Cream and Taclonex Ointment

	BDP at Week 4, Mean (SD)			BDP at Week 8, Mean (SD)		
	Above LLOQ	C_{max} (pg/mL)	AUC_{0-7h} (pg*h/mL)	Above LLOQ	C_{max} (pg/mL)	AUC_{0-7h} (pg*h/mL)
CAL/BDP Cream	3/27	22.4 (8.7)	160.3 (36.4)	0/19	20.0 (0.0)	148.4 (6.0)
Taclonex Ointment	3/27	29.0 (38.4)	158.0 (64.3)	N/A	N/A	N/A

Source: Reviewer's analysis

Concentrations below the LLOQ (20 pg/mL) were replaced with the LLOQ value for calculations.

Abbreviations: AUC_{0-7h} , area under the concentration-time curve from 0 to 7 hr; BDP, betamethasone dipropionate; CAL, calcipotriene; C_{max} , maximum concentration; LLOQ, lower limit of quantification

Table 15. Mean C_{max} and AUC_{0-7h} of B17P Following Once Daily Application of CAL/BDP Cream and Taclonex Ointment

	B17P at Week 4, Mean (SD)			B17P at Week 8, Mean (SD)		
	Above LLOQ	C_{max} (pg/mL)	AUC_{0-7h} (pg*h/mL)	Above LLOQ	C_{max} (pg/mL)	AUC_{0-7h} (pg*h/mL)
CAL/BDP Cream	13/27	95.9 (233.9)	419.1 (646.3)	7/19	31.4 (29.2)	204.7 (141.7)
Taclonex Ointment	14/27	60.1 (79.2)	337.9 (448.5)	N/A	N/A	N/A

Source: Reviewer's analysis

Concentrations below the LLOQ (20 pg/mL) were replaced with the LLOQ value for calculations.

Abbreviations: AUC_{0-7h} , area under the concentration-time curve from 0 to 7 hr; BDP, betamethasone dipropionate; CAL, calcipotriene; C_{max} , maximum concentration; LLOQ, lower limit of quantification; B17P, betamethasone 17-propionate

Table 16. Relative Bioavailability of BDP and B17P at Week 4 in CAL/BDP Cream and Taclonex Ointment Treatment Groups

Compound	PK Parameter	CAL/BDP Cream (Test) to Taclonex Ointment (Reference)	
		Ratio %Ref	90% CI
BDP (pg/mL) ¹	C _{max} (pg/mL)	93.06	77.92, 111.13
	AUC _{0-7h} (pg*h/mL)	103.68	94.53, 113.72
B17P (pg/mL) ¹	C _{max} (pg/mL)	102.74	66.36, 159.08
	AUC _{0-7h} (pg*h/mL)	108.51	75.66, 155.60
BDP (pg/mL) ²	C _{max} (pg/mL)	89.32	75.59, 105.55
	AUC _{0-7h} (pg*h/mL)	100.76	92.96, 109.22
B17P (pg/mL) ²	C _{max} (pg/mL)	90.01	61.29, 132.18
	AUC _{0-7h} (pg*h/mL)	98.33	70.91, 136.36

Source: Reviewer's analysis

¹ Analysis with all subjects (n=27 per treatment group)

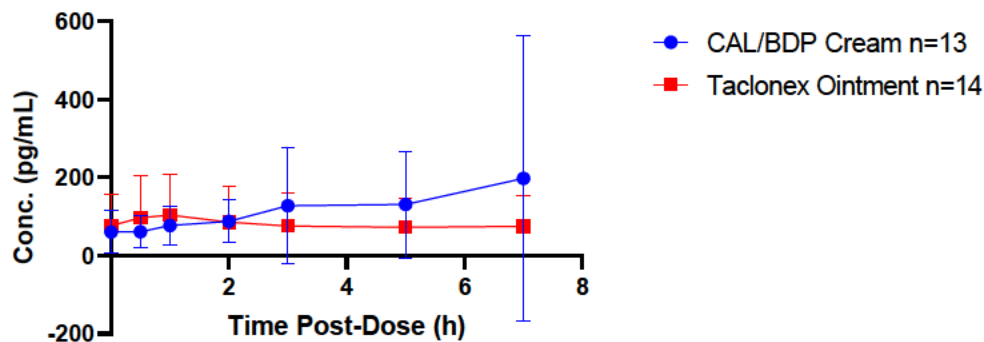
² Analysis without an outlier, Subject (b) (6) from the CAL/BDP Cream group

Abbreviations: AUC_{0-7h}, area under the concentration-time curve from 0 to 7 hr; BDP, betamethasone dipropionate; CAL, calcipotriene; CI, confidence interval; C_{max}, maximum concentration; B17P, betamethasone 17-propionate

The relative BA assessment for BDP is based on data for BDP and for its metabolite B17P, which were more quantifiable than BDP (Table 16). The subject with unusually high exposure was excluded. The results indicated comparable BA between CAL/BDP Cream and the LD, Taclonex Ointment. Although the confidence interval (CI) was outside the no-effect boundary of 80% to 125% for most parameters, with the exception of AUC_{0-7h} for BDP, the large CI range indicates high variability, and is considered to be nonsignificant.

The mean ± SD and individual plasma concentrations of B17P at Week 4 of subjects whose samples had a B17P plasma concentration above the LLOQ are illustrated in Figure 3 and Figure 4, respectively. The observed mean concentrations are generally similar in both treatment groups. The slightly higher mean concentrations in the CAL/BDP Cream group at later time points are most likely a result of one subject, Subject (b) (6), whose concentrations were markedly higher than those of the other subjects (Figure 4). The high exposure could not be explained. Although there was no clear trend between the concentrations of B17P and poststimulation cortisol levels according to the evaluation of HPA axis suppression (Figure 5), Subject (b) (6) showed HPA axis suppression at Week 4, and consequently was removed from the study at Week 4.

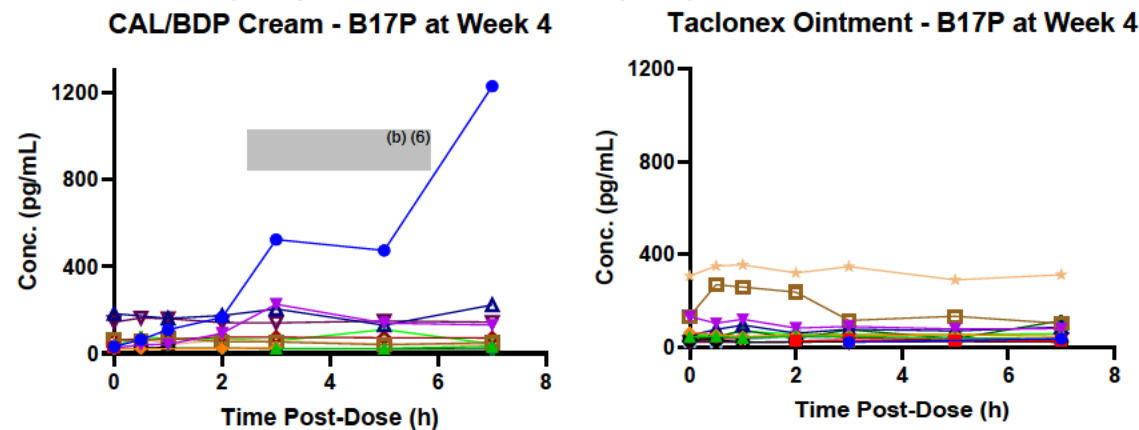
Figure 3. Mean $\pm$ SD Plasma Concentration of B17P at Week 4 Following Once Daily Application of CAL/BDP Cream and Taclonex Ointment
B17P at Week 4



Source: Reviewer's plot

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; B17P, betamethasone 17-propionate

Figure 4. Individual Plasma Concentration of B17P at Week 4 Following Once Daily Application of CAL/BDP Cream (n=13) and Taclonex Ointment (n=14)



Source: Reviewer's plot

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; B17P, betamethasone 17-propionate

Because only a small proportion of the subjects showed quantifiable levels of CAL and MC1080, the relative BA assessment for evaluation of a clinical bridge between the CAL/BDP Cream and Taclonex Ointment using data from these two analytes is not considered reliable. In general, the systemic exposures of CAL and MC1080 were low and close to the LLOQ of the bioanalytical assay. Furthermore, quantifiable concentrations were not available in a sufficient number of subjects to permit relative BA assessment. The bioanalytical assays are considered to be sensitive as per current standards. From a safety standpoint, there was no signal indicative of an effect on calcium metabolism in the maximal-use study (MC2-01-C3), indicating comparable safety of CAL/BDP Cream and Taclonex Ointment. In addition, there was no signal in the Phase 3 trial (MC2-01-C2) indicative of an effect on calcium metabolism for CAL/BDP Cream. Therefore, from a clinical pharmacology standpoint, the overall data support the establishment of a clinical bridge for calcipotriene.

The relative BA evaluation above suggests that there is no meaningful difference in systemic absorption of the four analytes following once daily application of CAL/BDP Cream and Taclonex Ointment. Therefore, the totality of evidence and the PK data from Study MC2-01-C3 support a clinical bridge between CAL/BDP Cream and Taclonex Ointment.

HPA Axis Suppression Potential

The HPA axis suppression potential of CAL/BDP Cream was evaluated in Study MC2-01-C3 by means of adrenocorticotrophic hormone (ACTH or cosyntropin) challenge test. The population comprised 30 subjects; their demographics and baseline characteristics are summarized in Table 17.

The ACTH challenge test was performed by assessing the serum cortisol concentration at Baseline, Week 4, and Week 8 (prior to application of CAL/BDP Cream), by collecting a predose blood sample, administering an intravenous bolus injection of 0.25 mg cosyntropin, and collecting a postdose blood sample at 30 min poststimulation.

Table 17. Summary of Demographics and Baseline Characteristics of HPA Population

Treatment Group	CAL/BDP Cream (N=30)
Age (years)	
Mean (SD)	51.4 (15.0)
Minimum, maximum	22, 78
Sex, n (%)	
Male	17 (56.7)
Female	13 (43.3)
Race, n (%)	
White	26 (86.7)
Black or African American	2 (6.7)
Asian	1 (3.7)
American Indian or Alaska Native	1 (3.7)
Ethnicity, n (%)	
Hispanic or Latino	21 (70.0)
Not Hispanic or Latino	9 (30.0)
Baseline PGA, n (%)	
3 – Moderate	27 (90.0)
4 – Severe	3 (10.0)
Baseline total BSA (%)	
Mean (SD)	24.3 (4.5)
Minimum, maximum ¹	20, 44
Scalp involvement, n (%)	
Yes	22 (73.3)
No	8 (26.7)

Source: Adapted from Table 14.1.2.2 of the clinical study report for MC2-01-C3

¹ One subject was enrolled with a total BSA exceeding the protocol-specified maximum of 30%.

Abbreviations: BDP, betamethasone dipropionate; BSA, body surface area; CAL, calcipotriene; HPA, hypothalamic–pituitary–adrenal; PGA, physician's global assessment

The Applicant submitted two sets of data analysis based on two different cutoff values of serum cortisol level (≤ 14 $\mu\text{g/dL}$ and ≤ 18 $\mu\text{g/dL}$) to define HPA axis suppression. The Applicant proposed that the analysis based on the lower cutoff value (≤ 14 $\mu\text{g/dL}$), together with an LC-MS/MS analytical method, be the primary means of evaluating HPA axis suppression over the higher cutoff value (≤ 18 $\mu\text{g/dL}$). The analyses based on these two cutoff values are presented in Table 18 and Table 19.

Table 18. Analysis of HPA Axis Suppression Based on a 30-Minute Poststimulation Cortisol Level of ≤ 18 $\mu\text{g/dL}$ (Sandoz Cosyntropin USPI, Polyclonal Antibody-Based Assay)

Evaluations		HPA Axis Suppression, n/N (%)
Week 4	Overall	6/26 (23.1)
Week 8	Overall	3/25 (12.0)
	HPA-axis suppressed both at Weeks 4 and 8 ¹	1/5 (20.0)
	HPA-axis suppressed at Week 8 only ²	2/20 (10.0)

Source: Adapted from Table 23, clinical study report of MC2-01-C3

¹ Denominator is the number of subjects HPA-axis suppressed at Week 4 and who had an HPA-axis assessment at Week 8.

² Denominator is the number of subjects not HPA-axis suppressed at Week 4 and who had an HPA-axis assessment at Week 8.

Abbreviations: HPA, hypothalamic–pituitary–adrenal; USPI, United States prescribing information

Table 19. Analysis of HPA Axis Suppression Based on a 30-Minute Poststimulation Cortisol Level of ≤ 14 $\mu\text{g/dL}$ ((b) (4) LC-MS/MS Assay)

Evaluations		HPA-Axis Suppression, n/N (%)
Week 4	Overall	1/27 (3.7)
Week 8	Overall	2/26 (7.7)
	HPA-axis suppressed both at Weeks 4 and 8 ¹	1/1 (100.0)
	HPA-axis suppressed at Week 8 only ²	1/25 (4.0)

Source: Adapted from Table 21 of the clinical study report of MC2-01-C3

¹ Denominator is the number of subjects HPA axis-suppressed at Week 4 and who had an HPA axis assessment at Week 8.

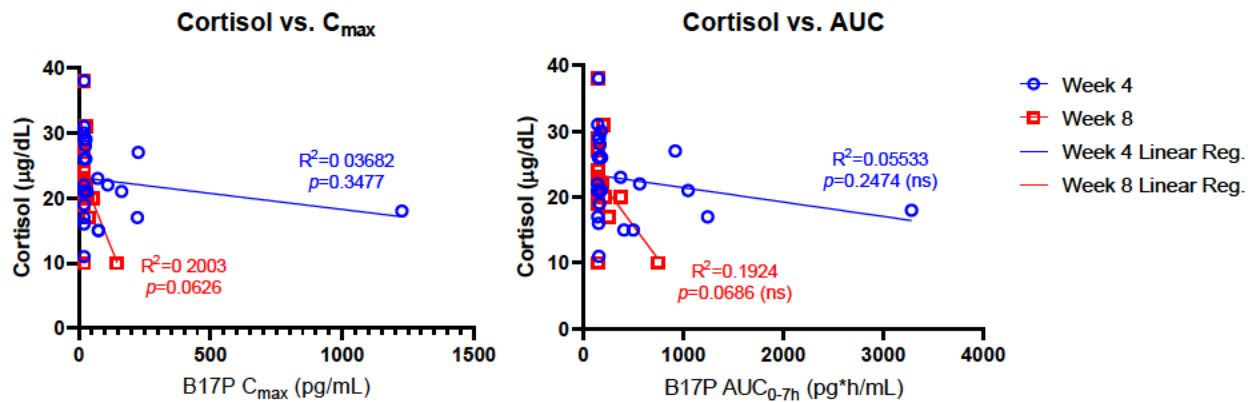
² Denominator is the number of subjects not HPA axis-suppressed at Week 4 and who had an HPA axis assessment at Week 8.

Abbreviations: HPA, hypothalamic–pituitary–adrenal; LC-MS/MS, liquid chromatography–tandem mass spectrometry

To date, the Agency has used ≤ 18 $\mu\text{g/dL}$ determined by immunoassay as the standard cutoff cortisol value for determining HPA axis suppression from an ACTH challenge test. Although LC-MS/MS may be more sensitive and selective than an immunoassay, as the Applicant stated; the new cutoff value, (b) (4) $\mu\text{g/dL}$, has not been adequately validated and hence not acceptable at this time. Thus, the analysis presented in Table 18 was used for review of the application and to inform the labeling recommendations regarding HPA axis suppression.

The possible correlations between the 30 min poststimulation cortisol level and systemic exposure of B17P and average weekly dose of CAL/BDP Cream administered were evaluated. As illustrated in Figure 5 and Figure 6, no meaningful correlation was found.

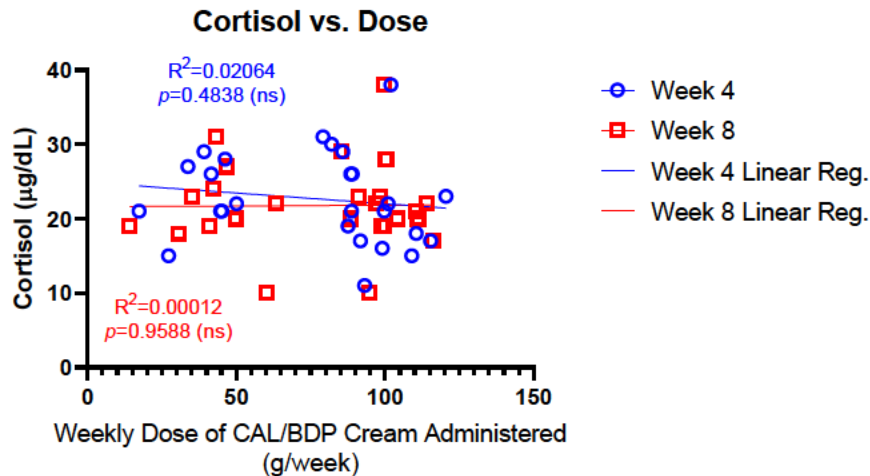
Figure 5. Poststimulation Cortisol Level vs. Systemic Exposure of B17P



Source: Reviewer's plot

Abbreviations: AUC_{0-7h} , area under the concentration-time curve from 0 to 7 hr; C_{max} , maximum concentration, B17P, betamethasone 17-propionate

Figure 6. Poststimulation Cortisol Level vs. Average Weekly Dose of CAL/BDP Cream Administered



Source: Reviewer's plot

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene

Effect on Calcium Metabolism

The effect on calcium metabolism of CAL/BDP Cream was evaluated in two studies—MC2-01-C3 and MC2-01-C2.

In Study MC2-01-C3, changes from Baseline to Week 4 or Week 8 in 24 hr urinary calcium excretion, urinary calcium to creatinine ratio, and albumin-corrected serum calcium level were evaluated in subjects treated with CAL/BDP Cream. The subjects were asked not to change their diet during the trial to limit diet-related variability in urinary calcium excretion. Specifically, the subjects were asked not to consume more than five servings of calcium daily and to keep a diary of their daily intake of dairy products, calcium-fortified products, and other specified calcium-rich products. No significant change in the daily intake of calcium was observed in these subjects.

The average 24 hr urine calcium excretion decreased from Baseline to Week 4 and Week 8 (Table 20). The number of subjects with a shift in the 24 hr urine calcium excretion is listed in Table 21. No significant concern was observed based on the data in the shift table.

The average urinary calcium to creatinine ratio from Baseline to Week 4 decreased by 0.24 and was unchanged from Baseline to Week 8 (Table 22). The number of subjects with a shift in 24 hr urine calcium excretion are listed in Table 23. No significant concern was observed based on the data in the shift table.

The average albumin-corrected serum calcium did not change from Baseline to Week 4 or Week 8 (Table 24). No subject had an albumin-corrected serum calcium level above the upper reference range, and no significant concern was observed according to the data in the shift table (Table 25).

The data in Table 20 to Table 25 suggest that once daily administration of CAL/BDP Cream did not result in meaningful changes in calcium metabolism in Study MC2-01-C3.

Table 20. Summary of 24 Hr Urinary Calcium Excretion (mmol/Day), Study MC2-01-C3

		Observed Value	Change From Baseline ¹
Baseline	N	30	-
	Mean (SD)	3.20 (2.35)	-
Week 4	N	25	24
	Mean (SD)	2.92 (1.76)	-0.56 (1.69)
Week 8	N	21	20
	Mean (SD)	2.69 (1.67)	-0.45 (1.08)

Source: Adapted from Table 28 in the clinical study report of MC2-01-C3

¹Subjects with both Baseline and Week 4 or Week 8 assessment.

Table 21. Summary of Shifts in 24 Hr Urinary Calcium Excretion From Baseline, Study MC2-01-C3

	Baseline to Week 4, n (%)	Baseline to Week 8, n (%)
Missing → Missing	7 (21.9)	11 (34.4)
Missing → Low Normal	1 (3.1)	1 (3.1)
Low Normal → Low Normal	8 (25.0)	8 (25.0)
Low Normal → Normal	2 (6.3)	1 (3.1)
Normal → Low Normal	1 (3.1)	
Normal → Normal	11 (34.4)	11 (34.4)
Normal → High Normal	1 (3.1)	
High Normal → Normal	1 (3.1)	

Source: Adapted from Table 30 in the clinical study report of MC2-01-C3

Table 22. Summary of Urinary Calcium to Creatinine Ratio, Study MC2-01-C3

		Observed Value	Change From Baseline ¹
Baseline	N	30	-
	Mean (SD)	2.63 (1.61)	-
Week 4	N	25	24
	Mean (SD)	2.40 (1.39)	-0.23 (1.49)
Week 8	N	21	20
	Mean (SD)	2.68 (1.60)	0.00 (1.32)

Source: Adapted from Table 29 in the clinical study report of MC2-01-C3

¹Subjects with both Baseline and Week 4 or Week 8 assessment

Reference ranges of the urinary calcium to creatinine ratio are 0.225 to 8.2 for females and 0.3 to 6.1 for males

Table 23. Summary of Shifts in Urinary Calcium to Creatinine Ratio From Baseline, Study MC2-01-C3

	Baseline to Week 4, n (%)	Baseline to Week 8, n (%)
Missing → Missing	7 (21.9)	11 (34.4)
Missing → Normal	1 (3.1)	1 (3.1)
Normal → Normal	22 (68.8)	20 (62.5)
Normal → High Normal	1 (3.1)	
High Normal → Normal	1 (3.1)	

Source: Adapted from Table 14.3.2.2.3 in the clinical study report of MC2-01-C3

Table 24. Summary of Albumin-Corrected Serum Calcium Level (mmol/L), Study MC2-01-C3

	Observed Value	Change From Baseline
Baseline	N Mean (SD)	32 - 2.21 (0.08) -
Week 4	N Mean (SD)	27 27 2.20 (0.10) -0.00 (0.09)
Week 8	N Mean (SD)	26 26 2.21 (0.09) 0.00 (0.07)

Source: Adapted from Table 31 in the clinical study report of MC2-01-C3

Table 25. Summary of Shifts in Albumin-Corrected Serum Calcium Level From Baseline, Study MC2-01-C3

	Baseline to Week 4, n (%)	Baseline to Most Extreme Postbaseline Value Up to Week 4, n (%)	Baseline to Week 8, n (%)	Baseline to Most Extreme Postbaseline Value Up to Week 8, n (%)
Missing → Missing	5 (15.6)	1 (3.1)	6 (18.8)	1 (3.1)
Low Normal → Low Normal	2 (6.3)	2 (6.3)	3 (9.4)	2 (6.3)
Low Normal → Normal	3 (9.4)	3 (9.4)	2 (6.3)	3 (9.4)
Normal → Low Normal	6 (18.8)	7 (21.9)	4 (12.5)	7 (21.9)
Normal → Normal	16 (50.0)	19 (59.4)	17 (53.1)	19 (59.4)

Source: Adapted from Table 32 in the clinical study report of MC2-01-C3

The effect of CAL/BDP Cream on changes in calcium metabolism was also evaluated in study MC2-01-C2 (Phase 3) by assessing the calcium to creatinine ratio and albumin-corrected serum calcium level.

In Study MC2-01-C2, three subjects in the CAL/BDP treatment group had a high albumin-corrected serum calcium level:

- Subject ID (b) (6) had a normal calcium level at Baseline and Week 4, but a high calcium level at the end-of-study visit. The urinary calcium to creatinine ratios of this subject were within the normal range throughout the study.
- Subject ID (b) (6) had a normal calcium level at Baseline, which shifted to high at Week 4. The level returned to within the normal range at Week 8. The urinary calcium to creatinine ratios for this subject were within the normal range throughout the study.

- Subject ID (b) (6) had a normal calcium level at Baseline, which shifted to high at Week 6 and to low at Week 8. The urinary calcium to creatinine ratios of this subject were within the normal range throughout the study.

One subject in the vehicle group had a normal calcium level at Baseline but had a high level at Week 4. This subject's calcium level returned to within the normal range at Week 8 and the urinary calcium to creatinine ratios of this subject were within the normal range throughout the study.

The calcium to creatinine ratios for the majority of subjects were within the normal range throughout the study. In the CAL/BDP Cream group, from Baseline to Week 4, one subject (0.3%) shifted from a normal to low, three subjects (0.9%) shifted from a high to normal, and two subjects (0.6%) shifted from a normal to high calcium to creatinine ratio. From Baseline to Week 8, one subject (0.3%) shifted from a normal to low and two subjects (0.6%) shifted from a high to normal calcium to creatinine ratio.

The results from Study MC2-01-C2 did not suggest that treatment with CAL/BDP Cream results in significant changes in calcium metabolism. For further information see the Clinical Review (Section 0).

Potency Classification

To support potency classification of CAL/BDP Cream, Study MC2-01-C4, a single-point vasoconstriction study, was conducted. Study MC2-01-C4 was an active- and vehicle-controlled, single-application, intraindividual comparison (n=7 sites) study in 36 healthy subjects. The demographics of these subjects are summarized in Table 26. The seven drug products listed in Table 27 were randomly applied to seven test sites of 2.2 cm diameter on the anterior surface of the forearms. Each test site was protected and covered with a nonocclusive gauze dressing for 16 hr of exposure. After 16 hr, remaining product was removed; after a further 2 hr, the degree of skin blanching was visually assessed by two independent, blinded investigators.

Table 26. Summary of Demographics, Study MC2-01-C4

Demographic	CAL/BDP Cream (N=36)
Sex	
Female	28 (77.8%)
Male	8 (22.2%)
Age (years)	
Mean ± SD	34.36±6.57
Min, max	22.0, 45.0
Skin type	
II	9 (25.0%)
III	24 (66.7%)
IV	3 (8.3%)
Weight (kg)	
Mean ± SD	68.46±14.15
Min, max	44.5, 117.0

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Demographic	CAL/BDP Cream (N=36)
Sex	
Height (cm)	
Mean ± SD	169.64±8.89
Min, max	156.0, 192.0

Source: Adapted from Table 5 in the clinical study report of MC2-01-C4
Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene

Table 27. Drug Products Used, Study MC2-01-C4

Brand Name	Generic Name	Group/ Class	Potency	Rationale
CAL/BDP (MC2-01) Cream	CAL/BDP, 0.005% 0.064%	-	-	-
CAL/BDP (MC2-01) Vehicle	-	-	-	-
Clobex® Lotion	Clobetasol propionate 0.05%	I	Super potent	Representative of super potency
Betamethasone Dipropionate (Augmented) Cream	Betamethasone dipropionate 0.05%	II	Potent	Representative of a potent group
Triamcinolone Acetonide Cream	Triamcinolone acetonide 0.1%	IV	Mid-strength	Representative of a mid- strength group
Locoid® Cream	Hydrocortisone-17- butyrate 0.1%	V	Lower mid- strength	Representative of a lower medium group
DesOwen® Cream	Desonide 0.05%	VI	Mild	Lowest potency used in psoriasis (face or folds)

Source: CRS of MC2-01-C4
Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene

The skin blanching visual scores are summarized in Table 28 and illustrated in Figure 7. The vasoconstrictive effect of CAL/BDP Cream was of significantly lesser magnitude than that of Clobex Lotion and Betamethasone Dipropionate 0.05% Cream, which are super-potent and potent corticosteroids, respectively. The vasoconstrictive effect of CAL/BDP Cream was comparable to that of Triamcinolone Acetonide Cream, a mid-strength corticosteroid.

Although the study results demonstrated that CAL/BDP Cream has a lesser vasoconstrictive effect than the two potent corticosteroids in Class I and Class II and a comparable effect to the mid-potent corticosteroid, there were no statistically significant differences among Locoid Cream, DesOwen Cream, and Triamcinolone Acetonide Cream. Hence, the data did not permit determination of the potency class of CAL/BDP Cream. Because current labeling practice does not distinguish between mid-strength class products as upper-mid, mid, and lower-mid (Class III, IV, and V, respectively), the extant data place this product in the mid-potency class but do not allow identification of the upper-mid, mid, and lower-mid potency class. The review team notes the very high variability in the data for DesOwen cream, which is considered a mild-potency topical corticosteroid. Because of their very high variability, the data for DesOwen cream would have little influence on decision making. Despite the weakness of the study, the results suggest that CAL/BDP Cream appears to be a mid-strength corticosteroid. This information is sufficient to support the labeling language in Section 12.2 of the labeling.

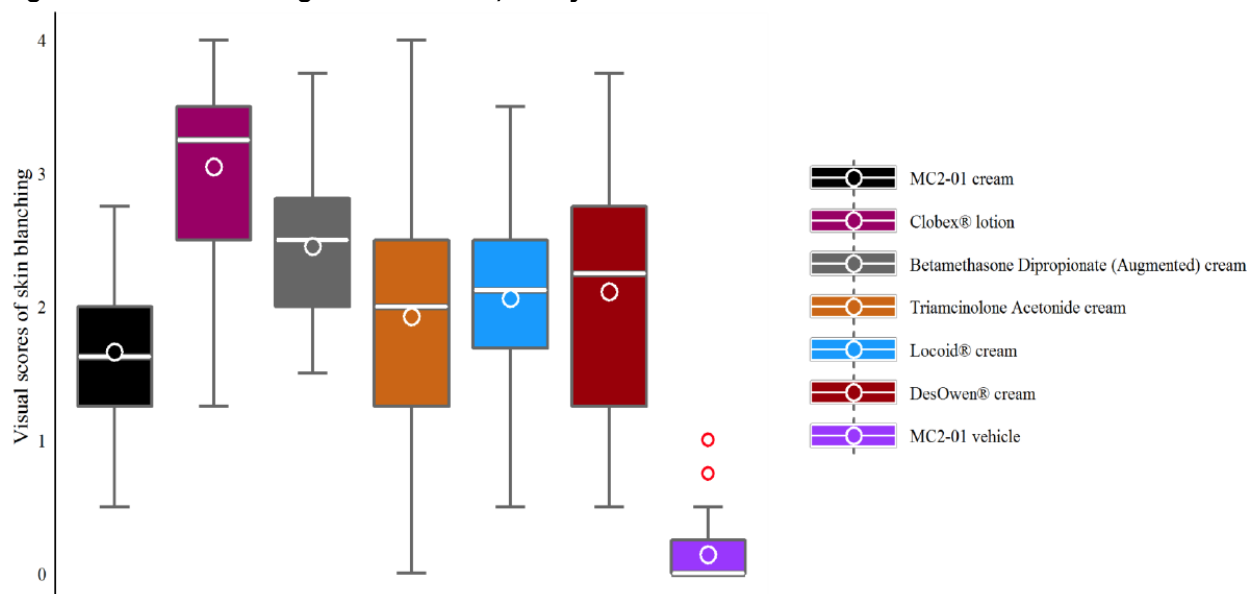
Table 28. Skin Blanching Visual Scores, Study MC2-01-C4

	CAL/BDP Cream	Clobex® Lotion	Betamethasone Dipropionate (Augmented) Cream	Triamcinolone Acetonide Cream	Locoid® Cream	DesOwen® Cream	MC2-01 Vehicle
N	36	36	36	36	36	36	36
Mean ± SD	1.66±0.57	3.05±0.65	2.45±0.61	1.92±0.89	2.06±0.70	2.11±0.85	0.14±0.25
Median	1.6	3.2	2.5	2.0	2.1	2.2	0.0
(Min,max)	(0.5,2.8)	(1.2,4.0)	(1.5,3.8)	(0.0,4.0)	(0.5,3.5)	(0.5,3.8)	(0.0,1.0)
p-value		<0.001	<0.001	0.210	0.015	0.005	<0.001
Estimate diff.		1.39	0.79	0.26	0.40	0.45	-1.52
95% CI		(1.0,1.7)	(0.4,1.1)	(-0.1,0.6)	(0.1,0.8)	(0.1,0.8)	(-1.9,-1.2)

Source: Adapted from Table 7 in the clinical study report of MC2-01-C4

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; CI, confidence interval

Figure 7. Skin Blanching Visual Scores, Study MC2-01-C4



Source: Figure 2 in the clinical study report of MC2-01-C4

White horizontal line, median; white circle, mean; box, interquartile range (IQR); whiskers, 1.5× IQR; red circles, outliers

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Not applicable. The purpose of the Clinical Pharmacology program in this NDA was to provide safety data; efficacy was not assessed.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen is appropriate and is supported by the systemic safety and bridging results from the maximal-use study (MC2-01-C3) and the efficacy and safety results from a Phase 3 trial (MC2-01-C2).

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The effect of intrinsic and extrinsic factors on the PK was not evaluated in this NDA because of the limited quantification of systemic concentrations.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food-drug interaction studies are not needed for topical products. Drug-drug interaction assessment was not needed for this product because this is a 505(b)(2) application and a clinical bridge with the LD was established.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 29. Clinical Trials Relevant to NDA 213422

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>								
MC2-01-C2	03308799	Phase 3, randomized, multicenter, investigator-blind, parallel-group trial	MC2-01 (CAL/BDP) cream MC2-01 vehicle Taclonex® Topical Suspension Applied topically once daily on trunk and/or limbs	<u>Primary efficacy:</u> Treatment success at Week 8, defined as minimum 2-point decrease from baseline to Week 8 in PGA score (i.e., a PGA of 0 or 1 if moderate disease at baseline; PGA of 0 if mild disease at baseline)	8 weeks	796	Adult patients with stable plaque psoriasis that involved the trunk and/or limbs with a PGA of 2 (mild) or 3 (moderate), mPASI ≥2, and BSA 2-30%	Fifty-five sites, all in the US
<i>Studies to Support Safety</i>								
MC2-01-C3	03462927	Phase 2, randomized, open-label MUsT	MC2-01 cream Taclonex® Ointment Applied topically once daily	PK of active ingredients and their main metabolites at Week 4; for MC2-01, PK of active ingredients and main metabolites at Week 8	MC2-01 cream: 8 weeks Taclonex® Ointment: 4 weeks	63	Adults with extensive psoriasis vulgaris; PGA of at least 3 (moderate) and BSA 20-30% on trunk, limbs, and scalp	Ten sites, all in the US

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Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
<i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i>								
MC2-01-C1		Vehicle and active-controlled, randomized, intrasubject, parallel group, observer-blind trial	MC2-01 cream MC2-01 (CAL) cream MC2-01 (BDP) cream MC2-01 vehicle Daivobet® Ointment ¹ Daivobet® Gel ² Applied topically once daily 6 days/week (50 µL per test field (1.5 cm ²))	Primary Efficacy: Absolute change in TCS from baseline visit (Day 1) to end of study visit (Day 29)	4 weeks	Randomized: N=33; completed: N=29	Adult patients with stable plaque psoriasis	Two sites in Germany
MC2-01-C4	03758365	Single-center, single-application, randomized, investigator-blinded, active- and vehicle-controlled trial with intraindividual comparison in healthy subjects	MC2-01 cream MC2-01 vehicle cream Clobex® (clobetasol propionate) Lotion, 0.05% Betamethasone Dipropionate (Augmented), 0.064% Triamcinolone Acetonide Cream, 0.1% Locoid® (hydrocortisone butyrate) Cream, 0.1% DesOwen® (desonide) Cream, 0.05% Topical (20 µL per test field [diameter 2.2 cm])	Primary: Mean of two (2) visual skin blanching scores for each treatment measured 2 hr after application for 16 hr under nonocclusive conditions	Single application for 16 hr	36	Healthy volunteers	One site in France

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WYNZORA (calcipotriene/betamethasone dipropionate) Cream, 0.005%/0.064%

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
MC2-16-C1		Vehicle- and active-controlled, randomized, intrasubject, observer-blind	MC2-01 cream MC2-01 (CAL) cream MC2-01 vehicle Daivobet® Ointment Daivonex® Cream ³ Daivonex® Ointment ⁴ Applied topically once daily 6 days/week (50 µL per test field [3 cm ²])	Primary efficacy: Absolute change in TCS from baseline to EOT	4 weeks	24	Adult patients with stable plaque psoriasis	One site in France
MC2-01-C9	03892564	Randomized, single-center, double-blind, controlled, within-subject comparison trial	MC2-01 cream MC2-01 cream vehicle	<u>Primary Objective:</u> To determine the phototoxic potential of MC2-01 cream when topical application to healthy skin was followed by light exposure	24 hr	35	Healthy volunteers	One site in the US
MC2-01-C10	03899064	Randomized, single-center, double-blind, controlled, within-subject comparison trial	MC2-01 cream MC2-01 cream vehicle	Primary objective: To determine the photoallergic potential of MC2-01 cream when topical application to healthy skin was followed by light exposure	In total seven series of applications, each of a duration of 24 hr (±4 hr)	58	Healthy volunteers	One site in the US

Source: Applicant's NDA submission, Module 5.2 and the clinical study reports of the listed studies.

¹ Daivobet (CAL/BDP) Ointment, 0.005%/0.064%, LEO Pharma Ltd., approved in Europe

² Daivobet (CAL/BDP) Gel, 0.005%/0.064%, LEO Pharma Ltd., approved in Europe

³ Daivonex® (CAL) Cream, 0.005%, LEO Pharma Ltd., approved in Europe

⁴ Daivonex® (CAL) Ointment, 0.005%, LEO Pharma Ltd., approved in Europe

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; DB, double-blind; EOT, end of treatment; MC2-01 cream; CAL/BDP, 0.005/0.064%; mPASI, modified Psoriasis Area and Severity Index; MUsT, maximal-usage trial; OL, open-label; PGA, Physician's Global Assessment; PK, pharmacokinetic; TCS, total clinical score (sum of the erythema, scaling, and infiltration subscores, each of which is scored from 0 to 4); BSA, body surface area

7.2. Review Strategy

Data Sources

The data sources used for the evaluation of the efficacy and safety of CAL/BDP Cream included the Applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. The submission was submitted in electronic common technical document format and was entirely electronic. Both Study Data Tabulation Model datasets and Analysis Data Model datasets were submitted. The analysis datasets used in this review are archived at:

- [Application 213422–Sequence 0001–Data Analysis Data](#) (Phase 3 trial MC2-01-C2)
- [Application 213422–Sequence 0001–Data Analysis Data](#) (Phase 2 trial MC2-01-C3)

Data and Analysis Quality

The statistical and clinical teams in conjunction with the JumpStart team evaluated the fitness of the data. In general, the data submitted by the Applicant to support the safety and efficacy of CAL/BDP Cream for the proposed indication appear to be adequate.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study Design and Endpoints

Trial MC2-01-C2 was a randomized, multicenter, investigator-blinded, vehicle and active-comparator controlled, parallel-group, Phase 3 trial to demonstrate noninferiority of CAL/BDP Cream, 0.005%/0.064% (CAL/BDP Cream; also referred by the Applicant as MC2-01) to Taclonex (CAL/BDP) Topical Suspension, 0.005%/0.064% in subjects with mild-to-moderate psoriasis on the body (i.e., trunk and/or limbs, excluding the genital skin). For enrollment, the protocol specified the following key inclusion criteria:

- At least 18 years of age
- Clinical diagnosis of plaque psoriasis of at least 6-month duration that involves the trunk and/or limbs and is amenable to topical treatment with a maximum of 100 g of trial medication per week
- PGA score of 2 (mild) or 3 (moderate) on the body (trunk and/or limbs); see Table 30
- Modified Psoriasis Area and Severity Index (mPASI) score of ≥ 2
- Treatment area involving 2% to 30% of the BSA

The trial was designed to enroll and randomize approximately 791 subjects from approximately 57 centers in the United States in a 3:3:1 ratio to CAL/BDP Cream (N=339), Taclonex Topical Suspension (N=339), or vehicle cream (N=113). The protocol specified that the randomization be stratified by investigational site and baseline severity (PGA score of 2 [mild] or 3

[moderate]). In addition, the protocol specified that the proportion of subjects with a baseline PGA score of 2 (mild) would be limited to approximately 30%.

The subjects topically applied the study product once daily in the evening to affected areas of the trunk and/or limbs, excluding the genital skin, for 8 weeks. The subjects were scheduled to attend eight study visits: Screening (Day -30 to -1), baseline (Day 0), and Weeks 1, 2 (telephone), 4, 6, 8 (end of treatment), and 10 (2-week follow-up).

The protocol-specified primary efficacy endpoint was the proportion of subjects with treatment success at Week 8. Treatment success was defined as a PGA score of 0 (clear) or 1 (almost clear) with at least a two-grade reduction from baseline. The protocol specified first comparing CAL/BDP Cream and Taclonex Topical Suspension against vehicle cream for superiority. If both active treatments are superior to vehicle cream, then the protocol specified testing for noninferiority of CAL/BDP Cream to Taclonex Topical Suspension.

The protocol specified the following as secondary efficacy endpoints:

- Percentage change from baseline in mPASI score at Week 8
- “Subject assessment of treatment convenience at Week 8 using a Psoriasis Treatment Convenience Scale”
- Absolute change from baseline on the itch NRS at Week 4 (CAL/BDP Cream vs. vehicle cream)
- Proportion of subjects with a four-point improvement from baseline on the itch NRS at Week 4 (CAL/BDP Cream vs. vehicle cream)

For the second secondary efficacy endpoint, the total PTCS score was calculated by summing the responses to the first five questions.

The protocol specified several other efficacy endpoints; however, it also stated that the statistical analyses for these endpoints will be “exploratory only and not for statistical inference.” Therefore, the results of these endpoints are considered exploratory and are not included in this review.

Table 30. Physician's Global Assessment Scale

Score	Grade	Definition
0	Clear	Plaque thickening = no elevation or thickening of normal skin Scaling = no evidence of scaling Erythema = none (no residual red colouration but post-inflammatory hypo or hyperpigmentation may be present)
1	Almost clear	Plaque thickening = none or possible thickening but difficult to ascertain whether there is a slight elevation above normal skin level Scaling = none or residual surface dryness and scaling Erythema = light pink colouration
2	Mild	Plaque thickening = slight but definite elevation Scaling = fine thin scales partially or mostly covering lesions Erythema = light red colouration
3	Moderate	Plaque thickening = moderate elevation with rounded or sloped edges Scaling = coarse scale layer at least partially covering most lesions Erythema = definite red colouration
4	Severe	Plaque thickening = marked or very marked elevation typically with hard or sharp edges Scaling = non-tenacious or thick tenacious scale predominates, covering most or all of the lesions Erythema = very bright red colouration, extreme red coloration, or deep red coloration

Source: Page 37 of the protocol

Modified Psoriasis Area and Severity Index

The Psoriasis Area and Severity Index (PASI) is a weighted sum score endpoint that typically ranges from 0 to 72. The mPASI score ranges from 0 to 64.8 because the calculation excludes involvement of the head. The extent of psoriatic involvement for each of the three areas (arms, trunk, and legs) was determined using the following scale:

- 0 = no involvement
- 1 = <10%
- 2 = 10% to 29%
- 3 = 30% to 49%
- 4 = 50% to 69%
- 5 = 70% to 89%
- 6 = 90% to 100%

Within each body area, the severity of psoriatic lesions for each of redness, thickness, and scaliness was evaluated according to the following scales:

- 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)

The sum of the three severity parameters is calculated for each body area, multiplied by the area score for that body area, and finally multiplied by the weight of the respective area (i.e., arms, 20%, trunk, 30%; and legs, 40%). The sum of the scores of the arms, trunk, and legs is the final mPASI score.

Psoriasis Treatment Convenience Scale

The PTCS consists of six disease-specific, self-report questions with a recall period of 1 week, and is rated on a scale of 1 to 10.

1. How easy was the treatment to apply to the skin?
2. How greasy was the treatment when applying it to the skin?
3. How moisturized did your skin feel after applying the treatment?
4. How greasy did your skin feel after applying the treatment?
5. How much did treating your skin disrupt your daily routine?
6. Overall, how satisfied were you with the medical treatment?

Itch Numerical Rating Scale

The itch NRS is an 11-point scale, the ends of which represent the two extremes of itch intensity; i.e., from 0 (no itch at all) to 10 (worst itch one can imagine).

8.1.2. Statistical Methodologies

The protocol specified that efficacy analyses be conducted using the following populations:

- ITT population: All randomized subjects
- Per-protocol (PP) population: All subjects in the ITT population who completed the trial without any major protocol violations. The protocol specified that subjects may be excluded from the PP population if any of the following criteria are met:
 - Failure to meet key inclusion/exclusion criteria; i.e., violation of inclusion/exclusion criteria that according to medical judgement may impact the primary endpoint analysis
 - Usage of restricted medications/treatments; i.e., medications/treatments that according to medical judgement may impact the primary endpoint analysis
 - Noncompliance with the visit schedule; at Week 8 $\pm$ 7 days
 - Noncompliance with the trial treatment regimen; compliance with the treatment schedule defined as application of IP as specified by the investigator for at least 80% of the days from Week 4 to Week 8
 - Noncompliance with the trial treatment regimen; compliance with the treatment schedule is defined as application of IP as per subject diary for at least 80% of the days from Day 1 to Week 8

The protocol-specified primary analysis population for testing for superiority was the ITT population. The PP population was specified as the primary analysis population for testing for noninferiority. The statistical analysis plan (SAP) defined the ITT population as all subjects who were randomized and dispensed the trial medication. The SAP specified that subjects who return all trial medications unused would be excluded from the ITT population.

The protocol specified stratifying the randomization by baseline severity (PGA score of 2 [mild] or 3 [moderate]) and investigational site. In the protocol, the Applicant stated that the aim is to randomize 14 subjects or more at each site. Sites that did not meet this minimum were specified to be combined based on geographical proximity. These combined sites as well as individual sites with a sufficient number of subjects are referred to as “analysis sites.”

For the primary efficacy endpoint (i.e., proportion of subjects with treatment success at Week 8), the protocol specified testing each of the two active treatments (i.e., CAL/BDP Cream and Taclonex Topical Suspension) against vehicle cream for superiority using logistic regression with treatment, baseline PGA score, and analysis site as factors in the model. If both CAL/BDP Cream and Taclonex Topical Suspension are superior to vehicle at the 0.05 level, then the protocol specified testing for noninferiority of CAL/BDP Cream to Taclonex Topical Suspension. The protocol and SAP did not specify testing CAL/BDP Cream against Taclonex Topical Suspension for superiority. The protocol specified calculating the 95%, two-sided CI for the difference between CAL/BDP Cream and Taclonex Topical Suspension. Noninferiority is claimed if the lower bound of the 95% CI is $\geq -10\%$. The protocol specified that the noninferiority margin be determined according to the FDA guidance for industry *Noninferiority Clinical Trials*. The Applicant determined their noninferiority margin using the results from three randomized trials; see Table 31. The M1 margin was determined to be 19.9% (i.e., the lower 99% CI limit of

the response difference between Taclonex Suspension and vehicle). For the M2 margin, the Applicant stated that the largest loss of effect that would be clinically acceptable is 10%.

Table 31. Efficacy Results at Week 8 Used to Determine Noninferiority Margin

	Taclonex Topical Suspension		Vehicle		Difference	
Study	N	PGA Success ¹ %	N	PGA Success ¹ %	%	99% CI
(Menter et al. 2013)	482	29.0	95	6.3	22.7	(14.4, 31.1)
(Langley et al. 2011)	183	39.9	91	5.5	34.4	(23.2, 45.6)
(Fleming et al. 2010)	162	27.2	40	0	27.2	(18.2, 36.2)
Overall					26.2	(19.9, 32.6)

¹ Success is defined as achievement of a PGA of 0 (clear) or 1 (almost clear) with at least a two-grade reduction from baseline.
Abbreviations: CI, confidence interval; PGA, Physician's Global Assessment

As with the primary efficacy endpoint, the protocol specified testing each of the two active treatment groups against vehicle cream for superiority for the secondary endpoint of percentage change from baseline in mPASI score at Week 8. The protocol-specified analysis method was analysis of covariance with treatment, baseline PGA score, baseline mPASI score, and analysis site as factors in the model. If both CAL/BDP Cream and Taclonex Topical Suspension were superior to vehicle cream, then the protocol specified testing for noninferiority of CAL/BDP Cream to Taclonex Topical Suspension. The protocol-specified noninferiority margin for this was -10%. For this secondary endpoint, the protocol and SAP did not specify testing CAL/BDP Cream against Taclonex topical suspension for superiority.

For the second secondary endpoint of subject assessment of treatment convenience at Week 8 using the PTCS, the protocol-specified analysis method was ANOVA with treatment and analysis site as factors in the model. The protocol specified that the PTCS total score is the sum of the scores for questions 1 to 5. For this secondary endpoint, the protocol and SAP only specified testing CAL/BDP Cream against Taclonex Topical Suspension for superiority.

For the third secondary endpoint of absolute change from baseline in itch NRS at Week 4, the protocol-specified analysis method was analysis of covariance with treatment, baseline PGA score, baseline itch NRS, and analysis site as factors in the model. For this secondary endpoint, the protocol and SAP only specified testing CAL/BDP Cream against vehicle cream for superiority.

For the fourth secondary endpoint (i.e., proportion of subjects with a ≥4-point improvement from baseline on the itch NRS at Week 4), the protocol-specified analysis method was logistic regression with treatment, baseline PGA score, baseline itch NRS, and analysis site as factors in the model. For this secondary endpoint, the protocol and SAP only specified only testing CAL/BDP Cream against vehicle cream for superiority.

To control the global Type I error rate, the protocol specified the following testing procedure:

- “Secondary endpoints will be tested only if the primary endpoint will reject the null hypothesis”
- “The two secondary endpoints ‘Percentage reduction from baseline in the mPASI score at Week 8,’ and ‘Subject assessment of treatment convenience at Week 8 using a PTCS’ will be tested with a loopback procedure with initial error probability weights of 2/3 for H1 (mPASI) and 1/3 for H2 (subject assessment of treatment convenience), resulting in $\alpha_1=0.0333$ and $\alpha_2=0.0167$. If any of the null hypotheses can be rejected, the respective error probability will be shuffled to the other hypothesis”
- “If and only if both noninferiority of MC2-01 to active comparator with respect to percentage reduction from baseline in mPASI as well as superiority of MC2-01 vs. active comparator with respect to psoriasis treatment convenience scale has been demonstrated, superiority of MC2-01 vs. vehicle with respect to the below endpoints will be tested in a hierarchical manner based on a significance level of 5%:
 - Change in itch intensity assessed on a numerical rating scale (itch by NRS) from baseline to Week 4
 - Percentage of subjects with four-point improvement on the numerical rating scale (itch by NRS) from baseline to Week 4 (in the subgroup of subjects with an NRS score ≥ 4 at baseline)”

For the analysis of the primary endpoint using the ITT population, the protocol-specified primary method for handling missing data was the multiple imputation approach. The protocol specified first using the Markov Chain Monte Carlo (MCMC) method to impute non-monotone missing PGA score data, after which imputation is performed using the regression method. The protocol specified including duration (days) of psoriasis, prior systemic biologic use for psoriasis (yes/no), baseline PGA score, and PGA scores at Weeks 1, 4, 6, and 8 in the model for imputation. The protocol specified imputing the missing data 100 times for each treatment group separately. The protocol specified using the last observation carried forward, baseline observation carried forward, and nonresponder imputation as sensitivity analyses for the handling of missing data. For the primary efficacy endpoint (i.e., binary endpoint), baseline observation carried forward and nonresponder imputation are the same because all subjects are nonresponders at baseline.

For the analysis of the secondary endpoints based on mPASI score and itch NRS using the ITT population, the SAP specified that missing data will be imputed by multiple imputation using a method similar to that described above for the primary endpoint.

As previously noted, the secondary endpoint based on the PTCS total score is the sum of the scores for questions 1 to 5. The protocol specified that the score is to be calculated if at most two of the questions have missing answers, in which case the missing answers will be imputed from the mean of the answered questions. If more than two questions have missing answers, the PTCS total score will be considered as missing. In addition, the protocol specified that a PTCS score is defined as “valid,” if subjects have used the study medication at some point

within 7 days prior to the day of the assessment. Missing and invalid PTCS scores are specified to be imputed using the last valid measure prior to the visit.

8.1.3. Subject Disposition, Demographics, and Baseline Disease Characteristics

Table 32 presents the subject disposition for trial MC2-01-C2. A total of 796 subjects from 55 investigational sites in the United States was enrolled and randomized (343 to CAL/BDP Cream, 338 to Taclonex Topical Suspension, and 115 to vehicle cream). Two subjects were excluded from the ITT population. One subject in the CAL/BDP Cream group was excluded because the study product was not dispensed and one subject in the Taclonex Topical Suspension group was excluded because the study product was returned sealed and unused. Subjects totaling 124 were excluded from the PP population; the reasons were primarily noncompliance with the visit scheduled at Week 8±7 days and noncompliance with the treatment regimen. The discontinuation rate was higher in the vehicle group compared to the two active groups. The primary reasons for discontinuations were withdrawal by subjects and loss to follow-up.

Table 32. Subject Disposition

	CAL/BDP Cream	Taclonex Topical Suspension	Vehicle Cream
Randomized	343	338	115
ITT population	342	337	115
PP population	302	282	88
<i>Reasons for exclusion from PP</i>			
Not in ITT	1	1	0
Usage of restricted medications/treatments	1	4	2
Noncompliance with the visit at Week 8±7 days	27	42	25
Noncompliance with trial treatment regimen	26	31	17
Subjects discontinued	22 (6%)	28 (8%)	21 (18%)
Adverse event	2 (1%)	1 (<1%)	2 (2%)
Death	1 (<1%)	0	1 (1%)
Withdrawal by subject	6 (2%)	15 (4%)	10 (9%)
Loss to follow-up	11 (3%)	8 (2%)	7 (6%)
Protocol withdrawal criterion	1 (<1%)	1 (<1%)	0
Other	1 (<1%)	3 (1%)	1 (1%)

Source: Statistical Reviewer's analysis (same as Applicant's analysis)

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; ITT, intent-to-treat; PP, per protocol

The demographics for trial MC2-01-C2 are presented in Table 33 and were generally comparable across the treatment groups. The subjects in the vehicle cream group were on average slightly younger than those in the two active treatment groups. In addition, the proportion of males in the Taclonex Topical Suspension group was slightly larger than that in the other two treatment groups. The baseline disease characteristics were generally comparable across the treatment groups and are presented in Table 34.

Table 33. Demographics (ITT Population)

	CAL/BDP Cream (N=342)	Taclonex Topical Suspension (N=337)	Vehicle Cream (N=115)
Age (years)			
Mean (SD)	52.0 (14.4)	52.6 (13.7)	50.4 (14.3)
Median	53.0	54.0	51.0
Range	19 to 89	18 to 89	20 to 81
Categories			
18 to 64	276 (81%)	272 (81%)	94 (82%)
≥65	66 (19%)	65 (19%)	21 (18%)
Sex			
Male	203 (59%)	221 (66%)	71 (62%)
Female	139 (41%)	116 (34%)	44 (38%)
Race			
White	290 (85%)	299 (89%)	102 (89%)
Black or African American	34 (10%)	20 (6%)	11 (10%)
Asian	10 (3%)	10 (3%)	1 (1%)
American Indian or Alaska Native	3 (1%)	3 (1%)	1 (1%)
Multiple	2 (1%)	3 (1%)	0
Native Hawaiian or Pacific Islander	2 (1%)	1 (<1%)	0
Other	1 (<1%)	1 (<1%)	0
Ethnicity			
Hispanic or Latino	101 (30%)	94 (28%)	31 (27%)
Not Hispanic or Latino	241 (70%)	243 (72%)	84 (73%)

Source: Statistical Reviewer's analysis (same as Applicant's analysis)

Abbreviations: ITT, intent-to-treat; BDP, betamethasone dipropionate; CAL, calcipotriene

The baseline disease characteristics were generally comparable across the treatment groups and are presented in Table 34.

Table 34. Baseline Disease Characteristics (ITT Population)

	CAL/BDP Cream (N=342)	Taclonex Topical Suspension (N=337)	Vehicle Cream (N=115)
PGA Score			
2 – mild	68 (20%)	57 (17%)	20 (17%)
3 – moderate	274 (80%)	280 (83%)	95 (83%)
mPASI Score			
Mean (SD)	7.3 (3.9)	7.7 (4.1)	7.1 (4.1)
Median	6.4	6.7	6.1
Range	1.2 to 22.5	1.8 to 28.8	2.0 to 19.4
Percentage BSA			
Mean (SD)	7.3 (6.0)	8.4 (7.0)	7.5 (6.1)
Median	5.0	6.0	5.0
Range	2.0 to 30.0	2.0 to 30.0	2.0 to 30.0

	CAL/BDP Cream (N=342)	Taclonex Topical Suspension (N=337)	Vehicle Cream (N=115)
Itch NRS Score ¹			
Mean (SD)	6.0 (2.8)	5.9 (2.7)	5.7 (2.9)
Median	6	6	6
Range	0 to 10	0 to 10	0 to 10
Categories			
Missing	3 (1%)	2 (<1%)	0
<4	64 (19%)	70 (21%)	29 (25%)
≥4	275 (80%)	265 (79%)	86 (75%)

Source: Statistical Reviewer's analysis (same as Applicant's analysis, except for itch NRS)

¹ Five subjects (three on CAL/BDP Cream and two on Taclonex Topical Suspension) that did not have baseline NRS scores. The Applicant's baseline disease characteristics table imputed these subjects using multiple imputation.

Abbreviations: BDP, betamethasone dipropionate; BSA, body surface area; CAL, calcipotriene; ITT, intent-to-treat; mPASI, modified Psoriasis Area and Severity Index; NRS, numerical rating scale; PGA, Physician's Global Assessment

8.1.4. Results of the Primary Efficacy Endpoint

Table 35 presents the results of the primary efficacy endpoint (i.e., treatment success at Week 8) for superiority against the vehicle cream in both the ITT and PP populations. CAL/BDP Cream was statistically superior to vehicle cream ($p < 0.001$) in both populations. The response rates were slightly higher in the PP population than the ITT population for all treatment groups.

Table 35. Primary Efficacy Endpoint Results at Week 8 for Superiority Against Vehicle Cream

	CAL/BDP Cream	Taclonex Topical Suspension	Vehicle Cream
ITT population ¹	N=342	N=337	N=115
Treatment success ² at Week 8	37.4%	22.8%	3.7%
Difference from vehicle (95% CI)	33.7% (27.4%, 40.0%)	19.1% (13.9%, 24.9%)	-
P-value ³	<0.001	<0.001	-
PP population	N=302	N=279	N=88
Treatment success ² at Week 8	40.1%	24.0%	4.5%
Difference from vehicle (95% CI)	35.5% (28.5%, 42.6%)	19.5% (12.8%, 26.1%)	-
P-value ³	<0.001	<0.001	-

Source: Statistical Reviewer's analysis (same as Applicant's analysis)

¹ Missing data were imputed using multiple imputation; the rates displayed are the averages over the 100 imputed datasets.

² Treatment success is defined as a PGA score of 0 (clear) or 1 (almost clear) with at least a two-grade reduction from baseline.

³ P-value based on logistic regression with treatment and baseline Physician's Global Assessment score as factors in the model.

Analysis site is not included in the model due to partial data separation. The comparison is against vehicle cream.

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; CI, confidence interval; ITT, intent-to-treat; PP, per protocol

Table 36 presents the results of the primary efficacy endpoint for noninferiority of CAL/BDP Cream to Taclonex Topical Suspension in both the PP and ITT populations. In both populations, noninferiority of CAL/BDP Cream to Taclonex Topical Suspension was demonstrated as the lower bound of the 95% CIs were $> -10\%$.

Table 36. Results of Primary Efficacy Endpoint at Week 8 for Noninferiority of CAL/BDP Cream to Taclonex Topical Suspension

	CAL/BDP Cream	Taclonex Topical Suspension
PP Population	N=302	N=279
Treatment success ¹ at Week 8	40.1%	24.0%
Difference	16.1%	-
95% CI	(8.6%, 23.5%)	-
ITT Population ²	N=342	N=337
Treatment success ¹ at Week 8	37.4%	22.8%
Difference	14.6%	-
95% CI	(7.6%, 21.6%)	-

Source: Statistical Reviewer's analysis (same as Applicant's analysis)

¹ Treatment success is defined as a Physician's Global Assessment score of 0 (clear) or 1 (almost clear) with at least a two-grade reduction from baseline.² Missing data were imputed using multiple imputation; the rates displayed are the averages over the 100 imputed datasets.

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; ITT, intent-to-treat; PP, per protocol; CI, confidence interval

Table 37 presents the number of subjects with missing data for the primary efficacy endpoint along with the results of the primary endpoint across the various prespecified imputation methods. The results were generally similar across the various methods.

Table 37. Results of Primary Efficacy Endpoint at Week 8 With Different Approaches for Handling Missing Data (ITT)

	CAL/BDP Cream (N=342)	Taclonex Topical Suspension (N=337)	Vehicle Cream (N=115)	Superiority CAL/BDP Cream vs. Vehicle Cream Difference (95% CI)	Noninferiority CAL/BDP Cream vs. Taclonex Topical Suspension Difference (95% CI)
Subjects with missing data	29 (6.7%)	47 (13.9%)	25 (21.7%)	-	-
MI (primary) ¹	37.4%	22.8%	3.7%	33.7% (27.4%, 40.0%)	14.6% (7.6%, 21.6%)
LOCF	38.2%	24.3%	3.6%	34.6% (28.4%, 40.8%)	13.9% (7.0%, 20.8%)
NRI	36.0%	20.8%	3.5%	32.5% (26.4%, 38.6%)	15.2% (8.5%, 21.9%)

Source: Statistical Reviewer's analysis (same as Applicant's analysis)

¹ Missing data were imputed using MI; the rates displayed are the averages over the 100 imputed datasets.

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; CI, confidence interval; ITT, intent-to-treat; LOCF, last observation carried forward; MI, multiple imputation; NRI, nonresponder imputation

8.1.5. Results of Secondary Efficacy Endpoints

Table 38 presents the results of the secondary efficacy endpoint of percentage reduction from baseline in mPASI score at Week 8. For this endpoint, CAL/BDP Cream was statistically superior to vehicle cream ($p < 0.001$) and noninferior to Taclonex Topical Suspension (lower bounds of the 96.7% CIs were $> -10\%$) in both the ITT and PP populations.

Table 38. Results of Secondary Efficacy Endpoint of Percentage Reduction From Baseline in mPASI Score at Week 8

	CAL/BDP Cream	Taclonex Topical Suspension	Vehicle Cream
Superiority Against Vehicle Cream			
ITT population ¹	N=342	N=337	N=115
Mean	62.9%	51.3%	22.9%
LS mean ²	63.2%	51.1%	22.8%
Difference from vehicle (95% CI)	40.4%	28.4%	-
	(32.7%, 48.1%)	(20.7%, 36.1%)	
P-value	<0.001	<0.001	-
PP population	N=302	N=279	N=88
Mean	64.8%	52.3%	25.7%
LS Mean ²	65.1%	52.0%	25.4%
Difference from vehicle (95% CI)	39.7%	26.6%	-
	(32.6%, 46.8%)	(19.4%, 33.7%)	
P-value	<0.001	<0.001	-
Noninferiority Against Taclonex Topical Suspension			
PP population	N=302	N=279	N=88
Mean	64.8%	52.3%	25.7%
LS mean ²	65.1%	52.0%	25.4%
Difference from Taclonex	13.1%	-	-
96.7% CI	(7.8%, 18.4%)	-	-
ITT population ¹	N=342	N=337	N=115
Mean	62.9%	51.3%	22.9%
LS mean ²	63.2%	51.1%	22.8%
Difference from Taclonex	12.0%	-	-
96.7% CI	(7.0%, 17.0%)	-	-

Source: Statistical Reviewer's analysis (same as Applicant's analysis).

¹ Missing data were imputed using multiple imputation.

² LS mean, difference, CI, and P-value are based on analysis of covariance, with treatment, baseline PGA score, baseline mPASI score, and analysis site as factors in the model.

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; CI, confidence interval; ITT, intent-to-treat; PP, per protocol; LS, least squares; mPASI, modified psoriasis area and severity index; PGA, Physician's Global Assessment

Table 39 presents the results of the secondary efficacy endpoint of PTCS total score at Week 8 for the ITT population. For this endpoint, CAL/BDP Cream was statistically superior to Taclonex Topical Suspension ($p < 0.001$). The results for the PP population (not shown) were similar to those for the ITT population.

Table 39. Results of Secondary Efficacy Endpoint of PTCS Total Score at Week 8 (ITT¹)

Endpoint	CAL/BDP Cream	Taclonex Topical Suspension	Vehicle Cream
PTCS total score at Week 8	N=338 ²	N=334 ²	N=110 ²
Mean	41.5	37.5	36.7
LS mean ³	41.5	37.5	36.7
Difference from Taclonex (98.3% CI)	4.0 (2.7, 5.3)	-	-
P-value	<0.001	-	-

Source: Statistical Reviewer's analysis (same as Applicant's analysis)

¹ Missing data were imputed using last valid measure prior to the visit.

² Subjects with valid PTCS total scores. The score is deemed valid if the subject used the study medication at some point within 7 days prior to the day of the assessment.

³ LS mean, difference, CI, and P-value are based on analysis of variance, with treatment, baseline Physician's Global Assessment score, and analysis site as factors in the model.

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; CI, confidence interval; ITT, intent-to-treat; LS, least squares; mPASI, modified psoriasis area and severity index; PTCS, psoriasis treatment convenience scale

Table 40 presents the results of the secondary efficacy endpoints based on the itch NRS at Week 4 for the ITT population. For both secondary efficacy endpoints, CAL/BDP Cream was statistically superior to vehicle cream ($p < 0.001$). The results for the PP population (not shown) were very similar to those for the ITT population.

Table 40. Results of Secondary Efficacy Endpoints Based on Itch NRS at Week 4 (ITT¹)

Endpoint	CAL/BDP Cream	Vehicle Cream	Taclonex Topical Suspension
Change (reduction) from baseline in itch NRS at Week 4	N=339 ²	N=115 ²	N=335 ²
Mean	3.5	1.0	3.2
LS mean ³	3.5	1.1	3.2
Difference from vehicle (95% CI)	2.4 (1.9, 2.9)	-	-
P-value	<0.001	-	-
≥4-Point improvement from baseline on itch NRS at Week 4	N=275 ⁴	N=86 ⁴	N=265 ⁴
Proportion	60.3%	21.4%	55.6%
Difference from vehicle (95% CI)	39.0% (28.2%, 49.7%)	-	-
P-value ⁵	<0.001	-	-

Source: Statistical Reviewer's analysis

¹ Missing data imputed using multiple imputation.

² Subjects with a baseline itch NRS score.

³ LS mean, difference, CI, and P-value are based on analysis of covariance, with treatment, baseline PGA score, baseline itch NRS score, and analysis site as factors in the model.

⁴ Subjects with a baseline itch NRS score ≥ 4.

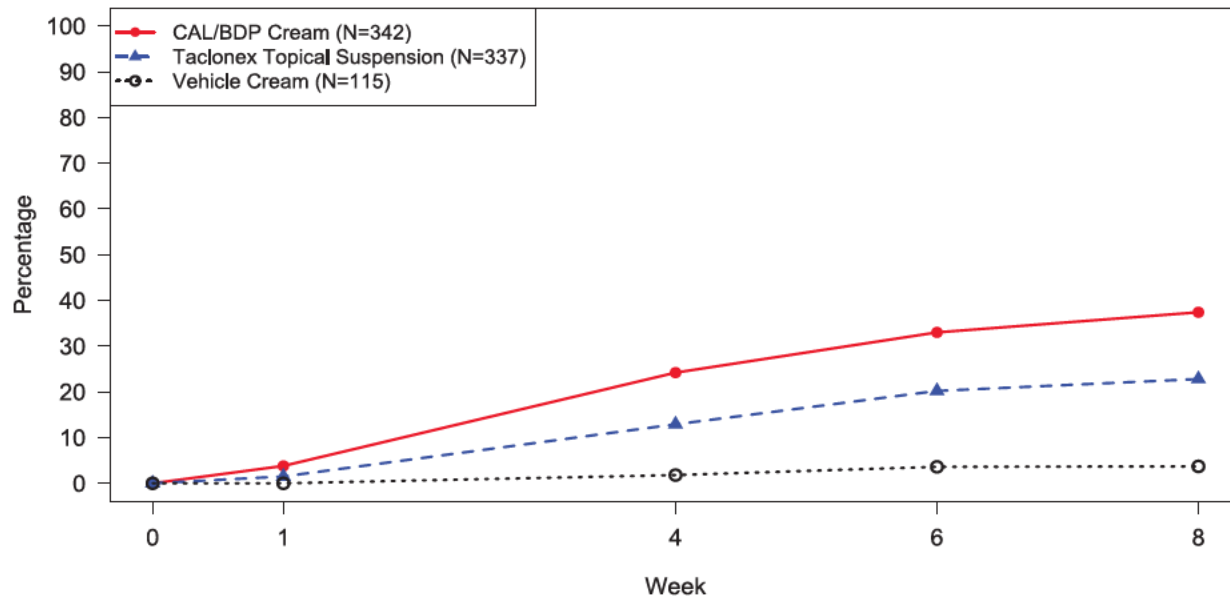
⁵ P-value based on logistic regression with treatment, baseline PGA score, baseline itch NRS score, and analysis site as factors in the model.

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; CI, confidence interval; ITT, intent-to-treat; LS, least squares; NRS, numerical rating scale; PGA, Physician's Global Assessment

8.1.6. Efficacy Over Time

Figure 8 presents the treatment success results (i.e., PGA score of 0 [clear] or 1 [almost clear] with at least a two-grade reduction from baseline) over time.

Figure 8. Results for Treatment Success¹ Over Time (ITT²)



Source: Statistical Reviewer's analysis

¹ Treatment success is defined as a Physician's Global Assessment score of 0 (clear) or 1 (almost clear) with at least a two-grade reduction from baseline.

² Missing data were imputed using multiple imputation; the rates displayed are the averages over the 100 imputed datasets.

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; ITT, intent-to-treat

8.1.7. Findings in Special/Subgroup Populations

Sex, Age, Race, and Baseline PGA Score

Table 41 presents the results of the primary efficacy endpoint at Week 8 by sex, age (<65 and ≥65 years), race (white and non-white), and baseline PGA score for the CAL/BDP Cream group vs. the vehicle cream group. The treatment effect was smaller in subjects with a baseline PGA score of 2 (mild) compared to those with a baseline PGA score of 3 (moderate).

Table 41. Results of Primary Efficacy Endpoint at Week 8 by Sex, Age, Race, and Baseline PGA Score for CAL/BDP Cream vs. Vehicle Cream (ITT¹)

Subgroups (n[C], n[V])	CAL/BDP Cream (N=342)	Vehicle Cream (N=115)	Difference	Difference (95% CI)
Sex				
Males (203, 71)	39.8%	3.0%	36.7%	
Females (139, 44)	33.9%	4.7%	29.3%	
Age (years)				
18-64 (276, 94)	35.0%	3.4%	31.7%	
65+ (66, 21)	47.2%	4.9%	42.3%	
Race				
White (290, 102)	36.7%	4.0%	32.7%	
Non-White (52, 13)	40.9%	0.5%	40.4%	
Baseline PGA				
2 - Mild (68, 20)	11.9%	0%	11.9%	
3 - Moderate (274, 95)	43.7%	4.4%	39.3%	
Overall	37.4%	3.7%	33.7%	

Source: Statistical Reviewer's analysis

¹ Missing data were imputed using multiple imputation; the rates displayed are the averages over the 100 imputed datasets.

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; CI, confidence interval; ITT, intent-to-treat; PGA, Physician's Global Assessment

Figure 9 presents the results of the primary efficacy endpoint at Week 8 by sex, age (<65 and ≥65 years), race (white and non-white), and baseline PGA score for the CAL/BDP Cream group vs. the Taclonex Topical Suspension group. The response rate for the CAL/BDP group was higher than that for the Taclonex Topical Suspension group in all of these subgroups, with the exception of subjects with a baseline PGA score of 2 (mild).

Figure 9. Results of Primary Efficacy Endpoint at Week 8 by Sex, Age, Race, and Baseline PGA Score for CAL/BDP Cream vs. Taclonex Topical Suspension (ITT¹)

Subgroups (n[C], n[T])	CAL/BDP Cream (N=342)	Taclonex Topical Suspension (N=337)	Difference	Difference (95% CI)
Sex				
Males (203, 221)	39.8%	24.0%	15.7%	
Females (139, 116)	33.9%	20.3%	13.6%	
Age (years)				
18-64 (276, 272)	35.0%	21.8%	13.3%	
65+ (66, 65)	47.2%	26.9%	20.3%	
Race				
White (290, 299)	36.7%	21.6%	15.2%	
Non-White (52, 38)	40.9%	32.0%	8.9%	
Baseline PGA				
2 - Mild (68, 57)	11.9%	14.2%	-2.3%	
3 - Moderate (274, 280)	43.7%	24.5%	19.2%	
Overall	37.4%	22.8%	14.6%	

Source: Statistical Reviewer's analysis

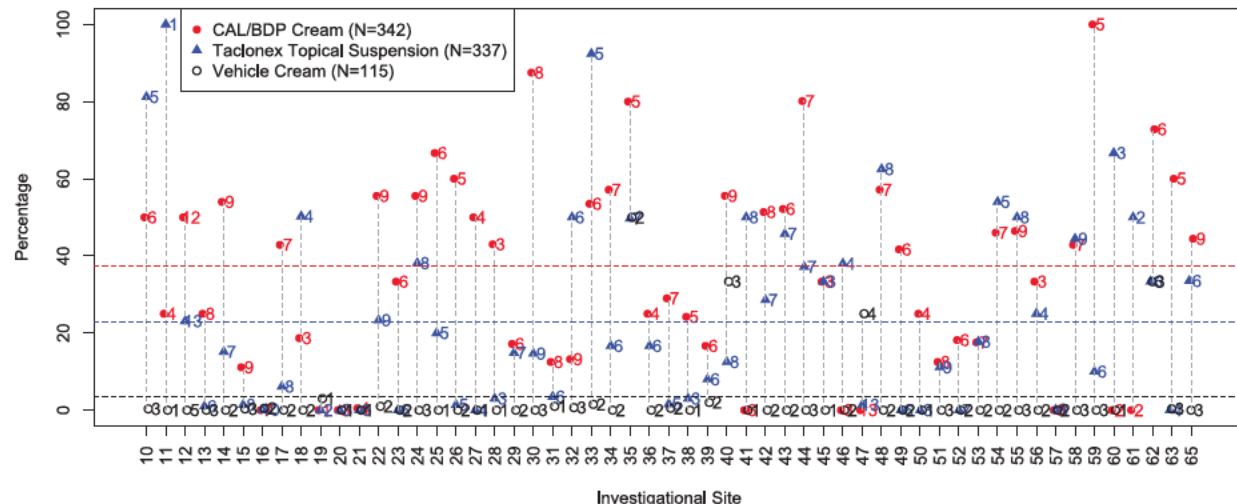
¹ Missing data were imputed using multiple imputation; the rates displayed are the averages over the 100 imputed datasets.

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; CI, confidence interval; ITT, intent-to-treat; PGA, Physician's Global Assessment

8.1.8. Investigational Site

Trial MC2-01-C2 enrolled and randomized subjects from 55 investigational sites in the United States. Figure 10 presents the results of the primary efficacy endpoint at Week 8 by investigational site in the ITT population. The response rate for CAL/BDP Cream was higher than that for vehicle cream at all but two sites. In addition, the majority of the sites had a response rate higher for CAL/BDP Cream than for Taclonex Topical Suspension.

Figure 10. Results of Primary Efficacy Endpoint at Week 8 by Investigational Site (ITT¹)



Source: Statistical Reviewer's analysis

¹ Missing data were imputed using multiple imputation; the rates displayed are the averages over the 100 imputed datasets.

² Dotted horizontal line denotes the overall result for each treatment group (red [top] for CAL/BDP Cream, blue [middle] for Taclonex Topical Suspension, and black [bottom] for vehicle cream).

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; ITT, intent-to-treat

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary review of safety for CAL/BDP Cream for the topical treatment of plaque psoriasis focuses on data from Phase 3 trial MC2-01-C2. Trial MC2-01-C2 was a randomized, multicenter, investigator-blind, parallel-group trial in adult subjects with stable plaque psoriasis.

The Phase 3 trial population included 794 subjects ≥ 18 years of age with mild-to-moderate plaque psoriasis, defined as a PGA score of 2 (mild) or 3 (moderate), mPASI score of ≥ 2 , and BSA of 2 to 30%. Subjects were randomized 3:1:3 to treatment with CAL/BDP Cream, vehicle cream, or Taclonex Topical Suspension.

During the Phase 3 trial, subjects applied the study product to affected areas of the trunk or limbs (i.e., not including the scalp, face, or intertriginous areas) once daily for up to 8 weeks. If a subject was classified as clear at any visit while on treatment, they were allowed to stop the treatment at the investigator's discretion. Such subjects would remain in the trial and attend all visits up to and including the follow-up visit. The study drug would continue to be dispensed,

and subjects could restart treatment at their own discretion. Investigators conducted safety and efficacy assessments at Baseline followed by Weeks 1, 4, 6, and 8. The safety population as defined and discussed in Section 8.2.2 and included 342 subjects treated with CAL/BDP Cream.

The Applicant also submitted supportive safety data from a Phase 2, open-label PK/BA trial conducted under MUsT conditions, a vasoconstriction study, two dermal safety studies, and two psoriasis plaque test (PPT) trials conducted in Europe.

To determine the safety profile of CAL/BDP Cream, the review team analyzed the following types of data: exposure, demographics, baseline characteristics, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, laboratory results, vital signs, and findings from physical examinations. In addition, the review team evaluated the effect of CAL/BDP Cream on calcium metabolism and the potential of CAL/BDP Cream to cause HPA axis suppression.

8.2.2. Review of the Safety Database

Overall Exposure

The primary analysis dataset for the review of safety for CAL/BDP Cream included data from Phase 3 trial MC2-01-C2. Data from the other trials were not integrated because of dissimilar study designs and different dose regimens.

The Phase 3 safety population includes all subjects who were randomized and dispensed the trial medication at Baseline (Day 0), excluding subjects who returned all the trial medication unused. The ITT and safety populations were identical (N=794). The safety population included 342 subjects treated with CAL/BDP Cream, 337 treated with Taclonex Topical Suspension, and 115 treated with vehicle cream.

For the Phase 3 trials, the Applicant summarized exposure by treatment duration in days as well as by the amount of study drug applied (g/day). The mean treatment duration was 54.5 days in the CAL/BDP Cream group, 53.8 days in the Taclonex Topical Suspension group, and 49.8 days in the vehicle cream group. The mean amount of drug used per week was 33.8 g in subjects treated with CAL/BDP Cream, 27.1 g in subjects treated with Taclonex Topical Suspension, and 42.7 g in subjects treated with vehicle cream.

Relevant Characteristics of the Safety Population

In the safety and ITT populations for the Phase 3 trial, the majority of subjects were white (87.0%), male (62.3%), and 40 to 64 years of age (60.5%). A total of 152 (19.1%) subjects was 65 years of age or older. The demographic characteristics of the two treatment groups were comparable. Most subjects were non-Hispanic or Latino (71.5%) Refer to Appendix 14.5 for the demographic characteristics of the subjects in the safety population.

Adequacy of the Safety Database

The total subject exposure to CAL/BDP Cream applied once daily for up to 8 weeks provides adequate data for the evaluation of safety. The demographics of the study population are sufficiently representative of the target population. Therefore, the safety database submitted by the Applicant is sufficient to characterize the safety profile of CAL/BDP Cream for the topical treatment of plaque psoriasis.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of CAL/BDP Cream for the topical treatment of plaque psoriasis in the adult population. Data quality and fitness were evaluated in conjunction with the JumpStart team. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

The Applicant defined an AE as "an untoward medical occurrence in any subject during the trial that does not necessarily have a causal relationship with the trial drug treatment." Also, the Applicant defined TEAEs as "those (AEs) that started after the first application of the trial medication or started before this and worsened in intensity after (first application of trial medication)." TEAEs form the primary basis of the review of safety.

Investigators assessed for AEs at each visit during the trial by nondirective questioning of the subjects, signs and symptoms detected during examinations, observations of trial personnel, and spontaneous reports from subjects. Investigators recorded all AEs in the electronic case report form, including a description of the AE, relationship to study product administration, start and stop dates, seriousness, severity, action taken and outcome. Investigators categorized the severity of the AE according to the following criteria:

- Mild: The subject was aware of the signs and symptoms but the signs and symptoms were easily tolerated and do not interfere with daily activity.
- Moderate: The signs and symptoms were sufficient to restrict, but did not prevent, usual daily activity for the subject. The subject is still able to function.
- Severe: The subject was unable to perform usual daily activity.

Investigators also assessed the relationship of the AE to treatment with the study drug using the following criteria:

- Not related: The AE is clearly explained by another cause not related to the trial product administration; the temporal relationship of the AE to IP administration makes a causal relationship unlikely, or, concomitant medication, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed AE.

- Possibly related: The AE and administration of trial product are temporally related, but the AE can be explained equally well by causes other than trial product administration.
- Probably related: The AE and use of trial product are temporally related, and the AE is more likely explained by trial product administration than by other causes.
- Definitely related: The AE and trial product administration are related in time, and a direct association can be demonstrated. Concomitant medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed AE.

An SAE was defined as an AE that met one of the following criteria:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect, or is an important medical event
- Other serious or important medical event

Investigators followed any AEs considered treatment related until resolved or until the medical condition of the subject was stable. Investigators classified the outcome of AEs as recovered, recovered with sequelae, recovering/resolving, ongoing, or death.

If a pregnancy occurred, treatment with the study drug was discontinued and investigators actively followed-up and documented the progress of the pregnancy until the outcome was reached.

Routine Clinical Tests

During the Phase 3 trial, investigators conducted safety assessments at Baseline followed by Weeks 1, 4, 6, and 8. In addition, a telephone visit was conducted at Week 2 to assess for AEs as well as compliance with treatment. The evaluation of safety included assessment for AEs at every visit as well as vital signs (blood pressure and heart rate), physical examination, and pregnancy testing at Baseline followed by Weeks 4 and 8.

Investigators conducted clinical laboratory testing at Baseline, Weeks 4 and 8, and Week 10 (only if needed to follow up abnormal results from Week 8). Laboratory assessments included serum biochemistry and urinalysis. Urine pregnancy testing was performed on female subjects of reproductive potential at Screening and/or Baseline, followed by Weeks 4 and 8.

Investigators conducted an active assessment for local skin reactions (LSRs) at all visits during the Phase 3 trial. LSRs included perilesional erythema, scaling, edema, atrophy, vesicles, and

erosion/ulceration, as well as lesional vesicles and erosion/ulceration. Subjects were also queried for the symptom of burning or pain at the application site. LSRs were scored as follows:

- 0 = absent
- 1 = mild
- 2 = moderate
- 3 = severe

8.2.4. Safety Results

Deaths

Two deaths occurred during the development program for CAL/BDP Cream. Both occurred during the Phase 3 trial MC2-01-C2. Brief narrative summaries for these subjects are provided below.

- A 74 y/o female (Subject (b) (6)) with a history of hypertension and hypercholesterolemia suffered a fatal myocardial infarction. She had been randomized to treatment with CAL/BDP Cream and was treated for 30 days prior to the event. The investigator considered the event not related to treatment. I concur with the investigator's assessment that this event was unrelated to treatment.
- A 58 y/o female (Subject (b) (6)) with a history of gastroesophageal reflux disease, xerosis, and throat infection died of an unknown cause. No further information was provided to the investigator. She had been randomized to treatment with vehicle and was treated for 16 days prior to the event. The investigator considered the event not related to treatment. I concur with the investigator's assessment that this event was unrelated to treatment.

Serious Adverse Events

During the Phase 3 trial, eight (8/342; 2.3%) subjects treated with CAL/BDP Cream reported nine SAEs, nine (9/337; 2.7%) subjects treated with Taclonex Topical Suspension reported 11 SAEs, and four (4/115; 3.5%) subjects treated with vehicle cream reported five SAEs. These SAEs are presented in Table 42.

Table 42. Treatment-Emergent SAEs, Phase 3 Safety Population

Body System or Organ Class Preferred Term	CAL/BDP Cream (N=342)	Taclonex Topical Suspension (N=337)	Vehicle Cream (N=115)
Cardiac disorders			
Angina pectoris	1 (0.3%)	0 (0.0%)	0 (0.0%)
Atrial fibrillation	0 (0.0%)	1 (0.3%)	0 (0.0%)
Myocardial infarction	1 (0.3%)	0 (0.0%)	1 (0.9%)
General disorders and administration site conditions			
Chest pain	0 (0.0%)	1 (0.3%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	1 (0.9%)
Pyrexia	0 (0.0%)	1 (0.3%)	0 (0.0%)
Hepatobiliary disorders			
Cholecystitis	0 (0.0%)	0 (0.0%)	1 (0.9%)

Body System or Organ Class Preferred Term	CAL/BDP Cream (N=342)	Taclonex Topical Suspension (N=337)	Vehicle Cream (N=115)
Infections and infestations			
Abscess	1 (0.3%)	0 (0.0%)	0 (0.0%)
Application site abscess	0 (0.0%)	1 (0.3%)	0 (0.0%)
Application site cellulitis	0 (0.0%)	1 (0.3%)	1 (0.9%)
Diverticulitis	0 (0.0%)	1 (0.3%)	0 (0.0%)
Nosocomial infection	1 (0.3%)	0 (0.0%)	0 (0.0%)
Pneumonia	1 (0.3%)	1 (0.3%)	0 (0.0%)
Injury, poisoning, and procedural complications			
Cervical vertebral fracture	1 (0.3%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders			
Dehydration	0 (0.0%)	1 (0.3%)	0 (0.0%)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)			
Cervix carcinoma	0 (0.0%)	1 (0.3%)	0 (0.0%)
Clear cell renal cell carcinoma	1 (0.3%)	0 (0.0%)	0 (0.0%)
Nervous system disorders			
Epilepsy	1 (0.3%)	0 (0.0%)	0 (0.0%)
Ischemic stroke	0 (0.0%)	0 (0.0%)	1 (0.9%)
Renal and urinary disorders			
Acute kidney injury	1 (0.3%)	0 (0.0%)	0 (0.0%)
Nephrolithiasis	0 (0.0%)	1 (0.3%)	0 (0.0%)
Respiratory, thoracic, and mediastinal disorders			
Chronic obstructive pulmonary disease	0 (0.0%)	1 (0.3%)	0 (0.0%)
Subjects	8 (2.3%)	9 (2.7%)	4 (3.5%)
Events	9	11	5

Source: Reviewer's table created in JReview using the ADSL and ADAE datasets

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; SAE, serious adverse event

Overall, SAEs were uncommon in the Phase 3 trial, and there was no imbalance in SAEs between the CAL/BDP Cream and vehicle cream groups. None of the SAEs was considered by the investigator to be related to the study drug. Narrative summaries of fatal SAEs were provided above. Brief narrative summaries for subjects treated with CAL/BDP Cream are presented below.

- A female subject "in her 70's" (Subject (b) (6)) experienced an abscess on the forearm on Day 3 of treatment. She was hospitalized for drainage of the abscess and treated with intravenous antibiotics. The event resolved and treatment with CAL/BDP Cream was resumed. The investigator considered the SAE not related to treatment because no psoriasis lesions were located, nor was the study drug administered near the application site.
- A female subject "in her 80's" (Subject (b) (6)) complained of shortness of breath at the Week 8 visit and had an abnormal electrocardiogram (ECG) showing nonspecific T changes. She was hospitalized and workup for myocardial infarction was negative. She was diagnosed with angina pectoris, which resolved 4 days after the start of the event. She had completed treatment with the study drug at the time of the event. The investigator considered the SAE of angina pectoris to not be related to treatment.
- A male subject "in his 70's" (Subject (b) (6)) was diagnosed with clear cell renal carcinoma on Day 40 of treatment and the study drug was discontinued. The outcome of the SAE was

reported as not recovered as of 82 days after the start of the event. The investigator considered the SAE of clear cell renal carcinoma to not be related to treatment.

- A male subject “in his 50’s” (Subject (b) (6)) sustained a nondisplaced cervical vertebral fracture in a motor vehicle accident on Day 27 of treatment. The study drug was continued, and the subject recovered from the fracture. The investigator considered the SAE of cervical vertebral fracture to not be related to treatment.
- A male subject “in his 40’s” (Subject (b) (6)) with a history of “mild epilepsy” had an epileptic seizure on Day 25 of treatment and was hospitalized. The study drug was discontinued during hospitalization but resumed after discharge. The SAE was reported as recovered on Day 31. The investigator considered the SAE of epileptic seizure to not be related to treatment.
- A male subject “in his 70’s” (Subject (b) (6)) was hospitalized with a sternal wound infection by *Candida albicans* on Day 7 of treatment with the study drug. His history was remarkable for recurrent sternal wound infections after a coronary artery bypass graft operation in 2016. He was treated with debridement, wound VAC, and fluconazole. The study drug was continued during his hospitalization. The SAE of nosocomial infection was reported as recovered with sequelae 66 days after onset of the event. The investigator considered the SAE of nosocomial infection to not be related to treatment.
- A male subject “in his 60’s” (Subject (b) (6)) was hospitalized on Day 26 with pneumonia and acute renal failure. The study drug was discontinued, and the outcome of the events was reported as recovered 7 days after the start of the event. The investigator considered the SAEs of acute kidney injury and pneumonia to not be related to treatment.

Dropouts and/or Discontinuations Caused by Adverse Effects

During the Phase 3 trial, discontinuations as a result of TEAEs were reported in two (2/342; 0.6%) subjects treated with CAL/BDP Cream, three (3/337; 0.9%) subjects treated with Taclonex Topical Suspension, and four (4/115; 3.5%) subjects treated with vehicle cream. One subject in the CAL/BDP Cream group with AEs leading to discontinuation was the male subject with an SAE of clear cell renal carcinoma and renal mass (Subject (b) (6); see the narrative above). The narrative for the other subject treated with CAL/BDP Cream who discontinued due to an AE is presented below.

- A male subject “in his 60’s” (Subject (b) (6)) experienced a TEAE of insomnia from Days 7 to 14 of treatment. The AE resolved on Day 14. However, the study drug was discontinued on Day 30. The investigator considered the AE of insomnia as probably related to treatment.

Of note, a male subject (Subject (b) (6)) with SAEs of pneumonia and acute renal failure also discontinued treatment on Day 26. However, the subject was not classified as a discontinuation because of an AE. No information was provided in the clinical study report regarding the reason the discontinuation was not classified as such.

Significant Adverse Events

During the Phase 3 trial, most TEAEs were of mild or moderate intensity. The following TEAEs of severe intensity were reported: six (6/342; 1.8%) subjects treated with CAL/BDP Cream had 8

SAEs, five (5/337; 1.5%) subjects treated with Taclonex Topical Suspension had 10 SAEs, and six (6/115; 5.2%) subjects treated with vehicle cream had 7 SAEs. SAEs by treatment group are presented in Table 43.

Table 43. Severe Treatment-Emergent Adverse Events, Phase 3 Safety Population

Body System or Organ Class Preferred Term	CAL/BDP Cream (N=342)	Taclonex Topical Suspension (N=337)	Vehicle Cream (N=115)
Cardiac disorders			
Atrial fibrillation	0 (0.0%)	1 (0.3%)	0 (0.0%)
Myocardial infarction	1 (0.3%)	0 (0.0%)	1 (0.9%)
General disorders and administration site conditions			
Application site pain	1 (0.3%)	0 (0.0%)	0 (0.0%)
Application site reaction	1 (0.3%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hepatobiliary disorders			
Cholelithiasis	0 (0.0%)	1 (0.3%)	0 (0.0%)
Infections and infestations			
Application site abscess	0 (0.0%)	1 (0.3%)	0 (0.0%)
Application site cellulitis	0 (0.0%)	1 (0.3%)	1 (0.9%)
Diverticulitis	0 (0.0%)	1 (0.3%)	0 (0.0%)
Pneumonia	1 (0.3%)	1 (0.3%)	0 (0.0%)
Musculoskeletal and connective tissue disorders			
Back pain	0 (0.0%)	0 (0.0%)	1 (0.9%)
Intervertebral disc protrusion	1 (0.3%)	0 (0.0%)	0 (0.0%)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)			
Cervix carcinoma	0 (0.0%)	1 (0.3%)	0 (0.0%)
Clear cell renal cell carcinoma	1 (0.3%)	0 (0.0%)	0 (0.0%)
Nervous system disorders			
Ischemic stroke	0 (0.0%)	0 (0.0%)	1 (0.9%)
Renal and urinary disorders			
Acute kidney injury	1 (0.3%)	0 (0.0%)	0 (0.0%)
Hematuria	0 (0.0%)	1 (0.3%)	0 (0.0%)
Hydronephrosis	0 (0.0%)	1 (0.3%)	0 (0.0%)
Nephrolithiasis	0 (0.0%)	1 (0.3%)	1 (0.9%)
Renal mass	1 (0.3%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders			
Psoriasis	0 (0.0%)	0 (0.0%)	1 (0.9%)
Subjects(filtered)	6 (1.8%)	5 (1.5%)	6 (5.2%)
Events	8	10	7

Source: Reviewer's table created in JReview using the ADSL and ADAE datasets

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene

Severe TEAEs in subjects treated with CAL/BDP Cream that were also classified as SAEs included one subject with clear cell renal carcinoma, one subject with acute kidney injury and pneumonia, and one subject with fatal myocardial infarction. These subjects are discussed in the SAE subsection above. The event of clear cell renal carcinoma also led to discontinuation of treatment with the study drug.

Two subjects treated with CAL/BDP Cream reported severe TEAEs involving the application site. One subject had application site pain beginning on Day 50 that resolved after 6 days. The other subject had an application site reaction (verbatim term: worsening of plaque psoriasis) beginning on Day 57 that resolved after 7 days.

Treatment-Emergent Adverse Events and Adverse Reactions

During the Phase 3 trial, TEAEs were reported by 90 (90/342; 26.3%) subjects in the CAL/BDP Cream group, 76 (76/337; 22.6%) in the Taclonex Topical Suspension group, and 32 (32/115; 27.8%) in the vehicle cream group. The most frequently reported TEAEs were in the system organ classes (SOCs) of Infections and Infestations as well as General Disorders and Administration Site Conditions. In the SOC of Infections and Infestations, the most commonly reported preferred terms (PTs) were nasopharyngitis and upper respiratory infections (URIs). In the SOC of General Disorders and Administration Site Conditions, the most commonly reported PTs were application site pruritus, dermatitis, irritation, and pain, as well as pyrexia.

For this topically applied product, application site reactions were of particular interest. Application site reactions reported as AEs are discussed here; the results from the active assessment of local safety are discussed in Section 8.2.5. We detected an imbalance between CAL/BDP Cream and vehicle in terms of application site irritation, which is discussed in detail below. TEAEs by SOC are presented in order of descending frequency in Table 44.

Table 44. Treatment-Emergent Adverse Event by System-Organ Class, Phase 3 Safety Population

Body System or Organ Class	CAL/BDP Cream (N=342)	Taclonex Topical Suspension (N=337)	Vehicle Cream (N=115)
Infections and infestations	45 (13.2%)	39 (11.6%)	18 (15.7%)
General disorders and administration site conditions	14 (4.1%)	11 (3.3%)	4 (3.5%)
Gastrointestinal disorders	7 (2.0%)	6 (1.8%)	3 (2.6%)
Nervous system disorders	6 (1.8%)	8 (2.4%)	2 (1.7%)
Respiratory, thoracic, and mediastinal disorders	8 (2.3%)	6 (1.8%)	1 (0.9%)
Injury, poisoning, and procedural complications	4 (1.2%)	4 (1.2%)	3 (2.6%)
Skin and subcutaneous tissue disorders	4 (1.2%)	5 (1.5%)	1 (0.9%)
Cardiac disorders	3 (0.9%)	6 (1.8%)	1 (0.9%)
Musculoskeletal and connective tissue disorders	4 (1.2%)	2 (0.6%)	3 (2.6%)
Investigations	2 (0.6%)	4 (1.2%)	2 (1.7%)
Metabolism and nutrition disorders	4 (1.2%)	2 (0.6%)	0 (0.0%)
Immune system disorders	2 (0.6%)	2 (0.6%)	2 (1.7%)
Renal and urinary disorders	2 (0.6%)	2 (0.6%)	2 (1.7%)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2 (0.6%)	3 (0.9%)	0 (0.0%)
Hepatobiliary disorders	2 (0.6%)	1 (0.3%)	1 (0.9%)
Psychiatric disorders	2 (0.6%)	2 (0.6%)	0 (0.0%)
Vascular disorders	0 (0.0%)	2 (0.6%)	1 (0.9%)
Eye disorders	0 (0.0%)	1 (0.3%)	1 (0.9%)

Body System or Organ Class	CAL/BDP Cream (N=342)	Taclonex Topical Suspension (N=337)	Vehicle Cream (N=115)
Reproductive system and breast disorders	1 (0.3%)	1 (0.3%)	0 (0.0%)
Endocrine disorders	1 (0.3%)	0 (0.0%)	0 (0.0%)
Ear and labyrinth disorders	0 (0.0%)	1 (0.3%)	0 (0.0%)
<i>Subjects</i>	90 (26.3%)	76 (22.6%)	32 (27.8%)

Source: Reviewer's table created in JReview using the ADSL and ADAE datasets

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene

Adverse Reactions

The Applicant proposed to include the following information in Section 6.1 (Adverse Reactions/Clinical Trials Experience) of the product labeling:



TEAEs that occurred in $\geq 1\%$ of subjects treated with CAL/BDP Cream and more frequently than among subjects treated with vehicle cream are listed in Table 45.

Table 45. Treatment-Emergent Adverse Events Occurring in $\geq 1\%$ of Subjects, CAL/BDP Group

	CAL/BDP Cream (n=342)	Taclonex Topical Suspension (n=337)	Vehicle Cream (n=115)
Preferred Term			
Pooled upper respiratory infection ¹	23 (6.7%)	18 (5.3%)	6 (5.2%)
Headache	5 (1.5%)	4 (1.2%)	0 (0.0%)
Application site irritation	3 (0.9%)	0 (0.0%)	0 (0.0%)

Source: Reviewer's table created in JReview using the ADSL and ADEX datasets

¹ Includes nasopharyngitis, upper respiratory tract infection (URTI), and viral URTI

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; TEAE, treatment-emergent adverse event

All TEAEs in Table 45 were of mild or moderate severity. To better characterize the frequency of URIs, we pooled the clinically related PTs of nasopharyngitis, upper respiratory tract infection (URTI), and viral URTI. Although the investigators considered none of the URIs to be related to treatment with CAL/BDP Cream, based on the information available in the submission, a relationship to treatment cannot be excluded. I recommend inclusion of URI in Section 6 (Adverse Reactions) of the product labeling.

Although the investigators considered headache to be treatment-related in only one subject in the CAL/BDP Cream group, it was also reported in 1.2% of the Taclonex Topical Suspension group. I recommend inclusion of headache in Section 6 of the product labeling. The investigators considered all cases of application site irritation to be related to treatment. I concur and recommend application site irritation be included in Section 6 of the product labeling.

The review team proposes inclusion of the following table in Section 6 (Adverse Reactions) of the product labeling:

Percentage of Subjects With Adverse Reactions at Week 8

Preferred Term	WYNZORA Cream (N=342)	Vehicle Cream (N=115)
Upper respiratory infection ¹	7%	5%
Headache	2%	0%
Application site irritation	1%	0%

Source: Reviewer's Table

¹ Includes nasopharyngitis, upper respiratory tract infection (URTI), and viral URTI

Abbreviations: CAL, calcipotriene; BDP, betamethasone dipropionate

Laboratory Findings

The investigators conducted clinical laboratory testing at Baseline, Weeks 4 and 8, and Week 10 (only if needed to follow up abnormal results from Week 8). The laboratory assessments included serum biochemistry and urinalysis. The serum biochemistry parameters assessed in the Phase 3 trial included serum calcium (albumin corrected), albumin, alkaline phosphatase, phosphate, and intact parathyroid hormone PTH. The mean changes from Baseline to Weeks 4 and 8 were small and comparable between the treatment groups.

The effect of CAL/BDP Cream on calcium metabolism is discussed in more detail in Section 6.3.1 of this review.

Vital Signs

Per the Applicant, no clinically relevant changes in heart rate or blood pressure from Baseline to Week 8 were observed.

Electrocardiograms/QT

Two subjects in the CAL/BDP Cream group had clinically significant, abnormal ECGs at Baseline. One subject had premature ventricular contraction and one had atrial fibrillation. Investigators considered ECG changes in the subject with atrial fibrillation to be clinically significant at Week 8. There were no other new, abnormal, clinically significant ECG changes in subjects treated with CAL/BDP Cream.

The Applicant submitted a request for waiver of the requirement to conduct a TQT study. The request for waiver included data from a MUSt that evaluated comparative systemic exposure to Taclonex Ointment. The trial demonstrated similar systemic exposure to active ingredients in CAL/BDP Cream and Taclonex Ointment under conditions of maximal use. Taclonex Ointment and Taclonex Topical Suspension are not labeled for QTc prolongation or dysrhythmia, nor does labeling for either product recommend routine ECG or other cardiac safety monitoring.

In a consult memorandum dated March 19, 2019, the QT-Interdisciplinary Review Team stated, "The Sponsor's proposed rationale for not conducting the thorough-QT study appears reasonable." The Division agreed and did not require a TQT study.

Immunogenicity

Because the proposed product is not a therapeutic protein, the Applicant did not assess the potential for immunogenicity.

8.2.5. Analysis of Submission-Specific Safety Issues

Refer to Section 6.3.1 of this review for a discussion of the evaluation of HPA axis suppression. The Applicant adequately evaluated the potential for HPA axis suppression associated with use of their product in adults. This will be included in Section 5.2 (Warnings and Precautions) of the product labeling.

Refer to Section 6.3.1 of this review for a discussion of the evaluation of the effect of CAL/BDP Cream on calcium metabolism. Although investigators observed no clinically meaningful effect on calcium metabolism during Phase 2 and 3 trials, the risk of hypercalcemia and hypercalciuria will be conveyed in Section 5.1 (Warnings and Precautions) of the product labeling.

During the Phase 3 trial MC2-01-C2, investigators assessed for the following local skin reactions (LSRs) at all visits: perilesional erythema, scaling, edema, atrophy, vesicles, and erosion/ulceration, as well as lesional vesicles and erosion/ulceration. Subjects were also queried for the symptom of burning or pain at the application site. LSRs were scored as follows:

- 0 = absent
- 1 = mild
- 2 = moderate
- 3 = severe

LSRs (all levels of severity combined) were analyzed at Baseline and Week 8. For vesicles and erosions/ulcerations, perilesional and lesional findings were combined. These results are presented in Table 46 and Table 47.

Table 46. Local Skin Reactions at Baseline, Phase 3 Trial MC2-01-C2

Parameter	Taclonex® Topical		
	CAL/BDP Cream (n=342)	Suspension (n=337)	Vehicle Cream (n=115)
Atrophy	24 (7.0%)	20 (5.9%)	7 (6.1%)
Burning or pain	84 (24.6%)	102 (30.3%)	30 (26.1%)
Edema	50 (14.6%)	41 (12.2%)	16 (13.9%)
Erosion/ulceration	38 (11.1%)	35 (10.4%)	18 (15.7%)
Erythema	95 (27.8%)	96 (28.5%)	33 (28.7%)
Scaling	94 (27.5%)	90 (26.7%)	33 (28.7%)
Vesicles	22 (6.4%)	20 (5.9%)	13 (11.3%)

Source: Reviewer's table created in JReview using the ADSL and ADCE datasets
Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene

Table 47. Local Skin Reactions at Week 8, Phase 3 Trial MC2-01-C2

Parameter	Taclonex® Topical		
	CAL/BDP Cream (n=313)	Suspension (n=292)	Vehicle Cream (n=90)
Atrophy	10 (3.2%)	6 (2.1%)	2 (2.2%)
Burning or pain	16 (5.1%)	9 (3.1%)	16 (17.8%)
Edema	13 (4.2%)	12 (4.1%)	5 (5.6%)
Erosion/ulceration	6 (1.9%)	6 (2.1%)	7 (7.8%)
Erythema	62 (19.8%)	55 (18.8%)	20 (22.2%)
Scaling	60 (19.2%)	48 (16.4%)	17 (18.9%)
Vesicles	2 (0.6%)	1 (0.3%)	1 (1.1%)

Source: Reviewer's table created in JReview using the ADSL and ADCE datasets
Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene

Most LSRs were mild or moderate in intensity. Three (3/313; 1.0%) subjects treated with CAL/BDP Cream reported severe application site burning or pain at Week 8; otherwise, no subject had an LSR of severe intensity at Week 8.

During the Phase 2 trial MC2-01-C3, LSRs were scored using the same scale as the Phase 3 trial. Our analysis of LSRs (all levels of severity combined) at Baseline and Weeks 4 and 8 in the Phase 2 trial is presented in Table 48, Table 49, and Table 50.

Table 48. Local Skin Reactions at Baseline, Phase 2 Trial MC2-01-C3

Parameter	Taclonex	
	CAL/BDP Cream (n=32)	Ointment (n=31)
Atrophy	4 (12.5%)	4 (12.9%)
Burning or pain	5 (15.6%)	8 (25.8%)
Edema	4 (12.5%)	4 (12.9%)
Erosion/ulceration	2 (6.3%)	2 (6.5%)
Erythema	11 (34.4%)	9 (29.0%)
Lesional erosion/ulceration	5 (15.6%)	3 (9.7%)
Lesional vesicles	4 (12.5%)	3 (9.7%)
Scaling	9 (28.1%)	8 (25.8%)
Vesicles	3 (9.4%)	3 (9.7%)

Source: Reviewer's table created in JReview using the ADSL and ADCE datasets
Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene

Table 49. Local Skin Reactions at Week 4, Phase 2 Trial MC2-01-C3

Parameter	Taclonex	
	CAL/BDP Cream (n=27)	Ointment (n=30)
Atrophy	2 (7.4%)	1 (3.3%)
Edema	1 (3.7%)	0 (0%)
Erosion/ulceration	2 (7.4%)	0 (0%)
Erythema	8 (29.6%)	5 (16.7%)
Lesional erosion/ulceration	2 (7.4%)	2 (6.7%)
Lesional vesicles	1 (3.7%)	1 (3.3%)
Scaling	6 (22.2%)	4 (13.3%)
Vesicles	2 (7.4%)	0 (0%)

Source: Reviewer's table created in JReview using the ADSL and ADCE datasets
Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene

Table 50. Local Skin Reactions at Week 8, Phase 2 Trial MC2-01-C3

Parameter	CAL/BDP Cream (n=26)
Atrophy	1 (3.8%)
Burning or pain	0
Edema	0
Erosion/ulceration	0
Erythema	3 (11.5%)
Lesional erosion/ulceration	2 (7.7%)
Lesional vesicles	1 (3.8%)
Scaling	5 (19.2%)
Vesicles	0

Source: Reviewer's table created in JReview using the ADSL and ADCE datasets

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene

Most LSRs reported at Week 4 and all at Week 8 during the Phase 2 trial were mild in intensity. The subject in the CAL/BDP Cream group with mild atrophy at Week 8 (Subject MC2-01-C3-^{(b) (6)}) also had mild atrophy at Baseline and Week 4. The other subject in the CAL/BDP Cream group reported to have atrophy at Week 4 (Subject MC2-01-C3-^{(b) (6)}) was reported to have severe atrophy at Baseline, mild atrophy at Week 4, and no atrophy at Week 8.

Although there was no allergic contact dermatitis based on AE related to the application site or the evaluation of LSRs, the risk of allergic contact dermatitis will be conveyed in Sections 5.3 and 5.4 (Warnings and Precautions) of the product labeling.

No ophthalmic adverse reactions (i.e., cataracts, glaucoma, or eye irritation) were reported during Phases 2 or 3 trials. However, the risk of these events will be conveyed as class labeling in Section 5.5 (Warnings and Precautions) of the product labeling.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

The Phase 3 trial protocol included the PTCS and an NRS for pruritus, which are PROs. ^{(b) (4)}

^{(b) (4)} Results from the pruritus NRS will be included in the labeling. ^{(b) (4)}

^{(b) (4)}

(b) (4)

8.2.7. Safety Analyses by Demographic Subgroup

The review team conducted additional analyses to evaluate the safety profile of CAL/BDP Cream in several demographic subgroups. Because the safety database consists of a single Phase 3 trial of limited size, the data should be interpreted with caution. Adverse reactions by age group, sex, and race are presented in Table 51, Table 52, and Table 53.

Table 51. Adverse Reactions by Age Group

Preferred Term	CAL/BDP Cream (N=342)		Taclonex Topical Suspension (N=337)		Vehicle Cream (N=115)	
	18–64 Yrs (N=276)	≥65 Yrs (N=66)	18–64 Yrs (N=272)	≥65 Yrs (N=65)	18–64 Yrs (N=94)	≥65 Yrs (N=21)
Pooled URI ¹	19 (6.9%)	4 (6.1%)	12 (4.4%)	6 (9.2%)	6 (6.4%)	0
Headache	5 (1.8%)	0	3 (1.1%)	1 (1.5%)	0	0
Application site irritation	3 (1.1%)	0	0	0	0	0

Source: Reviewer's table created in JReview using the ADSL and ADEX datasets

¹ Includes nasopharyngitis, upper respiratory tract infection (URTI), and viral URTI

Denominator is the total number of subjects of identical age/treatment group

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; URI, upper respiratory infection

(b) (4)

Table 52. Adverse Reactions by Sex

Preferred Term	CAL/BDP Cream (N=342)		Taclonex Topical Suspension (N=337)		Vehicle Cream (N=115)	
	Male (N=203)	Female (N=139)	Male (N=221)	Female (N=116)	Male (N=71)	Female (N=44)
Pooled URI ¹	9 (4.4%)	14 (10.1%)	11 (5.0%)	7 (6.0%)	5 (7.0%)	1 (2.3%)
Headache	2 (1.0%)	3 (2.2%)	2 (0.9%)	2 (1.7%)	0	0
Application site irritation	1 (0.5%)	2 (1.4%)	0	0	0	0

Source: Reviewer's table created in JReview using the ADSL and ADEX datasets

¹ Includes nasopharyngitis, upper respiratory tract infection (URTI), and viral URTI

Denominator is the total number of subjects of identical sex/treatment group

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; URI, upper respiratory infection

Table 53. Adverse Reactions by Race

Preferred Term	CAL/BDP Cream (N=342)		Taclonex Topical Suspension (N=337)		Vehicle Cream (N=115)	
	Non-White (N=52)	White (N=290)	Non-White (N=38)	White (N=299)	Non-White (N=13)	White (N=102)
Pooled URI ¹	1 (1.9%)	22 (7.6%)	2 (5.3%)	16 (5.4%)	0	6 (5.9%)
Headache	0	5 (1.7%)	0	4 (1.3%)	0	0
Application site irritation	0	3 (1.0%)	0	0	0	0

Source: Reviewer's table created in JReview using the ADSL and ADEX datasets

¹ Includes nasopharyngitis, upper respiratory tract infection (URTI), and viral URTI

Denominator is the total number of subjects of identical race/treatment group

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; URI, upper respiratory infection

Although several imbalances in AR between demographic subgroups were noted, because of the sample size, it cannot be concluded that these differences are clinically meaningful.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant submitted supportive safety data from a PK study conducted under conditions of maximal use, a vasoconstriction study, two dermal safety studies that evaluated phototoxicity and photoallergenicity, and two “psoriasis plaque test trials” conducted in Europe. The safety results from these studies are summarized below.

Maximal-Use PK Study MC2-01-C3

Study MC2-01-C3 was a Phase 2, randomized, open-label PK trial conducted under MUSt conditions in adult subjects with psoriasis vulgaris with baseline disease severity of a PGA score of at least 3 (moderate) and a BSA of 20% to 30% on the trunk, limbs, and scalp. Investigators randomized the subjects 1:1 to treatment with CAL/BDP Cream or Taclonex Ointment. The subjects applied the study product topically to affected areas of the scalp, trunk (including the neck), and limbs (i.e., not including the face or intertriginous areas). The subjects applied the study drug for 4 weeks (Taclonex Ointment group) or 8 weeks (CAL/BDP Cream group).

Refer to Section 6.2.1 for further details regarding the study design and PK results. The evaluation of safety included the following:

- AE/SAE
- Local skin reactions
- Clinical laboratory evaluation (hematology, chemistry, urinalysis)

- ECG
- Pregnancy testing
- Vital signs
- Physical examination
- Assessment for HPA axis suppression
- Calcium metabolism assessment

Refer to Sections 6.3.1 and 8.2.5 of this review for discussion of HPA axis suppression and the effect of the product on calcium metabolism. The only SAE reported was ankle fracture in one subject treated with Taclonex Ointment, and the SAE was considered not to be related to treatment. A total of six (6/32; 18.8%) subjects discontinued as a result of a TEAE. All of those six subjects were treated with CAL/BDP Cream and the TEAEs were considered probably or definitely related to treatment. TEAEs leading to discontinuation in the CAL/BDP Cream group included one subject with folliculitis and pruritus of the application site and five subjects with HPA axis suppression; of these, one also had hypercortisolism and one also had application site rash. The Applicant reports that eight subjects had treatment discontinued because of HPA axis suppression according to the protocol withdrawal criteria; however, only five were reported by investigators as discontinuation because of a TEAE.

From Baseline to Week 4, two (2/32; 6.3%) subjects treated with CAL/BDP Cream and five (5/31; 16.1%) subjects treated with Taclonex Ointment reported TEAEs. None of the TEAEs were of severe intensity. Of the reported TEAEs, investigators considered one event (application site folliculitis) in the CAL/BDP Cream group and three (cortisol deficiency, application site folliculitis, and pollakiuria) in the Taclonex Ointment group to be related to treatment. From Week 4 to Week 8 (i.e., subjects treated with CAL/BDP Cream), a total of six (6/32; 18.8%) subjects reported nine TEAEs. Investigators considered eight TEAEs in five (5/32; 15.6%) subjects to be related to treatment with CAL/BDP Cream (hypercorticism, application site rash, application site pruritus, and five cases of HPA axis suppression).

The evaluation of LSRs in trial MC2-01-C3 is discussed in Section 8.2.5 of this review.

Other PK and Dermal Safety Studies

Study MC2-01-C4 (Vasoconstriction Trial)

This was a single-center, single-application, randomized, investigator-blinded, active and vehicle-controlled trial with intraindividual comparison to evaluate the pharmacodynamic effect of CAL/BDP Cream in 36 healthy adult volunteers. Refer to Section 6.3.1 of this review for further details regarding the trial design. No deaths, SAEs, TEAEs, or LSRs were reported.

MC2-01-C9 (Phototoxicity Study)

This was a randomized, single-center, double-blind, controlled, within-subject comparison trial to determine the phototoxic potential of CAL/BDP Cream in healthy adult volunteers. Investigators marked four application sites (2×2 cm each) on the infrascapular region of each

subject's back. CAL/BDP Cream was applied to two sites and vehicle cream to two sites. The study product (0.2 g) was applied according to the randomization scheme under semiocclusive patch conditions once during the trial.

Study staff removed patches approximately 24 hr after application of the study product. Investigators then graded the sites for cutaneous reactions. Next, the designated sites were irradiated. One set of CAL/BDP Cream and one set of vehicle cream patches was designated for irradiation and the other set remained non-irradiated. An additional site on the back was marked and received no treatment but underwent irradiation to serve as an untreated irradiated control. The sites were examined at approximately 24 and 48 hr postirradiation and graded for reactions. Cutaneous reactions at the application sites were evaluated using a visual scale that rated the degree of erythema, edema, and other signs of cutaneous irritation.

A total of 35 subjects was randomized and 33 (94.3%) completed the trial. No AEs were reported during the trial. The Applicant reported that there were no statistically significant differences between irradiated CAL/BDP Cream sites, irradiated vehicle sites, and irradiated untreated control sites. There was a statistically significant difference between irradiated sites (CAL/BDP Cream, vehicle cream, and untreated control) and nonirradiated sites (CAL/BDP Cream and vehicle cream). The investigators attributed these to the light exposure itself. No subjects fulfilled the criteria for phototoxicity.

MC2-01-C10 (Photoallergenicity Study)

This was a randomized, single-center, double-blind, controlled, within-subject comparison trial to determine the photoallergic potential of CAL/BDP Cream in 58 healthy adult volunteers. Investigators marked eight application sites (2×2 cm each) on each subject's back. The sites were distributed so that four sites were on one side of the back for induction, and four sites were on the other side for challenge patches. The study product (CAL/BDP Cream or vehicle cream) was applied as two sets. One set of patches on the back was designated for irradiation after approximately 24 hr (±4 hr) of study product application and the other set remained nonirradiated. Investigators marked an additional site on the back during challenge, which was not treated with study product but was irradiated at challenge to serve as an untreated irradiated control.

Investigators irradiated a defined area (approximately 50 cm²) on the infrascapular region of each subject's back to determine the minimal erythema dose of ultraviolet light. During the 3-week induction phase of the study, investigators applied 0.2 g of each study product to two sites twice weekly (Monday and Thursday) for approximately 24 hr (±4 hr) under semi-occlusive patch conditions (six applications). After patch removal, all application sites were evaluated, and one site of application of each study product was irradiated with twofold the subject's minimal erythema dose using the full spectrum of a xenon lamp. Investigators reevaluated all sites at 48 to 72 hr postirradiation. Investigators performed these procedures each week for 3 weeks during the induction phase. Dermal reactions at the application sites were evaluated

using a visual scale that rated the degree of erythema, edema, and other signs of cutaneous irritation.

After the induction phase, subjects entered a rest period of 10 to 17 days, which was followed by the challenge phase. During the challenge phase, 0.2 g of each study product was applied to two naïve sites. At 24 hr (± 4 hr) after product application, all sites were evaluated, and one site of application of each product and an additional untreated site were irradiated. The sites were examined for dermal reactions at approximately 24 hr (± 4 hr), 48 h (± 4 hr), and 72 hr (± 4 hr) postirradiation. A rechallenge was performed if a cutaneous response observed during the challenge phase indicated possible photosensitization.

A total of 58 subjects was randomized and 51 (87.9%) completed the study. Two subjects reported a total of three TEAEs. One subject had URI of mild severity and the other had two events of headache (one of mild and one of moderate severity). The investigators considered all to be possibly related to treatment; none led to withdrawal from the study.

The investigators found no evidence of photosensitization for CAL/BDP Cream or vehicle cream.

Psoriasis Plaque Test Trials

Trial MC2-01-C1

This was a randomized, in-subject, observer-blind, vehicle- and active-controlled, multicenter Phase 2 trial to assess the efficacy and safety of the investigational products in subjects with psoriasis vulgaris (plaque psoriasis) using a PPT. The trial was conducted in two centers in Germany in adult subjects with stable plaque psoriasis, which was defined as a total clinical score (sum of the scores for erythema, scaling, and infiltration) of 5 to 12 (scores for erythema and infiltration of >2 , and for scaling of >1). In addition, the target plaque(s) must have been located on corresponding parts of the body (e.g., both arms, both upper legs, both lower legs, or trunk). The sum of the area of the target plaque(s) (not more than 2) must have been sufficient for application of six different products. The selected plaques must have had comparable intensities of psoriasis symptoms, according to the judgement of the investigator. The study products were: MC2-01 (CAL/BDP), MC2-01 (CAL), MC2-01 (BDP), MC2-01 vehicle, Daivobet (CAL/BDP) Ointment, and Daivobet (CAL/BDP) Gel. Each study product was applied to a 1.5 cm² test area once daily for 6 days/week for 28 days.

A total of 33 subjects was randomized and 29 (88%) completed the study. The Applicant reported that the treatment effect of MC2-01 (CAL/BDP) Cream was superior to that of each monad individually as well as vehicle cream, and comparable to those of the reference products Daivobet Ointment² and Daivobet Gel.³ Regarding safety, one SAE of worsening of psoriatic arthropathy was reported and led to discontinuation. The investigator considered the event not

² Daivobet (CAL/BDP) Ointment, 0.005%/0.064%, LEO Pharma Ltd., approved in Europe

³ Daivobet (CAL/BDP) Gel, 0.005%/0.064%, LEO Pharma Ltd., approved in Europe

to be related to treatment. No other TEAE led to discontinuation. A total of eight subjects reported 14 TEAEs; the investigators considered none of them to be related to treatment. These TEAEs are presented in Table 54.

Table 54. Overview of Treatment-Emergent Adverse Events in Trial MC2-01-C1

SOC Preferred term	Number of Patients n (%)	[AE]	Intensity	Nature (localization of AE)
Eye disorders	1 (3)	[1]		
Blepharitis	1 (3)	[1]	Mild	Dermatological (other location)
Gastrointestinal disorders	1 (3)	[1]		
Nausea	1 (3)	[1]	Moderate	Systemic
Infections and infestations	2 (6)	[3]		
Gastrointestinal infection	1 (3)	[1]	Mild	Systemic
Sinusitis	1 (3)	[1]	Moderate	Systemic
Tonsillitis	1 (3)	[1]	Moderate	Systemic
Injury, poisoning and procedural complications	1 (3)	[1]		
Ligament sprain	1 (3)	[1]	Moderate	Systemic
Musculoskeletal and connective tissue disorders	2 (6)	[4]		
Arthralgia	2 (6)	[2]	Moderate	Systemic
Psoriatic arthropathy	1 (3)	[2]	Severe	Systemic
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (3)	[1]		
Basal cell carcinoma	1 (3)	[1]	Mild	Dermatological (other location)
Nervous system disorders	3 (9)	[3]		
Headache	3 (9)	[3]	Mild (n=1)/ Moderate (n=2)	Systemic

Source: MC2-01-C1 clinical study report, text Table 12-6, p.111

Abbreviations: AE, adverse event; [AE], number of individual AEs that occurred among n patients; n, number of patients reporting at least one AE with the specification; %, percentage of patients of the total (N); SOC, system organ class

Trial MC2-16-C1

This was a single center, investigator-blinded, active- and vehicle-controlled, repeated-dose study with multiple intra-individual comparisons of mini-zones (n=6), involving 24 subjects with psoriasis vulgaris. The subjects were required to have stable plaque psoriasis with lesions located on the arms and/or legs and/or trunk. The subjects were required to have one or more plaques for the application of the six products, which had a sum of the scores for erythema, scaling, and infiltration of ≥ 5 , and a score for each of these items individually of ≥ 1 .

At Day 1, investigators selected six test sites of 2 cm diameter on predetermined psoriasis lesions (target plaques). During the 4-week treatment phase, 50 μ L of each study product were applied to the delimited area once daily, 6 days per week for 4 consecutive weeks. The study

products were: MC2-01 (CAL/BDP) Cream, MC2-01 (CAL) Cream, MC2-01 vehicle, Daivobet (CAL/BDP) Ointment, Daivonex (CAL) Cream,⁴ and Daivonex (CAL) Ointment.⁵

Twenty-four subjects were randomized; all completed the study. The evaluation of safety included monitoring of AEs and assessment of local tolerance on a four-point scale. A total of seven subjects (29.2%) experienced a total of 20 AEs. No deaths occurred during the study. One subject had AEs of syncope and hypoglycemia; both were of severe intensity and the syncope was reported as an SAE. The most commonly reported AEs were fever (n=2, 8.3%) and infection (n=2, 8.3%). All other AEs were reported by only one subject. The majority of AEs was of mild intensity; one was assessed as being of moderate intensity. The Applicant also reported that the evaluation of local tolerance revealed no signs of irritation during the study.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant did not conduct a clinical trial specifically to evaluate human carcinogenicity or tumor development. During the development program, the trial designs did not include specific assessments of carcinogenicity or safety signals related to malignancy. During the Phase 3 trial, malignancies were reported in two subjects treated with CAL/BDP Cream (one subject with basal cell carcinoma and one with clear cell renal carcinoma). In addition, malignancies were reported in two subjects treated with Taclonex (CAL/BDP) Topical Suspension, 0.005%/0.064% (one with basal cell carcinoma and one with carcinoma of the cervix). Investigators considered none of the events of malignancy to be related to treatment with CAL/BDP Cream or Taclonex (CAL/BDP) Topical Suspension, 0.005%/0.064%.

The Applicant submitted a 505(b)(2) application, using Taclonex (CAL/BDP) Topical Suspension, 0.005%/0.064% and Taclonex (CAL/BDP) Ointment, 0.005%/0.064% as the LDs. The Applicant intends to rely on nonclinical information from the approved labeling for the LD, including carcinogenicity. The carcinogenicity information contained in the labeling for the LD, Taclonex Ointment, will be conveyed in Section 13.1 of the labeling for CAL/BDP Cream. Refer to Section 5.5.3 of this review for further information regarding the nonclinical evaluation of carcinogenicity.

Human Reproduction and Pregnancy

During the Phase 3 trial, the Applicant required females of reproductive potential to have a negative pregnancy test at Screening and to use effective forms of contraception. In addition, during the Phase 3 trial urine pregnancy tests (UPTs) were performed on all females of reproductive potential at Baseline and at Weeks 4 and 8. This was also the case for the Phase 2 MUSt conditions.

⁴ Daivonex®(CAL) Cream, 0.005%, LEO Pharma Ltd., approved in Europe

⁵ Daivonex®(CAL) Ointment, 0.005%, LEO Pharma Ltd., approved in Europe

No pregnancies occurred during the development program for CAL/BDP Cream.

The Maternal Health Team reviewed the proposed labeling for compliance with the Pregnancy and Lactation Labeling Rule, and provided recommendations regarding the proposed language for applicable sections of the product labeling. Because the Maternal Health Team has archived several previous reviews for other dosage forms of this fixed combination, a review was not provided for CAL/BDP Cream (email communication, Dr. Jane Liedtka, April 17, 2020). Per the nonclinical toxicology reviewer, Dr. Carmen Booker, the fertility and early embryonic development information from the labeling for the LD Taclonex Ointment will be conveyed in Section 13.1 of the labeling for CAL/BDP Cream. Additionally, the embryo-fetal development and prenatal and postnatal development information from the labeling for the LD Taclonex Ointment will be conveyed in Section 8.1 of the labeling for CAL/BDP Cream. This is discussed in greater detail in Section 5.5.4 of this review.

Pediatrics and Assessment of Effects on Growth

As a new dosage form, CAL/BDP Cream triggers the requirement under the Pediatric Research Equity Act (PREA)(21 U.S.C. 355c) for assessment of the safety and effectiveness of the product for topical treatment of plaque psoriasis in pediatric patients unless said requirement is waived, deferred, or inapplicable.

(b) (4)

(b) (4) the Agency will not require postmarketing assessments under the Pediatric Research Equity Act on the grounds that CAL/BDP Cream fails to represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is unlikely to be used in a substantial number of pediatric age groups or the pediatric age group(s) (b) (4)

Refer to Section 10 of this review for further details.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

Per the Applicant, no overdoses occurred in subjects treated with CAL/BDP Cream. The Applicant also reports that the MUSt (MC2-01-C3) demonstrated low systemic exposure under conditions of maximal use. This is discussed in more detail in Section 6.2.2 of this review.

Drug Abuse Potential/ Withdrawal and Rebound

The Applicant did not evaluate abuse potential and did not design or conduct trials to evaluate subjects for withdrawal or rebound. However, based on the mechanism of action and low systemic exposure of CAL/BDP Cream, there is no reason to anticipate any potential for abuse or dependency. Therefore, Section 10 will be omitted from the product labeling.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

CAL/BDP Cream has not been marketed in any jurisdiction. Therefore, no postmarketing safety data are available.

Expectations on Safety in the Postmarket Setting

The fixed combination of CAL/BDP is approved in ointment, topical suspension, and topical foam dosage forms. The safety profile of the fixed combination of CAL/BDP is well established. The postmarketing experience for CAL/BDP Cream is expected to be similar to that for other products containing this fixed combination of CAL/BDP.

8.2.11. Integrated Assessment of Safety

The safety profile for CAL/BDP Cream was adequately characterized during the development program. The primary safety database consisted of 794 subjects from Phase 3 trial MC2-01-C2. The Phase 3 safety population includes all subjects who were randomized and dispensed the trial medication at Baseline (Day 0), excluding subjects who returned all of the trial medication unused. The safety data from this population were analyzed according to the treatment received by the subjects.

Based on a review of the safety data, no serious ARs were identified and therefore no contraindications will be included in Section 4 of the product labeling. This is consistent with the labeling for the LDs. Section 5 (Warnings and Precautions) will include information regarding HPA axis suppression, potential effects on calcium metabolism, allergic contact dermatitis, and ophthalmic ARs (e.g., glaucoma and cataracts). Although no meaningful changes in calcium metabolism parameters, allergic contact dermatitis, or ophthalmic ARs (glaucoma, cataracts, or eye irritation) were reported during the Phase 3 trial, these will be included in Section 5 as class labeling.

Treatment with CAL/BDP Cream was not associated with an increased risk of mortality or SAEs. Two deaths occurred during the development program; neither was related to treatment with CAL/BDP Cream. SAEs occurred in 2.3% of the subjects treated with CAL/BDP Cream, 2.7% of those treated with Taclonex Topical Suspension, and 3.5% of the subjects treated with vehicle cream. Among the subjects treated with CAL/BDP Cream, the SAEs included angina pectoris, myocardial infarction, abscess, nosocomial infection, pneumonia, cervical vertebral fracture, clear cell renal carcinoma, epilepsy, and acute kidney injury. The investigators considered none of the SAEs to be related to treatment with any of the study products.

The most common ARs were URI, headache, and application site irritation. URI was reported in 6.7% of the subjects treated with CAL/BDP Cream, 5.3% of those treated with Taclonex Topical Suspension, and 5.2% of the subjects treated with vehicle cream; headache was reported by 1.5% of the subjects treated with CAL/BDP Cream, 1.2% of those treated with Taclonex Topical Suspension, and 0% of the subjects treated with vehicle cream; application site irritation was

reported in 0.9% of the subjects treated with CAL/BDP Cream, 0% of those treated with Taclonex Topical Suspension, and 0% of the subjects treated with vehicle cream. URIs included the pooled preferred terms nasopharyngitis, URTI, and viral URTI. The Applicant also conducted active assessments of local tolerability, the results of which in subjects treated with CAL/BDP Cream at Week 8 (all levels of severity combined) were as follows: erythema (19.8%), scaling (19.2%), burning or pain (5.1%), edema (4.2%), atrophy (3.2%), erosion/ulceration (1.9%), and vesicles (0.6%). Local tolerability findings occurred at a similar or greater frequency in the vehicle cream group. The majority of the local tolerability findings were of mild or moderate severity.

No pregnancies occurred during the development program for CAL/BDP Cream. Per the recommendations of Dr. Jane Liedtka from the Maternal Health Team and the pharmacology/toxicology reviewer Dr. Carmen Booker, the fertility and early embryonic development information from the labeling for the LD Taclonex Ointment will be conveyed in Section 13.1 of the labeling for CAL/BDP Cream. Additionally, the embryo-fetal development and prenatal and postnatal development information from the labeling for the LD Taclonex Ointment will be conveyed in Section 8.1 of the labeling for CAL/BDP Cream.

The currently available data from the Phase 3 trial with a treatment period of 8 weeks demonstrate that CAL/BDP Cream appears to be safe for the topical treatment of plaque psoriasis in adults. The safety profile appears to be similar to that of the LDs. Postmarketing risk management will include professional labeling and routine pharmacovigilance. As the safety of this fixed combination is well characterized, the review team recommends no other risk management tools or assessments (risk evaluation and mitigation strategies or clinical postmarketing studies).

8.3. Summary and Conclusions

8.3.1. Statistical Issues

There were no major statistical issues affecting the overall conclusions. The treatment effect was generally consistent across endpoints and analysis populations. There were no substantial differences in efficacy among subgroups. In terms of handling missing data, the results were similar irrespective of the method used to impute missing data (see Table 37).

8.3.2. Conclusions and Recommendations

To establish the effectiveness of CAL/BDP Cream for the topical treatment of plaque psoriasis, the Applicant submitted data from a randomized, multicenter, investigator-blinded, vehicle- and active-comparator controlled, parallel-group, Phase 3 trial. The trial was conducted in subjects ≥ 18 years of age with mild-to-moderate psoriasis on the body (i.e., trunk and/or limbs, excluding the genital skin) with baseline disease severity defined as:

- PGA score of 2 (mild) or 3 (moderate) on the body (trunk and/or limbs)
- mPASI score of ≥ 2

- Treatment area involving 2 to 30% of the BSA

The subjects were randomized at a 3:3:1 ratio to CAL/BDP Cream, Taclonex Topical Suspension, or vehicle cream. The subjects applied the study product once daily in the evening to affected areas of the trunk and/or limbs. The protocol-specified primary efficacy endpoint was the proportion of subjects with treatment success at Week 8. Treatment success was defined as a PGA score of 0 (clear) or 1 (almost clear) with at least a two-grade reduction from baseline. The protocol specified the following secondary endpoints:

- Percentage change from Baseline in mPASI score at Week 8
- Subject assessment of treatment convenience at Week 8 using a PTCS
- Absolute change from Baseline on the itch NRS at Week 4 (CAL/BDP Cream vs. vehicle cream)
- Proportion of subjects with a four-point improvement from Baseline on the itch NRS at Week 4 (CAL/BDP Cream vs. vehicle cream)

CAL/BDP Cream was superior to vehicle cream ($p < 0.001$) and noninferior to CAL/BDP topical suspension, 0.005%/0.064% (difference [95% CI]: 14.6% [7.6%, 21.6%]) for the primary endpoint of treatment success at Week 8. Refer to Section 8.1.4 of this review for discussion of the primary endpoint and Section 8.1.5 for discussion of the secondary endpoints.

The Applicant conducted an adequate assessment of the safety of CAL/BDP Cream in the target population. The size of the safety database and the safety evaluations were adequate to identify local and systemic treatment-emergent ARs.

The submitted safety and efficacy data support approval of NDA 213422, WYNZORA (CAL/BDP) Cream, 0.005%/0.064% for the topical treatment of plaque psoriasis in patients 18 years of age and older.

9 Advisory Committee Meeting and Other External Consultations

The Agency did not conduct an Advisory Committee Meeting regarding this application because the safety profile of this fixed-combination is well characterized.

10 Pediatrics

Because CAL/BDP Cream is a new dosage form, it triggers the requirement under the PREA (21 USC 355c) for an assessment of its safety and effectiveness for the topical treatment of plaque psoriasis in pediatric patients unless said requirement is waived, deferred, or inapplicable.

(b) (4)

(b) (4)

After initial review of the safety and efficacy data in the NDA submission, the Division recommended a full waiver of the requirement to conduct studies in pediatric subjects less than 18 years of age on the grounds that the product fails to represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is unlikely to be used in a substantial number of pediatric age groups or the pediatric age group(s) for which a waiver is being requested. The Division noted that three dosage forms (ointment, topical suspension, and topical foam) of this fixed combination drug product have been approved for patients 12 years of age and older.

(b) (4)

(b) (4)

The Division presented this information to the PeRC at the meeting held on June 2, 2020. During this meeting, the PeRC agreed with the Division's recommendation to grant a full waiver of the requirement for studies in pediatric subjects. Therefore, postmarketing assessments under the PREA are not required.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant submitted proposed prescribing information (PI), patient package insert (PPI), instructions for use, and carton/container labels for CAL/BDP Cream. The review team provided recommendations regarding PI, which are provided throughout this review. Madhuri R. Patel, PharmD from the Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed PI, PPI, container labels, and carton labeling. DMEPA stated that "The container label and carton label can be improved to increase the prominence of important information, to minimize potential deteriorated drug errors, and to facilitate product identification." Dr. Patel made specific recommendations to address these concerns (refer to the review dated January

31, 2020). The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the proposed PI, PPI, and carton/container labeling and label. Refer to the OPDP review by Laurie Buonaccorsi, PharmD, dated May 11, 2020. These comments are reflected in the final labeling. Table 55 provides the location in this review of the discussion of each section of the product labeling.

Table 55. Locations of Discussion of Significant High-Level Labeling Changes

Section	Location of Reviewer Comments on Proposed Labeling
1 INDICATIONS AND USAGE	Section 1.1
2 DOSAGE AND ADMINISTRATION	Sections 1.1, 6.2.2
4 CONTRAINDICATIONS	Section 8.2.11
5 WARNINGS AND PRECAUTIONS	Sections 8.2.5, 8.2.11
6 ADVERSE REACTIONS	Section 8.2.4
7 DRUG INTERACTIONS	Section 6.3.2
8 USE IN SPECIFIC POPULATIONS	Sections 5.5, 8.2, 10, 14.3
12 CLINICAL PHARMACOLOGY	Section 6
14 CLINICAL STUDIES	Section 8.1
17 PATIENT COUNSELING INFORMATION	Reflects the data in other sections of labeling: Labeling Sections 2, 5, and 8

11.2. Patient Labeling

The Division of Medical Policy Programs and OPDP reviewed and provided comments regarding the PPI and instructions for use for CAL/BDP Cream. The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by Shawna Hutchins, MPH, BSN, RN and Laurie Buonaccorsi, PharmD, dated May 11, 2020.

12 Risk Evaluation and Mitigation Strategies

Based on the favorable safety profile of this product, risk mitigation measures beyond professional labeling and standard postmarketing surveillance are not warranted at this time.

13 Postmarketing Requirements and Commitment

None.

14 Appendices

14.1. References

Blauvelt, A and B Efst, 2015, Pathophysiology of Psoriasis, accessed July 1, 2020, <http://www.UptoDate.com>.

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Fleming, C, C Ganslandt, L Guenther, A Johannesson, C Buckley, J Simon, H Stegmann, and L Vestergaard Tingleff, 2010, Calcipotriol plus betamethasone dipropionate gel compared with its active components in the same vehicle and the vehicle alone in the treatment of psoriasis vulgaris: a randomised, parallel group, double-blind, exploratory study, *Eur J Dermatol*, 20(4):465-471.

Korman, N, 2017, Comorbid Disease in Psoriasis, accessed July 1, 2020, <http://www.UptoDate.com>.

Langley, R, A Gupta, K Papp, D Wexler, M Osterdal, and D Curcic, 2011, Calcipotriol plus betamethasone dipropionate gel compared with tacalcitol ointment and the gel vehicle alone in patients with psoriasis vulgaris: a randomized, controlled clinical trial, *Dermatology*, 222(2):148-156.

Menter, A, L Gold, M Bukhalo, S Grekin, S Kempers, B Boyce, C Ganslandt, J Villumsen, and M Lebwohl, 2013, Calcipotriene plus betamethasone dipropionate topical suspension for the treatment of mild to moderate psoriasis vulgaris on the body: a randomized, double-blind, vehicle-controlled trial, *J Drugs Dermatol*, 12(1):92-98.

Menter, A, A Gottlieb, S Feldman, A Van Voorhees, C Leonardi, K Gordon, M Lebwohl, J Koo, C Elmetts, N Korman, K Beutner, and R Bhushan, 2008, Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics, *J Am Acad Dermatol*, 58(5):826-850.

14.2. Financial Disclosure

In compliance with 21 CFR Part 54, the applicant provided Certification/Disclosure Forms from clinical investigators and subinvestigators who participated in the covered clinical studies for CAL/BDP Cream. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The covered clinical studies as defined in 21 CFR 54.2(e) were trials MC2-01-C3 and MC2-01-C2 which provided the primary data to establish effectiveness and safety of this product. Refer to Section 8.1.1 for the trial designs.

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Covered Clinical Study: MC2-01-C3

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>13</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
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: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) N/A

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Covered Clinical Study: MC2-01-C2

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>59</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
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: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) N/A

14.3. Nonclinical Pharmacology/Toxicology

Labeling Review

Recommended changes from the Applicant's proposed labeling are indicated below by means of ~~striking out~~ (deletions) and underlining (additions). It is recommended that all of the TM tradenames be removed from the following sections of the label.

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

WYNZORA™ Cream is a combination of calcipotriene, a vitamin D analog, and betamethasone dipropionate, a corticosteroid, indicated for the topical treatment of plaque psoriasis in patients 18 years of age and older.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data with WYNZORA™ Cream are not sufficient to evaluate a drug-associated risk for major birth defects, miscarriages, or adverse maternal or fetal outcomes. Although there are no available data on use of the calcipotriene component in pregnant women, systemic exposure to calcipotriene after topical administration of WYNZORA™ Cream is likely to be low [*see Clinical Pharmacology (12.3)*].

Observational studies suggest an increased risk of having low birthweight infants with the maternal use of potent or very potent topical corticosteroids (*see Data*) (~~see Data~~). Advise pregnant women that WYNZORA™ Cream may increase the potential risk of having a low birthweight infant and to use WYNZORA™ Cream on the smallest area of skin and for the shortest duration possible.

In animal reproduction studies, oral administration of calcipotriene to pregnant rats during the period of organogenesis resulted in an increased incidence of minor skeletal abnormalities, including enlarged fontanelles and extra ribs (*see Data*) (~~see Data~~). Oral administration of calcipotriene to pregnant rabbits during the period of organogenesis had no apparent effects on embryo-fetal development. Subcutaneous administration of betamethasone dipropionate to pregnant rats and rabbits during the period of organogenesis resulted in fetal toxicity, including fetal deaths, reduced fetal weight, and fetal malformations (cleft palate and crooked or short tail) (*see Data*) (~~see Data~~). The available data do not allow the calculation of relevant comparisons between the systemic exposures of calcipotriene and betamethasone dipropionate observed in animal studies to the systemic exposures that would be expected in humans after topical use of WYNZORA™ Cream.

The (b) (4) background risk of major birth defects and miscarriage of the indicated population is unknown. In the U.S. general population, the estimated background risk of major

birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Available observational studies in pregnant women did not identify a drug-associated risk of major birth defects, preterm delivery, or fetal mortality with the use of topical corticosteroids of any potency. However, when the dispensed amount of potent or very potent topical corticosteroids exceeded 300 g during the entire pregnancy, maternal use was associated with an increased risk of low birth weight in infants.

Animal Data

Embryo-fetal development studies with calcipotriene were performed by the oral route in rats and rabbits. Pregnant rats received dosages of 0, 6, 18, or 54 mcg/kg/Day (0, 36, 108, and 324 mcg/m²/day, respectively) on days 6-15 of gestation (the period of organogenesis). There were no apparent effects on maternal survival, behavior, or body weight gain, no effects on litter parameters, and no effects on the incidence of major malformations in fetuses. Fetuses from dams dosed at 54 mcg/kg/day exhibited a significantly increased incidence of minor skeletal abnormalities, including enlarged fontanelles and extra ribs.

Pregnant rabbits were dosed daily with calcipotriene at exposures of 0, 4, 12, or 36 mcg/kg/day (0, 48, 144, and 432 mcg/m²/day, respectively) on days 6-18 of gestation (the period of organogenesis). Mean maternal body weight gain was reduced in animals dosed at 12 or 36 mcg/kg/day. The incidence of fetal deaths was increased in the group dosed at 36 mcg/kg/day; reduced fetal weight was also observed in this group. The incidence of major malformations among fetuses was not affected. An increase in the incidence of minor skeletal abnormalities, including incomplete ossification of sternebrae, pubic bones, and forelimb phalanges, was observed in the group dosed at 36 mcg/kg/day.

Embryo-fetal development studies with betamethasone dipropionate were performed via subcutaneous injection in mice and rabbits. Pregnant mice were administered doses of 0, 156, 625, or 2500 mcg/kg/day (0, 468, 1875, and 7500 mcg/m²/day, respectively) on days 7 through 13 of gestation (the period of organogenesis). Betamethasone dipropionate induced fetal toxicity, including fetal deaths, reduced fetal weight, malformations (increased incidence of the cleft palate and crooked or short tail), and minor skeletal abnormalities (delayed ossification of vertebra and sternebrae). Fetal toxicity was observed at the lowest exposure that was evaluated (156 mcg/kg/day).

Pregnant rabbits were injected subcutaneously at dosages of 0, 0.625, 2.5, and 10 mcg/kg/day (0, 7.5, 30, and 120 mcg/m²/day, respectively) on days 6 through 18 of gestation (the period of organogenesis). Betamethasone dipropionate induced fetal toxicity, including fetal deaths, reduced fetal weight, external malformations (including malformed ears, cleft palate, umbilical hernia, kinked tail, club foot, and club hand), and skeletal malformations

(including absence of phalanges of the first digit and cranial dysplasia) at dosages of 2.5 mcg/kg/day and above.

Calcipotriene was evaluated for effects on peri- and post-natal development when orally administered to pregnant rats at dosages of 0, 6, 18 or 54 mcg/kg/day (0, 36, 108, and 324 mcg/m²/day, respectively) from gestation day 15 through day 20 postpartum. No remarkable effects were observed on any parameter, including survival, behavior, body weight, litter parameters, or the ability to nurse or rear pups.

Betamethasone dipropionate was evaluated for effects on peri- and post-natal development when orally administered to pregnant rats at dosages of 0, 100, 300, and 1000 mcg/kg/day (0, 600, 1800, and 6000 mcg/m²/day, respectively) from gestation day 6 through day 20 postpartum. Mean maternal body weight was significantly reduced on gestation day 20 in animals dosed at 300 and 1000 mcg/kg/day. The mean duration of gestation was slightly, but statistically significantly, increased at 100, 300, and 1000 mcg/kg/day. The mean percentage of pups that survived to day 4 was reduced in relation to dosage. On lactation day 5, the percentage of pups with a reflex to right themselves when placed on their back was significantly reduced at 1000 mcg/kg/day. No effects on the ability of pups to learn were observed, and the ability of the offspring of treated rats to reproduce was not affected.

12.1 Mechanism of Action

WYNZORA™ Cream combines the pharmacological effects of calcipotriene as a synthetic vitamin D3 analog and betamethasone dipropionate as a synthetic corticosteroid. However, while their pharmacologic and clinical effects are known, the exact mechanisms of their actions in plaque psoriasis are unknown.

13 NONCLINICAL TOXICOLOGY

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/m²/day), no significant changes in tumor incidence were observed when compared to control.

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/m²/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/m²/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/m²/day and 39 mcg/m²/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 120, ^{(b) (4)} 360, and 1200 mcg/m²/day), no significant changes in tumor incidence were observed when compared to control.

Calcipotriene did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, the human lymphocyte chromosome aberration test, or the mouse micronucleus test. Betamethasone dipropionate did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, or in the rat micronucleus test.

Studies in rats with oral doses of up to 54 mcg/kg/day (324 mcg/m²/day) of calcipotriene indicated no impairment of fertility or general reproductive performance. Studies in male rats at oral doses of up to 200 mcg/kg/day (1200 mcg/m²/day), and in female rats at oral doses of up to 1000 mcg/kg/day (6000 mcg/m²/day), of betamethasone dipropionate indicated no impairment of fertility.

14.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

14.4.1. Bioanalytical Methods for PK Data

The concentrations of CAL, MC1080, BDP, and B17P in human plasma from samples obtained from study MC2-01-C3 were quantified using validated LC-MS/MS methods. The method validation results for quantification of CAL and MC1080 are summarized in Table 56 and the bioanalysis performance results are summarized in Table 57. The method validation results for quantification of BDP and B17P are summarized in Table 58 and the bioanalysis performance results are summarized in Table 59.

The bioanalytical method was adequately validated and met the acceptance criteria suggested in the FDA Bioanalytical Method Validation Guidance. Incurred sample reanalysis for plasma samples was acceptable in terms of both sample size (at least 10% of the first 1000 samples and 5% of the remaining samples) and the results (>67% of the study samples evaluated within ±20% of the original sample concentrations). All samples were analyzed within the established long-term stability window.

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Table 56. Summary of LC-MS/MS Bioanalytical Method Validation for CAL and MC1080

Validation Report	(b) (4) 185135-3855/0001	
Matrix	Human plasma	
Anticoagulant	Disodium ethylene diamine tetra acetic acid/NaF	
Extraction method	Supported liquid extraction	
Analyte	CAL	MC1080
Internal standard	Calcipotriene-d4	MC1080-d4
Calibration curve range	30.0 to 500 pg/mL	29.1 to 485 pg/mL
LLOQ	30.0 pg/mL	29.1 pg/mL
QC levels	90.0, 250, 400 pg/mL	87.3, 243, 388 mL
Precision (% CV)		
Interassay	LLOQ: 11.4 LQC: 6.59 MQC: 3.66 HQC: 4.28	LLOQ: 7.97 LQC: 4.63 MQC: 3.10 HQC: 2.65
Intra-assay	LLOQ: ≤ 13.7 LQC: ≤ 7.33 MQC: ≤ 4.17 HQC: ≤ 4.68	LLOQ: ≤ 9.86 LQC: ≤ 5.96 MQC: ≤ 3.66 HQC: ≤ 3.23
Accuracy (% relative error)		
Interassay	LLOQ: -1.67 LQC: 1.22 MQC: 0.800 HQC: 2.75	LLOQ: 3.44 LQC: 1.95 MQC: 2.88 HQC: 4.12
Intra-assay	LLOQ: -7.33 to 5.33 LQC: -0.444 to 3.89 MQC: 0.00 to 1.60 HQC: 1.00 to 3.75	LLOQ: 0.344 to 8.25 LQC: 0.802 to 4.24 MQC: 1.65 to 3.70 HQC: 3.35 to 4.90
Freeze/thaw stability	4 cycles of freeze (-70°C) and thaw (4°C; ice bath)	
Bench-top stability	6 hr at 4°C (ice bath)	
Long-term stability	173 days at -70°C and -20°C	
Batch run storage stability	98 hr at 4°C with pierced caps	

Source: Reviewer's summary

Abbreviations: CAL, calcipotriene; CV, coefficient of variation; HQC, high quality control; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLOQ, lower limit of quantification; LQC, low quality control; MQC, mid quality control; QC, quality control; NaF, sodium fluoride

Table 57. Summary of Bioanalysis Performance for CAL and MC1080

Relevant clinical trial	MC2-01-C3
Bioanalytical method	Described in Table 56
Precision (% CV) – CAL	Intrarun: ≤4.17 to ≤13.7 Inter-run: 3.66 to 11.4
Accuracy (% relative error) – CAL	Intrarun: –7.33 to 5.33 Inter-run: –1.67 to 2.75
Precision (% CV) – MC1080	Intrarun: ≤3.23 to ≤9.86 Inter-run: 2.65 to 7.97
Accuracy (% relative error) – MC1080	Intrarun: 0.344 to 8.25 Inter-run: 1.95 to 3.44
Incurred sample reanalysis – CAL	
Total no. of incurred sample reanalysis	65 (10.5% of samples)
Total no. of sample whose % differences are within 20%	65
% of total no. of samples whose % differences are within 20%	100
Incurred sample reanalysis – MC1080	
Total no. of incurred sample reanalysis	65 (10.5% of total samples)
Total no. of sample whose % differences are within 20%	62
% of total no. of samples whose % differences are within 20%	95.4
Duration from time sample was first drawn to date of last sample analysis including ISR	161 days (within the established stability window of 173 days)
Sample storage temperature	–70°C

Source: Reviewer's summary

Abbreviations: CAL, calcipotriene; CV, coefficient of variation; ISR, individual safety report

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Table 58. Summary of LC-MS/MS Bioanalytical Method Validation for BDP and B17P

Validation report	(b) (4) 185139-3855/0001	
Matrix	Human plasma	
Anticoagulant	Disodium ethylene diamine tetra acetic acid/NaF	
Extraction method	Solid phase	
Analyte	BDP	BD17P
Internal standard	Betamethasone-d10 Dipropionate	Betamethasone 17-Propionate-d5
Calibration curve range	20.0 to 500 pg/mL	20.0 to 500 pg/mL
LLOQ	20.0 pg/mL	20.0 pg/mL
QC levels	40.0, 90.0, 400 pg/mL	40.0, 90.0, 400 pg/mL
Precision (% CV)		
Interassay	LLOQ: 9.00 LQC: 5.75 MQC: 7.16 HQC: 4.42	LLOQ: 6.90 LQC: 4.19 MQC: 4.58 HQC: 4.03
Intra-assay	LLOQ: ≤12.4 LQC: ≤5.56 MQC: ≤7.90 HQC: ≤4.42	LLOQ: ≤7.14 LQC: ≤5.96 MQC: ≤5.48 HQC: ≤4.48
Accuracy (% relative error)		
Interassay	LLOQ: 0.500 LQC: 1.75 MQC: -1.67 HQC: 1.25	LLOQ: 0.00 LQC: -4.76 MQC: -5.56 HQC: -8.53
Intra-assay	LLOQ: -3.50 to 5.00 LQC: -2.50 to 6.50 MQC: -6.44 to 3.22 HQC: -5.50 to 1.25	LLOQ: -3.00 to 5.00 LQC: -5.25 to -3.70 MQC: -7.78 to -2.56 HQC: -11.0 to -5.63
Freeze/thaw stability	4 cycles of freeze (-70°C) and thaw (room temperature)	
Bench-top stability	6 hr at room temperature	
Long-term stability	34 days at -70°C for BDP and B17P 34 days at -20°C for BDP only	
Batch run storage stability	133 hr at 4°C with pierced caps	

Source: Reviewer's summary

Abbreviations: CAL, calcipotriene; CV, coefficient of variation; HQC, high quality control; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLOQ, lower limit of quantification; LQC, low quality control; MQC, mid quality control; QC, quality control; B17P, betamethasone 17-propionate; NaF, sodium fluoride (NaF)

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WYNZORA (calcipotriene/betamethasone dipropionate) Cream, 0.005%/0.064%

Table 59. Summary of Bioanalysis Performance for BDP and B17P

Relevant clinical trial	MC2-01-C3
Bioanalytical method	Described in Table 58
Precision (% CV) – BDP	Intrarun: ≤4.42 to ≤12.4 Inter-run: 4.42 to 9.00
Accuracy (% relative error) – BDP	Intrarun: –3.50 to 6.50 Inter-run: –1.67 to 1.75
Precision (% CV) – B17P	Intrarun: ≤4.48 to ≤7.41 Inter-run: 4.03 to 6.90
Accuracy (% relative error) – B17P	Intrarun: –11.0 to 5.63 Inter-run: –8.53 to 0.00
Incurred sample reanalysis – BDP	
Total no. of incurred sample reanalysis	66 (10.4% of samples)
Total no. of sample whose % differences are within 20%	62
% of total no. of samples whose % differences are within 20%	93.9
Incurred sample reanalysis – B17P	
Total no. of incurred sample reanalysis	60 (10.4% of total samples)
Total no. of sample whose % differences are within 20%	66
% of total no. of samples whose % differences are within 20%	90.9
Duration from time sample was first drawn to date of last sample analysis including ISR	132 days (within the established stability window of 133 days); two ISR samples were stored for 140 and 141 days
Sample storage temperature	–70°C

Source: Reviewer's summary

Abbreviations: CAL, calcipotriene; CV, coefficient of variation; ISR, individual safety report; B17P, betamethasone 17-propionate

14.4.2. Bioanalytical Method for HPA Axis Suppression Evaluation (Cortisol)

The concentration of cortisol in human serum for evaluation of HPA axis suppression in study MC2-01-C3 was quantified using a validated LC-MS/MS method. The method validation results for quantification of cortisol are summarized in Table 60. The method appears acceptable.

Table 60. Summary of LC-MS/MS Bioanalytical Method Validation for Cortisol

Validation report	(b) (4) Serum Cortisol Assay Validation Report
Matrix	Human serum
Anticoagulant	Heparin or disodium ethylene diamine tetra acetic acid
Extraction method	Multiple HPLC system with on-line extraction
Internal standard	Cortisol-[¹³ C ₃]
Calibration curve range	0.1 – 100 µg/dL
LLOQ	0.1 µg/dL
QC levels	1.5, 20.0, 40.0, 80.0 µg/dL
Precision (%CV)	
Interassay	Level 1: 7.02% Level 2: 7.06% Level 3: 6.32% Level 4: 5.44%
Intra-assay	Level 1: 4.84% Level 2: 4.15% Level 3: 2.39% Level 4: 1.91%
Accuracy (recovery, %bias)	94.73%
Ambient stability (18 to 25°C)	14 days
Refrigerated stability (2 to 8°C)	21 days
Long-term stability	1 year at –30 to –10°C

Source: Reviewer's summary

Abbreviations: CV, coefficient of variation; HPLC, high-performance liquid chromatography; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLOQ, lower limit of quantification

14.4.3. Bioanalytical Method for Calcium

For quantitative determination of the calcium level in human serum, plasma, and urine in studies MC2-01-C3 and MC2-01-C2, the Applicant utilized a commercially available, validated and automated analysis system, the Siemens ADVIA® 1800. The method is based on colorimetric/ spectrophotometric detection and uses lithium heparin as an anticoagulant (for plasma samples). The analytical ranges are 0.5 to 16.0 mg/dL for serum/plasma samples and 1.0 to 32.0 mg/dL for urine samples. The method appears acceptable.

14.5. Clinical /Biostatistics

Table 61. Demographic Characteristics of Phase 3 Safety Population

Characteristic	CAL/BDP Cream n=342	CAL/BDP Topical Suspension n=337	Vehicle Cream n=115	Total n=794
Age				
Mean and SD	52.05 [14.39]	52.59 [13.71]	50.36 [14.28]	52.03 [14.09]
Median	53	54	51	53
Range	19-89	18-89	20-81	18-89
Age range 40-65, count subjects (%)				
40-64	207 (60.5%)	208 (61.7%)	65 (56.5%)	480 (60.5%)
<40	69 (20.2%)	64 (19.0%)	29 (25.2%)	162 (20.4%)
≥65	66 (19.3%)	65 (19.3%)	21 (18.3%)	152 (19.1%)
Sex, count subjects (%)				
M	203 (59.4%)	221 (65.6%)	71 (61.7%)	495 (62.3%)
F	139 (40.6%)	116 (34.4%)	44 (38.3%)	299 (37.7%)
Race, count subjects (%)				
White	290 (84.8%)	299 (88.7%)	102 (88.7%)	691 (87.0%)
Black or African American	34 (9.9%)	20 (5.9%)	11 (9.6%)	65 (8.2%)
Asian	10 (2.9%)	10 (3.0%)	1 (0.9%)	21 (2.6%)
American Indian or Alaska Native	3 (0.9%)	3 (0.9%)	1 (0.9%)	7 (0.9%)
Multiple	2 (0.6%)	3 (0.9%)	0 (0.0%)	5 (0.6%)
Native Hawaiian or other Pacific Islander	2 (0.6%)	1 (0.3%)	0 (0.0%)	3 (0.4%)
Other	1 (0.3%)	1 (0.3%)	0 (0.0%)	2 (0.3%)
Ethnicity, count subjects (%)				
Not Hispanic or Latino	241 (70.5%)	243 (72.1%)	84 (73.0%)	568 (71.5%)
Hispanic or Latino	101 (29.5%)	94 (27.9%)	31 (27.0%)	226 (28.5%)

Source: Reviewer's table created in JReview using the Applicant's ADSL dataset

Abbreviations: BDP, betamethasone dipropionate; CAL, calcipotriene; F, female; M, male

14.6. Additional Clinical Outcome Assessment Analyses

None.

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/s/

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