CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208079Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 208079	Submission Date(s): 4/6/2015, 7/15/2015, and 10/16/2015
Brand Name	Sernivo Spray, 0.05%
Generic Name	Betamethasone propionate spray, 0.05% w/w
Primary Reviewer	Doanh Tran, Ph.D.
Secondary Reviewer	Capt. E. Dennis Bashaw, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Dermatology and Dental Products
Sponsor	Promius Pharma
Relevant IND(s)	104853
Submission Type	Original NDA
Formulation; Strength(s)	Spray; 0.05%
Indication	Topical treatment of moderate plaque psoriasis in patients 18 years of age or older

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1 Executive Summary

The applicant has developed a new formulation of betamethasone dipropionate, Betamethasone Dipropionate Spray, 0.05%, for the topical treatment of moderate plaque psoriasis. Betamethasone dipropionate is a synthetic, fluorinated corticosteroid. Betamethasone Dipropionate Spray contains 0.05% betamethasone dipropionate (potency expressed as betamethasone) in a spray formulation. The spray is to be applied to affected areas twice daily for up to 4 weeks. The Applicant states that the spray dosage for is convenient for patients to use and dries completely leaving no sticky residue. Betamethasone dipropionate at the same 0.05% strength is commercially available as cream, ointment, and lotion formulations.

The clinical study data for Betamethasone Dipropionate Spray, 0.05% consist of ten clinical trials with Betamethasone Dipropionate Spray, 0.05%: seven Phase 1 studies (three vasoconstrictor assay studies and four safety studies of cumulative irritation, phototoxicity, photoallergy and sensitization), a Phase 2 hypothalamic-pituitary-adrenal (HPA) axis suppression and pharmacokinetic (PK) trial and two Phase 3 double-blind trials evaluating safety and efficacy in subjects with moderate plaque psoriasis. The listed drug, Diprolene (augmented betamethasone dipropionate) Lotion, 0.05%, was included for comparison in the Phase 1 vasoconstrictor studies, the Phase 2 HPA axis suppression trial and one of the Phase 3 safety and efficacy trials in order to construct a clinical bridge to the Agency's findings of safety for this approved product.

There is an agreed initial pediatric study plan (iPSP) dated 12/4/2014; however, the trial has not been completed. This trial will be included as a PREA post marketing requirement.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds NDA 208079 acceptable pending agreement on recommended labeling changes.

1.2 Phase IV Requirements and Commitments

The following post marketing requirement is recommended:

A trial evaluating the adrenal suppression potential and pharmacokinetic properties of twice daily betamethasone dipropionate spray, 0.05% under maximal use conditions in subjects 12 years to 16 years 11 months of age with plaque psoriasis.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

PK/HPA axis suppression:
The systemic exposure of Betamethasone Dipropionate Spray, 0.05% and Diprolene Lotion, 0.05% were compared using HPA axis suppression as a surrogate endpoint and

sparse pharmacokinetic sampling (1, 3 and 6 hours after application) (Trial BDS1307). Plasma cortisol was determined before and after adrenocorticotropic hormone (ACTH) stimulation in subjects with moderate to severe psoriasis treated twice daily with Betamethasone Dipropionate Spray, 0.05% (for 15 or 29 days) or Diprolene Lotion, 0.05% (for 15 days).

The incidence of HPA axis suppression was similar between the Betamethasone Dipropionate Spray, 0.05% 15-day and Diprolene Lotion, 0.05% 15-day groups at 20.8% (5 of 24) and 25.0% (5 of 20), respectively. HPA axis suppression was not observed in the Betamethasone Dipropionate Spray, 0.05% 29-day group (0 of 24). 7 of 10 suppressed subjects had follow up results and all returned to normal.

The majority of subjects in all groups had no measurable plasma concentration (<5.00 pg/mL) of betamethasone dipropionate at almost all time points just before and after the last application of study product at End of Treatment. In contrast, betamethasone dipropionate metabolites (i.e., betamethasone-17-propionate and betamethasone) were detected in the majority of subjects. Therefore, the bioavailability analysis focused on the metabolites concentrations.

Plasma concentrations at 0, 1, 3, and 6 hours appears to be at a plateau on Day 15 and Day 29. Summary of mean plasma Cmax is shown in Table 1. On Day 15 the Betamethasone Dipropionate Spray, 0.05% had similar mean Cmax for betamethasone-17-propionate and betamethasone compared to Diprolene lotion.

Subjects in the Betamethasone Dipropionate Spray, 0.05% 29-day group had lower concentration of metabolites betamethasone-17-propionate and betamethasone when compared with values at Day 15 in the Betamethasone Dipropionate Spray, 0.05% and Diprolene Lotion treatment groups. This was not the case for the parent moiety; however, this observation for the parent moiety may be due to limited measurable concentrations for the parent moiety.

Table 1: Mean (±SD) Maximum plasma concentration in Trial BDS1307

Analyte (pg/mL)	Sernivo Spray bid for 15 days	Sernivo Spray bid for 29 days	Diprolene lotion bid for 15 days
Betamethasone dipropionate	14.1 ± 10.2	101.5 ± 290.0	21.9 ±12.4
Betamethasone-17-propionate	119.9 ± 127.0	63.9 ± 52.6	121.9 ± 106.1
Betamethasone	119.0 ± 176.1	57.6 ± 55.9	112.6 ± 92.4

bid = twice a day

Potency classification:
The corticosteroid potency of Betamethasone Dipropionate Spray, 0.05% was compared to the listed drug, Diprolene Lotion, 0.05% and other corticosteroids of known potency in three studies using the vasoconstrictor method (Studies BDS1103, BDS1204, DFD01-CD-009). Study BDS1103 was a pilot trial that suggested the to-be-marketed formulation

was ranked as high to mid-potent. Follow up study BDS1204 to confirm potency did not show consistent results with the pilot trial and ranked it as low to mid-potent. A third study (study DFD01-CD-009) was conducted in a larger number of subjects (n=78 completers) to resolve the discrepancy. The results indicated it was a mid-potent corticosteroid.

The three vasoconstrictor studies all demonstrated that Betamethasone Dipropionate Spray, 0.05% is of lower potency compared to the listed drug, Diprolene Lotion, 0.05%.

Pediatric:
The applicant requested a deferral of pediatric studies for subjects 12 years to 16 years 11 months of age. There is an agreed iPSP dated 12/4/2014. As per the agreed iPSP initial pediatric study plan, the applicant will conduct a PK/HPA axis suppression trial in adolescents aged 12 years to 16 years 11 months with plaque psoriasis. This trial will be included as a PREA post marketing requirement.

Clinical versus to-be-marketed formulation:
The applicant stated that all 10 clinical trials were conducted with the final to-be-marketed Betamethasone Dipropionate Spray, 0.05% formulation (formulation F10), including the two Phase 3 studies, the HPA axis suppression study with pharmacokinetic sampling, and the Phase 1 vasoconstrictor and dermal safety studies.

Method validation:
Plasma betamethasone dipropionate, betamethasone and betamethasone-17-propionate and serum cortisol concentrations were evaluated using adequately validated assays.

2 Question-Based Review

2.1 General Attributes

2.1.1 What is betamethasone dipropionate?

Betamethasone dipropionate is a synthetic, fluorinated corticosteroid. Betamethasone Dipropionate Spray contains 0.05% betamethasone dipropionate (potency expressed as betamethasone) in a spray formulation. Betamethasone dipropionate at the same 0.05% strength is commercially available as cream, ointment, and lotion formulations.

2.1.2 What are the proposed indication and dosing regimen for Betamethasone Dipropionate Spray, 0.05%?

The proposed indication is for treatment of moderate plaque psoriasis in patients 18 years of age and older. The proposed dosing regimen is to shake well and apply to the affected area twice daily for up to 4 weeks. Rub in gently.

2.1.3 What is plaque psoriasis?

Psoriasis is a chronic autoimmune disease that manifests itself as inflammatory dermatosis and affects 1-3% of the US population. The most common type of psoriasis is plaque psoriasis, which is characterized by well-demarcated, pruritic, thick, scaly skin lesions. Psoriasis pathogenesis involves the abnormal regulation of the cells of the immune system (white blood cells including T lymphocytes, neutrophils, and other leucocytes) prompted by both environmental and genetic factors, which leads to a dysregulation of normal keratinocyte proliferation and an increase in proinflammatory cell signals.

2.2 General Clinical Pharmacology

2.2.1 What were the design features of the clinical pharmacology and clinical trials used to support Betamethasone Dipropionate Spray, 0.05%?

The clinical study data for Betamethasone Dipropionate Spray, 0.05% consist of ten clinical trials with Betamethasone Dipropionate Spray, 0.05%: seven Phase 1 studies (three vasoconstrictor assay studies and four safety studies of cumulative irritation, phototoxicity, photoallergy and sensitization), a Phase 2 hypothalamus pituitary adrenal (HPA) axis suppression and pharmacokinetic (PK) trial and two Phase 3 double-blind trials demonstrating safety and efficacy in subjects with moderate plaque psoriasis. The listed drug, Diprolene Lotion, 0.05%, was included for comparison in the Phase 1 vasoconstrictor studies, the Phase 2 HPA axis suppression trial and one of the Phase 3 safety and efficacy trials in order to construct a clinical bridge to the Agency's findings of safety for this approved product.

2.2.2 What is the systemic bioavailability of Betamethasone Dipropionate Spray, 0.05% under maximal use conditions and what is the relative bioavailability compared to Diprolene Lotion, 0.05%?

The systemic exposure of Betamethasone Dipropionate Spray, 0.05% and Diprolene Lotion, 0.05% were compared using HPA axis suppression as a surrogate endpoint and sparse PK sampling (1, 3 and 6 hours after application) in Trial BDS1307. This was a 15- or 29-day, randomized, multicenter, multi-dose, comparator-controlled, open-label study. Adult subjects with moderate to severe plaque psoriasis were randomized to treatment with Betamethasone Dipropionate Spray, 0.05% 15-day treatment, Betamethasone Dipropionate Spray, 0.05% 29-day treatment, or Diprolene Lotion 15-day treatment in a 1:1:1 ratio. These investigational products were applied twice daily to all affected areas on the body excluding face, scalp, groin, axillae, and other intertriginous areas. Subjects were to have 20 to 50% body surface area (BSA) treated to achieve maximal use exposure. The median total amount used during the entire study for Betamethasone Dipropionate Spray, 0.05% 15-day treatment, Betamethasone Dipropionate Spray, 0.05% 29-day treatment, and Diprolene Lotion 15-day treatment were 132 g, 179 g, and 98 g, respectively.

A PK blood sample was taken at the screening visit to obtain a baseline value (PK screening sample). At the End of Treatment Visit, subjects applied the last dose of study product at the clinic up to 60 minutes after a pre-treatment PK blood sample was taken (0 hour – End of Treatment Visit). PK blood samples were then collected at 1, 3, and 6 hours (± 5 minutes) after application of the study product.

The majority of subjects in all groups had no measurable plasma concentration (<5.00 pg/mL) of the parent betamethasone dipropionate at almost all time points just before and after the last application of study product at End of Treatment. However, betamethasone dipropionate metabolites, namely betamethasone-17-propionate and betamethasone, were detected in the majority of subjects. Therefore, the bioavailability analysis will focus on the metabolite concentrations.

Plasma concentrations at 0, 1, 3, and 6 hours appears to be at a plateau on Day 15 and Day 29. Summary of mean plasma Cmax (the maximum concentration among the 1, 3, and 6 hours concentration values) is shown in Table 2. On Day 15 the Betamethasone Dipropionate Spray, 0.05% had similar mean Cmax for betamethasone-17-propionate and betamethasone compared to Diprolene Lotion.

Subjects in the Betamethasone Dipropionate Spray, 0.05% 29-day group had lower concentration of metabolites betamethasone-17-propionate and betamethasone when compared with values at Day 15 in the Betamethasone Dipropionate, 0.05% and Diprolene Lotion treatment groups. This was not the case for the parent moiety; however, this observation for the parent moiety may be due to limited measurable concentrations for the parent moiety.

Table 2: Mean (±SD) Maximum plasma concentration in Trial BDS1307

Analyte (pg/mL)	Sernivo Spray bid	Sernivo Spray bid	Diprolene lotion bid

	for 15 days	for 29 days	for 15 days
Betamethasone dipropionate	14.1 ± 10.2	101.5 ± 290.0	21.9 ±12.4
Betamethasone-17-propionate	119.9 ± 127.0	63.9 ± 52.6	121.9 ± 106.1
Betamethasone	119.0 ± 176.1	57.6 ± 55.9	112.6 ± 92.4

bid = twice a day

2.2.3 What is the effect of Betamethasone Dipropionate Spray, 0.05% on suppressing the hypothalamic pituitary adrenal (HPA) axis?

In Trial BDS1307 described above in section 2.2.2, subjects were tested for HPA axis function using the adrenocorticotropin (ACTH) stimulation test (cosyntropin i.v. or i.m. injection) at the Screening Visit (at least 14 days and no more than 28 days prior to Baseline) and at the End of Treatment Visit (i.e., Day 15 for the two 15-day treatment arms or Day 29 for the 29-day treatment arm). If HPA axis was suppressed at the End of Treatment Visit, another test was administered 28 days later (at Day 43 or 57 as appropriate) to confirm recovery. The ACTH stimulation test was repeated every 28 days until recovery was confirmed (or until the cause of suppression was diagnosed).

The incidence of HPA axis suppression was similar between the Betamethasone Dipropionate Spray, 0.05% 15-day and Diprolene Lotion, 0.05% 15-day groups at 20.8% (5 of 24) and 25.0% (5 of 20), respectively. HPA axis suppression was not observed in the Betamethasone Dipropionate Spray, 0.05% 29-day group (0 of 24). 7 of 10 suppressed subjects had follow up results and all returned to normal at the first follow up visit.

2.2.4 What is the potency classification for Betamethasone Dipropionate Spray, 0.05%?

The corticosteroid potency of Betamethasone Dipropionate Spray, 0.05% was compared to the listed drug, Diprolene Lotion, 0.05% and other corticosteroids of known potency in three studies using the single point vasoconstrictor assay with visual assessment as the primary endpoint (Studies BDS1103, BDS1204, DFD01-CD-009). Study BDS1103 was a pilot trial that suggested the to-be-marketed formulation was ranked as high to mid-potent (Table 3). Follow up study BDS1204 to confirm potency did not show consistent results with the pilot trial and ranked it as low to mid-potent (Table 4). A third study (study DFD01-CD-009) was conducted in a larger number of subjects (n=78 completers) to resolve the discrepancy. The results indicated it was a mid-potent corticosteroid (Table 5).

The three vasoconstrictor studies all demonstrated that Betamethasone Dipropionate Spray, 0.05% is of lower potency compared to the listed drug, Diprolene Lotion, 0.05%.

Table 3: Potency ranking results based on visual assessment score from pilot study BDS1103. Betamethasone Dipropionate Spray, 0.05% is denoted as Test 2 (F-10).

Formulations		N	Mean	REGWQ Grouping*
Reference 8	Diprolene® (brand of augmented betamethasone dipropionate) Lotion 0.05%; Schering Corporation; Lot No. 0-EAW-101; Expiration Date: 08/12.	33	1.1136	A
Test 6 (F-18)	[redacted] (b) (4)			
Test 3 (F-11)				
Test 2 (F-10)	Betamethasone Dipropionate Spray 0.05% (Oleyl alcohol (b) (4); Mfd. by Dr. Reddy's Laboratories Limited for Promius Pharma, LLC; Lot No. DERCT-112/12-11; Mfg. Date: DEC-11; Retest Date: MAY-12.	33	0.7500	B, C
Test 7 (F-19)	[redacted] (b) (4)			
Test 4 (F-13)				
Test 1 (F-9)				
Test 5 (F-14)				
Reference 9	Cutivate® (fluticasone propionate) Cream 0.05%; Pharmaderm® A Division of Nycomed US Inc.; Lot No. 813K; Expiration Date: MAY 13.	33	0.3864	D

*Products with the same Ryan-Einot-Gabriel-Welsh Multiple Range Test (REGWQ) grouping letter are not significantly different.

Table 4: Potency ranking results based on visual assessment score from follow up study BDS1204. Betamethasone Dipropionate Spray, 0.05% is denoted as Test 1.

Formulations		N	Mean	REGWQ Grouping*
Reference 5	Elocon® Ointment, 0.1% (mometasone furoate ointment USP); Manufactured By: Schering-Plough Canada Inc.; Distributed by: Schering Corporation, a Subsidiary of Merck & Co. Inc.; Lot Number: 2UHK16; Expiration Date: 08/14	40	2.5000	A
Reference 2	Augmented Betamethasone Dipropionate Ointment, 0.05%; Manufactured for: (b) (4) (b) (4) Manufactured By: (b) (4) (b) (4) Lot Number: 2HYA09V; Expiration Date: 10/14	40	2.4000	A
Reference 4	Diprolene® AF (brand of augmented betamethasone dipropionate) Cream, 0.05%; Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of MERCK & CO., INC.; Manufactured By: Schering-Plough Canada, Inc.; Lot Number: 3EEW01V; Expiration Date: 01/15	40	2.2875	A,B
Reference 3	Diprolene® (brand of augmented betamethasone dipropionate) Lotion, 0.05%; Manufactured By: Schering-Plough Canada, Inc.; Distributed By: Schering Corporation a subsidiary of Merck & Co., Inc.; Lot Number: 2EAW02V; Expiration Date: 03/14	40	1.9750	B
Reference 6	Fluticasone Propionate Cream, 0.05%; Manufactured by: Perrigo; Distributed by: PERRIGO®; Lot Number: 3ET0369; Expiration Date: 04/15	40	1.1875	C
Test 1	Betamethasone Dipropionate Spray, 0.05%; Manufactured by: DPT Laboratories; Lot Number: FDP-C; Manufacturing Date: Jul 26, 2013	40	1.1375	C,D
Reference 7	Hydrocortisone Cream USP, 2.5%; Manufactured by: Perrigo; Distributed by: PERRIGO®; Lot Number: 2KT0038; Expiration Date: 09/15	40	0.8250	D,E
Untreated	No Treatment	40	0.5625	E

*Products with the same Ryan-Einot-Gabriel-Welsh Multiple Range Test (REGWQ) grouping letter are not statistically significantly different using a global 5% significance level.

Table 5: Potency ranking results based on visual assessment score from study DFD01-CD-009. Betamethasone Dipropionate Spray, 0.05% is denoted as Test 1.

Formulations		N	Mean	Standard Deviation	REGWQ Grouping*
Reference 2	Diprolene® Brand of Augmented Betamethasone Dipropionate Ointment, 0.05%; Manufactured for: Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., INC.; Manufactured By: Schering Plough Canada Inc.; Lot Number: 3HYA03; Expiration Date: 02/15	78	2.5064	0.5000	A
Reference 4	Diprolene® AF Brand of Augmented Betamethasone Dipropionate Cream, 0.05%; Manufactured for: Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., INC.; Manufactured By: Schering Plough Canada Inc.; Lot Number: 3EEW01V; Expiration Date: 01/15	78	2.0705	0.7633	B
Reference 3	Diprolene® Brand of Augmented Betamethasone Dipropionate Lotion, 0.05%; Manufactured for: Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., INC.; Manufactured By: Schering Plough Canada Inc.; Lot Number: 3EAW01V; Expiration Date: 02/15	78	2.0577	0.7385	B
Test 1	Betamethasone Dipropionate Spray, 0.05%; Promius Pharma, LLC; Lot Number: FDP-C; Manufacturing Date: Jul 26, 2013	78	1.2949	0.7091	C
Reference 6	Fougera® Fluticasone Propionate Cream, 0.05% E. Fougera & Co. A division of Fougera Pharmaceuticals Inc.; Lot Number: 840R; Expiration Date: APR 15	78	1.2628	0.8631	C
Reference 5	Fougera® Triamcinolone Acetonide Cream USP, 0.1% E. Fougera & Co. A division of Fougera Pharmaceuticals Inc.; Control No. 827R; Expiration Date: MAR 16	78	1.1539	0.7529	C
Reference 7	Fougera® Hydrocortisone Cream USP, 2.5% E. Fougera & Co. A division of Fougera Pharmaceuticals Inc.; Lot Number: DP3478; Expiration Date: AUG 16	78	0.6346	0.5564	D
Untreated	No Treatment	78	0.0513	0.1233	E

*Products with the same Ryan-Einot-Gabriel-Welsh Multiple Range Test (REGWQ) grouping letter are not statistically significantly different using a global 5% significance level.

2.3 Intrinsic Factors

2.3.1 What is the systemic exposure of Betamethasone Dipropionate Spray, 0.05% in pediatrics?

The applicant requested a deferral of pediatric studies for subjects 12 years to 16 years 11 months of age. There is an agreed initial pediatric study plan (iPSP) dated 12/4/2014. As

per the agreed iPSP initial pediatric study plan, the applicant will conduct a PK/HPA axis suppression trial in adolescents aged 12 years to 16 years 11 months with plaque psoriasis. This trial will be included as a PREA post marketing requirement. A waiver has been granted for studies in pediatrics <12 years of age in the agreed iPSP.

The pediatric study plan will be discussed with the pediatric review committee (PeRC) on 12/9/2015.

2.4 Extrinsic Factors

The applicant did not provide any information on the effect of extrinsic factors on the PK of Betamethasone Dipropionate Spray, 0.05%. Because the systemic bioavailability of Betamethasone Dipropionate Spray, 0.05% is similar to approved Diprolene Lotion, 0.05%, a request for additional studies is not warranted.

2.5 General Biopharmaceutics

2.5.1 What is the formulation composition of Betamethasone Dipropionate Spray, 0.05%?

The formulation composition of Betamethasone Dipropionate Spray, 0.05% is shown in Table 6 below.

Table 6: Formulation composition of Betamethasone Dipropionate Spray, 0.05%

S.No	Ingredients	Betamethasone Dipropionate Spray, 0.05%*
		%w/w
1	Betamethasone dipropionate USP, EP	0.0643
2	Sorbitan monostearate NF, (b) (4)	(b) (4)
3	Polyoxyl 20 cetostearyl ether, NF, (b) (4)	
4	Cetostearyl alcohol NF/EP, (b) (4)	
5	Mineral oil USP, (b) (4)	
6	Oleyl alcohol NF (b) (4)	
7	Propylparaben, NF	
8	Methylparaben, NF	
9	Butylated hydroxytoluene, NF/EP	
10	Hydroxyethyl cellulose, NF, (b) (4)	
11	Purified Water, USP/EP	

*Potency expressed as betamethasone

2.5.2 Was the to-be-marketed formulation used in the clinical trials?

Yes. The applicant stated that all 10 clinical trials were conducted with the final to-be-marketed Betamethasone Dipropionate Spray, 0.05% formulation (formulation F10), including the two Phase 3 studies, the HPA axis suppression study with pharmacokinetic sampling, and the Phase 1 vasoconstrictor and dermal safety studies.

2.6 Analytical

2.6.1 What bioanalytical methods were used to assess Betamethasone dipropionate, betamethasone, betamethasone-17-propionate and cortisol and were they adequately validated?

Plasma betamethasone dipropionate, betamethasone, and betamethasone-17-propionate:
The analysis of betamethasone dipropionate, betamethasone, and betamethasone-17-propionate in human plasma was done using 3 adequately validated LC/MS/MS assays. A summary of validation and incurred samples reanalysis is shown in Table 7 below.

Table 7: Summary of assay validation results

Parameter	Betamethasone dipropionate	Betamethasone propionate	Betamethasone
Assay range	5 – 5000 pg/mL	5 – 5000 pg/mL	5 – 5000 pg/mL
Intra-run precision	0.67 to 9.47%	1.52 to 8.81%	0.96 to 4.81%
Intra-run accuracy	-5.85 to 7.34%	-2.60 to 3.27%	-3.37 to 4.47%
Inter-run precision	2.87 to 9.86%	3.52 to 13.75%	3.19 to 11.23%
Inter-run accuracy	-1.00 to 1.70%	2.39 to 3.51%	-6.47 to -2.94%
Long term storage stability	245 days at -20ºC and -80°C	225 days at-80ºC and 78 days at -20ºC	253 days at -20°C and -80°C
Total number of samples tested	347	347	346
Incurred samples reanalysis	69.2% of 26 samples	100% of 50 samples	94% of 50 samples

Serum cortisol:
The analysis of serum cortisol concentration was done at (b) (4) using the validated commercial (b) (4) assay with a range of 0.2 – 75 µg/dL. Precision and accuracy assessments done at the testing laboratory were within acceptable limits (see Table 8).

Table 8: Summary of accuracy and precision assessments done at (b) (4)

Within Run Precision

Control	Level	N	Assayed Mean	SD	%CV	Verification Limit Within Run	Comment
40851	1	10	4.43	0.08	1.88	6.53 %CV	Within Acceptable Limits
40852	2	10	23.47	0.65	2.75	6.20 %CV	Within Acceptable Limits
40853	3	10	37.44	1.33	3.56	6.20 %CV	Within Acceptable Limits

Accuracy

Control	Level	N	Assayed Mean	Published Control Range	Comment
40851	1	10	4.43	3.30 - 5.30	Within Acceptable Limits
40852	2	10	23.47	21.00 - 25.00	Within Acceptable Limits
40853	3	10	37.44	29.90 - 45.00	Within Acceptable Limits

Storage stability:

For betamethasone dipropionate, betamethasone, and betamethasone-17-propionate, the bioanalytical reports indicate duration of storage was within the established storage stability.

For cortisol, no information on duration of storage or storage stability was provided in the initial NDA submission. The sponsor provided the information on 7/15/2015. The data showed that samples from 7 subjects (14 samples from total of 300 samples in the study) were analyzed outside of the 72 hours established stability for storage at 4 ºC (range from 79.3 – 201.0 hours). Of the 7 subjects, 4 of the test results showed a response within normal range (i.e., >18 µg/dL) and stability is not a concern. For the remaining 3 subjects with "abnormal" response (i.e., ≤18 µg/dL), the observed cortisol concentrations were significantly lower than the normal threshold. In addition, data from subjects 311001, where the screening samples were analyzed after 174 hours of storage, showed similar values at baseline compared to at 43 days after last dose which suggest there is not a significant stability issue with 174 hours of storage. Overall the data suggest that the 3 "abnormal" results are likely to be true and this reviewer recommends that results from all 7 subjects be included in the final dataset.

In response to Agency's question, the sponsor later clarified that all samples were actually analyzed within the demonstrated stability window (see discussion below). This would lead to the same conclusion as recommended above and therefore no further action was taken.

Applicant's response to request for further information:
The Applicant was requested to provide detailed information as to why the significant protocol deviations occurred and what corrective action they have taken to prevent future occurrence. In a reply submitted on 10/16/2015 the Applicant stated that upon further review and investigation following the Agency's question, the laboratory verified that their procedures is to analyze all samples on the day of receipt. The delay previously reported was related to a delay between sample analysis and reporting and not between when the sample was drawn and when they were analyzed. The sponsor provided updated listing showing that all samples were analyzed within the 3-day demonstrated stability.

The Applicant further stated that to prevent a recurrence, all CROs and internal personnel who are or may be involved with HPA axis studies in the future have been informed that future listings must include the date and time of collection and the date and time of analysis of cortisol samples to correctly calculate the duration between when a sample was collected and when it was analyzed.

3 Detailed Labeling Recommendations

The following changes are recommended for sections 5 and 12 of the label. For section 5, only edits to the data are noted here. This reviewer defers to the clinical reviewer to convert this section to be consistent with class labeling. Deletions are noted as ~~strikethrough~~ and additions are noted as double underlines.

5.1 Effects on Endocrine System

SERNIVO Spray can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency. This may occur during or after withdrawal of treatment. Factors that predispose to HPA axis suppression include the use of high-potency steroids, large treatment surface areas, prolonged use, use of occlusive dressings, altered skin barrier, liver failure, and young age.

Evaluation for HPA axis suppression may be done by using the adrenocorticotropic hormone (ACTH) stimulation test.

In a study including (b) (4) 48 evaluable subjects 18 years of age or older with moderate to severe plaque psoriasis (b) (4) abnormal ACTH stimulation test results suggestive of adrenal suppression were identified in 5 out of 24 (20.8%) subjects after treatment with SERNIVO Spray twice daily for 15 days (b) (4) . No subject (0 out of 24) had abnormal ACTH stimulation test results after treatment with SERNIVO Spray twice daily for 29 days.

If HPA axis suppression is documented, gradually withdraw the drug, reduce the frequency of application, or substitute with a less potent corticosteroid. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Cushing's syndrome and hyperglycemia may also occur with topical corticosteroids. These events are rare and generally occur after prolonged exposure to excessively large doses, especially of high-potency topical corticosteroids.

Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios. *[see Use in Specific Populations (8.4)]*

12.1 Mechanism of Action

Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action of SERNIVO Spray in psoriasis is unknown.

12.2 Pharmacodynamics

Vasoconstrictor studies performed with SERNIVO Spray in healthy subjects indicate that it is in the (b) (4) range (b) (4) of potency as compared with other topical corticosteroids; however, similar blanching scores do not necessarily imply therapeutic equivalence.

The potential for HPA axis suppression was evaluated in a study of (b) (4) 52 adult subjects with moderate to severe plaque psoriasis (b) (4) . SERNIVO Spray was applied twice daily for 15 or 29 days (b) (4)

[redacted]. The subjects had psoriasis involving a mean of 29.0% and 26.5% body surface area at baseline across the 2 treatment duration arms, respectively. [redacted] Forty eight ([redacted]48) subjects were evaluated for HPA axis suppression at end of treatment. The proportion of subjects demonstrating HPA axis suppression was 20.8% (5 out of 24) in subjects treated with SERNIVO Spray for 15 days [redacted] No subjects (0 out of 24) treated with SERNIVO Spray for 29 days had HPA axis suppression. In this study HPA axis suppression was defined as serum cortisol level ≤18 mcg/dL 30-minutes post-cosyntropin stimulation. In the [redacted]4 subjects with available follow-up values, all subjects had normal ACTH stimulation tests at follow-up.

12.3 Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids can be absorbed through normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption. [redacted]

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 HPA axis suppression trial in [redacted] subjects with psoriasis [*see Clinical Pharmacology (12.2)*]. 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 the majority of subjects (Table 2). There was high variability in the data but there was a trend toward higher systemic exposure at day 15 and lower systemic exposure at day 29.

Table 2: Mean (±SD) Maximum Plasma Concentrations (pg/mL) of Betamethasone Dipropionate Metabolites after 15 or 29 Days of Treatment with SERNIVO Spray [redacted]

Analyte (pg/mL)	SERNIVO Spray *b.i.d.* (15 days)	SERNIVO Spray *b.i.d.* (29 days)	[redacted]
Betamethasone-17-propionate	120 ± 12765 [redacted])	63.9 ± 52 [redacted]	[redacted]

Analyte (pg/mL)	SERNIVO Spray *b.i.d.* (15 days)	SERNIVO Spray *b.i.d.* (29 days)	(b) (4)
Betamethasone	119 ± 176 (b) (4)	57.6 ± 55. (b) (4)	(b) (4)
(b) (4)			

4 Appendix

4.1 Individual Study Reviews

Trial BDS1307

Title:
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.

Studied period:
Date first subject randomized: 14 March 2014
Date last subject exited: 04 November 2014

Objectives:
- To evaluate the potential of Betamethasone Dipropionate Spray, 0.05% to suppress the hypothalamic-pituitary-adrenal (HPA) axis when applied twice daily for 15 days or when applied twice daily for 29 days, as compared to Diprolene (augmented betamethasone dipropionate) Lotion, 0.05%, when applied twice daily for 15 days, in subjects with moderate to severe plaque psoriasis under maximal use conditions with the final-to-be-marketed formulation.
- To compare the plasma concentrations of betamethasone dipropionate and its metabolites after multiple uses of Diprolene (augmented betamethasone dipropionate) Lotion, 0.05% to Betamethasone Dipropionate Spray, 0.05% under maximal use condition with the final-to-be- marketed formulation.

Methods:
This was a 15- or 29-day, randomized, multicenter, multi-dose, comparator-controlled, open-label study. Subjects, who were at least 18 years old, with moderate to severe plaque psoriasis, were randomized to treatment with either Betamethasone Dipropionate Spray, 0.05% 15-day treatment, Betamethasone Dipropionate Spray, 0.05% 29-day treatment, or Diprolene Lotion 15-day treatment in a 1:1:1 ratio. These investigational products were applied twice daily to all affected areas on the body excluding face, scalp, groin, axillae, and other intertriginous areas. Subjects were to have 20 to 50% body surface area (BSA) treated to achieve maximal use exposure.

Subject visits took place at Screening, Baseline (Day 1), Day 8, Day 15, Day 29 (as appropriate), and Day 43 or 57 (if needed to confirm recovery). Clinical determinations of disease severity were conducted using the Investigator's Global Assessment (IGA) for overall severity at each visit. Subjects were tested for HPA axis function using the adrenocorticotropin (ACTH) stimulation test (cosyntropin i.v. or i.m. injection) at the Screening Visit (at least 14 days and no more than 28 days prior to Baseline) and at the End of Treatment Visit (i.e., Day 15 for the two 15-day treatment arms or Day 29 for the

29-day treatment arm). If HPA axis was suppressed at the End of Treatment Visit, another test was administered 28 days later (at Day 43 or 57 as appropriate) to confirm recovery. The ACTH stimulation test was repeated every 28 days until recovery was confirmed (or until the cause of suppression was diagnosed).

At the time of the screening ACTH stimulation test, a PK blood sample was taken to obtain a baseline value (PK screening sample). At the End of Treatment Visit, subjects applied the last dose of study product at the clinic up to 60 minutes after a pre-treatment PK blood sample was taken (0 hour – End of Treatment Visit). PK blood samples were then collected at 1, 3, and 6 hours (± 5 minutes) after application of the study product.

Local cutaneous safety evaluations (including atrophy, telangiectasia, pruritus, pain, and burning/stinging) were performed at each visit. Other safety assessments included vital signs (blood pressure, pulse), urine pregnancy tests, and collection of adverse event (AE) data.

Main inclusion criteria:
This study included subjects who were male or female, 18 years of age or older, in good general health, with a clinical diagnosis of stable (at least three months) plaque-type psoriasis involving 20 to 50% BSA, not including the face, scalp, groin, axillae, and other intertriginous areas, and an IGA Grade of at least 3 (moderate) at the Baseline Visit.

Test product and dose:
Test Article: Betamethasone Dipropionate Spray, 0.05%, Batches FDP-C and GBB-C.

Administration: The investigational product was applied topically to all affected areas (i.e., those areas that were affected at Baseline, even if resolved, and new lesions that developed at any time during the treatment period) twice daily, approximately 12 hours apart. The target dose was 5 to 7 g per day (15 to 20 pumps, twice daily). Product was not to be applied to face, scalp, groin, axillae, or other intertriginous areas. Subjects treated affected areas for either 15 days or 29 days. The total study duration was 15 or 29 days plus any wash-out period. Some subjects may have needed to return for a follow-up visit at Day 43 or 57.

Reference product and dose:
Reference Therapy: Diprolene Lotion (augmented betamethasone dipropionate) 0.05%, Batch 3-EAW-01V.

Administration: The control product was applied the same way as the investigational product. Subjects treated affected areas for 15 days.

Pharmacokinetic assessment:
Plasma concentrations of betamethasone dipropionate and its metabolites, betamethasone-17-propionate and betamethasone, were assessed. Maximum (Cmax) and average concentrations post-treatment are presented.

A screening PK blood sample was taken at the time of the screening ACTH stimulation test to obtain a baseline value.

At the End of Treatment Visit, subjects applied the last dose of study product at the clinic up to 60 minutes after a pre-treatment PK blood sample was taken (0 hour – End of Treatment Visit). PK blood samples were then collected at 1, 3, and 6 hours (± 5 minutes) after application of the study product.

Blood (approximately 10 mL) was collected in NaF/Na2EDTA blood collection tubes at each timepoint. Approximately a total of 50 mL of blood per subject was drawn for drug assays during the study.

HPA assessment:
The primary safety variable is the proportion of subjects with abnormal cortisol response for ACTH stimulation test at the end of treatment (cortisol level ≤18 µg/dL at 30 minutes post stimulation). Subjects were tested for HPA axis function using the ACTH stimulation test (cosyntropin i.v. or i.m. injection) at a Screening Visit and at the End of Treatment Visit. If HPA axis was suppressed at the end of treatment, another test was administered at Day 43 or 57, as appropriate, to confirm recovery. The ACTH stimulation test was repeated until recovery or until the cause of suppression was diagnosed. The test was conducted between the hours of 7:00 and 9:30 AM. The End of Treatment test was performed within 1 hour of the time when the Screening Visit test was performed. A normal response was defined as a serum cortisol level of >18 µg/dL at 30 minutes post stimulation. An abnormal response at end of treatment was to be recorded as an AE.

Bioanalytical assay:
See section 2.6 of this review.

Results:

Demographic:
Demographic characteristics were comparable across the treatment groups. Subjects were 20 to 72 years old, with a median age of 47.5 to 52 years across the treatment groups. Most subjects (64.0% to 77.8%) were male in each treatment group, and 48.0% to 68.2% of subjects were Hispanic or Latino. Most subjects (80.0% to 90.9% across the treatment groups) were White. Demographic information is summarized in Table 9 below.

Table 9: Summary of subject demographic (safety population) (Source: study report Table 9)

	Diprolene Lotion 15 Days (N=22)	Betamethasone Dipropionate Spray 15 Days (N=25)	Betamethasone Dipropionate Spray 29 Days (N=27)
Age (years)			
N	22	25	27
Mean	45.4	47.6	46.8
SD	11.32	13.71	9.99
Median	47.5	52.0	48.0
Min. to Max.	20 to 59	20 to 72	26 to 68
Sex			
N	22	25	27
Male	16 (72.7%)	16 (64.0%)	21 (77.8%)
Female	6 (27.3%)	9 (36.0%)	6 (22.2%)
Ethnicity			
N	22	25	27
Hispanic or Latino	15 (68.2%)	12 (48.0%)	17 (63.0%)
Not Hispanic or Latino	7 (31.8%)	13 (52.0%)	10 (37.0%)
Not Reported	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)
Race			
N	22	25	27
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	1 (4.5%)	2 (8.0%)	1 (3.7%)
Black or African American	1 (4.5%)	3 (12.0%)	2 (7.4%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
White	20 (90.9%)	20 (80.0%)	24 (88.9%)
Other[a]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Multiple[a]	0 (0.0%)	0 (0.0%)	0 (0.0%)

[a] See Listing 16.2.4.1 for a complete list of all other/multiple races.

Baseline disease characteristics were similar across the treatment groups (Table 10). The BSA affected by psoriasis ranged between 20% and 50%, with a median of 22% to 25.5% across the treatment groups. Most subjects had psoriasis of moderate severity. All subjects had normal ACTH stimulation test results at Screening.

Table 10: Subject baseline characteristics (safety population) (Source: study report Table 10)

	Diprolene Lotion 15 Days (N=22)	Betamethasone Dipropionate Spray 15 Days (N=25)	Betamethasone Dipropionate Spray 29 Days (N=27)
Percent body surface area affected			
N	22	25	27
Mean	26.8	29.0	26.5
SD	6.32	11.04	8.61
Median	25.5	24.0	22.0
Min. to Max.	20 to 40	20 to 50	20 to 50
Investigator's Global Assessment			
N	22	25	27
None	0 (0.0%)	0 (0.0%)	0 (0.0%)
Minimal or almost clear	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	21 (95.5%)	22 (88.0%)	20 (74.1%)
Severe/very severe	1 (4.5%)	3 (12.0%)	7 (25.9%)
ACTH Stimulation Test (Screening)			
N	22	25	27
Normal	22 (100.0%)	25 (100.0%)	27 (100.0%)
Abnormal[a]	0 (0.0%)	0 (0.0%)	0 (0.0%)

[a] Abnormal is defined as a plasma cortisol level less than or equal to 18 (µg/dL) 30 minutes after ACTH administration.

Dosing:

A summary of number of application and amount applied is shown in Table 11. The median total amount of drug used during the entire study was greater in the Betamethasone Dipropionate Spray 15-day group (132.15 g) compared with the Diprolene Lotion 15-day group (98.30 g); and was the greatest in the Betamethasone Dipropionate Spray 29-day group (178.55 g). The median amount of study drug used for the final application (on the day of the PK sampling) was greater in the Betamethasone Dipropionate Spray 15-day and 29-day groups (5.05 and 5.85 mg, respectively) than in the Diprolene Lotion 15-day group (3.9 mg).

Table 11: Summary of drug application

	Diprolene Lotion 15 Days (N=22)	Betamethasone Dipropionate Spray 15 Days (N=25)	Betamethasone Dipropionate Spray 29 Days (N=27)
Number of Applications			
N	22	24	26
Mean	28.8	29.6	56.2
SD	3.59	2.64	5.39
Median	29.0	29.0	57.0
Min. to Max.	17 to 33	23 to 34	39 to 69
Amount of Drug Used for Final Application (g)			
N	19	22	24
Mean	4.02	6.82	7.08
SD	1.940	3.957	4.491
Median	3.90	5.05	5.85
Min. to Max.	1.5 to 7.1	2.8 to 17.0	0.6 to 19.2
Total Amount of Drug Used (g)			
N	20	22	24
Mean	102.63	129.66	238.22
SD	40.358	58.570	155.522
Median	98.30	132.15	178.55
Min. to Max.	44.2 to 212.6	30.4 to 230.2	87.8 to 805.3

SOURCE: Table 14.3.0.1

PK:

The majority of subjects in all groups had no measurable plasma concentration (< 5.00 pg/mL) of betamethasone-17,21-dipropionate at almost all time points just before and after the last application of study product at End of Treatment (Table 12). However, the metabolites, betamethasone-17-propionate (Table 13) and betamethasone (Table 14), were detected in the majority of subjects. Therefore, the bioavailability analysis will focus on the metabolite concentrations.

Among subjects with measurable concentrations of betamethasone-17- propionate, the mean concentrations just before the last dose (0 hour) in the Diprolene Lotion 15-day group (100 pg/mL) and the Betamethasone Dipropionate Spray 15-day group (117 pg/mL) were approximately twice the concentration seen in the Betamethasone Dipropionate Spray 29-day group (48 pg/mL). A similar trend was seen for the mean of the average of the 1-, 3-, and 6-hour plasma concentrations and the mean Cmax. Results were similar for the other metabolite, betamethasone. A similar observation is made for Cmax (the maximum concentration among the 1, 3, and 6 hours concentration values).

The mean concentration at 0 hour was similar to the mean concentrations at 1, 3, and 6 hours after application of the last dose and similar to the mean Cmax for both metabolites. In addition, the metabolites' concentrations were lower on Day 29 compared to Day 15 (cross cohort comparison). These results suggest that steady-state was achieved by Day 15.

Table 12: Summary of Betamethasone-17,21-Dipropionate (pg/mL) Concentrations (Safety Population - Subjects with Data)

Betamethasone-17, 21-Dipropionate (pg/mL)	After Last Application at End of Treatment					
	0 Hour	1 Hour	3 Hours	6 Hours	Average [a]	C_{max} [b]
Diprolene Lotion 15 Days						
N with data	0	3	3	2	6	6
Mean		18.710	27.713	6.915	20.008	21.928
SD		6.4853	14.2643	1.8173	12.8695	12.4471
Median		20.390	23.680	6.915	16.528	22.035
Min.		11.55	15.90	5.63	8.20	8.20
Max.		24.19	43.56	8.20	43.56	43.56
95% LCL		2.600	0	0	6.502	8.866
95% UCL		34.820	63.148	23.242	33.513	34.991
Betamethasone Dipropionate Spray 15 Days						
N with data	7	3	6	5	11	11
Mean	9.190	10.623	15.035	11.766	12.577	14.050
SD	2.8253	2.6676	11.5147	10.4232	8.6960	10.1623
Median	8.950	9.340	10.730	5.570	9.340	9.340
Min.	5.36	8.84	5.84	5.52	5.54	5.54
Max.	14.31	13.69	33.74	29.59	33.74	33.74
95% LCL	6.577	3.997	2.951	0	6.735	7.223
95% UCL	11.803	17.250	27.119	24.708	18.419	20.877
Betamethasone Dipropionate Spray 29 Days						
N with data	6	5	9	5	15	15
Mean	44.495	259.680	30.361	14.558	64.024	101.521
SD	71.2839	496.2318	28.2595	5.8484	152.6779	290.0495
Median	13.645	18.500	17.680	15.990	15.750	15.750
Min.	5.56	15.68	5.13	8.45	5.13	5.13
Max.	187.65	1144.80	77.68	21.18	606.63	1144.80
95% LCL [c]	0	0	8.639	7.296	0	0
95% UCL [d]	119.303	875.833	52.083	21.820	148.574	262.145

[a] Average concentration of 1, 3, and 6 hours after last application.
[b] C_{max} is the maximum concentration of 1, 3, and 6 hours concentration values.
[c] LCL = lower confidence limit
[d] UCL = upper confidence limit
Note: Plasma concentrations from samples taken more than 1 hour off-schedule are not included.
Lower confidence limits less than zero are set to zero for the table presentation.
SOURCE: Table 14.3.1.1.4

Table 13: Summary of Betamethasone-17-propionate (pg/mL) Concentrations (Safety Population – Subjects with Data)

Betamethasone-17-Propionate (pg/mL)	After Last Application at End of Treatment					
	0 Hour	1 Hour	3 Hours	6 Hours	Average [a]	C_{max} [b]
Diprolene Lotion 15 Days						
N with data	16	18	18	18	18	18
Mean	100.000	92.683	101.331	110.838	101.617	121.942
SD	77.7100	73.1720	84.3467	101.3533	82.1375	106.1138
Median	78.580	83.000	83.480	80.420	87.457	92.825
Min.	13.31	6.46	6.32	8.06	6.95	8.06
Max.	327.97	295.79	339.08	404.25	307.12	404.25
95% LCL	58.591	56.295	59.387	60.436	60.771	69.173
95% UCL	141.409	129.070	143.276	161.240	142.463	174.711
Betamethasone Dipropionate Spray 15 Days						
N with data	22	21	23	23	23	23
Mean	117.235	94.996	104.014	100.013	101.558	119.930
SD	149.3787	99.7246	119.6918	108.6101	109.8296	126.9911
Median	45.650	50.230	56.350	50.630	52.020	64.940
Min.	5.16	16.43	6.75	8.58	7.67	8.58
Max.	600.52	395.46	490.16	388.29	424.64	490.16
95% LCL	51.004	49.602	52.256	53.046	54.065	65.015
95% UCL	183.465	140.390	155.773	146.979	149.052	174.845
Betamethasone Dipropionate Spray 29 Days						
N with data	24	24	24	24	24	24
Mean	47.781	49.468	56.014	59.627	55.036	63.892
SD	42.8104	47.5930	53.5698	50.8340	50.0467	52.6058
Median	32.165	34.975	35.040	43.405	41.033	52.180
Min.	8.70	7.38	10.20	9.33	9.94	10.29
Max.	172.43	204.34	224.85	205.16	211.45	224.85
95% LCL [c]	29.704	29.371	33.393	38.162	33.903	41.678
95% UCL [d]	65.859	69.565	78.634	81.092	76.169	86.105

[a] Average concentration of 1, 3, and 6 hours after last application.
[b] C_{max} is the maximum concentration of 1, 3, and 6 hours concentration values.
[c] LCL = lower confidence limit
[d] UCL = upper confidence limit
Note: Plasma concentrations from samples taken more than 1 hour off-schedule are not included.
Lower confidence limits less than zero are set to zero for the table presentation.
SOURCE: Table 14.3.1.1.4

Table 14: Summary of Betamethasone (pg/mL) Concentrations (Safety Population – Subjects with Data)

Betamethasone (pg/mL)	After Last Application at End of Treatment					
	0 Hour	1 Hour	3 Hours	6 Hours	Average [a]	C_{max} [b]
Diprolene Lotion 15 Days						
N with data	16	17	18	18	18	18
Mean	109.841	114.794	106.229	102.509	105.822	112.649
SD	83.3514	85.7231	85.3474	87.2076	86.1742	92.3796
Median	97.925	93.480	93.705	81.170	88.580	93.705
Min.	8.22	9.56	5.62	5.59	5.61	5.62
Max.	253.83	265.76	274.56	286.73	275.68	286.73
95% LCL	65.426	70.719	63.787	59.142	62.969	66.710
95% UCL	154.256	158.868	148.672	145.876	148.675	158.589
Betamethasone Dipropionate Spray 15 Days						
N with data	21	21	22	23	24	24
Mean	118.806	117.836	118.659	111.232	111.112	118.969
SD	186.8859	180.2183	163.0590	167.2217	165.6113	176.3710
Median	54.350	54.510	52.925	49.670	51.703	53.730
Min.	11.71	11.46	5.06	5.19	5.06	5.06
Max.	788.01	760.88	666.85	709.64	712.46	760.88
95% LCL	33.737	35.801	46.362	38.920	41.181	44.494
95% UCL	203.876	199.870	190.955	183.544	181.044	193.444
Betamethasone Dipropionate Spray 29 Days						
N with data	24	23	24	24	24	24
Mean	53.174	57.305	54.698	53.118	54.366	57.649
SD	52.9972	55.4209	52.6565	51.9005	53.0796	55.8650
Median	40.555	43.100	42.150	39.045	40.852	42.150
Min.	5.71	6.78	7.36	10.05	8.49	10.05
Max.	206.93	222.98	202.39	216.05	213.81	222.98
95% LCL [c]	30.795	33.339	32.463	31.202	31.952	34.059
95% UCL [d]	75.552	81.271	76.932	75.034	76.779	81.239

[a] Average concentration of 1, 3, and 6 hours after last application.
[b] C_{max} is the maximum concentration of 1, 3, and 6 hours concentration values.
Note: Plasma concentrations from samples taken more than 1 hour off-schedule are not included.
[c] LCL = lower confidence limit
[d] UCL = upper confidence limit
Lower confidence limits less than zero are set to zero for the table presentation.
SOURCE: Table 14.3.1.1.4

HPA axis suppression:

A similar percentage of subjects in the Diprolene Lotion 15-day and Betamethasone Dipropionate Spray 15-day groups had an abnormal ACTH stimulation test result at the end of treatment suggestive of adrenal suppression, whereas no subjects in the Betamethasone Dipropionate Spray 29-day group had an abnormal ACTH stimulation test result suggestive of adrenal suppression (Table 15). A few subjects had missing end of treatment ACTH test results in each group, and the incidence of abnormal results was calculated based on the population of subjects with data.

Table 15: Summary of ACTH Stimulation Test at End of Treatment (Safety Population – Subjects with data)

	Diprolene Lotion 15 Days (N=20)	Betamethasone Dipropionate Spray 15 Days (N=24)	Betamethasone Dipropionate Spray 29 Days (N=24)
ACTH Stimulation Test Results			
Normal	15 (75.0%)	19 (79.2%)	24 (100.0%)
Abnormal [a]	5 (25.0%)	5 (20.8%)	0 (0.0%)

[a] Abnormal is defined as a plasma cortisol level less than or equal to 18 µg/dL 30 minutes after ACTH administration.

Seven of 10 subjects with abnormal ACTH stimulation test at end of treatment returned for follow up testing. For these 7 subjects (3 subjects in the Diprolene Lotion 15-day group and 4 subjects in the Betamethasone Dipropionate Spray 15-day group, and including Subject 302003), all had normal ACTH stimulation tests at follow-up.

Efficacy and other safety assessments:
Please see Clinical review.

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/s/

DOANH C TRAN
12/08/2015

EDWARD D BASHAW
12/08/2015

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208079	**SDN**	1
Applicant	Promius Pharma	**Submission Date**	4/6/2015
Generic Name	Betamethasone dipropionate spray, 0.05%	**Brand Name**	Sernivo
Drug Class	Topical corticosteroid		
Indication	Topical treatment of moderate plaque psoriasis in patients 18 years of age or older		
Dosage Regimen	Shake well and apply spray to the affected skin areas twice daily. Rub in gently.		
Dosage Form	Topical spray	**Route of Administration**	Topical
OCP Division	Division of Clinical Pharmacology 3	**OND Division**	Division of Dermatology and Dental Products

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Doanh Tran, Ph.D	Capt. E. Dennis Bashaw, Pharm. D.
Pharmacometrics		
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	6/5/2015	**74-Day Letter Date**	6/19/2015
Review Due Date	12/7/2015	**PDUFA Goal Date**	2/6/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☑ Yes

☐ No

If yes list comment(s)

Please see comments for applicant at end of filing memorandum.

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		

☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☑ Multiple Dose	1	HPA/PK Study BDS1307
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☑ Healthy Subjects		3	Vasoconstrictor assay studies BDS1103, BDS1204, and DFD01-CD-009
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**	0	**In Vivo**	4
Total Number of Studies to be Reviewed		0		4

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memorandum

Clinical Pharmacology Review

NDA: **208079**
Compound: Betamethasone dipropionate spray, 0.05% w/w (based on betamethasone)
Applicant: Promius Pharma, LLC

Date: 4/29/2015
Reviewer: **Doanh Tran**

Background:
The applicant has developed a new formulation of betamethasone dipropionate, Betamethasone Dipropionate Spray, 0.05%, for the topical treatment of moderate plaque psoriasis. Betamethasone dipropionate is a synthetic, fluorinated corticosteroid. Betamethasone Dipropionate Spray contains 0.05% betamethasone dipropionate (potency expressed as betamethasone) in a spray formulation. The spray is to be applied to affected areas twice daily for up to 4 weeks. Betamethasone dipropionate at the same 0.05% strength is commercially available as cream, ointment, and lotion formulations.

The clinical study data for Betamethasone Dipropionate Spray, 0.05% consist of ten clinical studies with Betamethasone Dipropionate Spray, 0.05%: seven Phase 1 studies (three vasoconstrictor assay studies and four safety studies of cumulative irritation, phototoxicity, photoallergy and sensitization), a Phase 2 HPA axis suppression and systemic absorption study and two Phase 3 double-blind studies demonstrating safety and efficacy in subjects with moderate plaque psoriasis. The reference listed drug, Diprolene Lotion, 0.05%, was included for comparison in the Phase 1 studies, the Phase 2 HPA axis suppression study 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.

Bioavailability:
The systemic exposure of Betamethasone Dipropionate Spray, 0.05% and Diprolene Lotion, 0.05% were compared using hypothalamic-pituitary-adrenal (HPA) axis suppression as a surrogate endpoint and sparse pharmacokinetic sampling (1, 3 and 6 hours after application) (Study BDS1307). Plasma cortisol was determined before and after adrenocorticotropic hormone (ACTH) stimulation in subjects with moderate to severe psoriasis treated twice daily with Betamethasone Dipropionate Spray, 0.05% (for 15 or 29 days) or Diprolene Lotion, 0.05% (15 days).

The incidence of HPA axis suppression was similar between the Betamethasone Dipropionate Spray, 0.05% 15-day and Diprolene Lotion, 0.05% 15-day groups at 20.8% and 25.0%, respectively (Table 2.5.3.2). HPA axis suppression was not observed in the Betamethasone Dipropionate Spray, 0.05% 29-day group.

The majority of subjects in all groups had no measurable plasma concentration (<5.00 pg/mL) of

betamethasone dipropionate at almost all time points just before and after the last application of study product at End of Treatment. In contrast, betamethasone dipropionate metabolites (betamethasone-17-propionate and betamethasone) were detected in the majority of subjects. Subjects in the Betamethasone Dipropionate Spray, 0.05% 29-day group had lower median Cmax for betamethasone-17-propionate and betamethasone plasma concentrations when compared with values at Day 15 in the Betamethasone Dipropionate, 0.05% and Diprolene Lotion treatment groups.

Table 1: Maximum Plasma Concentrations (pg/mL) of Betamethasone Dipropionate Metabolites after 15 or 29 Days of Treatment with Betamethasone Dipropionate Spray, 0.05% or 15 Days of Treatment with Diprolene Lotion, 0.05%

Analyte	**Betamethasone Dipropionate Spray, 0.05% *b.i.d.* (15 days)**	**Betamethasone Dipropionate Spray, 0.05% *b.i.d.* (29 days)**	**Diprolene Lotion, 0.05% *b.i.d.* (15 days)**
Betamethasone-17-propionate	65 (9, 490)	52 (10, 225)	93 (8, 404)
Betamethasone	54 (5, 761)	42 (10, 223)	94 (6, 287)

Data represent median of maximum plasma concentrations (C_{max}) (minimum, maximum)

Vasoconstrictor assay studies:
The corticosteroid potency of Betamethasone Dipropionate Spray, 0.05% was compared to the listed drug, Diprolene Lotion, 0.05% and other corticosteroids of known potency in three studies using the vasoconstrictor method (Studies BDS1103, BDS1204, DFD01-CD-009). Study BDS1103 was a pilot trial that suggested the to-be-marketed formulation was ranked as high to mid-potent. Follow up study BDS1204 to confirm potency did not show consistent results with the pilot trial and ranked it as low to mid-potent. A third study (study DFD01-CD-009) was conducted in a larger number of subjects to resolve the discrepancy. The results indicated it was a mid- to upper mid-potent corticosteroid, consistent with the pilot study.

The three vasoconstrictor studies sponsored by Promius all demonstrated that Betamethasone Dipropionate Spray, 0.05% is of lower potency compared to the listed drug, Diprolene (augmented betamethasone dipropionate) Lotion, 0.05%.

Pediatrics:
An agreed iPSP is available (dated 12/4/2014). The applicant plans to conduct a PK/HPA trial in adolescent subjects age 12 - <17 years.

Clinical vs. to-be-marketed formulation:
The applicant stated that all pivotal clinical trials were conducted with the final to-be-marketed Betamethasone Dipropionate Spray, 0.05% formulation (formulation F10), including the two Phase 3 studies, the HPA axis suppression study with pharmacokinetic sampling, and the Phase 1 vasoconstrictor and dermal safety studies.

Method validation:

Method validation reports and bioanalytical reports for plasma betamethasone dipropionate, betamethasone, betamethasone-17-propionate, and cortisol are available for review. For betamethasone dipropionate, betamethasone, and betamethasone-17-propionate, the bioanalytical reports indicate duration of storage was within the established storage stability. For cortisol, no information on duration of storage or storage stability was provided. A request will be made for this information for trial BDS1307.

Recommendation:
The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 208079 is fileable.

Comments for sponsor:
For the analysis of plasma cortisol in trial BDS1307, provide the duration and conditions of sample storage from collection to time of sample analysis. Provide storage stability data to support the duration and storage temperature of all samples in this trial.

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

/s/

DOANH C TRAN
05/14/2015

EDWARD D BASHAW
05/14/2015