CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208079Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208079
Priority or Standard	Standard
Submit Date(s)	04-06-2015
Received Date(s)	04-06-2015
PDUFA Goal Date	02-06-2015
Division / Office	DDDP / ODE3
Reviewer Name(s)	Hon-Sum Ko
Review Completion Date	12-28-2015
Established Name	Betamethasone dipropionate
(Proposed) Trade Name	SERNIVO Spray
Therapeutic Class	Corticosteroid
Applicant	Promius Pharma, LLC
Formulation(s)	Spray, 0.05%
Dosing Regimen	Twice daily for up to 4 weeks
Indication(s)	Moderate plaque psoriasis (proposed)
Intended Population(s)	18 years of age or older

Template Version: March 6, 2009

Table of Contents

Table of Tables

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval, contingent upon agreement of labeling

1.2 Risk Benefit Assessment

SERNIVO (betamethasone dipropionate) Spray, 0.05% is a corticosteroid proposed for topical treatment of plaque psoriasis. The applicant recommends twice daily dosing for up to 4 weeks. The container provides for 60 or 120 mL of the drug product.

Plaque psoriasis is a chronic disease characterized by symmetrically distributed, sharply demarcated, scaly, erythematous plaques, which often involve extensor surfaces of the extremities, but may present anywhere from scalp to soles of the feet. The extent of body surface area affected is variable. Disease of limited extent may be effectively managed with topical treatment. There are many approved topical corticosteroids available for the treatment of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, which include plaque psoriasis. There are also several approved topical corticosteroids, alone or as fixed combination with a vitamin D analog approved for the indication of plaque psoriasis. SERNIVO Spray, 0.05% is a new dosage form for betamethasone diproionate.

There are some betamethasone dipropionate formulations which have been classified as “superpotent” or “high” in potency with the vasoconstriction assay (e.g., Diprolene formulations, of which Diprolene Lotion, 0.05% is the reference product for SERNIVO Spray, 0.05%). There are other betamethasone dipropionate formulations classified as of “medium” potency. SERNIVO Spray is of “medium” (or “mid-”) potency by the vasoconstriction assays. Although the reference product, Diprolene Lotion, has dosage limitations for use of no more than 50 mL/week and no more than 2 consecutive weeks, SERNIVO Spray has been studied for longer time frame (4 weeks) without greater risk of systemic adverse effects such as hypothalamic-pituitary-adrenal (HPA) axis suppression.

A risk-benefit assessment suggests that SERNIVO Spray is effective in the treatment of plaque psoriasis of moderate severity and likely carries lower risks of systemic and local adverse effects of topical corticosteroids than its reference product, Diprolene Lotion, which is of higher potency. Therefore, this reviewer concludes that the benefits of SERNIVO Spray, 0.05% outweigh its risks. It is reasonable to extrapolate and approve this new formulation for the treatment of mild to moderate plaque psoriasis at the recommended dosage for up to 4 weeks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Recommending routine pharmacovigilance and product labeling for postmarket risk evaluation and mitigation

1.4 Recommendations for Postmarket Requirements and Commitments

Pediatric Research Equity Act (PREA) postmarketing requirement (PMR) with deferred pediatric study to include assessment of HPA axis suppression under maximal use conditions in adolescents 12 years to 16 years 11 months of age having plaque psoriasis, and evaluation of pharmacokinetic parameters

The recommended timeline for the PMR (as per accepted iPSP) is:

- Final Protocol Submission: 06-30-2015
- (b) (4)
- Final Report Submission: 07-31-2018

See Section 7.6.3 of this review for additional discussion on pediatric development.

2 Introduction and Regulatory Background

2.1 Product Information

The applicant proposes marketing of SERNIVO (betamethasone dipropionate) Spray, 0.05% for the topical treatment of moderate plaque psoriasis in adults. Betamethasone dipropionate is a corticosteroid, and SERNIVO Spray, 0.05% is a new dosage form shown to be of mid-potency by the vasoconstriction assay.[1] Section 2.3 of this review discusses availability of the active ingredient, betamethasone dipropionate, and Section 4.1 contains details of the product's composition.

The applicant proposes dosing twice daily for up to 4 weeks.

Unless otherwise noted, SERNIVO Spray in this review refers to the to-be-marketed formulation with betamethasone dipropionate 0.05%. The term "betamethasone diproprionate spray, 0.05%" is used synonymously with the proprietary name "SERNIVO Spray." Although the actual concentration of betamethasone dipropionate in this product is 0.643 mg per gram, the strength has been traditionally labeled as 0.05%, with consideration of only the steroid portion of the ester molecule (e.g., in Diprolene formulations). However, the diester itself is an active moiety and has enhanced affinity

1 Valencia IC, Kerdel FA. Chapter 216. Topical Corticosteroids. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K. eds. *Fitzpatrick's Dermatology in General Medicine, 8e.* New York, NY: McGraw-Hill; 2012.

to the glucocorticoid receptor, with the steroid portion being an active metabolite of the complete betamethasone dipropionate molecule.

2.2 Tables of Currently Available Treatments for Proposed Indications

The proposed indication is the topical treatment of moderate plaque psoriasis in patients 18 years of age or older. Products available as prescription drugs for the topical treatment of plaque psoriasis include those listed in Table 1.

Table 1: Topical prescription treatments for plaque psoriasis

Product Class	Example
Corticosteroid*	Clobetasol ointment
Synthetic vitamin D_3 derivative	Calcipotriene cream
Synthetic vitamin D_3 derivative/corticosteroid combination product	Calcipotriene and betamethasone dipropionate ointment
Retinoid	Tazarotene gel

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

In addition, there are active ingredients monographed for the over-the-counter indication of "relief" or "control" of psoriasis symptoms (21 CFR Part 358). These active ingredients are listed in Table 2.

Table 2: Over-the-counter treatments for plaque psoriasis

Active Ingredient	Strength
Coal tar*	0.5 to 5.0%
Salicylic acid	1.8 to 3.0%

*When a coal tar solution, derivative, or fraction is used as the source of the coal tar, the labeling is to specify the identity and concentration of the coal tar source used.

Apart from topical treatment, approved therapies for plaque psoriasis of higher severity also include systemic therapy (e.g., retinoids, corticosteroids, cyclosporine, biologics, etc.) and phototherapy (psoralen plus ultraviolet radiation). These are not pertinent to the current discussion on SERNIVO Spray, 0.05%, as the target population is one with less severe disease and requires primarily topical treatment.

2.3 Availability of Proposed Active Ingredient in the United States

The betamethasone dipropionate moiety was first approved on January 29, 1975 as a medium-potency topical corticosteroid cream "indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 13 years and older" (Diprosone Cream; NDA 17536). However, this product and other subsequent dosage forms of the Diprosone series for betamethasone dipropionate (Diprosone Ointment under NDA 17691 and Diprosone Lotion under NDA 17781) have been discontinued.

There have been newer topical formulations of betamethasone dipropionate since the 1980s, and the currently marketed dosage forms are “augmented” formulations under the proprietary name “Diprolene” or “Diprolene AF”, which are shown in Table 3.

Table 3: Marketed topical monotherapy products with betamethasone dipropionate

NDA	Drug Name	Strength	Potency*	Status
18741	Diprolene Ointment	0.05%	Superpotent	Approved July 27, 1983
19555	Diprolene AF Cream	0.05%	High potency	Approved August 27, 1987
19716	Diprolene Lotion	0.05%	Superpotent	Approved August 1, 1988

*Potency as determined by the vasoconstriction assay

Betamethasone dipropionate is currently also marketed as a component of fixed combination products with the vitamin D analog, calcipotriene, for topical treatment of plaque psoriasis (Taclonex Ointment and Suspension, and Enstilar Foam). As well, it is available in combination with the antifungal, clotrimazole, for topical treatment of symptomatic inflammatory tinea pedis, tinea cruris, and tinea corporis (Lotrisone Cream and Lotion).

In addition to the innovators, topical products for betamethasone dipropionate are marketed as generic drugs, both as monotherapy and as combination products.

2.4 Important Safety Issues with Consideration to Related Drugs

Prescription topical corticosteroids, including betamethasone dipropionate products, are labeled for potential systemic and local risks:

- Potential systemic risks include reversible hypothalamic-pituitary adrenal (HPA) axis suppression, manifestations of Cushing’s syndrome, hyperglycemia, and glycosuria.
- Potential local safety risks include skin atrophy, striae, telangiectasias, burning or stinging, pruritus, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infections, hypertrichosis, and miliaria.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The product was developed under IND 104,853. Important interactions, especially those with respect to clinical issues include those described below.

Pre-IND Meeting of June 17, 2009

- The sponsor proposed studying betamethasone dipropionate spray, 0.05% for moderate(b) (4) plaque psoriasis under 505(b)(2) pathway, with Diprolene Lotion, 0.05% as the reference product.
- There were no clinical questions in the meeting package, and the agency provided general comments on clinical development for topical corticosteroids, in addition to advice for 505(b)(2) submission.

Advice Letter of November 17, 2010
The agency provided guidance on vasoconstriction assay studies.

Guidance Meeting of March 16, 2011
In this meeting, the agency explained the requirements for 505(b)(2) submission and clinical bridging to the reference product.

Advice Letter of April 28, 2011
Based on the lack of absorbance in the 290-700 nm portion of the ultraviolet-visible light spectrum, the agency waived nonclinical phototoxcicity studies and reminded the sponsor that photocarcinogenicity studies had been waived previously.

Advice Letter of January 15, 2013
The agency provided guidance on the draft phase 3 protocols regarding Investigator Global Assessment scoring, body surface area involvement for moderate (b) (4) psoriasis, time point for primary efficacy (agency recommending Day 29), and target lesion as secondary endpoint.

Advice Letter of August 1, 2013
The agency provided guidance on the following issues:

- Comparison with the reference product (Diprolene Lotion, 0.05%) should be done with usage under its labeled conditions (twice daily for up to 2 weeks).
- (b) (4) the agency advised studying moderate to severe plaque psoriasis.
- The Investigator Global Assessment scoring scale was acceptable.

Advice Letter of March 3, 2014
The agency provided guidance on statistical issues for phase 3 trials, and reiterated previous recommendation of analysis of primary efficacy to be at Day 29.

Advice Letter of October 2, 2014
The agency gave advice on dermal carcinogenicity study: "We have reviewed the 13-week dermal dose range-finding study in rats (13-2355). Based on the extent of test article induced immunosuppression noted in the 13 week dermal dose range finding study in rats, conduct of a 2-year dermal carcinogenicity study is not practical with your topical drug product. Therefore, you should submit a waiver request to the IND for conduct of a 2-year dermal carcinogenicity study in rats with your topical drug product." As well, the agency informed the sponsor that another 28-day study on non-rodents was not required.

Advice Letter of October 20, 2014
The agency provided statistical comments on phase 3 trials, including the sponsor's choice of Day 15 as primary endpoint: "You have not provided a rationale for continuing treatment for 28 days when the primary efficacy assessment is Day 15. A secondary

endpoint assessment at Day 28 may not be sufficient for including 4-week data in labeling." As noted above, the agency had advised primary efficacy endpoint to be at Day 29.

Pre-NDA Meeting of January 12, 2015

- The agency discussed with the sponsor about submission of CDISC-compliant datasets in SDTM and ADaM, as well as pooling of study data for the integrated summaries.
- In addition, the agency agreed that the two phase 3 efficacy studies (BDS1205 and BDS1206) and the HPA axis suppression study (BDS1307) could support filing of SRNIVO Spray, 0.05% for the treatment for up to 4 weeks of moderate plaque psoriasis in patients 18 years of age and older.

2.6 Other Relevant Background Information

Other relevant background information includes the development of a pediatric study plan, leading to acceptance by the agency of the final iPSP in December, 2014. The applicant has proposed waiver for studying pediatric patients between 0 and 11 years 11 months of age, and deferral of pediatric assessment of adolescents between 12 and 16 years 11 months of age. The deferred study will evaluate HPA axis suppression and pharmacokinetic parameters in adolescent subjects with plaque psoriasis treated with SERNIVO Spray under maximal use conditions.

The Division of Medication Error Prevention and Analysis (DMEPA) concluded that the proposed proprietary name SERNIVO for betamethasone dipropionate spray, 0.05% was acceptable. A letter to that effect was sent to the IND sponsor on November 10, 2014.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The application was sufficiently complete and organized, such that it could be reviewed without difficulty.

3.2 Compliance with Good Clinical Practices

The applicant stated that the clinical studies were conducted in accordance with Good Clinical Practices.

Data from individual study sites for the pivotal clinical trials, BDS1205 and BDS1206, were evaluated by this Reviewer and the Statistical Reviewer, Dr. K. Fritsch. We determined that there was no single site which could carry sufficient weight to affect the outcome of each of the clinical trials. In addition, as betamethasone dipropionate is a

well-studied molecular entity in past clinical trials, auditing of the clinical sites in this NDA by OSI is optional. The OSI Reviewer, Dr. Roy Blay, agrees with this approach and site inspections have been waived.

3.3 Financial Disclosures

In this NDA submission, the applicant has certified the following:

- The applicant has not entered into any financial arrangement with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the trial.
- Each clinical investigator who was required to disclose to the applicant whether he/she had a proprietary interest in this product or a significant equity in the applicant did not disclose any such interests.
- No investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The drug product of the NDA is betamethasone dipropionate lotion co-packaged with a manual spray pump for installation by the pharmacist prior to dispensing.

Composition of the drug product is shown in Table 4.

Table 4: Composition of SERNIVO Spray, 0.05%*

Ingredients	Quality standard	% w/w	Function
Betamethasone dipropionate	USP/EP	0.0643	Active
Sorbitan monostearate	(b) (4)		
Polyoxyl 20 cetostearyl ether			
Cetostearyl alcohol			
Mineral oil			
Oleyl alcohol			
Propylparaben			
Methylparaben			
Butylated hydroxytoluene			
Hydroxyethyl cellulose			
Purified water			

*Potency expressed as betamethasone (0.05%)

The quality sections of this NDA have been reviewed by a CMC team (Drug substance Reviewer: Sam Bain, Ph.D., Drug product Reviewer: Hamid Shafiei, Ph.D., Biopharmaceutics Reviewer: Vidula Kolhatkar, Ph.D., Process Reviewer: Yaodong

Huang, Ph.D., Micro Reviewer: Erika Pfeiler, Ph.D., Facility Reviewer: Tony Wilson, Ph.D.) under the technical leadership of Yichun Sun, Ph.D., with the recommendation for approval pending labeling. Although no IVRT data have been submitted, adequacy of the proposed IVRT method and the proposed in vitro release acceptance criteria will not affect approvability.

The CMC Review has not revealed significant issues impacting safety or efficacy of SERNIVO Spray, 0.05%.

In summary, Dr. Sun has the following conclusions and recommendation:

- The applicant of this NDA has provided sufficient CMC information to assure the identity, purity, strength and quality of the drug substance and drug product.
- The facility review team from the Office of Facility and Process has issued an "Approval" recommendation for the facilities involved in this application.
- The issues on labels/labeling related to CMC are completely resolved at this time.
- Therefore, from the OPQ perspective, this NDA is recommended for approval with an expiration dating period of 24 months.

4.2 Clinical Microbiology

The product is not an antimicrobial.

4.3 Preclinical Pharmacology/Toxicology

Jill Merrill, Ph.D. is the pharmacology/toxicology reviewer for this NDA. She concludes that SERNIVO Spray, 0.05% is "approvable from a pharmacology/toxicology perspective."

As a 505(b)(2) application, the applicant relies on FDA's findings of safety for Diprolene® Lotion, 0.05% to support the systemic safety of SERNIVO Spray, 0.05%. Consistent with the labeling of Diprolene Lotion, the prescribing information for SERNIVO Spray states that betamethasone was negative in bacterial and mammalian mutagenicity assays, positive in the in vitro chromosomal aberration assay, and equivocal in the in vivo mouse micronucleus assay. Intramuscular administration resulted in dose-related increase in fetal resorptions in rabbits and mice. Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the intramuscular route at doses of 0.05 mg/kg.

Nonclinical studies conducted by the applicant provided data consistent with corticosteroid effect:

- In a 13-week repeat dose dermal toxicity study in rats, topical administration of betamethasone dipropionate spray at dose levels up to up to 0.5 mg/kg/day in males and 0.25 mg/kg/day in females resulted in reduced body weight gain and adrenal atrophy consistent with the reported toxicological effects of synthetic corticosteroids. Based on the test article-induced immunosuppression, a waiver for 2-year dermal carcinogenicity study has been granted.

- In a 28-day dermal toxicity study in minipigs, betamethasone dipropionate spray up to 1.5 mg/kg/day in males and 1.0 mg/kg/day in females was administered. The study was terminated early due to severe dermal irritation attributed to vehicle. The clinical pathology, organ weight and microscopic changes were consistent with anti-inflammatory and immunosuppressive effects of corticosteroids. Additional dermal toxicity study in another nonrodent model has not been considered necessary.
- Betamethasone dipropionate, 0.05% spray did not elicit a delayed contact hypersensitivity response in guinea pigs nor was it a dermal or ocular irritant when tested in rabbits.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The applicant proposed similar language in labeling for mechanism of action of SERNIVO Spray, 0.05% as that for the reference drug, Diprolene Lotion, 0.05%: "Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action in psoriasis is unknown." This is acceptable.

4.4.2 Pharmacodynamics

There have been three vasoconstriction assay studies and one study on HPA axis suppression, details of which can be found in the Clinical Pharmacology Review by Dr. D. Tran. The following summarizes the findings from these trials:

- The vasoconstrictor studies in healthy subjects (BDS1103, BDS1204 and DFD01-CD-009) show that SERNIVO Spray, 0.05% is in the mid-range of potency.
- The HPA axis suppression study (BDS1307) included 75 adult subjects with moderate to severe plaque psoriasis involving 20% to 50% of their body surface area (BSA) who were administered the cosyntropin stimulation test. SERNIVO Spray was applied twice daily for 15 or 29 days and Diprolene Lotion, 0.05% was applied twice daily for 15 days. Of the 68 subjects evaluated with cosyntropin stimulation at the end of treatment, HPA axis suppression was demonstrated in 20.8% (5 out of 24) of subjects treated with SERNIVO Spray for 15 days and 25.0% (5 out of 20) of those treated with Diprolene Lotion for 15 days, but not in subjects (0 out of 24) treated with SERNIVO Spray for 29 days. In this study, HPA axis suppression was defined as serum cortisol level ≤18 µg/dL 30-minutes post-cosyntropin stimulation. In the 7 subjects with available follow-up values, all subjects showed normal stimulation at follow-up.

4.4.3 Pharmacokinetics

The HPA axis suppression study (BDS1307) included a component for pharmacokinetic evaluation. Plasma concentrations of betamethasone dipropionate, betamethasone-17-propionate, and betamethasone were measured at baseline, and before and after the

last dose (1, 3, and 6 hours) in the trial. Most subjects had no measurable plasma concentration of betamethasone dipropionate (<5.00 pg/mL), while the metabolites, betamethasone-17-propionate and betamethasone, were detected in the majority of subjects.

Table 5: Mean (±SD) maximum plasma levels (pg/mL) of betamethasone dipropionate metabolites after 15 or 29 days of treatment with SERNIVO Spray

Analyte (pg/mL)	SERNIVO Spray *b.i.d.* (15 days)	SERNIVO Spray *b.i.d.* (29 days)
Betamethasone-17-propionate	120 ± 127	63.9 ± 52.6
Betamethasone	119 ± 176	57.6 ± 55.9

Modified from Clinical Pharmacology Review by Dr. D. Tran.

High variability was observed, but there was a trend towards higher systemic exposure at day 15 and lower exposure at day 29.

In conclusion, Dr. D. Tran, the Clinical Pharmacology Reviewer, concludes: "The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds NDA 208079 acceptable pending agreement on recommended labeling changes."

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The applicant's [redacted] (b) (4) SERNIVO Spray, 0.05% consisted of ten studies shown in Tables 6 and 6a:

Table 6: List of clinical studies conducted by applicant to support SERNIVO Spray, 0.05%

Study Type	Study No.	Title
Vasoconstriction assay studies	BDS1103	A Randomized, Evaluator-Blinded, Within-Subject, Single-Center Vasoconstrictor Study to Compare the Relative Potency of Seven Different Betamethasone Dipropionate Spray Formulations to Two Currently Marketed Topical Corticosteroid Formulations of Known Potency in Healthy Adult Subjects
	BDS1204	A Randomized, Evaluator-Blinded, Within-Subject, Single-Center, Vasoconstrictor Study to Determine the Potency of a Betamethasone Dipropionate 0.05% Spray (Formulation compared to Six Currently Marketed Topical Corticosteroid Formulations of Known Potency in Healthy Adult Subjects
	DFD01-CD-009	A Randomized, Evaluator-Blinded, Within-Subject, Single-Center Vasoconstrictor Study to Determine the Potency of a Betamethasone Dipropionate 0.05% Spray (Promius Pharma LLC) Formulation Compared to Six Currently Marketed Topical Corticosteroid Formulations of Known Potency under Non-occluded Conditions in Healthy Adult Subjects
Dermal safety studies	DFD01-CD-008	A Double-Blind, Randomized, Controlled, Cumulative Irritation Patch Test Study of Betamethasone Dipropionate Spray

	DFD01-CD-010	A 4-Day, Randomized, Vehicle-Controlled, Patch Test Study to Evaluate the Phototoxic Potential of Betamethasone Dipropionate Spray
	DFD01-CD-011	A 6-Week, Randomized Study to Evaluate the Potential of Betamethasone Dipropionate Spray to Induce a Photoallergic Skin Reaction in Healthy Volunteers, Using a Controlled Photopatch Test Design
	DFD01-CD-012	A Randomized, Double-Blind, Vehicle-Controlled, Repeat Insult Patch Test Study to Assess the Sensitization Potential of Betamethasone Dipropionate Spray
HPA axis suppression study	BDS1307	A Randomized, Parallel, Open Label, Multicenter Study to Assess the Potential for Adrenal Suppression and Systemic Drug Absorption Following Multiple Dosing with Betamethasone Dipropionate Spray 0.05% versus Diprolene® (augmented betamethasone dipropionate) Lotion 0.05% in Subjects with Moderate to Severe Plaque Psoriasis
Phase 3 safety and efficacy studies ("pivotal" clinical trials) and bridging to RLD (BDS1205)	BDS1205	A Randomized, Double-Blind, Vehicle-Controlled, Multicenter, Parallel Group Study of the Safety of Betamethasone Dipropionate Spray 0.05% versus Diprolene® (augmented betamethasone dipropionate) Lotion 0.05% and the Efficacy of Betamethasone Dipropionate Spray 0.05% versus Vehicle Spray in the Treatment of Moderate Plaque Psoriasis
	BDS1206	A Randomized, Double-Blind, Vehicle-Controlled, Multicenter, Parallel Group Study of the Efficacy and Safety of Betamethasone Dipropionate Spray 0.05% in the Treatment of Moderate Plaque Psoriasis

Table 6a: Summary of clinical studies supporting NDA 208079 in the Integrated Summary of Safety of the NDA

Study ID	No. of Ctrs.[a]	Study Dates (Start–Completion)	Total Enrollment (Planned/Actual)	Design / Control	Route and Regimen	Healthy Subjects or Diagnosis of Patients	No. of Subjects by Treatment (Entered/ Completed)	Treatment Duration	Gender (M/F) Age (Range) Race
Pharmacodynamics									
BDS1103	1	03 Mar 2012 – 04 Mar 2012	30 to 40/33	Patch test Randomized, evaluator-blinded, within-subject, single-center Vasoconstrictor potency study Active and listed drugs	Topical single application of 10 µL of each formulation	Healthy	33/33 for each treatment: Betamethasone dipropionate spray formulations F9, F10 (final to-be-marketed formulation), F11, F13, F14, F18, F19; Diprolene Lotion 0.05%; Cutivate Cream 0.05%	Single application of each treatment for 16 hours (non-occluded)	M: 16 / F: 17 Age: 21 to 62 years Race: Asian: 1 Black: 9 White: 20 Other: 3

Study ID	No. of Ctrs.[a]	Study Dates (Start–Completion)	Total Enrollment (Planned/Actual)	Design / Control	Route and Regimen	Healthy Subjects or Diagnosis of Patients	No. of Subjects by Treatment (Entered/ Completed)	Treatment Duration	Gender (M/F) Age (Range) Race
BDS1204	1	11 Nov 2013 – 12 Nov 2013	30 to 40/40	Patch test Randomized, evaluator-blinded, within-subject, single-center Vasoconstrictor potency study Active, listed drug, and placebo	Topical single application of 10 µL of each formulation	Healthy	40/40 for each treatment: Betamethasone Dipropionate Spray, 0.05%, (F10-final to-be-marketed formulation) Augmented Betamethasone Dipropionate Ointment, 0.05% Diprolene Lotion, 0.05% Diprolene AF Cream, 0.05% Elocon Ointment Fluticasone propionate cream, 0.05% Hydrocortisone cream, 2.5% Placebo spray	Single application of each treatment for 16 hours (non-occluded)	M: 6 / F: 34 Age: 18 to 64 years Race: Asian: 3 Black: 2 White: 16 Other: 19

Study ID	No. of Ctrs.[a]	Study Dates (Start–Completion)	Total Enrollment (Planned/Actual)	Design / Control	Route and Regimen	Healthy Subjects or Diagnosis of Patients	No. of Subjects by Treatment (Entered/ Completed)	Treatment Duration	Gender (M/F) Age (Range) Race
DFD01-CD-009	1	28 Feb 2014 – 08 Mar 2014	Up to 80/80	Patch test Randomized, evaluator-blinded, within-subject, single-center Vasoconstrictor potency study Active, listed drug, and vehicle	Topical single application of 10 µL of each formulation	Healthy	80/78 for all: Betamethasone Dipropionate Spray, 0.05%, (F 10-final to-be-marketed formulation) Diprolene Ointment, 0.05%, Diprolene Lotion, 0.05%, Diprolene AF Cream, 0.05%, Triamcinolone acetonide cream, 0.1%, Fluticasone propionate cream, 0.05%, Hydrocortisone cream, 2.5%, Vehicle Spray	Single application of each treatment for 16 hours (non-occluded)	M: 23 / F: 55* Age: 18 to 64 years Race: White: 37 Other: 36 Asian: 5 *for ITT population (n=78)

Study ID	No. of Ctrs.[a]	Study Dates (Start–Completion)	Total Enrollment (Planned/Actual)	Design / Control	Route and Regimen	Healthy Subjects or Diagnosis of Patients	No. of Subjects by Treatment (Entered/ Completed)	Treatment Duration	Gender (M/F) Age (Range) Race
Safety									
DFD01-CD-008	1	19 Sep 2013 – 11 Oct 2013	Approximately 40/40	Patch test Double-blind, randomized, single-center, within-subject Irritation potential Vehicle, negative, positive	Topical Once daily	Healthy	40/34 for each: Betamethasone Dipropionate Spray, 0.05% Vehicle Spray Diprolene Lotion vehicle Sodium lauryl sulfate 0.2% Saline 0.9%	21 days	M: 11 / F: 29 Age: 36 to 75 years Race: White: 36 Black: 2 Other : 2
DFD01-CD-010	1	22 Jul 2014 – 31 Jul 2014	Approximately 35/33	Patch test Double-blind randomized, within-subject, single-center Phototoxic potential Active, listed drug, and vehicle	Topical one application of 10 µL of each formulation to two sites	Healthy	33/33 for each: Betamethasone Dipropionate Spray, 0.05% Vehicle Spray Diprolene Lotion, 0.05%	24 hours	M: 7 / F: 26 Age: 17 to 74 years Race: White: 33

Study ID	No. of Ctrs.[a]	Study Dates (Start–Completion)	Total Enrollment (Planned/Actual)	Design / Control	Route and Regimen	Healthy Subjects or Diagnosis of Patients	No. of Subjects by Treatment (Entered/ Completed)	Treatment Duration	Gender (M/F) Age (Range) Race
DFD01-CD-011	1	04 Aug 2014 – 24 Oct 2014	Approximately 50/53	Patch test Double-blind randomized, within-subject, single-center Photoallergic potential Negative, listed drug, and vehicle	Topical, once daily, of each formulation	Healthy	53/45 for each: Betamethasone Dipropionate Spray, 0.05% Vehicle Spray Diprolene Lotion, 0.05% Saline, 0.9%	2 times per week for 3 weeks plus challenge application	M: 13 / F: 40 Age: 19 to 75 years Race: White: 53
DFD01-CD-012	1	21 Jul 2014 – 9 Oct 2014	Approximately 240/226	Patch test Double-blind randomized, within-subject, single-center Sensitization and irritation potential Negative, positive, listed drug, and vehicle	Topical, once daily	Healthy	226/200 for each: Betamethasone Dipropionate Spray, 0.05% Vehicle Spray Diprolene Lotion, 0.05% Sodium lauryl sulfate 0.2% Saline 0.9%	3 times per week for 3 weeks plus challenge application	M: 74 / F: 152 Age: 18 to 75 years Race: Asian: 4 Black: 82 Native Hawaiian: 1 White: 137 Multiple: 2

Study ID	No. of Ctrs.[a]	Study Dates (Start–Completion)	Total Enrollment (Planned/Actual)	Design / Control	Route and Regimen	Healthy Subjects or Diagnosis of Patients	No. of Subjects by Treatment (Entered/ Completed)	Treatment Duration	Gender (M/F) Age (Range) Race
BDS1307	11	03 Mar 2014 – 11 Nov 2014	Approximately 75 but no more than 90/75	Randomized, parallel, open label, multicenter HPA axis suppression study Listed drug	Topical, twice daily	Moderate to severe plaque psoriasis	Betamethasone Dipropionate Spray, 0.05% 29-day treatment: 27/25 Diprolene Lotion: 23/21 Betamethasone Dipropionate Spray, 0.05% 15-day treatment: 25/24	15 days or 29 days	M: 53 / F: 21* Age: 20 to 72 years Race: Asian: 4 Black: 6 White: 64 *for safety population which is one less than entered

Study ID	No. of Ctrs.[a]	Study Dates (Start–Completion)	Total Enrollment (Planned/Actual)	Design / Control	Route and Regimen	Healthy Subjects or Diagnosis of Patients	No. of Subjects by Treatment (Entered/ Completed)	Treatment Duration	Gender (M/F) Age (Range) Race
Adequate and Well-Controlled Studies									
BDS1205	39	05 Nov 2013 – 06 Jan 2015	Approximately 396 but no more than 450/394	Randomized double-blind parallel, multicenter Pivotal psoriasis study	Topical, twice daily	Moderate plaque psoriasis	Betamethasone Dipropionate Spray, 0.05%: 174/166 Vehicle Spray: 87/81 Diprolene Lotion, 0.05%: 90/88 Vehicle Lotion: 43/38	28 days	M: 242 / F: 152 Age: 18 to 86 years Race: American Indian/Alaska native: 2 Asian: 20 Black: 28 Native Hawaiian: 1 White: 337 Other: 3 Multiple: 3
BDS1206	28	04 Dec 2013 – 31 Jul 2014	Approximately 264 but no more than 300/277	Randomized double-blind parallel, multicenter Pivotal psoriasis study	Topical, twice daily	Moderate psoriasis	Betamethasone Dipropionate Spray, 0.05%: 182/174 Vehicle Spray: 95/87	28 days	M: 172 / F: 105 Age: 19 to 86 years Race: Asian: 11 Black: 21 Native Hawaiian: 1 White: 233 Other: 5 Multiple: 6

[a]Ctrs=centers; F=female; HPA= hypothalamic-pituitary-adrenal; M=male;
Summary Tables in Integrated Summary of Safety section of the application (Module 5, Section 5.3.5.3)

All of the clinical studies have used the to-be-marketed formulation of betamethasone dipropionate spray, 0.05% (“F10”, or SERNIVO Spray, 0.05%). For the vasoconstriction assay study BDS1103, several formulations of betamethasone dipropionate 0.05% were also included, out of which the to-be-marketed formulation (“F10”) was chosen for further studies.

5.2 Review Strategy

The vasoconstriction assay studies (BDS1103, BDS1204 and DFD01-CD-009) and the HPA axis suppression study (BDS1307) have been reviewed by Dr. D. Tran, the Clinical Pharmacology Reviewer. With respect to these studies, the focus in this clinical review will be on the safety data.

The two phase 3 trials, BDS1205 and BDS1206 will be discussed in Section 6 "Review of Efficacy" with respect to efficacy, while the safety data will be discussed in Section 7 "Review of Safety", and the four dermal safety studies, DFD01-CD-008, DFD01-CD-010, DFD01-CD-011, and DFD01-CD-012 also in Section 7 "Review of Safety" (subsection 7.4.5).

5.3 Discussion of Individual Studies/Clinical Trials

Study BDS1103 A Randomized, Evaluator-Blinded, Within-Subject, Single-Center Vasoconstrictor Study to Compare the Relative Potency of Seven Different Betamethasone Dipropionate Spray Formulations to Two Currently Marketed Topical Corticosteroid Formulations of Known Potency in Healthy Adult Subjects

Single point, randomized, evaluator-blinded, within-subject, single-center potency ranking study.

Investigator: William F. Lamberton, M.D.
Novum Pharmaceutical Research Services
5900 Penn Avenue
Pittsburgh, PA 15206

Objective: To use the vasoconstriction assay to evaluate the relative potency of seven test formulations of topical betamethasone dipropionate spray and two marketed topical corticosteroid formulations

Selection of Subjects:
Inclusion Criteria
1. Non-tobacco-using adult subjects, 18 to 65 years of age, inclusive.
2. Demonstrated blanching response to Cutivate® (fluticasone propionate) Cream 0.05% (visual assessment score of at least 1).
3. Body mass index (BMI) of 30 kg/m² or less.
4. Good health as determined by lack of clinically significant abnormalities in medical history and clinical assessment, as judged by the Investigator.
5. A Fitzpatrick skin type of 4 (IV) or less.
6. Signed and dated informed consent form.

Exclusion Criteria

1. History of allergy to any systemic or topical corticosteroid (especially betamethasone or fluticasone) or to any cream, lotion, ointment, gel, spray, cotton, soap, cosmetic, rubber or tape which in the opinion of the Investigator would compromise safety.
2. Presence of any skin condition or coloration that would interfere with placement of test articles at test sites or the response or assessment of skin blanching.
3. Significant history or current evidence of chronic infectious disease, systemic disorder (especially hypertension or circulatory disease) or organ dysfunction.
4. Presence of a medical condition requiring regular treatment with prescription drugs.
5. Drug or alcohol addiction requiring treatment (in-patient or out-patient) in the 12 months prior to dosing.
6. Use of any topical dermatological drug therapy on flexor surface of the ventral forearms in the 30 days prior to dosing.
7. Use of any tobacco products in the 30 days prior to dosing.
8. Receipt of any drug as part of a research study within 30 days prior to initial study dosing (Day 1).
9. Pregnant or lactating.
10. A Fitzpatrick skin type greater than 4 (IV).

Treatment:
Evaluation of the vasoconstriction properties of seven different test formulations of topical betamethasone dipropionate spray, (0.05% for formulations F9, F10, F11, F13, F14, (b) (4) F18, F19) and two marketed topical corticosteroids formulations (augmented formulation of Diprolene® 0.05% Lotion and Cutivate® 0.05% Cream) of known potency:

- A 10 µl amount of each formulation was applied to a single application site on the flexor surfaces of each subject's forearms and kept in place for 16 hours. Two untreated control sites were designated on each forearm as ChromaMeter reference sites. The degree of vasoconstriction was measured using visual scoring and a ChromaMeter (a-scale reading) at pre-dose (in duplicate) and at ~18 hours after drug application (~2 hours after washing the test sites to remove study drug).

Vasoconstriction Assay Data:
Thirty-three (33) asymptomatic, healthy, non-tobacco-using adult subjects pre-screened to show a vasoconstriction response to Cutivate® (fluticasone propionate) Cream, 0.05% were enrolled, and all 33 subjects completed the study. For vasoconstriction assay data, see review by Dr. D. Tran.

Safety Data:
No adverse events were reported by any subjects in this study.

Study BDS1204 A Randomized, Evaluator-Blinded, Within-Subject, Single-Center, Vasoconstrictor Study to Determine the Potency of a Betamethasone Dipropionate 0.05% Spray (Formulation compared to Six Currently Marketed Topical Corticosteroid Formulations of Known Potency in Healthy Adult Subjects

Single point, randomized, evaluator-blinded, within-subject, single-center potency ranking study.

Investigator: Robert A. Weaver, M.D., CPI
Novum Pharmaceutical Research Services
11300 Richmond Avenue
Houston, TX 77082

Objective: To use the vasoconstriction assay to determine potency of a test formulation of topical betamethasone dipropionate 0.05% spray and compare that to vehicle spary and to 6 marketed topical corticosteroid formulations of known potency: augmented betamethasone dipropionate 0.05% ointment, Diprolene® (brand of augmented betamethasone dipropionate) 0.05% lotion, Diprolene® AF (brand of augmented betamethasone dipropionate) 0.05% cream, Elocon® (mometasone furoate) 0.1% ointment, fluticasone propionate 0.05% cream, and hydrocortisone cream 2.5%

Selection of Subjects:
The eligibility criteria for this study are similar to those for BDS1103, except for Fitzpatrick skin type (≤3 for this study; ≤4 for BDS1103).

Treatment:
Ten sites were designated on the flexor surface of each forearm. An open washer was placed over each of the 10 sites and taped in place on its edges with hypoallergenic tape. Sites were labeled by number for ease of identification (sites 1-10 on the right arm; sites 11-20 on the left arm), and evaluated before dosing for any skin condition (e.g., coloration, freckles, moles, scratches, etc.) that might interfere with assessment.

A 10 µl application of each test, control, and reference formulation was applied to one site on the ventral surface of each forearm (total of 8 products each forearm) for ~16 hours before simultaneous removal at Time 0 (0 hour) and cleansed. Sites remained non-occluded throughout the study. Two untreated control sites were designated on each forearm, and were similarly cleaned and wiped at the same time as the treated sites (Time 0). Vasoconstriction was measured using visual scoring and a ChromaMeter (a-scale reading) at pre-dose (in duplicate) and at ~18 hours after drug application (~2 hours after washing the test sites to remove study drug).

Vasoconstriction Assay Data:
Forty (40) asymptomatic, healthy, non-tobacco-using adult subjects pre-screened to show a vasoconstriction response to fluticasone propionate cream, 0.05% were enrolled, and all 40 subjects completed the study. For vasoconstriction assay data, see review by Dr. D. Tran.

Safety Data:

No adverse events were reported by any subjects in this study.

DFD01-CD-009 A Randomized, Evaluator-Blinded, Within-Subject, Single-Center Vasoconstrictor Study to Determine the Potency of a Betamethasone Dipropionate 0.05% Spray (Promius Pharma LLC) Formulation Compared to Six Currently Marketed Topical Corticosteroid Formulations of Known Potency under Non-occluded Conditions in Healthy Adult Subjects

Single point, randomized, evaluator-blinded, within-subject, single-center potency ranking study.

Investigator: Robert A. Weaver, M.D., CPI
Novum Pharmaceutical Research Services
11300 Richmond Avenue
Houston, TX 77082

Objective: To use the vasoconstriction response to determine the potency of a test formulation of betamethasone dipropionate 0.05% spray (Promius Pharma, LLC) compared to vehicle spray and 6 marketed topical corticosteroid formulations of known potency (Diprolene® brand of augmented betamethasone dipropionate 0.05% ointment, Diprolene® brand of augmented betamethasone dipropionate 0.05% lotion, Diprolene® AF brand of augmented betamethasone dipropionate 0.05% cream, Fougera® triamcinolone acetonide 0.1% cream, Fougera® fluticasone propionate 0.05% cream and Fougera® hydrocortisone 2.5% cream)

Selection of Subjects:
The eligibility criteria for this study are the same as those for BDS1204, except for adding a lower limit for the BMI requirement (18-30 kg/m^2).

Treatment:
Ten sites were designated on the flexor surface of each forearm. An open washer placed over each of the 10 sites and taped in place on its edges with hypoallergenic tape. Sites were labeled by number for ease of identification (sites 1-10 on the right arm; sites 11-20 on the left arm), and evaluated before dosing for any skin condition (e.g., coloration, freckles, moles, scratches, etc.) that might interfere with assessment.

A 10 µl amount of each formulation was applied to a single application site on the flexor surfaces of each subject's forearms (left and right) and kept in place for 16 hours. In addition, two untreated control sites were designated on each forearm. The degree of vasoconstriction was measured using visual scoring and the ChromaMeter (a-scale reading) at pre-dose (in duplicate) and at 18 hours after the application of the formulations (~2 hours after washing the test sites to remove study drug).

Vasoconstriction Assay Data:

Eighty (80) asymptomatic, healthy, non-tobacco-using adult subjects pre-screened to show a vasoconstriction response to Fougera fluticasone propionate cream, 0.05% were enrolled, and 78 subjects completed the study. Two subjects (#64 and #69) did not return for Day 2 evaluation 18 hours after drug application. For vasoconstriction assay data, see review by Dr. D. Tran.

Safety Data:
Two adverse events were reported by one subject (#28) in this study: macular rash and pruritus on the right arm, and both were of mild severity. They were considered to be not related to study drug but due to the tape used to hold down the washers for drug application. The events resolved upon use of hydrocortisone cream, 1% applied topically.

BDS1307 A Randomized, Parallel, Open Label, Multicenter Study to Assess the Potential for Adrenal Suppression and Systemic Drug Absorption Following Multiple Dosing with Betamethasone Dipropionate Spray 0.05% versus Diprolene® (augmented betamethasone dipropionate) Lotion 0.05% in Subjects with Moderate to Severe Plaque Psoriasis

Randomized, multicenter (11 sites), multi-dose, comparator-controlled, open-label study on the potential for HPA axis suppression and pharmacokinetics of SERNIVO Spray upon maximal use conditions for 15 or 29 days in psoriasis subjects

Investigators:
The clinical investigators are shown in the following Table.

Table 7: Investigators for Study BDS1307

Site#	Principal Investigator	Investigational Site Name, City, and State
301	Syed Ali MD	Suzanne Bruce and Associates, PA The Center for Skin Research Katy/Cinco Ranch, Katy, TX 77494
302	Alicia Bucko, DO	Academic Dermatology Associates, Albuquerque, NM 87106
303	Zoe Diane Draelos, MD	Dermatology Consulting Services, High Point, NC 27262
304	Janet DuBois, MD	DermResearch, Inc., Austin, TX 78759
305	Michael H. Gold, MD	Tennessee Clinical Research Center, Nashville, TN 37215
306	Adelaide Hebert, MD	The University of Texas Health Science Center at Houston, Houston, TX 77030
307	Jennifer L. Parish, MD	Paddington Testing Company, Inc. Philadelphia, PA 19103
309	Jeffrey Sugarman, MD., PhD	Redwood Dermatology Research, Santa Rosa, CA 95403
311	Stephen K. Tyring, MD, PhD	Center for Clinical Studies, LTD., LLP Houston, TX 77004
312	Miriam S. Bettencourt, MD	Bettencourt Skin Center, Henderson, NV 89074
313	Tooraj Raoof, MD	Encino Research Center, Encino, CA 91436

Objectives:
• To evaluate the potential of SERNIVO Spray, 0.05% to suppress the HPA axis when applied twice daily for 15 days or 29 days, as compared to Diprolene Lotion, 0.05%, applied twice daily for 15 days [Diprolene Lotion being labeled for not more than 2

consecutive weeks of use], in subjects with moderate to severe plaque psoriasis under maximal use conditions, and
• To compare the plasma levels of betamethasone dipropionate and its metabolites after multiple uses of Diprolene (augmented betamethasone dipropionate) Lotion, 0.05% to those after multiple uses of SERNIVO Spray, 0.05% under maximal use condition

Selection of Subjects:
Inclusion Criteria
1. Subject understood study procedures and agreed to participate by giving written informed consent; willing to authorize use and disclosure of protected health information collected for the study.
2. Subject was at least 18 years of age.
3. Subject presented with a clinical diagnosis of stable (at least three months) plaque-type psoriasis.
4. Subject had psoriasis involving 20 to 50% of BSA, not including the face, scalp, groin, axillae, and other intertriginous areas.
5. Subject had an IGA Grade of at least 3 (moderate) at the Baseline Visit.
6. Female subjects of childbearing potential agreed to use contraception during the study which could have included abstinence with an adequate secondary option should the subject become sexually active. All women of childbearing potential must have completed a urine pregnancy test (UPT) (test must have had a sensitivity of at least 25 IU/L for human chorionic gonadotropin) at the Baseline Visit (Visit 2), and the test result must have been negative to be eligible for enrollment.

A female was considered of childbearing potential unless she was:

a. Pre-menarche
b. Postmenopausal for at least 12 months prior to study drug administration
c. Without a uterus and/or both ovaries; or had been surgically sterile for at least 6 months prior to study drug administration

Reliable methods of contraception were:

a. Hormonal methods or intrauterine device in use ≥ 90 days prior to study drug administration
b. Barrier methods plus spermicide in use at least 14 days prior to study drug administration
c. Partner had a vasectomy at least 3 months prior to study drug administration

Exception: Sexually inactive females of childbearing potential were not required to practice reliable method of contraception and might be enrolled at discretion of investigator if they were counseled to remain sexually inactive for the duration of the study, understood possible risks of getting pregnant during the study, and would use an acceptable form of contraception, if needed.

7. Subject was in good general health as determined by investigator and supported by medical history and normal or not clinically significant abnormal vital signs (blood pressure and pulse).

8. Subjects whose results from the screening ACTH stimulation test were considered normal (cortisol level >18 µg/dL at 30 minutes post stimulation) and showed no other signs of abnormal HPA function or adrenal response.

Exclusion Criteria

1. Current diagnosis of unstable forms of psoriasis including guttate, erythrodermic, exfoliative, or pustular psoriasis.
2. History of organ transplant requiring immunosuppression, human immunodeficiency virus, or other immunocompromised state.
3. Had received treatment for any type of cancer within 5 years of the Baseline Visit except that skin cancer and cervical cancer (in situ) were allowed if at least one year before the Baseline Visit.
4. Used within 60 days prior to the Baseline Visit:
    a. Immunosuppressive drugs (e.g., tacrolimus, pimecrolimus)
    b. Systemic antipsoriatic treatment (e.g., methotrexate, cyclosporine, hydroxyurea)
5. Used within 30 days prior to the Baseline Visit:
    a. Topical antipsoriatic drugs (salicylic acid, anthralin, coal tar, calcipotriene)
    b. Psoralen + ultraviolet light A (PUVA) therapy
    c. Systemic anti-inflammatory agents (e.g., mycophenolate mofetil, sulfasalazine, 6-thioguanine)
    d. Ultraviolet light B (UVB) therapy
6. Used within 30 days prior to the Screening Visit a product containing corticosteroid, including inhaled, intraocular, intranasal corticosteroids, etc.
7. Known hypersensitivity to betamethasone dipropionate or any component of SERNIVO Spray.
8. Known hypersensitivity to Diprolene Lotion AF or of its components.
9. Subjects who had an abnormal sleep schedule or work at night.
10. Subjects who had participated in a study of an investigational drug 60 days prior to the Baseline Visit.
11. Subjects unable to comply with study requirements.
12. Female subjects who were pregnant (or planning to become pregnant) or breast-feeding.
13. Subjects with a known history of acute adrenal crisis, Addison's disease or decreased adrenal output, low pituitary function or pituitary tumors.
14. Subjects who had a history of an adverse reaction to cosyntropin injection or similar test reagents.

Treatment:

Subjects were randomized to treatment with SERNIVO Spray, 0.05% 15-day treatment, SERNIVO Spray, 0.05% 29-day treatment, or Diprolene Lotion, 0.05% 15-day treatment in a 1:1:1 ratio. They were instructed to apply the study products topically, twice daily, ~12 hours apart, to all affected areas on the body (i.e., those areas that were affected at Baseline, even if resolved, and new lesions that developed at any time during treatment

period) excluding face, scalp, groin, axillae, and other intertriginous areas. The target dose was 5 to 7 g per day (15 to 20 pumps, twice daily).

The study product was to be sprayed or applied directly onto affected areas and rubbed in gently and completely. It was applied after bathing, if applicable. The subjects were not to use study product on the morning of a visit day if the appointment was scheduled before 12 noon, but to apply after the visit, if possible.

HPA Axis Suppression and Pharmacokinetics Data:
HPA axis suppression was evaluated by ACTH stimulation. The study included 75 adult subjects with moderate to severe plaque psoriasis involving 20% to 50% of their body surface area (BSA) who were administered the cosyntropin stimulation test. For details of the HPA axis suppression and pharmacokinetics data, see review by Dr. D. Tran. A brief summary is given here:

- SERNIVO Spray was applied twice daily for 15 or 29 days and Diprolene Lotion, 0.05% was applied twice daily for 15 days. Of 68 subjects evaluated at the end of treatment with cosyntropin stimulation, HPA axis suppression was found in 20.8% (5 out of 24) of subjects treated with SERNIVO Spray for 15 days, and 25.0% (5 out of 20) of those treated with Diprolene Lotion for 15 days, but not in subjects (0 out of 24) treated with SERNIVO Spray for 29 days. Suppression was defined as serum cortisol level ≤18 µg/dL 30-minutes post-cosyntropin stimulation. In the 7 subjects with available follow-up values, all showed normal stimulation at follow-up.
- Plasma levels of betamethasone dipropionate, betamethasone-17-propionate, and betamethasone were measured at baseline, and before and after the last dose (1, 3, and 6 hours) in the trial. The majority of subjects had no measurable plasma concentration (<5.00 pg/mL) of betamethasone dipropionate, while the metabolites, betamethasone-17-propionate and betamethasone, were detected in most subjects. There was a trend towards lower plasma levels after 29 days of treatment (betamethasone mean levels being 119 pg/mL after 15 days of treatment and 58 pg/mL after 29 days of treatment, and the corresponding mean levels for betamethasone-17-propionate being 120 pg/mL and 64 pg/mL).

Safety Data:
There were no deaths, serious adverse events, or adverse events leading to discontinuation from the study or from study product.

The frequency of adverse events in this study is shown in Table 8 below. The adverse events considered having relationship to treatment by the Investigator are shown in Table 9. Most of the events considered related to treatment are HPA axis suppression as shown by cosyntropin stimulation test. They were not associated with clinical evidence of adrenal insufficiency. The only other event considered related to treatment is application site pruritus.

Table 8: Adverse event table for Study BDS1307

System Organ Class Preferred Term	Diprolene Lotion 15 Days (N=22)	Betamethasone Dipropionate Spray 15 Days (N=25)	Betamethasone Dipropionate Spray 29 Days (N=27)
Endocrine disorders	5 (22.7%)	5 (20.0%)	0
Hypothalamic pituitary adrenal axis suppression	5 (22.7%)	5 (20.0%)	0
Gastrointestinal disorders	0	1 (4.0%)	0
Vomiting	0	1 (4.0%)	0
General disorders and administration site conditions	1 (4.5%)	1 (4.0%)	4 (14.8%)
Application site pain	0	0	1 (3.7%)
Application site pruritus	1 (4.5%)	1 (4.0%)	2 (7.4%)
Chest pain	0	0	1 (3.7%)
Infections and infestations	0	0	2 (7.4%)
Gingival infection	0	0	1 (3.7%)
Nasopharyngitis	0	0	1 (3.7%)
Injury, poisoning and procedural complications	0	1 (4.0%)	0
Muscle strain	0	1 (4.0%)	0
Musculoskeletal and connective tissue disorders	0	0	1 (3.7%)
Back pain	0	0	1 (3.7%)
Nervous system disorders	0	2 (8.0%)	0
Headache	0	2 (8.0%)	0
Skin and subcutaneous tissue disorders	0	0	1 (3.7%)
Acne	0	0	1 (3.7%)

Note: MedDRA Version: 16.1
Source: Table 14 on p.52 of study report for BDS1307.

Table 9: Adverse events considered by Investigator to be related to treatment for Study BDS1307

	Diprolene Lotion 15d N=22	SERNIVO Spray 15d N=25	SERNIVO Spray 29d N=27
Total AE related to treatment	4 (18.2%)	3 (12.0%)	1 (3.7%)
HPA axis suppression	3 (13.6%)	2 (8.0%)	0
Application site pruritus	1 (4.5%)	1 (4.0%)	1 (3.7%)

Adapted from Table 14.3.1.2.5 of study report

Local cutaneous safety evaluations at study visits included assessments for atrophy, telangiectasia, burning/stinging, pain, and itching. "Clinically significant" atrophy or telangiectasia was not observed. The incidence of burning/stinging, pain, and itching decreased from Baseline to Day 15 in all groups (Table 10); however, these three are also symptoms of psoriasis which may be expected to ameliorate with treatment.

Table 10: Local cutaneous safety evaluations for Study BDS1307

	Baseline	Day 8	Day 15	Day 29
Atrophy	None in any group from baseline to end of treatment			
Telangiectasia	None in any group from baseline to end of treatment			
Burning/stinging				
Diprolene 15d*	4/22 (18.2%)	2/22 (9.1%)	0/21 (0)	-
SERNIVO 15d	7/25 (28.0%)	1/24 (4.2%)	1/24 (4.2%)	-
SERNIVO 29d	3/27 (11.1%)	2/27 (7.4%)	2/26 (7.7%)	1/25 (4.0%)

Pain				
Diprolene 15d	3/22 (13.6%)	0/22 (0)	0/21 (0)	-
SERNIVO 15d	4/25 (16.0%)	1/24 (4.2%)	0/24 (0)	-
SERNIVO 29d	1/27 (3.7%)	0/27 (0)	0/26 (0)	0/25 (0)
Itching				
Diprolene 15d	16/22 (72.7%)	10/22 (45.5%)	6/21 (28.6%)	-
SERNIVO 15d	19/25 (76.0%)	12/24 (50.0%)	6/24 (25.0%)	-
SERNIVO 29d	20/27 (74.1%)	10/27 (37.0%)	10/26 (38.5%)	5/25 (20.0%)

*Diprolene 15d = Diprolene Lotion twice daily for 15 days, SERNIVO 15d = SERNIVO Spray twice daily for 15 days, and SERNIVO 29d = SERNIVO Spray twice daily for 29 days. Adapted from Table 14.3.1.1.1 of study report;

In conclusion, safety data from this study confirm the potential for HPA axis suppression and local cutaneous effects of SERNIVO Spray, 0.05%, which are consistent with the effects from topical glucocorticoids. No unusual systemic or local toxicities have been observed in this study.

In addition, this study and the vasoconstriction assays have partially established a clinical bridge between SERNIVO Spray, 0.05% and the reference product, Diprolene Lotion, 0.05%. The vasoconstriction assays show that SERNIVO Spray is of lower "potency" (mid-strength), and the proportion of subjects showing HPA axis suppression with SERNIVO Spray is slightly lower than that for Diprolene Lotion after 15 days of use (20.8% vs 25.0%).

6 Review of Efficacy

Efficacy Summary

This is a 505(b)(2) application with Diprolene Lotion, 0.05% as the reference product. The applicant has conducted two phase 3 trials in subjects with moderate plaque psoriasis, one of which included comparison with Diprolene Lotion, 0.05% as a clinical bridge. The design of these two trials has been shown above (Table 6a) and the results summarized in Table 11.

In Study BDS1205, which was a 4-arm trial including SERNIVO Spray, Diprolene Lotion and their vehicles with twice daily application for 4 weeks (Diprolene Lotion arm switching to vehicle lotion for the second 2 weeks of study) in subjects with moderate psoriasis, the treatment success rate at Day 15 was 19% for both SERNIVO Spray and Diprolene Lotion, and SERNIVO Spray was superior to vehicle spray (19.0% vs 2.3%, $p < 0.001$). At Day 29, SERNIVO Spray was also superior to vehicle spray (34.5% vs 13.6%, $p < 0.001$). Treatment success was defined as 0 (none) or 1 (minimal or almost clear), and at least 2-grade reduction in the Investigator Global Assessment (IGA) scale for disease severity.

In Study BDS1206, which was a 2-arm trial comparing SERNIVO Spray with its vehicle upon twice daily application for 4 weeks in subjects with moderate psoriasis, SERNIVO Spray was also superior to vehicle spray for treatment success (defined as in BDS1205)

rates at Days 15 and 29 (21.5% vs 7.4%, p = 0.002 at Day 15, and 42.7% vs 11.7%, p < 0.001 at Day 29).

The two phase 3 trials have independently demonstrated superiority of SERNIVO Spray over vehicle spray in the treatment of moderate plaque psoriasis. Although the Diprolene Lotion and vehicle lotion arms in Study BDS1205 were not designed for efficacy analyses (the applicant indicating these arms to be for clinical bridging for safety) the treatment success rates for SERNIVO Spray and the reference product, Diprolene Lotion were almost the same numerically after 15 days of treatment.

Table 11: Efficacy summary of phase 3 trials BDS1205 and BDS1206*

Study Number	Treatment Group (Number of Subjects - ITT Population)	Primary Efficacy Endpoint	Secondary Efficacy Endpoints/Results
BDS1205	Betamethasone Dipropionate Spray, 0.05% (n=174) Vehicle Spray (n = 87) Diprolene Lotion (n=90) Vehicle Lotion (n = 43)	The primary efficacy analysis demonstrated a statistically significant and clinically relevant superiority of Betamethasone Dipropionate Spray, 0.05% over Vehicle Spray as measured by the proportion of subjects with treatment success[a] at Day 15 in the ITT population (19.0% vs. 2.3% in the Betamethasone and Vehicle groups, respectively, $P < .001$).	The secondary efficacy analysis demonstrated statistically significantly greater proportion of subjects with treatment success[a] in the Betamethasone Dipropionate Spray, 0.05% group compared with the Vehicle Spray group at the Day 29 visit (34.5% versus 13.6%, respectively, $P < .001$) and at the Day 8 visit (10.0% versus 1.2%, respectively, $P = .003$). The proportion of subjects with a reduction of at least 50% in the TSS at the Day 4 visit was significantly greater in the Betamethasone Dipropionate Spray, 0.05% group compared with the Vehicle Spray group (12.1% versus 2.3%, respectively, $P = .004$).
BDS1206	Betamethasone Dipropionate Spray, 0.05% (n = 182) Vehicle Spray (n = 95)	The primary efficacy analysis demonstrated a statistically significant and clinically relevant superiority of Betamethasone Dipropionate Spray, 0.05% over Vehicle Spray as measured by the proportion of subjects with treatment success [a] at Day 15 in the ITT population (21.5% vs. 7.4% in the Betamethasone and Vehicle groups, respectively, $P = .002$).	The secondary efficacy analysis demonstrated a significantly greater proportion of subjects with treatment success[a] at the Day 29 visit in the Betamethasone Dipropionate Spray, 0.05% group compared with the Vehicle Spray group (42.7% vs. 11.7%, respectively, $P < .001$). There was a notable difference between the treatment groups at Day 8 (12.7% versus 7.4%, respectively; $P = .156$); however, this did not attain statistical significance. The proportion of subjects with a reduction of at least 50% in the TSS at the Day 4 visit was 14.3% in the Betamethasone Dipropionate Spray, 0.05% group and 10.5% in the Vehicle Spray group; no testing was performed for this efficacy endpoint as defined in the step-down strategy.

IGA = Investigator's Global Assessment; ITT = intent-to treat; TSS = Total Sign Score.
[a]Treatment success was defined as IGA = 0 or 1 and at least a 2 grade reduction from Baseline.
*Source: Integrated Summary of Efficacy, p.14 Table 4 (Module 5, section 5.3.5.3)

6.1 Indication

The proposed indication is: treatment of moderate plaque psoriasis in patients 18 years of age or older.

Since the phase 3 trials have demonstrated effectiveness in moderate plaque psoriasis, and the safety profile under maximal use conditions in moderate to severe psoriasis with 20 to 50% BSA involvement (HPA axis suppression Study BDS1307) has posed no special concerns, it is reasonable to extrapolate use to psoriasis of milder severity which is anticipated to incur less drug exposure. Thus, SERNIVO Spray, 0.05% is recommended for the treatment of mild to moderate plaque psoriasis in adults.

6.1.1 Methods

The applicant conducted two adequate and well-controlled phase 3 clinical trials to support the marketing application: one 4-arm study including SERNIVO Spray and the reference product, Diprolene Lotion as well as their vehicles, and a second study with 2 arms including SERNVIO Spray and its vehicle, BDS1205 and BDS1206, respectively.

Protocols for phase 3 trials BDS1205 and BDS1206

BDS1205 A Randomized, Double-Blind, Vehicle-Controlled, Multicenter, Parallel Group Study of the Safety of Betamethasone Dipropionate Spray 0.05% versus Diprolene® (augmented betamethasone dipropionate) Lotion 0.05% and the Efficacy of Betamethasone Dipropionate Spray 0.05% versus Vehicle Spray in the Treatment of Moderate Plaque Psoriasis

BDS1206 A Randomized, Double-Blind, Vehicle-Controlled, Multicenter, Parallel Group Study of the Efficacy and Safety of Betamethasone Dipropionate Spray 0.05% in the Treatment of Moderate Plaque Psoriasis

Study Objectives:

BDS1205 – (a) To compare the safety and efficacy of SERNIVO Spray, 0.05% to vehicle spray for topical treatment of moderate plaque psoriasis after 3, 7, 14 and 28 days of treatment and (b) To compare the safety of SERNIVO Spray, 0.05% to Diprolene (augmented betamethasone dipropionate) Lotion, 0.05% for topical treatment of moderate plaque psoriasis over 14 days

BDS1206 – To compare the efficacy and safety of SERNIVO Spray, 0.05% to vehicle spray after 3, 7, 14, and 28 days of treatment for moderate plaque psoriasis

Study Design:

BDS1205 – Phase 3 multicenter, randomized, vehicle-controlled, double-blind, parallel-group study in the US planned for ~396 subjects with moderate plaque psoriasis to be randomized to treatment arms of SERNIVO Spray, 0.05%, Diprolene Lotion, 0.05%, vehicle spray, or vehicle lotion in a 4:2:2:1 ratio, using study drug twice daily for 4 weeks. Subjects in the Diprolene Lotion arm were to switch to vehicle lotion after the initial 2-week period of Diprolene Lotion use.

BDS1206 – Phase 3 multicenter, randomized, vehicle-controlled, double-blind, parallel-group study in the US planned for ~264 subjects with moderate plaque psoriasis to be randomized to treatment arms of SERNIVO Spray, 0.05% or vehicle spray in a 2:1 ratio, using study drug twice daily for 4 weeks.

Instructions for Use and Application:

In each phase 3 study, subjects applied SERNIVO Spray, 0.05% or vehicle spray to affected areas twice daily with ~12 hours between applications for 28 days. In Study BDS1205, for the purposes of safety assessment, subjects who were in the Diprolene Lotion treatment group applied Diprolene Lotion, 0.05% twice daily for 14 days followed

by crossover to vehicle lotion twice daily for 14 days, while subjects in the vehicle lotion group used vehicle spray twice daily for 28 days. The cross-over design was to limit the treatment duration of Diprolene Lotion to 14 days per approved labeling.

All baseline affected areas and newly affected areas were treated until the end of the study even if cleared. Subjects were provided a study instruction sheet along with a diagram of the affected areas to be treated. The diagram was updated at each visit with any new affected areas added. In addition, subjects documented the dates of any missed application on a diary card.

Inclusion Criteria (both studies):

1. Subject understood the study procedures and agreed to participate by giving written informed consent. Subject was willing to authorize use and disclosure of protected health information collected for the study.
2. Subject was at least 18 years of age.
3. Subject presented with a clinical diagnosis of stable (at least 3 months) plaque-type psoriasis.
4. Subject had psoriasis involving 10% to 20% of BSA, not including the face, scalp, groin, axillae, and other intertriginous areas. The upper limit of 20% for BSA was included to limit the maximum drug product exposure to approximately 7 grams per day, and was not meant to be a measure of disease severity.
5. Subject had an IGA grade of 3 (moderate) at the Baseline Visit.
6. Female subjects of childbearing potential agreed to use contraception during the study which could have included abstinence with an adequate secondary option should the subject become sexually active. All women of childbearing potential were to have completed a urine pregnancy test (UPT) (test must have had a sensitivity of at least 25 mIU/mL for human chorionic gonadotropin) at the Baseline Visit (Visit 2), and the test results were to have been negative to be eligible for enrollment.

    A female was considered of childbearing potential unless she was:

    a. Pre-menarche
    b. Postmenopausal for at least 12 months prior to study drug administration
    c. Without a uterus and/or both ovaries; or had been surgically sterile for at least 6 months prior to study drug administration

    Reliable methods of contraception were:

    a. Hormonal methods or intrauterine device in use ≥ 90 days prior to study drug administration
    b. Barrier methods plus spermicide in use at least 14 days prior to study drug administration
    c. Partner had a vasectomy at least 3 months previous to study drug administration

    Exception: Sexually inactive female subjects of childbearing potential were not required to practice a reliable method of contraception, and might have been enrolled at the investigator's discretion provided that they were counseled to remain sexually inactive for the duration of the study, understood the possible risks involved in getting pregnant during the study and would use an acceptable form of contraception, if needed.
7. Subject was in good general health as determined by the investigator and supported by the medical history and normal or not clinically significant abnormal vital signs (blood pressure and pulse).

Exclusion Criteria (both studies):

1. Current diagnosis of unstable forms of psoriasis including guttate, erythrodermic, exfoliative, or pustular psoriasis.
2. Other inflammatory skin disease that might have confounded the evaluation of the plaque psoriasis (e.g., atopic dermatitis, contact dermatitis, tinea corporis).

3. Presence of pigmentation, extensive scarring, or pigmented lesions or sunburn which could have interfered with the rating of efficacy parameters.
4. History of psoriasis unresponsive to topical treatments.
5. History of organ transplant requiring immunosuppression, HIV, or other immunocompromised state.
6. Used biologic treatment for psoriasis (e.g., infliximab, adalimumab, etanercept, ustekinumab, or alefacept) within 180 days prior to Baseline Visit.
7. Had received treatment for any type of cancer within five years of the Baseline Visit except that skin cancer and cervical cancer (in situ) were allowed within one year of the Baseline Visit.
8. Used within 60 days prior to the Baseline Visit:
    a. Immunosuppressive drugs (e.g., tacrolimus, pimecrolimus)
    b. Systemic antipsoriatic treatment (e.g., methotrexate, cyclosporine, hydroxyurea)
    c. Oral retinoids (e.g., acitretin, isotretinoin)
9. Used within 30 days prior to the Baseline Visit:
    a. Systemic steroids
    b. Psoralen + ultraviolet light A (PUVA) therapy
    c. Systemic anti-inflammatory agents (e.g., mycophenolate mofetil, sulfasalazine, 6-thioguanine)
    d. Ultraviolet light B (UVB) therapy

Inhaled, intraocular, and intranasal steroids were allowed.
10. Used within 14 days prior to the Baseline Visit:
    a. Topical antipsoriatic drugs (e.g., salicylic acid, anthralin, coal tar, calcipotriene)
    b. Topical retinoids (e.g., tazarotene, tretinoin)
    c. Topical corticosteroids
11. Required use of the following medications during the 180 days prior to the Baseline Visit with a medical history that these medications affected the subject's psoriasis; except that these medications were allowed if the subject had been using the medication routinely during the 180 days prior to the Baseline Visit.
    a. Beta blockers
    b. Lithium
    c. Angiotensin-converting enzyme (ACE) inhibitors
    d. Nonsteroidal anti-inflammatory drugs (NSAIDs) (indomethacin, ibuprofen, aspirin, naproxen)
12. Known hypersensitivity to betamethasone dipropionate or any component of SERNIVO Spray, 0.05% and Diprolene Lotion.
13. Had participated in a study of an investigational drug within 60 days prior to the Baseline Visit.
14. Unable to comply with study requirements.
15. Female subjects who were pregnant (or planning to become pregnant) or breast-feeding.

Efficacy Assessments (both studies):

The study schedules for Studies BDS1205 and BDS1206 were almost identical. Subjects were randomized to treatment at Baseline (Day 1) and study visits were scheduled on Days 4, 8, 15 and 29. The clinical determinations of disease severity were performed using Investigator's Global Assessment (IGA) for overall severity (Table 12), and Total Sign Score (TSS) (Table 13) for the target lesion, which was selected at baseline by the
investigator as being representative of overall disease severity, not the least severe or the most severe and not the smallest or the largest.

Table 12: Scoring for Investigator's Global Assessment (IGA) in BDS1205 and BDS1206

Score	Grade	Definition
0	None	No plaque elevation above normal skin level May have residual non-erythematous discoloration No psoriatic scale No erythema
1	Minimal or Almost clear	No more than: Very slight elevation above normal skin level Faint light pink coloration Occasional very fine scale partially covering some of the lesions
2	Mild	No more than: Slight but definite elevation of plaque above normal skin level Light red coloration Fine scale with some lesions partially covered
3	Moderate	No more than: Definite elevation with rounded or sloped edges to plaque Definite red coloration Somewhat coarse scale with most lesions partially covered
4	Severe/Very Severe	At least one: Marked elevation with hard, sharp edges to plaque Dark red coloration Coarse, thick scale with virtually all lesions mostly covered and a rough surface

Table 13: Scoring for Clinical Signs of Target Lesions of Psoriasis (TSS*) in BDS1205 and BDS1206

Score	Grade	Erythema	Scaling	Plaque Elevation
0	Clear	No evidence of erythema	No evidence of scaling	No elevation of lesion above normal skin level
1	Slight to Mild	Faint to light red coloration	Fine scale partially covering the lesion	Trace elevation to slight but definite elevation above normal skin surface
2	Moderate	Definite red coloration	Somewhat coarse scale partially covering the lesion	Definite elevation with rounded or sloped edges
3	Severe to Very Severe	Dark red to beet red coloration	Coarse/thick scale, mostly to completely covering the lesion and a rough surface	Marked elevation with hard, distinct edges

*TSS (total sign score) is obtained by summing scores of erythema, scaling and plaque elevation.

The two studies did not include body surface area involvement or pruritus as part of efficacy evaluation. BSA was evaluated at screening and baseline for the purpose of eligibility assessment (inclusion criterion #4). Pruritus was considered a local safety evaluation measure.

Other Assessments:

The following Table shows the schedule of assessments for Study BDS1205, which includes safety and other assessments besides efficacy evaluations. Study BDS1206 had similar arrangements for these assessments.

Table 14: Schedule of assessments in BDS1205

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Screen[a, b]	Day 1	Day 4[c]	Day 8[c]	Day 15[c]	Day 29[d]
Vital signs (blood pressure, pulse)	X[e]	X	X	X	X	X
Urine pregnancy test (UPT)[f]		X			X	X
Body surface area (BSA)	X[e]	X				
Assess Investigator's Global Assessment (IGA)	X[e]	X	X	X	X	X
Total Sign Score (TSS) (erythema, scaling, elevation) for target lesion		X	X	X	X	X
Local safety evaluation for atrophy, telangiectasis, itching, pain, and burning/stinging		X	X	X	X	X
Diagram of affected areas to be treated[e]		X	X	X	X	
Adverse event assessment		X[g]	X	X	X	X

[a]No more than 60 days before Visit 2, [b]Visits 1 and 2 can be combined, [c]Allowed visit window ± 1 day, [d]Allowed visit window ± 3 days, [e]Record on source only, [f]For female subjects of childbearing potential, [g]Related to study procedures only

Source: adapted from Table 4 of BDS1205 study report, p.33

Efficacy Endpoint(s):

In both phase 3 studies, efficacy was demonstrated if SERNIVO Spray, 0.05% was superior to vehicle spray for IGA success at Day 15. The primary efficacy variable in both studies was the proportion of subjects with treatment success (defined as IGA = 0 or 1 and at least a 2-grade reduction from Baseline) at the Day 15.

The primary endpoint was analyzed with a Cochran-Mantel-Haenszel (CMH) test stratified by analysis center with the intent-to-treat (ITT) population. Handling of missing efficacy data was based on estimation using the method of Markov Chain Monte Carlo (MCMC) imputation.

Pre-specified efficacy analyses were limited to the SERNIVO Spray, 0.05% and vehicle spray treatment groups. Diprolene Lotion, 0.05% was included as a comparator for safety purposes to support a clinical bridge to FDA's finding of safety of Diprolene Lotion, 0.05%, and vehicle lotion was included for blinding purposes. The Diprolene Lotion and vehicle lotion arms were not included in efficacy analyses.

Reviewer Comment:

While it is recognized that the reference product has a dosing regimen of no more than 2 weeks, and it is important to evaluate the treatment effect at Day 14, however, as the proposed dosing regimen is up to 4 weeks, the primary efficacy endpoint should be at Day 29. This issue has been discussed with the IND sponsor in the advice letters of January 15, 2013 and of March 3, 2014. In another advice letter to the IND sponsor dated October 21, 2014, the agency stated:

- *You have not provided a rationale for continuing treatment for 28 days when the primary efficacy assessment is Day 15. A secondary endpoint assessment at Day 28 may not be sufficient for including 4-week data in labeling.*

For the purpose of supporting a 4-week dosing regimen, this review will regard the Day 29 assessment of treatment success as important as that on Day 15.

Secondary efficacy endpoints in both phase 3 studies include:

1. proportion of subjects with treatment success at the Day 29 visit,
2. proportion of subjects with treatment success at the Day 8 visit, and
3. proportion of subjects with reduction of at least 50% for TSS at the Day 4 visit.

Secondary endpoints were analyzed with a CMH test stratified by analysis center. The type 1 error was controlled using a step-wise gate-keeping strategy. If the primary efficacy endpoint analysis at Day 15 achieved $P < 0.05$, statistical significance testing for the secondary efficacy endpoints used a step-down approach, according to the following pre-specified order:

- treatment success at Day 29, and if treatment success at Day 29 $P < 0.05$, then:
- treatment success at Day 8, and if treatment success at Day 8 $P < 0.05$, then:
- reduction of at least 50% for TSS at Day 4.

Investigators and Enrollment:

Tables 15 and 16 list the Investigators for Studies BDS1205 and BDS1206, respectively, and the number of subjects enrolled in treatment arms at each site.

Table 15: Investigators and enrollment in BDS1205

Site#	Principal Investigator	Investigational Site Name, City, and State	#Subjects/Arm			
			SERNIVO Spray	Vehicle Spray	Diprolene Lotion	Vehicle Lotion
101	Javier Alonso-Llamazares, MD	International Dermatology Research, Inc. Miami, FL	14	7	6	3
102	Suzanne Bruce, MD	Suzanne Bruce and Associates, PA The Center for Skin Research Houston, TX	4	0	1	1
103	Alicia Bucko, DO	Academic Dermatology Associates Albuquerque, NM	9	4	4	2
104	Fran E. Cook-Bolden, MD	Fran Cook-Bolden, MD New York, NY	6	3	4	1
105	Sunil Dhawan, MD	Center for Dermatology Clinical Research, Inc. Fremont, CA	6	4	3	1
106	Zoe Diane Draelos, MD	Zoe Diane Draelos, MD, PA High Point, NC	5	2	3	1
107	David P. Fivenson, MD	David Fivenson, MD, Dermatology, PLLC Ann Arbor, MI	6	2	2	2
108	Joseph F. Fowler, MD	Dermatology Specialists Research Louisville, KY	4	2	2	1
109	Michael H. Gold, MD	Tennessee Clinical Research Center Nashville, TN	1	2	2	0
110	Scott T. Guenthner, MD	The Indiana Clinical Trials Center Plainfield, IN	4	3	2	1
111	David M. Pariser, MD	Virginia Clinical Research, Inc. Norfolk, VA	2	0	0	0
112	Holly Hake Harris, MD	The South Bend Clinic, LLP South Bend, IN	5	4	4	2

113	Angela S. Hutcheson, MD	Carolina Dermatology of Greenville, PA Greenville, SC	2	1	0	0
114	Michael Jarratt, MD	DermResearch, Inc. Austin, TX	6	3	4	2
115	Hershel E. Stoller, MD	Quality Clinical Research, Inc. Omaha, NE	3	2	2	1
116	Francisco A. Kerdel, MD	Florida Academic Center Research and Education Miami, FL	2	2	1	0
117	Keith H. Loven, MD, CPI	Rivergate Dermatology Clinical Research Center, PLLC Goodlettsville, TN	0	0	2	0
118	Leslie A. Mark, MD	Skin Surgery Medical Group, Inc. San Diego, CA	1	1	0	0
120	Adnan Nasir, MD	Wake Research Associates, LLC Raleigh, NC	7	3	3	1
121	Elyse Rafal, MD	DermResearch Center of New York Stony Brook, NY	6	3	2	2
122	Ronald C. Savin, MD	The Savin Center, PC New Haven, CT	2	1	1	1
125	Jan-Marie Kroh, MD	Compliant Clinical Research Inc. Olathe, KS	6	3	3	1
126	Dow B. Stough, MD	Burke Pharmaceutical Research Hot Springs, AR	3	0	1	0
127	Jeffrey Sugarman, MD., PhD	Redwood Dermatology Research Santa Rosa, CA	6	3	3	1
128	Leonard J. Swinyer, MD	Dermatology Research Center, Inc. Salt Lake City, UT	1	1	0	0
129	William P. Werschler, MD	Premier Clinical Research Spokane, WA	4	2	3	1
130	David C. Wilson, MD	The Education & Research Foundation, Inc. Lynchburg, VA	0	0	0	1
131	Cynthia Strout, MD	Coastal Carolina Research Center Mt. Pleasant, SC	1	0	1	0
132	Jerry Bagel, MD	Psoriasis Treatment Center of Central NJ East Windsor, NJ	8	4	4	1
133	Lawrence J. Green, MD	Lawrence J. Green, MD, LLC Rockville, MD	5	4	4	2
134	Robert Haber, MD	Haber Dermatology & Cosmetic Surgery, Inc. Beachwood, OH	4	3	2	2
135	Terry M. Jones, MD	J & S Studies, Inc. College Station, TX	4	2	2	2
136	Jonathan P. Wilson, DO	PMG Research of Winston-Salem Winston-Salem, NC	4	2	2	1
137	Amy M. Morris, MD	Horizon Research Group, Inc. Mobile, AL 36608	0	0	1	1
138	Tooraj Raoof, MD	Encino Research Center T. Joseph Raoof MD, Inc. Encino, CA	16	7	8	4
139	Stacy R. Smith, MD	California Dermatology and Clinical Research Institute Encinitas, CA	6	2	2	1
140	J. Michael Maloney, III, MD	Cherry Creek Research, Inc. Denver, CO	4	2	1	1
141	James M. Swinehart, MD	Colorado Medical Research Center, Inc. Denver, CO	0	1	2	0
142	Patricia C. Lee, MD	Center for Clinical Studies Webster, TX	7	2	3	2
			174	87	90	43

Table 16: Investigators and Enrollment in BDS1206

Site#	Principal Investigator	Investigational Site Name, City, and State	#Subjects/Arm	
			SERNIVO Spray	Vehicle Spray
201	Susan Barker, MD	MOORE Clinical Research, Inc. Tampa, FL	10	6
202	Miriam S. Bettencourt, MD	Bettencourt Skin Center Henderson, NV	14	7
203	Belin Frederick Bodie, MD	Coastal Clinical Research, Inc. Mobile, AL	5	3
204	Steven A. Davis, MD	Dermatology Clinical Research Center of San Antonio San Antonio, TX	8	4
206	Steven K. Grekin, DO	Grekin Skin Institute Warren, MI	7	3
207	Iltefat Hamzavi, MD	Hamzavi Dermatology Fort Gratiot, MI	6	3
208	Charles P. Hudson, MD	Hudson Dermatology/Clinical Research Advantage, Inc. Evansville, IN	0	1
209	Melissa L.F. Knuckles, MD	MLF Knuckles MD, PSC Corbin, KY	6	3
210	Nancy Krywonis, MD	Horizons Clinical Research Center, LLC Denver, CO	6	3
211	Mark Lee, MD	Progressive Clinical Research, PA San Antonio, TX	3	2
212	Anne M. Loebl, MD	Augusta Centre for Dermatology and Skin Renewal, LLC Augusta, GA	7	4
213	Anna Magee, MD	Charlottesville Medical Research Center, LLC Charlottesville, VA	6	3
215	Walter K. Nahm, MD, PhD	University Clinical Trials, Inc. San Diego, CA	8	5
216	Michael Noss, MD	Radiant Research, Inc. Cincinnati, OH	5	2
217	Jennifer L. Parish, MD	Paddington testing Company, Inc. Philadelphia, PA	8	4
218	Marta Rendon, MD	Skin Care Research, Inc. Boca Raton, FL	6	3
219	Joseph Samady, MD	Dermatology Specialist, Inc. Oceanside, CA	1	1
220	Joel Schlessinger, MD	Skin Specialists, P.C Omaha, NE	2	0
221	Eileen Smith, MD	Eastern Washington Dermatology Walla Walla, WA	1	0
222	Shondra L. Smith, MD	Shondra L. Smith, MD Dermatology & Advanced Aesthetics Lake Charles, LA	3	1
223	Linda Stein Gold, MD	Henry Ford Medical Center, New Center One Detroit, MI	5	2
224	Tory P. Sullivan, MD	Dr. Tory P. Sullivan, MD, PA N. Miami Beach, FL	1	1
225	John H. Tu, MD	Skin Search of Rochester, Inc. Rochester, NY	8	4
226	Stephen K. Tyring, MD, PhD	Center for Clinical Studies, LTD, LLP Houston, TX	15	8
227	Kyle L. Wagamon, MD	Brodell Medical, Inc. Waren, OH	8	4
228	Jonathan S. Weiss, MD	Gwinnett Clinical Research Center, Inc. Snellville, GA	4	3

229	Hector Wiltz, MD	FXM Research Corp. Miami, FL	18	9
230	Paul S. Yamauchi, MD, PhD	Clinical Science Institute Santa Monica, CA	11	6
			182	95

6.1.2 Demographics

Demographics of the treatment arms and their baseline disease characteristics in the phase 3 trials are shown in Tables 17and 18, respectively. The treatment arms across the two phase 3 trials are comparable. Disease severity in terms of the clinical signs plaque elevation, erythema, and scaling is also similar between the treatment groups. The majority of subjects showed moderate severity for each of the three clinical signs, consistent with the IGA score of 3 (moderate).

Table 17: Demographic characteristics of Studies BDS1205 and BDS1206

Variable Statistic	Study BDS1206		Study BDS1205			
	SERNIVO Spray (N=182)	Vehicle Spray (N=95)	SERNIVO Spray (N=174)	Vehicle Spray (N=87)	Diprolene Lotion (N=90)	Vehicle Lotion (N=43)
Age (years)						
Mean (SD)	50.3 (14.72)	49.9 (12.90)	49.0 (14.54)	50.2 (14.12)	51.0 (12.75)	51.6 (12.67)
Median	51.0	50.0	49.0	52.0	51.0	52.0
Min, Max	19, 86	22, 78	18, 86	20, 82	18, 78	26, 81
Sex, n (%)						
Male	114 (62.6)	58 (61.1)	111 (63.8)	51 (58.6)	56 (62.2)	24 (55.8)
Female	68 (37.4)	37 (38.9)	63 (36.2)	36 (41.4)	34 (37.8)	19 (44.2)
Ethnicity, n (%)						
Hispanic/Latino	55 (30.2)	28 (29.5)	49 (28.2)	28 (32.2)	25 (27.8)	8 (18.6)
Not Hispanic/Latino	119 (65.4)	63 (66.3)	125 (71.8)	59 (67.8)	63 (70.0)	35 (81.4)
Not reported	7 (3.8)	4 (4.2)	0 (0.0)	0 (0.0)	2 (2.2)	0 (0.0)
Unknown	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Race, n (%)						
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.3)	0 (0.0)	0 (0.0)
Asian	11 (6.0)	0 (0.0)	10 (5.7)	5 (5.7)	4 (4.4)	1 (2.3)
Black or African American	13 (7.1)	8 (8.4)	14 (8.0)	3 (3.4)	8 (8.9)	3 (7.0)
Native Hawaiian or Other Pacific Islander	1 (0.5)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
White	147 (80.8)	86 (90.5)	146 (83.9)	76 (87.4)	77 (85.6)	38 (88.4)
Other	5 (2.7)	0 (0.0)	1 (0.6)	1 (1.1)	0 (0.0)	1 (2.3)
Multiple	5 (2.7)	1 (1.1)	2 (1.1)	0 (0.0)	1 (1.1)	0 (0.0)

Max = maximum; Min = minimum; SD = standard deviation.
Source: Study BDS1205 Table 14.1.1.1 and Study BDS1206 Table 14.1.1.1.

Table 18: Baseline disease characteristics in Studies BDS1205 and BDS1206

Variable Statistic	Study BDS1206		Study BDS1205			
	SERNIVO Spray (N=182)	Vehicle Spray (N=95)	SERNIVO Spray (N=174)	Vehicle Spray (N=87)	Diprolene Lotion (N=90)	Vehicle Lotion (N=43)
Percent body surface affected						
Mean (SD)	13.7 (3.72)	13.4 (3.49)	13.1 (3.20)	13.1 (3.45)	13.6 (3.39)	12.9 (3.23)
Median	12.0	12.0	12.0	12.0	13.0	12.0
Min, Max	10, 20	10, 20	10, 20	10, 20	10, 20	10, 20
Investigator Global Assessment (IGA), n (%)						
Grade 3-Moderate	182 (100.0)	95 (100.0)	174 (100.0)	87 (100.0)	90 (100.0)	43 (100.0)
Location of target lesion, n (%)						
Elbow	49 (26.9)	23 (24.2)	47 (27.0)	21 (24.1)	20 (22.2)	9 (20.9)
Knee	19 (10.4)	14 (14.7)	18 (10.3)	13 (14.9)	12 (13.3)	10 (23.3)
Trunk	33 (18.1)	13 (13.7)	37 (21.3)	19 (21.8)	16 (17.8)	8 (18.6)
Extremities	75 (41.2)	41 (43.2)	63 (36.2)	30 (34.5)	39 (43.3)	13 (30.2)
Other	6 (3.3)	4 (4.2)	9 (5.2)	4 (4.6)	3 (3.3)	3 (7.0)
Total Sign Score (TSS)						
Mean (SD)	6.4 (0.96)	6.5 (0.95)	6.2 (0.75)	6.3 (0.71)	6.3 (0.80)	6.2 (0.80)
Median	6.0	6.0	6.0	6.0	6.0	6.0
Min, Max	4, 9	5, 9	4, 9	5, 9	5, 9	4, 9

IGA = Investigator's Global Assessment; Max = maximum; Min = minimum; SD = standard deviation.
Source: Study BDS1206 Table 14.1.2.1 and Study BDS1205 Table 14.1.2.1.

6.1.3 Subject Disposition

Disposition of subjects in the phase 3 trials is shown in Table 19. Apart from the vehicle lotion arm in BDS1205, discontinuation rates were lower than 10%, and discontinuation rates for SERNIVO Spray were lower than 5%. The most common reason for discontinuation was "lost to follow-up", which actually does not provide adequate reasoning for the discontinuation.

Table 19: Subject disposition – Studies BDS1205 and BDS1206

	Study BDS1206		Study BDS1205			
	SERNIVO Spray (N=182)	Vehicle Spray (N=95)	SERNIVO Spray (N=174)	Vehicle Spray (N=87)	Diprolene Lotion (N=90)	Vehicle Lotion (N=43)
Completed study, n (%)	174 (95.6)	87 (91.6)	166 (95.4)	81 (93.1)	88 (97.8)	38 (88.4)
Reason for discontinuation (n)						
AE related	1	1	0	1	0	2
AE not related	1	1	0	0	0	0
Lack of efficacy	0	0	1	0	0	1

Lost to follow-up	5	2	5	3	1	2
Protocol violations	0	0	1	0	0	0
Withdrawal by subject not due to AE	1	3	1	1	1	0
Worsening condition	0	1	0	1	0	0

Source: Study BD1205 Table 14.0.3 and Study BD1206 Table 14.0.3.

6.1.4 Analysis of Primary Endpoint(s)

The following analysis of primary endpoint "treatment success" (defined as IGA = 0 or 1 and at least a 2-grade reduction from Baseline) is according to that from the Statistical Reviewer, Dr. K. Fritsch.

Table 20: Primary endpoint analysis in Studies 1205 and 1206

	Study 1205				Study 1206	
	SERNIVO Spray N=174	Vehicle Spray N=87	Diprolene Lotion* N=90	Vehicle Lotion N=43	SERNIVO Spray N=182	Vehicle Spray N=95
Treatment Success Day 15	19.0%	2.3%	18.9%	9.3%	21.5%	7.4%
	p<0.001				p=0.002	

*Diprolene Lotion data not compared with other arms, as protocol indicates this arm is for safety data bridging.
-P-values are for SERNIVO Spray vs. vehicle spray.
-Treatment Success missing data are handled with multiple imputation for SERNIVO Spray and vehicle spray and LOCF for Diprolene Lotion and vehicle lotion.
Source: pg 134, 136 of bds1205-body.pdf and pg 118, 120 of bds1206-body.pdf and reviewer analysis.

SERNIVO Spray was superior to vehicle spray for the primary endpoint, treatment success at Day 15.

6.1.5 Analysis of Secondary Endpoints(s)

The following secondary endpoint analyses are also according to those of the Statistical Reviewer, Dr. K. Fritsch.

Table 21: Secondary endpoint analysis in Studies 1205 and 1206

	Study 1205				Study 1206	
	SERNIVO Spray N=174	Vehicle Spray N=87	Diprolene Lotion* N=90	Vehicle Lotion N=43	SERNIVO Spray N=182	Vehicle Spray N=95
Treatment Success Day 29	34.5%	13.6%	21.1%	9.3%	42.7%	11.7%
	p<0.001				p<0.001	
Treatment Success Day 8	10.0%	1.2%	6.7%	2.3%	12.7%	7.4%
	p=0.003				p=0.156	
TSS50 Day 4	12.1%	2.3%	5.6%	2.3%	14.3%	10.5%
	p=0.004				Not tested	

*Diprolene Lotion data not compared with other arms, as protocol indicates this arm is for safety data bridging. For the Day 29 data, Diprolene Lotion arm used vehicle lotion for the second two weeks after initial use of Diprolene Lotion in the first 2 weeks.
-P-values are for SERNIVO Spray vs. vehicle spray.
-Secondary endpoints were evaluated in sequential order to control the Type I error.
-Treatment Success missing data are handled with multiple imputation for SERNIVO Spray and vehicle spray and LOCF for Diprolene Lotion and vehicle lotion.
-TSS50 missing data are handled with baseline carried forward.
Source: pg 134, 136 of bds1205-body.pdf and pg 118, 120 of bds1206-body.pdf and reviewer analysis.

These data indicate that:

- SERNIVO Spray was superior to vehicle spray in both studies for treatment success at Day 29, the first ranked secondary efficacy endpoint.
- For the next ranked secondary endpoint of treatment success at Day 8, superiority was only demonstrated in Study BDS1205, but not Study BDS1206.
- For the final ranked secondary endpoint of ≥ 50% reduction in Total Symptom Score at Day 4, superiority was also only demonstrated in Study 1205, but was not tested in Study 1206, because sequential testing stopped after treatment success at Day 8 was not statistically significant.

Reviewer Comment:
As indicated earlier, the Day 29 treatment success is important for support of a dosing regimen of 4 weeks. The data showing SERNIVO Spray's superiority over vehicle spray in treatment success on Day 29 support a regimen of up to 4 weeks. The data also demonstrate that SERNIVO Spray, 0.05% was superior over vehicle spray after 14 days of treatment for moderate psoriasis.

In conclusion, the phase 3 trials support efficacy claims based on both the primary efficacy endpoint and the first ranked secondary endpoint (treatment success at Days 15 and 29).

6.1.6 Other Endpoints

Scores of the clinical signs plaque elevation, scaling, and erythema improved with time upon treatment with SERNIVO Spray and vehicle spray, as reflected by TSS50 (≥50% reduction of TSS) for the pooled data from BDS1206 and BDS1206 (Table 22).

Table 22: Number and percent subjects with TSS reduction of ≥50% from baseline *

	Day 4	Day 8	Day 15	Day 29
SERNIVO Spray	47/356 (13.2%)	120/346 (34.7%)	177/347 (51.0%)	201/340 (59.1%)
Vehicle spray	12/182 (6.6%)	40/176 (22.7%)	37/171 (21.6%)	51/168 (30.4%)

*adapted from Integrated Summary of Efficacy, p.69, Table 14.2.2.1.2 in Module 5, Section 5.3.5.3

These data on TSS improvement are consistent with those for treatment success using IGA scores.

6.1.7 Subpopulations

The applicant conducted subgroup analyses for the primary efficacy (Day 15) endpoint for the ITT population with respect to gender, age, ethnicity, and race in the individual studies and in the pooled data analysis. Age was dichotomized to less than and greater than or equal to the median age of subjects in the respective population. These subgroup analyses were done for individual studies and upon pooling (Tables 23 and 24, respectively) did not identify any demographic characteristic that potentially predicted a lack of treatment response. The subset analyses by race category did not

result in meaningful conclusions due to the small number of subjects in categories other than White.

Table 23: Subgroup analyses of the primary efficacy endpoint - treatment success at Day 15 (intent-to-treat population) – individual studies (Studies BDS1205 & BDS1206)

Subgroup	BDS1206				BDS1205			
	SERNIVO Spray (N=182)		Vehicle Spray (N=95)		SERNIVO Spray (N=174)		Vehicle Spray (N=87)	
	N	TrSucc[a]	N	TrSucc[a]	N	TrSucc[a]	N	TrSucc[a]
Gender								
Males	114	23.7%	58	8.7%	111	16.2%	51	0.0%
Females	68	17.8%	37	5.4%	63	23.8%	36	5.6%
Age Group								
< 51 years	86	17.6%	48	6.3%	90	21.7%	42	0.0%
≥ 51 years	96	25.0%	47	8.6%	84	16.0%	45	4.4%
Ethnicity								
Hispanic/Latino	55	25.6%	28	14.3%	49	17.4%	28	0.0%
Not Hispanic/Latino	119	18.5%	63	4.8%	125	19.6%	59	3.4%
Race								
Black or African American	13	0.0%	8	0.0%	14	17.8%	3	0.0%
White	147	23.2%	86	8.2%	146	18.2%	76	2.6%
American Indian or Alaska Native	0	-	0	-	0	-	2	0.0%
Asian	11	27.3%	0	-	10	30.0%	5	0.0%
Native Hawaiian or Other Pacific Islander	1	100.0%	0	-	1	0.0%	0	-
Other or Multiple	10	10.0%	1	0.0%	3	33.3%	1	0.0%

IGA = Investigator Global Assessment, - = not applicable.
[a]TrSucc = treatment success defined as IGA = 0 or 1 with at least a 2-grade reduction from Baseline. Source: Study BDS1205 Table 14.2.7 and Study BDS1206 Table 14.2.7.

Table 24: Subgroup analyses of the primary efficacy endpoint - treatment success at Day 15 (intent-to-treat population) – pooled analyses (Studies BDS1205 and BDS1206)

Subgroup	SERNIVO Spray, 0.05% (N=356)		Vehicle Spray (N=182)	
	N	Treatment Success[a]	N	Treatment Success[a]
Gender				
Male	225	20.0%	109	4.6%
Female	131	20.7%	73	5.5%
Age Group				
< 51 years	176	19.7%	90	3.3%
≥ 51 years	180	20.8%	92	6.6%
Ethnicity				
Hispanic/Latino	104	21.7%	56	7.1%
Not Hispanic/Latino	244	19.1%	122	4.1%

Race				
Black or African American	27	9.2%	11	0.0%
White	293	20.7%	162	5.6%
American Indian or Alaska Native	0	-	2	0.0%
Asian	21	28.6%	5	0.0%
Native Hawaiian or Other Pacific Islander	2	50.0%	0	-
Other or multiple	13	15.4%	2	0.0%

IGA = Investigator Global Assessment, - = not applicable.
[a]Treatment success defined as IGA = 0 or 1 with at least a 2-grade reduction from Baseline.
Source: Integrated Summary of Efficacy Appended Table 14.2.7.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dose-finding studies were not conducted. Dosing of SERNIVO Spray, 0.5% has been based on the dosing regimen for the reference product, Diprolene Lotion, 0.05% (twice daily). However, because SERNIVO Spray is of lower potency than Diprolene Lotion, the phase 3 trials have studied the efficacy of SERNIVO Spray with 15- and 29-day dosing (Diprolene Lotion limitation of use up to 2 weeks), both of which showed superiority over vehicle spray in the treatment of plaque psoriasis of moderate severity. Studies exploring variations in strength or dosing frequency have not been conducted.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The applicant has not evaluated persistence of efficacy and/or tolerance effects.

6.1.10 Additional Efficacy Issues/Analyses

There are no other efficacy issues.

7 Review of Safety

Safety Summary

This application includes 7 phase 1 studies (3 vasoconstriction assay studies and 4 dermal safety studies) in normal subjects, one safety study on HPA axis suppression and pharmacokinetics in patients with moderate to severe plaque psoriasis, and 2 pivotal phase 3 studies in patients with moderate plaque psoriasis. A total of 477 healthy adult male and female subjects and 741 adult patients with psoriasis were included in these studies.

The safety evaluation of SERNIVO Spray, 0.05% focused on two areas: systemic glucocorticoid adverse effects and local cutaneous safety:

- Systemic glucocorticoid adverse effects include HPA axis suppression with the potential for adrenal insufficiency, iatrogenic Cushing's syndrome, impaired glucose tolerance and other metabolic changes. None of these manifestations were observed in the phase 3 clinical trials on SERNIVO Spray, 0.05%. The study on HPA axis suppression in patients with moderate to severe plaque psoriasis under maximal use conditions provided a risk estimate for suppression of ~21% after 15 days of twice daily use when tested with cosyntropin stimulation. No suppression was observed after 29 days of twice daily use. Diprolene Lotion, 0.05%, the reference product, showed a rate of HPA axis suppression of 25% in this study.
- The most common adverse effects (≥1%) observed in the phase 3 trials were application site reactions, including pruritus, burning/stinging, pain, and skin atrophy. However, pruritus and pain are also manifestations of psoriasis, and the vehicle spray appeared to be associated with a greater proportion of subjects showing these effects. Since SERNIVO Spray is a topical corticosteroid product which has anti-inflammatory effects, this safety profile may be reasonably anticipated. Dermal safety studies on irritancy, sensitization, phototoxicity, and photoallergenicity did not yield positive evidence for the potential of SERNIVO Spray, 0.05% to cause these phenomena.

There were no deaths or serious adverse events considered related to treatment in the phase 3 clinical trials for SERNIVO Spray, 0.05%. Five (5) subjects discontinued treatment but none of the discontinuations was considered to be related to treatment with SERNIVO Spray, 0.05%. Vital sign observations during the clinical trials did not indicate any clinically significant changes. Routine clinical laboratory testing and ECG studies were not conducted in the clinical development program because clinically meaningful changes were not anticipated from use of a topical corticosteroid product containing betamethasone dipropionate.

In conclusion, the clinical program involved studies in adults and the data thus far suggest an acceptable safety profile. The applicant will have a postmarketing requirement to conduct a study on HPA axis suppression and pharmacokinetics in adolescent patients with plaque psoriasis in order to ascertain safety in this pediatric population.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety of SERNIVO Spray, 0.05% was evaluated by monitoring adverse events (AEs) during the clinical pharmacology studies including 3 vasoconstriction assay studies (Studies BDS1103, BDS1204, DFD01-CD-009), and 1 HPA axis suppression study (Study BDS1307), as well as the two phase 3 safety and efficacy trials (Studies BDS1205 and BDS1206). There were also 4 dermal safety studies to determine the potential for skin irritancy, sensitization, phototoxicity, and photoallergenicity (Study

DFD01-CD-008, Study DFD01-CD-012, Study DFD01-CD-010, and Study DFD01-CD-011, respectively). Summary Tables of these studies have been presented above (Table 6 and 6a in Section 5.1 of this review).

In addition, the applicant is relying on safety data that formed the basis of approval for the listed drug, Diprolene Lotion, 0.05%. Diprolene Lotion was included in the phase 1 dermal safety studies, the study on HPA axis suppression potential and systemic absorption, and one of the phase 3 safety and efficacy studies in order to construct a clinical bridge to the agency's findings of safety for this approved product.

As the study designs are similar, safety data from SERNIVO Spray-treated groups and the vehicle spray-treated groups from the two phase 3 studies, BDS1205 and BDS1206, have been pooled. In Study BDS1205, an active control, Diprolene Lotion, was used for 14 days (label recommending use not to exceed 14 days), followed by vehicle lotion for another 14 days to preserve blinding. This treatment arm and its control (vehicle lotion) serve to support the 505(b)(2) application by providing safety data of the reference product and assures sensitivity of the system being studied.

7.1.2 Categorization of Adverse Events

The applicant coded adverse events using the Medical Dictionary for Regulatory Activities (MedDRA), version 16.1. Verbatim terms were mapped into a MedDRA system organ class (SOC) and preferred term (PT). If a subject had more than one adverse event within a preferred term, the subject was counted once in that preferred term. This strategy was also applied if a subject had more than one adverse event within a system organ class.

The applicant has summarized "treatment emergent adverse events" (TEAE's) for each treatment group by SOC and preferred term. TEAE's are defined as those adverse events occurring after the first dose of study treatment. For the purpose of this review, the term TEAE is not used, as only adverse events post-baseline are included for consideration. Pre-baseline conditions are considered under the medical history domain.

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

See Section 7.1.1. Although Study BDS1205 included two additional treatment arms (Diprolene Lotion, 0.05%, and vehicle lotion), the two phase 3 trials BDS1205 and BDS1206 were under a similar basic design with corresponding eligibility criteria, schedule of procedures, safety and efficacy evaluations, and statistical analysis plan for primary and secondary endpoints. The safety data from the SERNIVO Spray treatment groups and the vehicle spray groups in these two trials are appropriate for pooling in the analyses for safety. This procedure allows for greater power for statistical comparison.

The Diprolend Lotion, 0.05% treatment arm in BDS1205 was included to establish clinical bridging to the reference product, but not required for comparison to demonstrate safety or efficacy of SERNIVO Spray, 0.05%.

7.2 Adequacy of Safety Assessments

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

Overall exposure at appropriate doses/durations
The proposed dosing regimen for SERNIVO Spray, 0.05% is twice daily for up to 4 weeks.

The phase 1 dermal safety studies and vasoconstriction assay studies were done with protocols pertaining to their respective testing methodologies and not intended to support clinical dosing. Although the HPA axis suppression study, BDS1307, was conducted with twice daily dosing for 29 days, the enrollment involved subjects with moderate to severe plaque psoriasis having disease over 20% to 50% BSA. These patients' disease was greater in severity and extent than the target population's. The phase 3 trials, BDS1205 and BDS1206 enrolled patients with moderate plaque psoriasis involving 10% to 20% BSA assigned to twice daily regimen for up to 4 weeks. This is reflective of the condition of the target population and their usage of SERNIVO Spray, 0.05%. Therefore, the discussion on overall exposure will focus on the phase 3 study population.

Overall drug exposure in the phase 3 studies (combined data of BS1205 and BDS1206) is shown in Tables 25 and 26. Six (6) subjects are not included in the overall analyses for the combined data from the two phase 3 studies (Studies BDS1205 and BDS1206) due to lack of post-baseline safety evaluation (SERNIVO Spray, 0.05%, n = 4 and vehicle spray, n = 2).

Table 25: Extent of exposure - safety population (BDS1205 and BDS1206 pooled)

Characteristic: Weeks of Exposure (n, [%])	**SERNIVO Spray, 0.05% (N=352)**	**Vehicle Spray (N=180)**
Number of subjects with < 1 week of exposure	7 (2.0)	7 (3.9)
Number of subjects with 1 week to < 2 weeks of exposure	2 (0.6)	4 (2.2)
Number of subjects with 2 weeks to < 3 weeks of exposure	3 (0.9)	2 (1.1)
Number of subjects with 3 weeks to < 4 weeks of exposure	38 (10.8)	18 (10.0)
Number of subjects with ≥ 4 weeks of exposure	302 (85.8)	149 (82.8)

Source: iss appended Table 14.3.0.1.2

In addition, the HPA axis suppression study (Study BDS1307) included 25 subjects with moderate to severe plaque psoriasis exposed to SERNIVO Spray for 4 weeks or longer.

Together with the subjects in SERNIVO treatment arms in the phase 3 trials BDS1205 and BDS1206, there were a total of 365 psoriasis subjects from all studies exposed for 3 to 4 weeks or more.

Table 26: Number of applications - safety population for SERNIVO Spray and vehicle spray vs Diprolene Lotion (BDS1205 and BDS1206 Pooled)

Characteristic:	SERNIVO Spray, 0.05% (N=352)	Vehicle Spray (N=180)	Diprolene Lotion, 0.05% (N=90)
Number of Applications Day 1 to Day 15			
Number of subjects	348	176	89
Mean (SD)	28.1 (3.60)	28.0 (4.70)	28.1 (3.17)
Median	28.0	28.0	28.0
Min to Max	14 to 55	1 to 53	14 to 43
Number of Applications Day 1 to Day 29			
Number of subjects	345	174	-
Mean (SD)	54.6 (5.69)	54.0 (8.54)	-
Median	56.0	56.0	-
Min to Max	14 to 88	1 to 64	-

- = not applicable: Diprolene Lotion 0.05% subjects were only treated for 14 days and crossed-over to vehicle lotion at the Day 15 visit (Study BDS1205). Source: iss rappended Table 14.3.0.1.2, CSR Study BDS1205 Table 14.3.0.1.2

The majority of subjects had 3 to ≥4 weeks of exposure to SERNIVO Spray, 0.05% or vehicle spray (97% and 93%, respectively) with median number of applications being 56 for both (twice daily application for 4 weeks). The Diprolene Lotion, 0.05% treatment arm in Study BDS1205 had a mean number of applications of 28.1 and median 28, reflecting the twice daily dosing for 2 weeks.

These two studies did not measure the weight of the product container when dispensed, at study visits, or at final collection. Thus, the actual amount of drug use between time intervals is not known.

Demographics and baseline characteristics of target population

The target population for the applicant's proposed indication is patients with plaque psoriasis of moderate severity. Table 27 shows demographics and baseline characteristics of the target population studied with pooled data from Studies BDS1205 and BDS1206. Study 1307 is not included because it enrolled patients with moderate to severe plaque psoriasis, which is not the intended target population of this application.

Table 27: Demographic and baseline characteristics (BDS1205 and BDS1206 pooled) (safety population)

Characteristic	SERNIVO Spray, (N=352)	Vehicle Spray (N=180)	Diprolene Lotion, (N=90)
Age (years)			
Mean (SD)	49.8 (14.59)	50.1 (13.53)	51.0 (12.75)
Min to Max	18 to 86	20 to 82	18 to 78
Gender (n, [%])			

Male	223 (63.4)	107 (59.4)	56 (62.2)
Female	129 (36.6)	73 (40.6)	34 (37.8)
Ethnicity (n, [%])			
Hispanic or Latino	103 (29.3)	56 (31.1)	25 (27.8)
Not Hispanic or Latino	242 (68.8)	120 (66.7)	63 (70.0)
Not reported	6 (1.7)	4 (2.2)	0
Unknown	1 (0.3)	0	2 (2.2)
Race (n, [%])			
American Indian or Alaska Native	0	2 (1.1)	0
Asian	21 (6.0)	5 (2.8)	4 (4.4)
Black or African American	27 (7.7)	11 (6.1)	8 (8.9)
Native Hawaiian or other Pacific Islander	2 (0.6)	0	0
White	290 (82.4)	160 (88.9)	77 (85.6)
Other race	6 (1.7)	1 (0.6)	0
Multiple races	6 (1.7)	1 (0.6)	1 (1.1)
Percent body surface area affected			
Mean (SD)	13.5 (3.49)	13.3 (3.47)	13.6 (3.39)
Range	10 to 20	10 to 20	10 to 20
Investigator's Global Assessment (IGA) (n, [%])			
Moderate	352 (100)	180 (100)	90 (100)
Location of target lesion (n, [%])			
Elbow	95 (27.0)	43 (23.9)	20 (22.2)
Knee	37 (10.5)	26 (14.4)	12 (13.3)
Trunk	70 (19.9)	32 (17.8)	16 (17.8)
Extremities	136 (38.6)	71 (39.4)	39 (43.3)
Other	14 (4.0)	8 (4.4)	3 (3.3)
Total Sign Score (TSS)			
Median	6.0	6.0	6.0
Range	4 to 9	5 to 9	5 to 9

Source: appended Table 14.1.1.2 and Table 14.1.2.2, CSR Study BDS1205 Table14.1.1.2 and Table 14.1.2.2

The demographics and baseline disease condition were comparable between subjects treated with SERNIVO Spray, 0.05%, Diprolene Lotion, 0.05%, and vehicle spray when data of the phase 3 trials were pooled.

7.2.2 Explorations for Dose Response

The applicant has developed SERNIVO Spray, 0.05% using the 505(b)(2) pathway with Dirpolene Lotion, 0.05% as the reference product. Formal dose ranging studies were not performed. The phase 3 program included a treatment arm with Diprolene Lotion, 0.05% to establish clinical bridging. Both products contain the same concentration of betamethasone dipropionate, and are intended for twice daily dosing.

As Diprolene Lotion, 0.05% is considered to be a "superpotent" topical corticosteroid, it has limitations for use - up to 50 Gm per week and no more than use over 2 consecutive weeks. SERNIVO Spray, 0.05%, however, is of "mid-potency", and the applicant has developed this product for a longer time frame of use, i.e., up to 4 weeks. In both the HPA axis suppression study (BDS1307) and the phase 3 trials (BDS1205 and BDS1206), the applicant explored safety of use up to 2 weeks and up to 4 weeks.

These data have been discussed in the Clinical Pharmacology Review and in this review (Sections 7.3 to 7.5). Use of SERNIVO Spray, 0.05% for 4 weeks has posed no additional safety concerns over use for 2 weeks. Thus, it is appropriate to label SERNIVO Spray, 0.05% for dosing up to 4 weeks.

7.2.3 Special Animal and/or In Vitro Testing

See Section 4.3 of this Review.

7.2.4 Routine Clinical Testing

Routine clinical laboratory testing has not been included in the clinical development program. Betamethasone dipropionate has been marketed for 40 years as topical products in the United States, and the systemic safety profile is well known. The agency has found the clinical study protocols acceptable during the IND stage. No additional useful information was anticipated from routine clinical testing.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

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

The adverse event profile is well-established for topical corticosteroids.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in the clinical studies on SERNIVO Spray, 0.05%.

7.3.2 Nonfatal Serious Adverse Events

Six (6) nonfatal serious adverse events in the clinical program occurred in the phase 3 trials, BDS1205 and BDS1206. Four (4) of them are shown in Table 28.

Table 28: Subject listing for non-fatal serious adverse events: Studies BDS1206 and BDS1206

Study#	Subject ID	Preferred Term[a]/Onset Day	Intensity	Treatment	Relationship to Study Drug	Outcome Resolution Day
BDS1205	138016	Diabetes Mellitus/Day 5	Moderate	Vehicle Spray	Not related	Resolved Day 10
BDS1206	204010[b]	Upper gastrointestinal haemorrhage/Day 10	Moderate	SERNIVO Spray	Not related	Resolved Day 12

BDS1206	208002[b]	Localized infection/ Day Unknown	Severe	Vehicle Spray	Not related	Unknown Day Unknown
BDS1206	227009	Schizophrenia, paranoid type/Day 9	Severe	Vehicle Spray	Not related	Resolved Day 13

[a] MedDRA Version: 16.1
[b] Resulted in discontinuation from the study.
Source: CSR Study BDS1205 Listing 16.2.7.3 and CSR Study BDS1206 Listing 16.2.7.3.

In addition, there were 2 subjects in the Diprolene Lotion group of BDS1205 who experienced serious adverse events after Day 15 in Study BDS1205, when they had crossed over to receive vehicle lotion (CSR Study BDS1205 Listing 16.2.7.3 and CSR Study BDS1205 Report Body Section 12.3.2.1):

- Subject 120005 experienced serious adverse events of mild fall, severe hyponatremia, mild metabolic acidosis, moderate convulsion, and severe alcohol withdrawal syndrome on Day 24 and moderate urinary tract infection on Day 26. None were considered related to study treatment and all resolved.
- Subject 136008 experienced a serious adverse event of severe chronic obstructive lung disease on Day 20 considered not related to study treatment and resolved.

7.3.3 Dropouts and/or Discontinuations

In the pooled phase 3 studies (BDS1205 and BDS1206), 5 subjects discontinued study treatment and/or discontinued from the studies due to adverse events (2 [0.6%] subjects in the SERNIVO Spray, 0.05% group and 3 [1.7%] in the vehicle spray group). Application site pruritus resulted in discontinuation for 2 subjects in the vehicle spray group; other adverse events resulting in discontinuation were single occurrences. Of the 5 events leading to discontinuation, 3 were considered related to study treatment: 1 in the SERNIVO Spray group (hyperglycemia) and 2 in the vehicle spray group (pruritus and pain at application site).

Table 29: Subject listing for discontinuations due to adverse events: Studies BDS1206 and BDS1206

Study No.	Subject ID	Preferred Term[a]/Onset Day	Serious AE	Intensity	Treatment	Relationship to Study Drug
BDS1205	127012	Application site pain /Day 7	No	Moderate	Vehicle Spray	Probably related
		Application site pruritus /Day 7	No	Moderate		Probably related
		Application site pain (burning/stinging)/Day 7	No	Moderate		Probably related
BDS1206	204010	Upper gastrointestinal hemorrhage/Day 10	Yes	Moderate	SERNIVO Spray	Not related
BDS1206	225002	Hyperglycemia/Day 9	No	Moderate	SERNIVO Spray	Possibly related
BDS1206	201028	Application site pruritus/Day 5	No	Mild	Vehicle Spray	Possibly related
BDS1206	208002	Localized infection/Day Unknown	Yes	Severe	Vehicle Spray	Not related

BDS1206	209009[b]	Influenza/Day Unknown	Unknown	Unknown	SERNIVO Spray	Not related

[a] MedDRA Version: 16.1
[b] Not included in summary statistics due to unknown status
Source: CSR Study BDS1205 Listing 16.2.1.2.2 and CSR Study BDS1206 Listing 16.2.1.2.2.

7.3.4 Significant Adverse Events

One additional subject in the SERNIVO Spray, 0.05% group of BDS1206 (209009) was lost to follow-up, and the subject might have discontinued due to an adverse event of influenza based on comments from relatives that could not be confirmed with the subject.

7.3.5 Submission Specific Primary Safety Concerns

There are two specific safety concerns for this submission about SERNIVO Spray, 0.05%: systemic effects, especially HPA axis suppression, and local cutaneous effects.

- Topical corticosteroids can be absorbed to produce systemic effects, especially if used at above the recommended doses and over prolonged time periods. The applicant has conducted a study (BDS1307) on HPA axis suppression in plaque psoriasis patients administering SERNIVO Spray under maximal use conditions over 29 days. The results suggest slightly lower risk of HPA axis suppression after 15 days of use as compared to Diprolene Lotion use for 15 days, and at the end of 29 days, HPA axis suppression was not observed. This has been discussed in Section 4.4.2 of this review. Details on this study can be found in the Clinical Pharmacology Review by Dr. D. Tran.
- Local cutaneous toxicity of topical corticosteroids include skin atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, hypertrichosis, and miliaria. The HPA axis study (BDS1307) and the phase 3 trials (BDS1205 and BDS1206) include evaluation of changes at application site. There have not been additional concerns observed in these studies. The findings will be incorporated into labeling.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the phase 3 trials (BDS1205 and BDS1206), subjects with moderate plaque psoriasis of the body applied SERNIVO Spray or vehicle spray twice daily for 4 weeks or Diprolene Lotion, 0.05% twice daily for 2 weeks. A total of 352 subjects applied SERNIVO Spray and 90 subjects applied Diprolene Lotion, 0.05%. The adverse events occurring at a rate of 1% or higher in any one group are shown in Table 30.

Table 30: Number (%) of subjects with adverse events occurring in ≥1% of subjects: BDS1205 and BDS1206

Preferred Term[b]	SERNIVO Spray 14 days (N=352)	SERNIVO Spray 28 days (N=352)	Diprolene Lotion[a] 14 days (N=90)	Vehicle Spray 28 days (N=180)
Application site pruritus	21 (6.0)	27 (7.7)	6 (6.7)	26 (14.4)
Application site pain	15 (4.3%)	23 (6.5)	13 (14.4)	22 (12.2)
Nasopharyngitis	4 (1.1%)	6 (1.7)	1 (1.1)	1 (0.6)
Upper respiratory tract infection	5 (1.4%)	5 (1.4)	0	1 (0.6)
Application site atrophy	2 (0.6%)	4 (1.1)	0	3 (1.7)
Arthralgia	0	0	0	2 (1.1)
Erythema	0	0	0	2 (1.1)
Gastroenteritis	0	0	1 (1.1)	0
Palpitations	0	0	1 (1.1)	0
Procedural pain	1 (0.3)	1 (0.3)	1 (1.1)	0
Sinus congestion	1 (0.3)	1 (0.3)	1 (1.1)	0

a Study BDS1205: Diprolene Lotion subjects were only treated for 14 days and crossed-over to Vehicle Lotion at Day 15 visit.
b MedDRA Version: 16.1
Source: appended Table 14.3.1.2.3 and CSR Study BDS1205 Table 14.3.1.3.6

Adverse reactions (events considered attributable to treatment) occurring at a rate of 1% or higher in any one treatment group are shown in Table 31.

Table 31: Number (%) of subjects with adverse reactions occurring in ≥1% of subjects: BDS1205 and BDS1206

Preferred Term[b]	SERNIVO Spray 14 days (N=352)	SERNIVO Spray 28 days (N=352)	Diprolene Lotion[a] 14 days (N=90)	Vehicle Spray 28 days (N=180)
Number of subjects with Adverse Reactions	31 (8.8%)	42 (11.9%)	13 (14.4%)	27 (15.0%)
Application site atrophy	2 (0.6%)	4 (1.1%)	0	3 (1.7%)
Application site pruritus	16 (4.5%)	21 (6.0%)	6 (6.7%)	17 (9.4%)
Application site burning and/or stinging	11 (3.1%)	16 (4.5%)	12 (13.3%)	18 (10%)
Application site pain	5 (1.4%)	8 (2.3%)	2 (2.2%)	7 (3.9%)

a Study BDS1205: Diprolene Lotion subjects were only treated for 14 days and crossed-over to Vehicle Lotion at Day 15 visit.
b MedDRA Version: 16.1
Source: appended Table 14.3.1.3.3 and 14.3.1.2.3 and CSR Study BDS1205 Table 14.3.1.3.6

Similar to the HPA axis suppression study BDS1307 (see Section 5.3), the phase 3 protocols included dedicated assessment of the following local events – “clinically

significant" atrophy, "clinically significant" telangiectasia, burning/stinging, pain, and itchiness. Responses were recorded as "yes" or "no", and "yes" even if not worse than baseline; an adverse event would be reported if worse than baseline. However, the protocol has not provided guidance on what would constitute "clinically significant." The results are shown in the Table below (Table 32).

Table 32: Local cutaneous safety evaluations for Studies BDS1205 and 1206 combined

		Baseline	Day 8	Day 15	Day 29
"Clinically significant" atrophy	SERNIVO Spray	0/352*	0/346	2/347 (0.6)	3/340 (0.9)
	Vehicle Spray	1/180 (0.6)	3/176 (1.7)	3/171 (1.8)	3/168 (1.8)
	Diprolene Lotion	0/90	0/89	0/88	-
"Clinically significant" telangiectasia	SERNIVO Spray	0/352	0/346	1/347 (0.3)	2/340 (0.6)
	Vehicle Spray	0/180	0/176	0/171	0/168
	Diprolene Lotion	0/90	0/89	0/88	-
Burning/Stinging	SERNIVO Spray	73/352 (20.7)	19/346 (5.5)	8/347 (2.3)	19/340 (5.6)
	Vehicle Spray	31/180 (17.2)	18/176 (10.2)	18/171 (10.5)	15/168 (8.9)
	Diprolene Lotion	19/90 (21.1)	7/89 (7.9)	12/88 (13.6)	-
Pain	SERNIVO Spray	55/352 (15.6)	15/346 (4.3)	10/347 (2.9)	10/340 (2.9)
	Vehicle Spray	21/180 (11.7)	7/176 (4.0)	5/171 (2.9)	8/168 (4.8)
	Diprolene Lotion	8/90 (8.9)	2/89 (2.2)	2/88 (2.3)	-
Pruritus	SERNIVO Spray	227/352 (64.5)	104/346 (30.1)	84/347 (24.2)	79/340 (23.2)
	Vehicle Spray	105/180 (58.3)	60/176 (34.1)	60/171 (35.1)	45/168 (26.8)
	Diprolene Lotion	60/90 (66.7)	30/89 (33.7)	26/88 (29.5)	-

*Values expressed as ratio of the number of subjects with the condition/total number of subjects at the visit, with percentage in parentheses except when that is zero (0); - = not applicable, as Diprolene Lotion subjects were only treated for 14 days and crossed over to vehicle lotion at Day 15 visit in Study BDS1205. No imputation was made for missing data.
Source: appended Table 14.3.1.1.1 of Integrated Summary of Safety; Study report of BDS1205 Table 14.3.1.1.

Reviewer Comment
The incidence of "clinically significant" atrophy or telangiectasia has been low. This is consistent with the findings in BDS1307. The incidence of burning/stinging, pain, and itching decreased from Baseline to Day 15 in all groups (Table 32); however, these three are also symptoms of psoriasis which may be expected to ameliorate with treatment.

7.4.2 Laboratory Findings

Urine pregnancy test at Baseline, Day 15 and Day 29 was the only clinical laboratory evaluation in the phase 3 trials (BDS1205 and BDS1206). No subjects became pregnant during the study.

For the HPA axis suppression study (BDS1307), cosyntropin stimulation testing required measurement of plasma cortisol levels. This study also sampled blood for measurement of betamethasone dipropionate and its metabolites. The findings have been discussed above in Section 4.4.3, and details are available in the Clinical Pharmacology Review by Dr. D. Tran.

7.4.3 Vital Signs

Vital signs (blood pressure and pulse rate) were measured at screening and at the study visits of Days 1, 8, 15, and 29 in the HPA axis suppression study (BDS1307) and the two phase 3 trials (BDS1205 and BDS1206; phase 3 trials also at Day 4 visit). Changes from baseline over the time course of the studies were unremarkable. There were no clinically meaningful changes within the treatment groups over time or differences between the treatment groups in the vital sign parameters or changes from baseline.

7.4.4 Electrocardiograms (ECGs)

ECG assessments were not in the clinical development program of SERNIVO Spray, 0.05%. The active ingredient, betamethasone dipropionate, has been marketed since 1975 without signals for cardiovascular events, and systemic exposure to betamethasone dipropionate is very low in the HPA axis suppression study (BDS1307) in which plasma levels were measured for pharmacokinetic parameters, with only a small number of subjects showing measurable levels.

There have been studies on glucocorticoids such as fluticasone furoate which showed lack of association with QTc prolongation in healthy subjects[2]. The applicant is basing the safety of SERNIVO Spray, 0.05% partly on FDA's finding of safety of the reference drug, Diprolene Lotion, 0.05%. None of the currently marketed topical corticosteroid products have labeling on cardiac toxicity, including QTc prolongation. The agency had indicated to the applicant that if a clinical bridge is established between SERNIVO Spray and the reference product, TQT studies could be waived. As this application has included studies BDS1307 (HPA axis suppression) and BDS1205 (phase 3 trial) which establish the clinical bridge between SERNIVO Spray and Diprolene Lotion, it is reasonable to waive TQT studies on this product.

7.4.5 Special Safety Studies/Clinical Trials

There have been 5 dedicated human safety studies on SERNIVO Spray, 0.05%: one HPA axis suppression study (BDS1307), and 4 dermal safety studies, including the testing of SERNIVO Spray, 0.05% for its potential for irritancy (DFD01-CD-008), phototoxicity (DFD01-CD-010), photoallergenicity (DFD01-CD-011), and contact sensitization (DFD01-CD-012).

- *HPA axis suppression study*

The HPA axis suppression study (BDS1307) has been discussed above in Section 4.4.2 of this review, and details are to be found in the Clinical Pharmacology Review by Dr. D. Tran.

[2] Kempsford R, Allen A, Kelly K, Saggu P, Crim C. A repeat-dose thorough QT study of inhaled fluticasone furoate/vilanterol combination in healthy subjects. Br J Clin Pharmacol. 2014;77(3):466-79.

- *Dermal Safety Studies*

The four dermal safety studies are discussed in this section. They were all conducted using the to-be-marketed formulation ("F10"). The term "Betamethasone Dipropionate Spray" in the following discussion on these four dermal safety studies is meant to represent the to-be-marketed formulation, SERNIVO Spray, 0.05%.

The Investigator for all four dermal safety studies was Dr. Jonathan Dosik in the Clinical Research Organization TKL Research, Inc. at 4 Forest Avenue, Paramus, NJ 07652. Dr. Dosik is a board certified dermatologist and Medical Director of TLK Research, Inc. He is qualified to conduct the research on dermal safety testing.

Reviewer Comment
Although the drug product did not show absorbance over the ultraviolet-visible light spectrum (290 to 700 nm), the applicant had conducted the phototoxicity and photoallergenicity studies using the to-be-marketed formulation. These two studies would have been waived at the request of the IND sponsor.

The 4 dermal safety studies all enrolled healthy subjects, and their demographics is shown together in the following Table (Table 33).

Table 33: Demographics of study population in dermal safety studies

Characteristics	DFD01-CD-008	DFD01-CD-010	DFD01-CD-011	DFD01-CD-012
N (randomized)	4	3	53	22
Age (years)				
Mean	58.8	50.8	45.9	46.7
Standard Deviation	11.9	17.61	15.7	14.3
Median	59.4	55.0	48.0	49.0
Range	36.8 - 75.2	17 - 74	19 - 75	18 - 75
Sex, n (%)				
Male	11 (27.5)	7 (21.2)	13 (24.5)	74 (32.7)
Female	29 (72.5)	26 (78.8)	40 (75.5)	152 (67.3)
Race, n (%)				
White	36 (90.0)	33 (100.0)	53 (100.0)	137 (60.6)
Black or African American	2 (5.0)	0 (0.0)	0 (0.0)	82 (36.3)
Asian	NR	0 (0.0)	0 (0.0)	4 (1.8)
American Indian or Alaskan Native	NR	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	NR	0 (0.0)	0 (0.0)	1 (0.45%)
Other	2 (5.0)	0 (0.0)	0 (0.0)	1 (0.45%)
Ethnicity, n (%)				
Hispanic or Latino	7 (17.5)	5 (15.2)	18 (34.0)	56 (24.8)
Not Hispanic or Latino	33 (82.5)	28 (84.8)	35 (66.0)	170 (75.2)
Fitzpatrick Skin Type, n (%)				
I	2 (5.0)	1 (3.0)	4 (7.5)	5 (2.2)
II	14 (35.0)	23 (69.7)	28 (52.8)	11 (4.9)
III	20 (50.0)	9 (27.3)	21 (39.6)	70 (31.0)

IV	4 (10.0)	0 (0.0)	0 (0.0)	121 (53.5)
V	0 (0.0)	0 (0.0)	0 (0.0)	19 (8.4)

ND = not determined; NR = not reported
Source: Module 2.7 clin-summary-safety.pdf page 16, Table 2.7.4.1.3:

More details of these studies follow.

DFD01-CD-008 A Double-Blind, Randomized, Controlled, Cumulative Irritation Patch Test Study of Betamethasone Dipropionate Spray

Objective: To assess the irritation potential of betamethasone dipropionate spray to-be-marketed formulation after repeated topical application to healthy skin of humans under controlled conditions

Design: Randomized, double-blind, single-center, vehicle-controlled, within-subject comparison, patch test study of betamethasone dipropionate spray to-be-marketed formulation, vehicle spray, vehicle lotion (corresponding to excipients of Diprolene Lotion), sodium lauryl sulfate (SLS) 0.2% and saline 0.9% for irritation potential when repeatedly applied to the skin under semi-occlusive conditions in healthy volunteers.

Subjects received applications of each study product to intact skin at randomly assigned, adjacent sites on the back. Evaluators and subjects were masked for identity of test product at the patch test sites. Test products were applied under semi-occlusive patch conditions using a 2 cm x 2 cm patch to either side of the infrascapular area of the back. Evaluation of dermal reactions at the application sites was by a visual scale that rates the degree of erythema, edema, and other signs of cutaneous irritation. A total of 21 patch applications was made over a period of 21 days.

Subject number and eligibility:

Forty (40) subjects were to be enrolled. Healthy males and females 18 years of age and older, of any skin type which allowed discernment of erythema and free of any systemic or dermatologic disorder. See Table 33 for demographics of enrolled population.

Test products, dose and mode of administration, batch number:

- Betamethasone Dipropionate Spray was applied daily for 3 weeks (21 applications) in the amount of 0.2 mL topically to skin on the infrascapular area of the back under semi-occlusive patch conditions. The batch number was FDP-C.
- Vehicle spray was applied similarly. The batch number was FDN-C.
- Vehicle lotion was applied similarly. The batch number was RD-13018.

Controls with sterile saline and 0.2% sodium lauryl sulfate (SLS) were also used.

Criteria for evaluation:

Patch test site evaluations: Patch sites were assessed 21 times during the study and the assigned score was used for statistical analysis.

Cumulative irritancy: Mean and total score were tested pairwise for product differences using Fisher's least significant differences in the randomized block analysis of variance (ANOVA), taking study product as the analysis unit and subject as the blocking stratum. The scoring system consisted of numerical and notational grading:

Table 34: Integer grading scale of skin responses for Study DFD01-CD-008

Grade	Response	Score
0	No evidence of irritation	0
1	Minimal erythema, barely perceptible	1
2	Definite erythema, readily visible; or minimal edema; or minimal papular response	2
3	Erythema and papules	3
4	Definite edema	3
5	Erythema, edema, and papules	3
6	Vesicular eruption	3
7	Strong reaction spreading beyond test site	3

Notations (see Table 35) were made in place of a grade to designate particular circumstances preventing the assignment of a grade or in addition to a grade to identify damage to the epidermis and/or spreading of a reaction.

Table 35: Notations to grading in the response scale for Study DFD01-CD-008

Notation	Definition
X	Subject absent
PD	Patch dislodged
NA	Patch not applied
NP	No patch due to limiting irritation
I	Itching
D	Damage of the epidermis: oozing, crusting, and/or superficial erosions
P	Papular response
Pv	Papulovesicular response
S	Spreading of reaction beyond patch site (ie, reaction where study material did not come in contact with skin)

Results:

- Forty (40) subjects were enrolled and 34 subjects completed the study. One subject, No. 3014 developed an exclusion criterion while on the study (use of an exclusionary medication (Augmentin)); 5 other subjects requested discontinuation. None of the subjects discontinued had patches discontinued due to limiting irritation at any of the patch sites.

- Mean irritancy scores and comparisons are shown in Table 36.

Table 36: Mean irritancy scores and summary comparisons for Study DFD01-CD-008

	SERNIVO Spray	Vehicle Spray	Vehicle Lotion	SLS 0.2%	Sterile Saline 0.9%
Mean total irritation score (SD)	0.24 (0.99)	1.15 (4.27)	3.06 (9.26)	4.59 (7.86)	0.03 (0.17)

SD = standard deviation
Source: Table 14.2.6 and 14.2.6 of study report.

There was significantly more irritation at the Vehicle Lotion site and 0.2% SLS site than at the Betamethasone Dipropionate Spray site, Vehicle Spray site and 0.9% sterile saline site ($p < 0.05$ for total irritation scores). There was no significant difference in irritation between Vehicle Lotion site and 0.2% SLS site, and no significant difference between the Betamethasone Dipropionate Spray site and Vehicle Spray site, the Betamethasone Dipropionate Spray site and the 0.9% sterile saline site, or the Vehicle Spray site and 0.9% sterile saline site.

- Two of the 40 subjects (5%) each experienced an adverse event: flu-like symptoms (#3014) and blood in urine (#3022) during the study. Both events were mild in severity and considered to be not related to the study product.

Conclusion:
It was concluded that under exaggerated conditions of use, with continuous exposure under semi-occlusion for 21 days, the betamethasone dipropionate spray to-be-marketed formulation and its vehicle spray produced no evidence of significant irritation. In comparison, the vehicle lotion produced irritation similar to that by 0.2% SLS site, a known irritant.

Reviewer Comment:
Out of the 40 subjects enrolled, 34 completed the 21-day testing. Although there is a dropout rate of 15%, the data appear to be robust enough for acceptance of the conclusion.

DFD01-CD-010 A 4-Day, Randomized, Vehicle-Controlled, Patch Test Study to Evaluate the Phototoxic Potential of Betamethasone Dipropionate Spray

Objectives: To assess the phototoxic potential of betamethasone dipropionate spray to-be-marketed formulation

Design:
On Day 1, betamethasone dipropionate spray to-be-marketed formulation 0.05%, Diprolene Lotion 0.05%, and vehicle spray each was applied to 2 sites on the infrascapular area of the back under fully occlusive patches for ~24±2 hours.

Minimal erythema dose (MED) irradiation was also performed for each subject on Day 1.

After patch removal on Day 2, all application sites were evaluated and one application site of each study product was irradiated with 16 J/cm^2 of ultraviolet A (UVA) followed by 0.5 times the MED of UVA/ultraviolet B (UVB) irradiation. An additional site was also irradiated with 16 J/cm^2 of UVA followed by 0.5 times the MED of UVA/UVB and served as an untreated control.

On Day 3, ~24±2 hours after irradiation and Day 4, ~48 hours±2 hours after irradiation, all application sites and the untreated control site were evaluated.

Subject number and eligibility:
Thirty-three (33) subjects were to be enrolled. The main eligibility criteria were: healthy males and females 18 years of age and older, who had Fitzpatrick Skin Type I, II, or III, and free of any systemic or dermatologic disorder. Female subjects of childbearing potential had to have negative urine pregnancy test results performed on Day 1. For demographics of the enrolled population, see Table 33.

Test products, dose and mode of administration, batch number:

- Betamethasone dipropionate spray to-be-marketed formulation 0.05% was applied in an amount of 0.2 mL under occlusive patch conditions to 2 sites (2 cm x 2 cm each) on the infrascapular area of the back once for ~24±2 hours. Lot #: GBB-C, Bottle ID #s: 20, 21
- Diprolene Lotion 0.05% and vehicle spray were applied similarly. Diprolene Lotion Lot #: 3EAW01V, Bottle ID #s: 28 and 29; Vehicle Spray Lot #: FDN-C, Bottle ID #s: 24 and 25.

Criteria for evaluation:

- Scoring for patch sites is as follows:
  - for erythema: No reaction = 0, Mild, but definite erythema = 1, Moderate erythema = 2, Marked/severe erythema =3;
  - for edema: No reaction = 0, Mild, but definite edema = 1, Definite edema with erosion/vesiculation = 2.
- A study product is considered to be phototoxic if meeting any of the following:

  1) Score of the irradiated study product minus score of the irradiated control was ≥2 points above score of the non-irradiated study product in ≥3 subjects, or

  2) Score of the irradiated study product minus score of the irradiated control was ≥1 point above score of the non-irradiated study product in ≥9 subjects.

Results:

- All 33 enrolled subjects completed the study. All female subjects of childbearing potential had negative urine pregnancy test results performed on Day 1 and at end of study.
- The criteria for phototoxicity (i.e., multiple subjects with a phototoxic response pattern) were not met for any study product. For the pairwise comparisons, there was a significant difference (P<.0001) between the scores for the irradiated and non-irradiated sites for each study product and between the scores for the non-irradiated study product site and the untreated control irradiated site.
- There were no adverse events, serious adverse events, or deaths reported during the 4-day study.

Conclusion:
There was no evidence of phototoxicity for the betamethasone dipropionate spray to-be-marketed formulation, vehicle spray or Diprolene Lotion.

DFD01-CD-011 A 6-Week, Randomized Study to Evaluate the Potential of Betamethasone Dipropionate Spray to Induce a Photoallergic Skin Reaction in Healthy Volunteers, Using a Controlled Photopatch Test Design

Objective: To determine the photoallergic potential of betamethasone dipropionate spray to-be-marketed formulation

Design:
- During the 3-week Induction Phase, the betamethasone dipropionate spray to-be-marketed formulation, Diprolene Lotion, 0.05%, vehicle spray, and saline 0.9% were each applied 2 times per week (Monday and Thursday) to 2 sites on the infrascapular area of the back under semi-occlusive patch conditions for ~24±2 hours. MED irradiation was also performed for each subject on Day 1.
- After patch removal, the application sites were evaluated and one application site of each test product was irradiated with 2 times the MED using the full Xenon lamp spectrum. The sites were evaluated ~48±2 hours later when irradiated on Tuesdays and 72±2 hours later when irradiated on Fridays.
- At challenge, betamethasone dipropionate spray to-be-marketed formulation, 0.05%, Diprolene Lotion, 0.05%, vehicle spray, and saline 0.9% were each applied once to 2 naive sites on the infrascapular area of the back under semi-occlusive patch conditions for ~24±2 hours. After patch removal, all application sites were evaluated and one site of each study product was irradiated with 6 J/cm^2 of ultraviolet A (UVA) followed by 0.5 times the MED of UVA/ultraviolet B (UVB). An additional untreated site was also irradiated at challenge to serve as untreated control. Each site was evaluated again at ~24±2 hours, 48±2 hours, and 72±2 hours following irradiation.

- A rechallenge was performed if a cutaneous response observed during challenge phase indicated possible photosensitization or at the discretion of the Investigator.

Subject number and eligibility:

The protocol plan was to provide 45 completed subjects. Fifty-three (53) subjects were enrolled. These were to be healthy males and females 18-75 years of age, who had Fitzpatrick Skin Type I, II, or III, and free of any systemic or dermatologic disorder. Female subjects of childbearing potential had to have negative urine pregnancy test results at Day 1. See Table 33 for demographics of the enrolled population.

Test products, dose and mode of administration, batch number:

- The betamethasone dipropionate spray to-be-marketed formulation was applied topically 2 times each week at 0.2 mL each time for 24±2 hours under semi-occlusive patch conditions to 2 sites for 3 weeks during the Induction Phase, and once to 2 naive sites at challenge. Lot #: GBB-C, Bottle ID #:s 40, 41 and 42.
- Diprolene Lotion, 0.05% and vehicle spray were applied similarly. Diprolene Lotion, 0.05% Lot #: 3EAW01V, Bottle ID #: 50, 51 and 52; and Vehicle Spray Lot #: FND-C, Bottle ID #s: 47, 48 and 49.
- Saline 0.9% which served as negative control was applied. TKL purchased commercially available sterile saline 0.9%.

A 3-week Induction Phase was followed by a rest period of 10-17 days and a Challenge Phase which consisted of one 24-hour topical application to naïve sites.

Criteria for evaluation:

- The scoring system is the same as that in the phototoxicity study, DFD01-CD-011:
  - for erythema: No reaction = 0, Mild, but definite erythema = 1, Moderate erythema = 2, Marked/severe erythema =3;
  - for edema: No reaction = 0, Mild, but definite edema = 1, Definite edema with erosion/vesiculation = 2.
- The diagnosis of a photosensitization response was made by the Investigator based on review of the observed skin responses after Challenge. All assigned scores during Induction and Challenge were summarized by frequency counts by time point and treatment. The incidence of reactions was summarized by frequency counts for each treatment. The guidelines for determination of photosensitization are as follows:
  - Not all observations of erythema and edema were considered as indicative of photosensitivity.
  - However, only if erythema and edema were observed can a reaction be suspected of being a positive photosensitivity reaction, and an increase in the intensity of the reaction over time further supported an assessment of photosensitivity.
  - If reactions were observed at both the irradiated and non-irradiated study product sites (i.e., if contact sensitization occurred), the reaction at the irradiated site upon Rechallenge was to be at least 1 grade more intense than at the non-irradiated site for the reaction to be suspected of being photosensitivity reaction.

Results:

- Fifty-three subjects were enrolled and 45 (85%) completed the study: four subjects withdrew, 3 discontinued due to adverse events (see below), and 1 was lost to follow-up.
- All female subjects of childbearing potential had negative urine pregnancy test results at Day 1, at the end of the Induction Phase and at end of study.
- Under the conditions in this study, there was no evidence of photosensitization to the betamethasone dipropionate spray to-be-marketed formulation, Diprolene Lotion 0.05%, or vehicle spray.
- There were no deaths or serious adverse events reported. Seven (7) subjects (13.2%) had 8 adverse experiences, and all were single occurrences. Six (6) of the 8 events were mild in severity, and all 8 adverse events resolved. Treatment-related adverse events were observed in 2 subjects (3.8%): rash and application site papules, and 3 subjects (5.7%) were discontinued from the study due to adverse events (rash at center of back in Subject 2006, hemorrhoids in Subject 2017, and blepharitis in Subject 2743).

Conclusion:
There was no evidence of photosensitization to the betamethasone dipropionate spray to-be-marketed formulation, Diprolene Lotion, 0.05%, or vehicle spray.

DFD01-CD-012 A Randomized, Double-Blind, Vehicle-Controlled, Repeat Insult Patch Test Study to Assess the Sensitization Potential of Betamethasone Dipropionate Spray

Objectives: To assess the contact sensitization potential of betamethasone dipropionate spray to-be-marketed formulation after repeated topical application to the skin of healthy human volunteers under controlled conditions, and secondarily, its irritation potential during the Induction Phase

Design:
The betamethasone dipropionate spray to-be-marketed formulation, Diprolene Lotion, 0.05%, vehicle spray, sodium lauryl sulfate (SLS) 0.2%, and saline 0.9% were applied under semi-occlusive patch conditions to intact skin 3 times a week for 3 weeks during the Induction Phase. Patches remained in place for 48 hours (or 72 hours over the weekend). Subjects returned 10 to 14 days after completion of the Induction Phase for challenge patches that remained in place for 48 hours. Patch test sites were scored for cutaneous reactions before each patch application during the Induction Phase, and 30 minutes and 1, 2, and 3 days following patch removal during the Challenge Phase.

Subject number and eligibility:

The protocol plan was to provide 200 completed healthy male and female subjects 18 years of age and older, of any skin type or race which allowed discernment of erythema and free of any systemic or dermatologic disorder. Female subjects of childbearing potential had to have negative urine pregnancy test results at Day 1. See Table 33 for demographics of the enrolled population.

Test products, dose and mode of administration, batch number:

- The betamethasone dipropionate spray to-be-marketed formulation was applied topically 3 times a week for 3 weeks (9 applications) during Induction Phase and once at Challenge Phase (10 total applications) in the amount of 0.2 mL to intact sites on the infrascapular area of the back under semi-occlusive patch conditions; Lot #: GBB-C.
- Diprolene Lotion, 0.05% was applied similarly; Lot #: 3EAW01V.
- Vehicle spray was also applied similarly; Lot #: FDN-C.

A three-week Induction Phase was followed by a 10- to 14-day resting period and a Challenge Phase, which consisted of one 48-hour topical application.

Criteria for evaluation:

- The safety endpoints for this study were irritation responses during the Induction Phase, positive responses at Challenge (i.e., reactions indicative of a sensitization response) and adverse events.
- The scoring system for the patch site changes is the same as that in the irritancy study, DFD01-CD-008, consisting of numerical grading and notational grading with letters (see above in discussion of Study DFD01-CD-008).
- Cumulative Irritancy: The mean and total of the scores (excluding the baseline reading) were calculated for each subject and product/condition.
- Sensitization Potential: A 95% 2-sided confidence interval on the proportion of subjects who showed a positive sensitization response at Challenge was computed.

Results:

- There were 226 subjects enrolled. Although 202 subjects were included in the primary analysis for incidence of sensitization, 200 (88.5%) were considered to have completed the study. The 26 discontinuations were due to:

Lost to Follow-up -	14 (6.2%)
Withdrawal of informed consent -	5 (2.2%)
Subject's Request -	5 (2.2%)
Adverse events/SAEs -	2 (0.9%)

- All female subjects of childbearing potential had negative urine pregnancy test results on Day 1 and at end of study.
- Only very mild reactions of minimal erythema, barely perceptible (a score of 1) were observed for a few subjects (6%) in response to the betamethasone dipropionate spray to-be-marketed formulation at Challenge. These reactions were

not considered indicative of sensitization. Results were similar for the controls. The mean of the subject's mean irritation score for betamethasone dipropionate spray during the Induction Phase was 0.01 on a scale of 0 to 3. A few subjects (8%) had scores of 1 (minimal erythema, barely perceptible) during the study, and no subject had a score of more than 1. Results were similar for the controls.

- A total of 3 non-treatment-related adverse events were reported by 3 subjects: tingling in the arm of a female subject and change in color of her fingers followed by a diagnosis of moderate Raynaud's phenomenon, another subject experiencing sialoadenitis, and a third subject with chronic obstructive lung disease leading to discontinuation. The chronic obstructive lung disease was reported as a serious adverse event. Two subjects discontinued from study due to adverse events: chronic obstructive lung disease and Raynaud's phenomenon.

Conclusion
There was no evidence of sensitization to the study products: the betamethasone dipropionate spray to-be-marketed formulation, Diprolene Lotion or Vehicle Spray. The study products were also non-irritating under the conditions of this study during the Induction Phase.

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose ranging studies have not been performed to allow observing dose-dependency of adverse events.

7.5.2 Time Dependency for Adverse Events

Although no pattern for time dependency for adverse events was observed in the phase 3 trials for SERNIVO Spray, the HPA axis suppression study, BDS1307, showed that in contrast to use for 15 days (HPA axis suppression rate in 20.8% of tested subjects), cosyntropin stimulation testing after SENIVO Spray, 0.05% twice daily for 29 days in moderate to severe plaque psoriasis did not show evidence of adrenal suppression. It is possible that systemic absorption may be reduced upon healing of skin lesions with improvement in the skin barrier function, and hence reduction of systemic effects. However, prolonged use of topical corticosteroids may also result in skin atrophy, and thinning of skin allows increased potential for systemic absorption and systemic effects. Thus, the net result can be hard to predict.

7.5.3 Drug-Demographic Interactions

No safety signals were identified when age, gender, ethnic or race demographic subgroups were examined.

Age

- Pediatric patients. Because of a higher ratio of skin surface area to body mass, pediatric patients are at greater risk for systemic adverse effects with use of topical corticosteroids, including betamethasone dipropionate. The applicant has not conducted clinical studies in pediatric subjects, but will have a postmarketing requirement under PREA to assess pediatric patients age 12 to 16 years 11 months for HPA axis suppression and pharmacokinetic parameters.
- Geriatric Patients. There were 57 subjects 65 years of age or older treated with SERNIVO Spray, 0.05% in the phase 3 studies. The small number studied renders it difficult to have meaningful assessment of the drug in the geriatric population.
- Additional age analyses. The combined data in the phase 3 trials showed 51 as the median age of the study population. The applicant analyzed age differences using age 51 as cut-off between younger and older subjects in the phase 3 trials. The ≥51 age group appears to have a lower incidence of application site pruritus in the SERNIVO Spray arm compared to the vehicle spray arm for periods Day 1 to Day 15 and Day 1 to Day 29 (5% vs 16%, p = 0.003, and 6% vs 17%, p = 0.005, respectively), whereas the <51 age group appears to show lower incidence for application site pain in the SERNIVO Spray treatment group vs vehicle spray group during Day 1 to Day 15 (5% vs 13%, p = 0.041). These incidence rates of application site events are based on the all adverse event profile, as this approach can be more conservative when treatment site events are considered. However, such post-hoc analyses are not definitive and only serve for hypothesis generation.

Other drug-demographic interactions: gender, ethnicity, and race

Other analyses for drug-demographic interactions in the phase 3 trials are shown in Table 37. The applicant analyzed the adverse event data between SERNIVO Spray and vehicle spray for males and females, for Hispanics and non-Hispanics, and for different races. Comparisons using the all event profile Day 1 to Day 29 are presented in the Table, which shows only those events with statistical significance between treatments (p values highlighted in red). This approach can be more conservative when treatment site events are considered. However, such post-hoc analyses are not definitive and only serve for hypothesis generation.

Table 37: Drug-demographic interactions: gender, ethnicity, and race for adverse events* with statistical significance between SERNIVO Spray and vehicle spray treatment groups

	Application site pain			Application site pruritus		
	SERNIVO**	vehicle	p-value	SERNIVO	vehicle	p-value
Sex						
Males	13/223 (5.8%)	15/107 (14.0%)	0.019	10/223 (4.5%)	15/107 (14.0%)	0.003
Females	10/129 (7.8%)	7/73 (9.6%)	0.793	17/129 (13.2%)	11/73 (15.1%)	0.832
Ethnicity (Hispanic N=159, Non-Hispanic=362): no statistically significant differences between treatments for any AE						

Race						
White	12/290 (4.1%)	17/160 (10.6%)	0.009	16/290 (5.5%)	20/160 (12.5%)	0.011
Asian	1/21 (4.8%)	1/5 (20%)	0.354	1/21 (4.8%)	1/5 (20.0%)	0.354
Black	2/27 (7.4%)	1/11 (9.1%)	1.000	1/27 (3.7%)	0/11 (0%)	1.000
American Indian or Alaska native	-	0/2 (0)	-	-	0/2 (0)	-
Pacific Islander	0/2 (0)	-	-	0/2 (0)	-	-
Other	0/12 (0)	0/2 (0)	-	3/12 (25.0%)	2/2 (100.0%)	0.110

*from all adverse events profile Day 1 to Day 29; **SERNIVO = SERNIVO Spray, 0.05%, vehicle = vehicle spray.
Source: integrated summary of safety sections 5.3.3, 5.3.5, and 5.3.6. Module 5, Section 5.3.5.3.

Although these data might suggest lower incidence of application site pruritus and application site pain in SERNIVO Spray-treated subjects as compared to vehicle spray-treated subjects among males but not females, and among whites but not other races, this may be due to the larger sample sizes for males and for whites, as the finding actually reflects the overall trend in the entire study population. The sample sizes of subjects in the non-white groups are too small for meaningful analysis.

7.5.4 Drug-Disease Interactions

Drug-disease interaction analyses were not done. SERNIVO Spray, 0.05% has not been specifically evaluated in subjects with renal or hepatic impairment. However, in the phase 3 trials, there were subjects with liver or kidney disease in the medical history, as shown in the following (verbatim terms):

Study BDS1205
Subject 103011 renal calculi
Subject 103014 kidney stones
Subject 107010 renal insufficiency
Subject 110002 fatty liver
Subject 112011 chronic renal calculi
Subject 112012 chronic renal calculi
Subject 127003 liver cirrhosis
Subject 142013 liver cirrhosis due to alcohol

Study BDS1206
Subject 216008 increased liver enzymes
Subject 227003 elevated liver function tests

No specific safety issues concerning the liver or kidney conditions of these subjects were presented in the trials.

7.5.5 Drug-Drug Interactions

No drug-drug interactions are known for topical use of betamethasone dipropionate. The applicant did not conduct specific drug interaction studies.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Although corticosteroids may have an immunosuppressive effect, and carry a theoretical predisposition to malignancies, such occurrence is rare, especially with topical corticosteroids.

In the clinical trials for SERNIVO Spray, 0.05% on plaque psoriasis, one 67-year-old male Caucasian subject in Study BDS1205 was reported to have non-superficial basal cell carcinoma (Subject ID 134004). However, the subject started treatment with SERNIVO Spray on 01-14-2014, and the event was reported on 01-15-2014. He had electrodessication and curettage 5 days later. This event has been considered to be unrelated to treatment with SERNIVO Spray.

7.6.2 Human Reproduction and Pregnancy Data

Protocols for all clinical studies excluded pregnant and/or nursing women. There is no information on the use of SERNIVO Spray, 0.05% in pregnant or lactating women.

7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant has discussed pediatric assessment required under PREA in the agreed-upon iPSP dated December 4, 2014. In this application, the applicant is proposing waiver for assessment in the age group 0 to 11 years 11 months because the incidence of psoriasis in this age group is low, and studies would be impractical (section 505B(a)(4)(B)(i) of the Act). This Reviewer notes that there have been previous studies on psoriasis in patients below age 12, and it is more appropriate to grant a waiver on the basis of the absence of meaningful therapeutic benefit over existing alternatives and the unlikely use by a substantial number of pediatric patients in that age group (section 505B(a)(4)(B)(iii) of the Act).

For the age group 12 to 16 years 11 months, the applicant will have a postmarketing requirement to conduct a deferred study, because the drug product is ready for approval for use in adults before pediatric studies are completed (section 505B(a)(3)(A)(i) of the Act). This will be a study on HPA axis suppression and pharmacokinetic parameters in patients 12 to 16 years 11 months of age. The study protocol has been submitted and study initiated with estimated completion date of March 31, 2018 and submission of study report by July 31, 2018.

Prolonged use of corticosteroids, including topical corticosteroids, may result in growth retardation. The assessment on growth effect will require long-term studies, and the growth differences are difficult to measure. As this adverse effect is already in the

labeling of topical corticosteroids, including in the draft label of SERNIVO Spray, 0.05%, additional assessment is not necessary.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There are no data on SERNIVO Spray, 0.05% regarding overdose, drug abuse potential or withdrawal and rebound.

However, it is well known that topical corticosteroids may produce HPA axis suppression and other endocrine adverse effects such as Cushing's syndrome, hyperglycemia, and glycosuria when excessive doses have been administered over a prolonged period of time. A maximal use study with SERNIVO Spray, 0.05% in moderate to severe psoriasis in adults showed a potential rate of HPA axis suppression of ~21% after 15 days of use, but none after 29 days. Prolonged use of topical corticosteroids may result in skin atrophy, striae, and telangiectasia.

In patients with HPA axis suppression, withdrawal of exogenous corticosteroids may be associated with adrenal insufficiency, which potentially requires systemic corticosteroid supplementation. Adrenal insufficiency has not been observed in the clinical development program of SERNIVO Spray, 0.05%. As well, rebound effects have not been observed in clinical trials with SERNIVO Spray, 0.05%.

7.7 Additional Submissions / Safety Issues

The applicant submitted the four-month Safety Update on October 8, 2015.

There were no new data from clinical studies on SERNIVO Spray, 0.05% during this period. Three clinical publications[3] were identified by the applicant as potentially containing new safety indications and/or new indications for betamethasone (not betamethasone dipropionate). The types of adverse events reported are mild and, when specified, are not new for corticosteroids used topically. The applicant considers no new safety issues as having been identified in the published literature during the reporting period that warrants revision of the draft labeling.

[3] The 3 publications are:

- Beer H, Southern KW, Swift AC. Topical nasal steroids for treating nasal polyposis in people with cystic fibrosis. *Cochrane Database Syst Rev*. 2015;6:CD008253.
- Li L; Wu Y; Li L; et al. Triple combination treatment with fractional CO2 laser plus topical betamethasone solution and narrowband ultraviolet B for refractory vitiligo: a prospective, randomized half-body, comparative study. *Dermatol Ther*. 2015;28(3):131-134.
- Muro M, Kawakami H, Matsumoto Y, Abe N, Tsuboi R, Okubo Y. Topical combination therapy with vitamin D3 and corticosteroid ointment for palmoplantar pustulosis: A prospective, randomized, left-right comparison study. *J Dermatolog Treat*. 2015. [Epub ahead of print].

8 Postmarket Experience

SERNIVO Spray, 0.05% has not been marketed.

9 Appendices

9.1 Literature Review/References

This reviewer has not conducted a literature review for this application.

9.2 Labeling Recommendations

Labeling negotiations are ongoing as this review closed. If the application is approved, final labeling will be attached to the approval letter.

As this application was submitted prior to the new Pregnancy and Lactation Labeling Final Rule (PLLR) coming into effect (June 30, 2015), the prescribing information may use the existing format at the time of submission, and have conversion into PLLR format by June 30, 2019.

The draft label contained an Instructions-For-Use (IFU) brochure, but did not include a patient package insert (PPI). Upon advice from the agency, the applicant has submitted a draft PPI, which is also currently under labeling negotiation.

9.3 Advisory Committee Meeting

This application was not discussed at an advisory committee meeting.

9.4 Clinical Investigator Financial Disclosure Review Template

Clinical Investigator Financial Disclosure
Review Template

Application Number: 208079

Submission Date(s): April 6, 2015

Applicant: Promius Pharma, LLC

Product: SERNIVO (betamethasone dipropionate) Spray, 0.05%

Reviewer: Hon-Sum Ko, M.D.

Date of Review: December 17, 2015

Covered Clinical Study (Name and/or Number): BDS1103
BDS1204
DFD01-CD-009
BDS1307
DFD01-CD-008
DFD01-CD-010
DFD01-CD-011
DFD01-CD-012
BDS1205
BDS1206

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: 73		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
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: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0		

Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Not applicable	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Not applicable	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Not applicable	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[4] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The applicant has certified in Form 3454 that there were no financial arrangements with the clinical investigators, and that the clinical investigators do not have proprietary interest in the product proposed for marketing, or a significant equity in the applicant.

The disclosed information does not affect approvability of this application.

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

/s/

HON SUM KO
12/29/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 208079 **Applicant:** Promius **Stamp Date:** 04-06-2015
Drug Name: Sernivo **NDA Type:** 505(b)(2)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	eCTD			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			In Module 2 – under "Clinical Overview"
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	505(b)(2)			
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?	Diprolene Lotion AF 0.05%			
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	X			
15.	Describe the scientific bridge (e.g., BA/BE studies)	PK/PD studies including HPA axis suppression study; clinical trial including Sernivo and its vehicle, and Diprolend Lotion 0.05% and its vehicle			
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	This is a 505(b)(2) application referencing Diprolene Lotion 0.05%, with clinical bridge to be established in the clinical trials.
EFFICACY					
17.	On its face, do there appear to be the requisite number of adequate and well controlled studies in the application? Pivotal Study #1- BDS1205 Indication: treatment of moderate* plaque psoriasis Pivotal Study #2 - BDS1206 Indication: same as BDS 1205	X			*Agency advised studying moderate to severe psoriasis. Pivotal studies limited enrollment to moderate disease.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.		X		FDA recommended using Day 29 for primary endpoint.
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			No specific manner requested by DDDP
22.	Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	505(b)(2) application referencing safety of RLD
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			Product not marketed; literature on BD presented
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA 16.1 is used for studies and iss.
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Dermal safety studies are included.
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	review of the patient data?				
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			Primary endpoint (IGA = 0 or 1, and ≥2-grade IGA reduction from Baseline) is dependent on IGA; the raw data on IGA are submitted.
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			Division also asked for CRF of subjects with "severe" AEs.
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?		X		Statements present in clinical study reports (Section 5 of each report: "Ethics")

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____Yes___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No issues

Hon-Sum Ko 05-21-2015

Reviewing Medical Officer and Acting Clinical Team Leader Date

---

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

/s/

HON SUM KO
05/21/2015