CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	208079 / 000
Drug Name:	Sernivo (betamethasone dipropionate) spray, 0.05%
Indication(s):	Psoriasis
Applicant:	Promius
Dates:	Submitted: 4/6/2015 PDUFA: 2/6/2016
Review Priority:	Standard review
Biometrics Division:	Division of Biometrics III
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Keywords: Psoriasis, 505(b)(2), secondary endpoints

Table of Contents

1 Executive Summary

Betamethasone dipropionate spray, 0.05% was superior to vehicle spray in the treatment of psoriasis in two studies. Studies 1205 and 1206 enrolled subjects age 18 and older with stable plaque psoriasis involving 10-20% body surface area not including the face, scalp, groin, axillae, and other intertriginous areas, and an investigator's global assessment (IGA) of 'moderate'. Subjects applied treatment twice daily for 28 days. One of the studies also included a treatment arm for the listed drug of this 505(b)(2) application, betamethasone lotion, and a treatment arm for vehicle lotion. Subjects on the betamethasone lotion arm applied betamethasone lotion for 14 days followed by vehicle lotion for 14 days, because betamethasone lotion is only labeled for 14 days use.

Both studies had statistically significant results for the primary efficacy endpoint of treatment success (clear or almost clear (0 or 1) on the IGA with at least 2 grades reduction from baseline) at Day 15 for betamethasone spray versus vehicle spray ($p \leq 0.002$). The secondary endpoints were assessed in sequential order. The first ranked secondary endpoint of treatment success at Day 29 was also statistically significant in both studies ($p < 0.001$). Thus, efficacy has been established for treatment success at Days 15 and 29. However, the second ranked secondary endpoint of treatment success at Day 8 was significant in Study 1205 ($p=0.003$), but was not significant in Study 1206 ($p=0.156$). Consequently the final ranked secondary endpoint of at least a 50% reduction in the total symptom score at Day 4 was not evaluated in Study 1206. The secondary assessments at Days 8 and 4 were only statistically significant in one of the studies, and thus efficacy has not been established for these endpoints. See Table 1.

Table 1 – Efficacy Results in Studies 1205 and 1206

	Study 1205				Study 1206	
Primary	Beta Spray N=174	Vehicle Spray N=87	Beta / Veh Lotion N=90	Vehicle Lotion N=43	Beta Spray N=182	Vehicle Spray N=95
Trt Succ. at Day 15	19.0%	2.3%	18.9%	9.3%	21.5%	7.4%
	p<0.001				p=0.002	
Secondary						
Trt Succ. at Day 29	34.5%	13.6%	21.1%	9.3%	42.7%	11.7%
	p<0.001				p<0.001	
Trt Succ. at Day 8	10.0%	1.2%	6.7%	2.3%	12.7%	7.4%
	p=0.003				p=0.156	
TSS50 at Day 4	12.1%	2.3%	5.6%	2.3%	14.3%	10.5%
	p=0.004				Not tested	

Note: Secondary endpoints were evaluated in sequential order to control the Type I error.

2 Introduction

2.1 Overview

2.1.1 Clinical Studies

The applicant, Promius, is developing Sernivo (betamethasone dipropionate) spray, 0.05% for the treatment of psoriasis under the 505(b)(2) pathway. The listed drug is Diprolene (augmented betamethasone dipropionate) lotion, 0.05%, which was approved in 1988. Betamethasone spray was evaluated in two Phase 3 trials. One trial was a two-arm trial (betamethasone spray and vehicle spray) and one trial was a four-arm trial (betamethasone spray, vehicle spray, Diprolene lotion, and vehicle lotion). The design details for these two trials are summarized in Table 2. Both trials were conducted in the U.S.

Table 2 – Clinical Studies Overview

Study Numbers	1205 and 1206				
Study Design	Study 1205 (4-arm): betamethasone spray vs. vehicle spray vs. betamethasone lotion vs. vehicle lotion Study 1206 (2-arm): betamethasone spray vs. vehicle spray				
Inclusion criteria	Age 18 and older with psoriasis (10-20% BSA, moderate on IGA)				
Treatment regimen	Twice daily for 4 weeks (subjects randomized to betamethasone lotion applied betamethasone lotion for 2 weeks and vehicle lotion for 2 weeks)				
Primary endpoint	-Treatment success on the IGA defined as clear or almost clear with at least 2 grades reduction at Day 15				
Secondary endpoints	-Treatment success on the IGA at Day 29 -Treatment success on the IGA at Day 8 -≥50% on the Total Symptom Score (sum of erythema, scaling, and plaque elevation) at Day 4				
Treatment arms and Sample Size		Beta.Spray	Veh. Spray	Beta. Lotion	Veh. Lotion
	Study 1205	174	87	90	43
	Study 1206	182	95	--	--
Study location	US				
Study dates	Study 1205: Nov. 2013 – Jan. 2015 Study 1206: Nov. 2013 – July 2014				

2.1.2 Regulatory History

The IND for betamethasone spray was opened in June 2010 with a Phase 1 vasoconstrictor study. The applicant conducted vasoconstrictor potency studies, an HPA axis suppression and systemic drug absorption study, dermal safety studies, and two Phase 3 studies. The applicant did not conduct any Phase 2 dose ranging studies with betamethasone spray. The following meetings were scheduled with the sponsor:

- Pre-IND Meeting (6/17/2009)
- Guidance (3/16/2011; converted to written responses)
- Pre-NDA (1/12/2015)

Both Phase 3 protocols were submitted to the Agency for review. The applicant's original proposal for Study 1205 was to have (b) (4) . The applicant later revised the protocol to have one primary endpoint of IGA success at Day 15 with assessments of IGA success at Day 29 and 8 as sequentially ordered secondary endpoints. Study 1206 was also subsequently designed to have one primary endpoint of IGA success at Day 15 with assessments of IGA success at Day 29 and 8 as sequentially ordered secondary endpoints. The two studies also included a third secondary endpoint that evaluated a 50% reduction from baseline to Day 4 in the Total Symptom Score (sum of scores for erythema, scaling, and plaque elevation).

2.2 Data Sources

This reviewer evaluated the applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. The submission was submitted in eCTD format and was entirely electronic. Both SDTM and analysis datasets were submitted. The analysis datasets used in this review are archived at \\cdsesub1\evsprod\nda208079\0000\m5\datasets\.

3 Statistical Evaluation

3.1 Data and Analysis Quality

The databases for the studies required minimal data management prior to performing analyses. However, the Agency requested statistical programs for conducting multiple imputation analyses, as the statistical analysis plan did not contain sufficient detail regarding models, transformations, and randomization seeds for these analyses to replicate the analyses without the statistical programs.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Statistical Analysis

Study 1205 was a randomized, double-blind, four-arm study evaluating betamethasone dipropionate spray, vehicle spray, Diprolene (augmented betamethasone dipropionate) lotion, and vehicle lotion in the treatment of psoriasis. Study 1206 was a randomized, double-blind, two-arm study evaluating betamethasone dipropionate spray versus vehicle spray in the treatment of psoriasis. The studies enrolled subjects age 18 and older with stable plaque psoriasis involving 10-20% body surface area (BSA) not including the face, scalp, groin, axillae, and other intertriginous areas, and an investigator's global assessment of moderate. Subjects in Study 1205 were randomized in a 4:2:2:1 ratio to betamethasone spray, vehicle spray, betamethasone lotion, or vehicle lotion, respectively. Subjects in Study 1206 were randomized in a 2:1 ratio to betamethasone spray or vehicle spray. Subjects applied treatment twice daily for 28 days. Subjects randomized to betamethasone lotion applied betamethasone lotion twice daily for 14 days, followed by vehicle lotion twice daily for 14 days, because Diprolene is only labeled for 14 days use. Subjects were evaluated at screening, baseline, Day 4, Day 8, Day 15, and Day 29.

Efficacy was assessed using the Investigator's Global Assessment (IGA) and the Total Sign Score (TSS) for the target lesion. These two scales were defined as follows:

Investigator's Global Assessment (IGA)

Score	Grade	Description
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

Total Sign Score (TSS)

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	Course/thick scale, mostly to completely covering the lesion and a rough surface	Marked elevation with hard, distinct edges

The individual assessments for erythema, scaling, and plaque elevation were summed together to get a total score ranging from 0 to 9.

The primary efficacy endpoint was treatment success at Day 15 where treatment success was defined as clear or almost clear (0 or 1) on the IGA with at least 2 grades reduction

from baseline. The secondary endpoints were treatment success at Day 29, treatment success at Day 8, and at least a 50% reduction in the TSS at Day 4.

Success rates (betamethasone spray vs. vehicle spray) were analyzed with the Cochran-Mantel-Haenszel (CMH) test stratified on analysis center. Multiplicity among the secondary endpoints was controlled by analyzing the three secondary endpoints in sequential order.

The ITT population was defined as all subjects who were randomized and dispensed study product. The per protocol population included subjects who met all inclusion and exclusion criteria, did not take any prohibited medications through Day 15, completed the Day 15 visit within ± 1 day, and was compliant with the dosing regimen through Day 15.

The primary method of handling missing data was multiple imputation using Markov Chain Monte Carlo (MCMC) imputation. For each study, the number of imputations was 5 times the maximum number of missing values from the betamethasone spray and vehicle spray groups. Missing IGA scores were imputed using MCMC and rounded to the nearest integer (0 to 4). For each imputed data set, success rates were analyzed using the CMH test. Before combining the results of the individual analyses, the CMH general association statistic from the *m*th imputation (labeled $cmh^{(m)}$ with df=1 for the binary endpoint) was transformed using the Wilson-Hilferty transformation

$$st_{wh\_cmh}^{(m)} = \frac{\sqrt[3]{\frac{cmh^{(m)}}{df}} - \left(1 - \frac{2}{9 \times df}\right)}{\sqrt[2]{\frac{2}{9 \times df}}}$$

so that the transformed statistic would have an approximately standard normal distribution.

The protocols specified two sensitivity analyses for handling missing data: observed values analyzed using a repeated measures logistic regression, and another multiple imputation analysis using logistic regression for the imputation and analysis model. In the statistical analysis plan, the applicant also stated that an LOCF analysis would be conducted.

Small centers were combined into analysis centers for the analyses. Sites that enrolled fewer than 8 subjects in the betamethasone spray arm and 4 subjects in the vehicle spray arm were pooled. Within such centers, the smallest center was pooled with the largest center. If additional subjects were needed to make the minimum, the next smallest center was also combined. This process was continued until all analysis centers met the minimum enrollment numbers. For testing consistency of response, a logistic regression analysis was conducted on the treatment response rate at Day 15 with terms for treatment, analysis center, and treatment-by-analysis center. If the interaction term is significant at the 0.10 level, then additional assessment will be conducted to identify extreme analysis centers that may impact the results.

3.2.2 Subject Disposition

Study 1205 randomized 394 subjects: 174 to betamethasone spray, 87 to vehicle spray, 90 to betamethasone lotion, and 43 to vehicle lotion. Study 1206 randomized 277 subjects: 182 to betamethasone spray and 95 to vehicle spray. Approximately 4-5% of betamethasone spray subjects discontinued, while 7-8% of vehicle spray subjects discontinued. The most common reason for study discontinuation was lost to follow-up. See Table 3.

Table 3 – Disposition of Subjects in Studies 1205 and 1206

	Study 1205				Study 1206	
	Beta. Spray	Veh. Spray	Beta. Lotion	Veh. Lotion	Beta. Spray	Veh. Spray
Subjects Randomized	174	87	90	43	182	87
Discontinued	8 (5%)	6 (7%)	2 (2%)	5 (12%)	8 (4%)	8 (8%)
Adverse event (related)	--	1 (1%)	--	2 (5%)	1 (<1%)	1 (1%)
Adverse event (not related)	--	--	--	--	1 (<1%)	1 (1%)
Lack of efficacy	1 (<1%)	--	--	1 (2%)	--	--
Lost to follow-up	5 (3%)	3 (3%)	1 (1%)	2 (5%)	5 (3%)	2 (2%)
Protocol violation	1 (<1%)	--	--	--	--	--
Withdrawal by subject	1 (<1%)	1 (1%)	1 (1%)	--	1 (<1%)	3 (3%)
Worsening of condition	--	1 (1%)	--	--	--	1 (1%)

Source: pg 42 of bds1205-body.pdf and pg 38 of bds1206-body.pdf.

3.2.3 Baseline Characteristics

Baseline demographics were generally balanced across the treatment groups in the two studies, except that Study 1206 randomized a greater proportion of non-white subjects (particularly those identifying as Asian or 'Other') to the betamethasone spray arm than the vehicle spray arm. The mean age was approximately 50 years, with 13% of subjects age 65 and older. The majority of subjects were male (62%), white (85%), and non-Hispanic (69%). See Table 4.

Table 4 – Demographics in Studies 1205 and 1206

	Study 1205				Study 1206	
	Beta. Spray N=174	Veh. Spray N=87	Beta. Lotion N=90	Veh. Lotion N=43	Beta. Spray N=182	Veh. Spray N=95
Age (years)						
Mean	49.0	50.2	51.0	51.6	50.3	49.9
Range	18-86	20-82	18-78	26-81	19-86	22-78
18 to 64 years	150 (86%)	75 (86%)	79 (88%)	36 (84%)	158 (87%)	84 (88%)
65 + years	24 (14%)	12 (14%)	11 (12%)	7 (16%)	24 (13%)	11 (12%)
Gender						
Female	63 (36%)	36 (41%)	34 (38%)	19 (44%)	68 (37%)	37 (39%)
Male	111 (64%)	51 (59%)	56 (62%)	24 (56%)	114 (63%)	58 (61%)
Race						
White	146 (84%)	76 (87%)	77 (86%)	38 (88%)	147 (81%)	86 (91%)
Black or Afric.-Amer.	14 (8%)	3 (3%)	8 (9%)	3 (7%)	13 (7%)	8 (8%)
Am. Ind./ AK Native	--	2 (2%)	--	--	--	--
Asian	10 (6%)	5 (6%)	4 (4%)	1 (2%)	11 (6%)	--
Native HI/ Pac. Islander	1 (<1%)	--	--	--	1 (<1%)	--
Other	1 (<1%)	1 (1%)	--	1 (2%)	5 (3%)	--
Multiple	2 (1%)	--	1 (1%)	--	5 (3%)	1 (1%)
Ethnicity						
Hispanic or Latino	49 (28%)	28 (32%)	25 (28%)	8 (19%)	55 (30%)	28 (30%)
Not Hispanic or Latino	125 (72%)	59 (68%)	63 (70%)	35 (81%)	119 (65%)	63 (66%)
Not Reported	--	--	--	--	7 (4%)	4 (4%)
Unknown	--	--	2 (2%)	--	1 (<1%)	--

Source: pg 89-90 of bds1205-body.pdf and pg 79-80 of bds1206-body.pdf and reviewer analysis.

To be enrolled in the study, subjects were to have an IGA of moderate, and a percent BSA of 10-20%. All subjects met the IGA and BSA inclusion criteria, and the mean baseline BSA was about 13%. The baseline disease characteristics were balanced across treatment arms. See Table 5.

Table 5 – Baseline Disease Characteristics in Studies 1205 and 1206

	Study 1205				Study 1206	
	Beta. Spray N=174	Veh. Spray N=87	Beta. Lotion N=90	Veh. Lotion N=43	Beta. Spray N=182	Veh. Spray N=95
IGA						
Moderate	174 (100%)	87 (100%)	90 (100%)	43 (100%)	182 (100%)	95 (100%)
Scaling						
Slight/Mild	7 (4%)	1 (1%)	3 (3%)	--	5 (3%)	1 (1%)
Moderate	143 (82%)	73 (84%)	76 (84%)	38 (88%)	139 (76%)	72 (76%)
Severe	24 (14%)	13 (15%)	11 (12%)	5 (12%)	38 (21%)	22 (23%)
Erythema						
Slight/Mild	4 (2%)	2 (2%)	1 (1%)	1 (2%)	4 (2%)	1 (1%)
Moderate	152 (87%)	75 (86%)	76 (84%)	37 (86%)	153 (84%)	81 (85%)
Severe	18 (10%)	10 (12%)	11 (12%)	5 (12%)	25 (14%)	13 (14%)
Plaque Elev.						
Slight/Mild	10 (6%)	4 (5%)	2 (2%)	3 (7%)	8 (4%)	2 (2%)
Moderate	146 (84%)	74 (85%)	80 (89%)	37 (86%)	147 (81%)	78 (82%)
Severe	18 (10%)	9 (10%)	8 (9%)	3 (7%)	27 (15%)	15 (16%)
BSA						
Mean	13.1	13.1	13.6	12.9	13.7	13.4
Std deviation	3.20	3.45	3.39	3.23	3.72	3.49

Source: pg 97-99 of bds1205-body.pdf and pg 87-89 of bds1206-body.pdf.

3.2.4 Efficacy Endpoints

Bethamethasone spray was superior to vehicle spray in both studies on the primary efficacy endpoint of treatment success at Day 15, where treatment success was defined as clear or almost clear (0 or 1) on the IGA with at least 2 grades reduction from baseline. Betamethasone spray was also superior to vehicle spray in both studies of the first ranked secondary efficacy endpoint of treatment success at Day 29. However, the next ranked secondary endpoint of treatment success at Day 8 was only statistically significant in Study 1205, but not Study 1206. The final ranked secondary endpoint of at least a 50% reduction in Total Symptom Score at Day 4 was statistically significant in Study 1205, but was not tested in Study 1206, because sequential testing stopped after treatment success at Day 8 was not statistically significant. Consequently the studies only support efficacy claims based on the primary efficacy endpoint and the first ranked secondary endpoint (treatment success at Days 15 and 29). See Table 6.

Table 6 – Efficacy Results in Study 1205 and 1206

	Study 1205				Study 1206	
Primary	Beta Spray N=174	Vehicle Spray N=87	Beta / Veh Lotion N=90	Vehicle Lotion N=43	Beta Spray N=182	Vehicle Spray N=95
Trt Succ. at Day 15	19.0%	2.3%	18.9%	9.3%	21.5%	7.4%
	p<0.001				p=0.002	
Secondary						
Trt Succ. at Day 29	34.5%	13.6%	21.1%	9.3%	42.7%	11.7%
	p<0.001				p<0.001	
Trt Succ. at Day 8	10.0%	1.2%	6.7%	2.3%	12.7%	7.4%
	p=0.003				p=0.156	
TSS50 at Day 4	12.1%	2.3%	5.6%	2.3%	14.3%	10.5%
	p=0.004				Not tested	

-P-values are for bethamethasone 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 betamethasone spray and vehicle spray and LOCF for betamethasone 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.

Missing data for the betamethasone spray and vehicle spray arms was handled with multiple imputation, using MCMC imputation and the Wilson-Hilferty transformation on the CMH statistic. In the protocol and statistical analysis plan, the sponsor proposed three sensitivity analyses: LOCF, observed values analyzed using a repeated measures logistic regression, and another multiple imputation analysis using logistic regression for the imputation and analysis model. These analyses led to similar conclusions as the primary multiple imputation analysis. See Table 7.

Table 7 – Sensitivity Analyses for Handling Missing Data for Treatment Success at Day 15

	Study 1205		Study 1206	
	Betamethasone Spray N=174	Vehicle Spray N=87	Betamethasone Spray N=182	Vehicle Spray N=95
LOCF	18.4%	2.3%	21.4%	7.4%
	<0.001		0.001	
Repeated measures	20.0%	2.5%	22.7%	9.4%
	<0.001		<0.001	
Logistic regression multiple imputation	19.1%	2.7%	17.8%	5.7%
	<0.001		0.003	

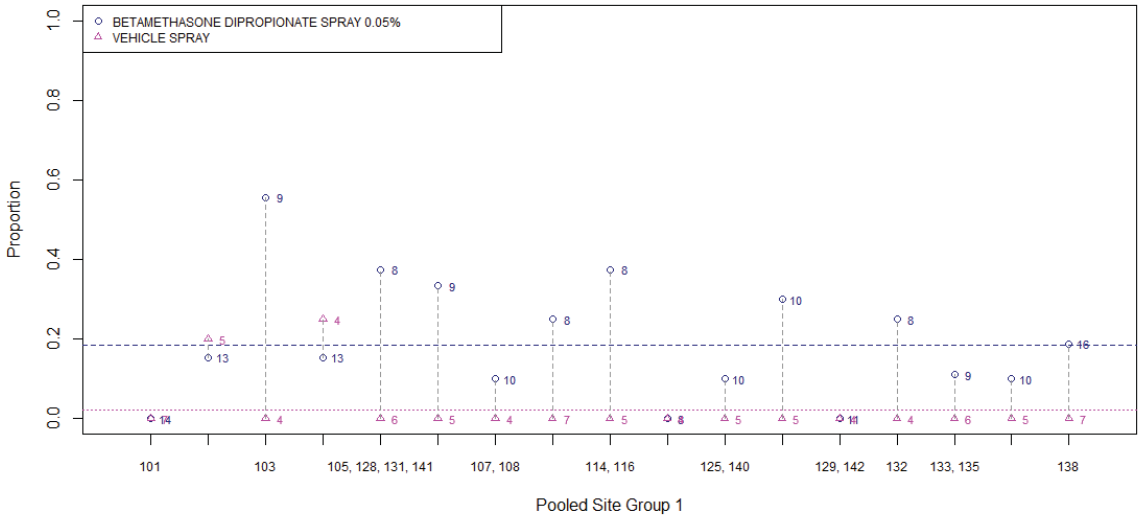
Source: pg 138 of bds1205-body.pdf and pg 122 of bds1206-body.pdf.

3.2.5 Efficacy by Center

Study 1205 was conducted at 39 sites, which were pooled into 17 analysis sites. Study 1206 was conducted at 28 sites, which were pooled into 18 analysis sites. The response rates were somewhat variable but the p-values from an interaction test from a logistic

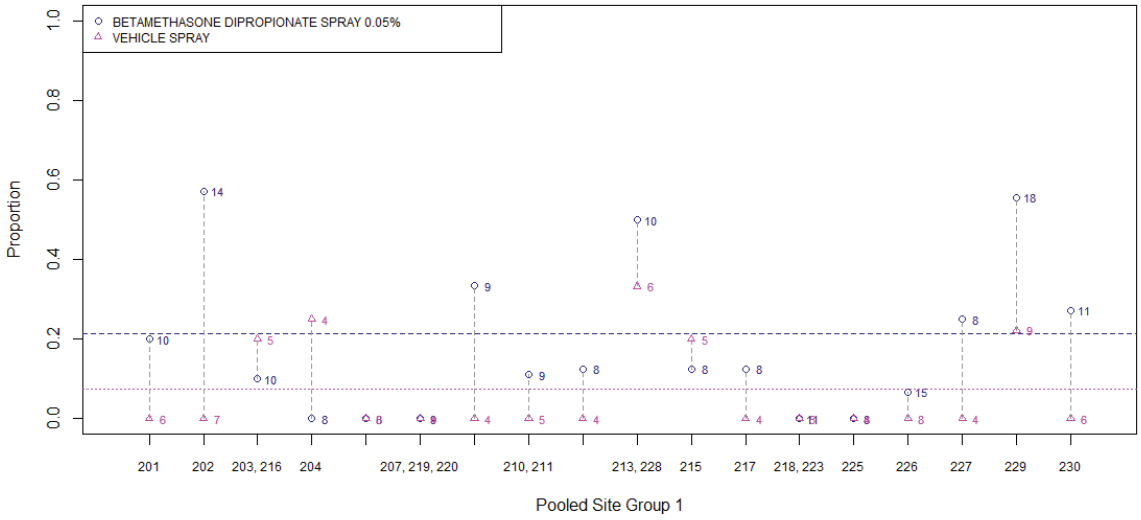
regression model were non-significant in both studies (0.999 for treatment-by-site and 0.984 for treatment-by-analysis center in Study 1205 and 0.986 for treatment-by-site and 0.956 for treatment-by-analysis center in Study 1206). Treatment success rates at Day 15 by analysis center (restricted to the betamethasone spray and vehicle spray arms in Study 1205) are presented in Figure 1 and Figure 2.

Figure 1 – Treatment Success at Day 15 by Analysis Center in Study 1205



Source: reviewer analysis. Numbers represent the sample size on the treatment arm for the analysis center.

Figure 2 – Treatment Success at Day 15 by Analysis Center in Study 1206



Source: reviewer analysis. Numbers represent the sample size on the treatment arm for the analysis center.

3.3 Evaluation of Safety

3.3.1 Extent of Exposure

The treatment regimen was to apply treatment twice a day for 28 days. Subjects randomized to betamethasone lotion were to apply betamethasone lotion twice daily for 14 days followed by vehicle lotion for 14 days. Subjects applied similar number of applications on each arm. During the first two weeks the subjects in the treatment groups applied an average of between 27.2 and 28.5 applications. Similarly, during the second two weeks (when the subjects on the betamethasone lotion arm switched to vehicle lotion), the treatment groups applied an average of between 25.1 and 26.8 applications. See Table 8.

Table 8 – Extent of Exposure in Studies 1205 and 1206 (Safety Population)

	Study 1205				Study 1206	
	Beta. Spray N=173	Veh. Spray N=87	Beta/Veh Lotion N=90	Veh. Lotion N=43	Beta. Spray N=179	Veh. Spray N=93
Number of Applications on Days 1-15	*N=170*	*N=85*	*N=89*	*N=42*	*N=178*	*N=91*
Mean (SD)	27.6	27.5	28.1	27.2	28.5	28.5
Range	14-55	1-34	14-43	15-42	17-55	13-53
Number of Applications on Days 15-29	*N=168*	*N=83*	*N=89*	*N=41*	*N=177*	*N=91*
Mean (SD)	26.7	26.8	26.6	26.1	26.2	25.1
Range	0-39	0-36	0-35	0-40	0-49	0-37

Source: pg 62 of bds1205-body.pdf and pg 58 of bds1206-body.pdf.

3.3.2 Adverse Events

Adverse events were reported by 28% of betamethasone spray subjects in Study 1205 and 17% of betamethasone spray subjects in Study 1206. Administration site conditions were the most commonly reported adverse events. The most common administration site conditions were application site pain and pruritus, which were more common on the vehicle spray arm than the betamethasone spray arm. Table 9 presents the total number of adverse events and the adverse events in the administration site conditions class. The other reported adverse events not included in this table were spread out over the other system organ classes.

Table 9 – Total Adverse Events and Administration Site Conditions (Safety Population)

	Study 1205				Study 1206	
	Beta. Spray N=173	Veh. Spray N=87	Beta/Veh Lotion N=90	Veh. Lotion N=43	Beta. Spray N=179	Veh. Spray N=93
Adverse Events	49 (28%)	20 (23%)	28 (31%)	21 (49%)	31 (17%)	27 (29%)
Administration site conditions						
Pain	18 (10%)	12 (14%)	15 (17%)	10 (23%)	5 (3%)	10 (11%)
Pruritus	15 (9%)	12 (14%)	8 (9%)	14 (33%)	12 (7%)	14 (15%)
Atrophy	4 (2%)	1 (1%)	--	1 (2%)	--	2 (2%)
Telangiectasia	2 (1%)	--	--	--	--	--
Dermatitis	1 (<1%)	--	--	--	--	--
Discoloration	1 (<1%)	--	--	--	--	--
Erosion	1 (<1%)	--	--	--	--	--
Rash	1 (<1%)	--	--	--	--	--
Dryness	--	--	--	--	--	1 (1%)

Source: pg 223, 228-229 of bds1205-body.pdf and pg 137,143 of bds1206-body.pdf.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, Age, and Geographic Region

Treatment effects were generally consistent across age group, gender, and race, although some of the subgroups were small. All subjects were enrolled in the United States. See Table 10.

Table 10 – Treatment Success Rates at Day 15 by Subgroup

	Study 1205		Study 1206	
	Betamethasone Spray N=174	Vehicle Spray N=87	Betamethasone Spray N=182	Vehicle Spray N=95
Age (years)				
< 65	28/147 (19.0%)	2/75 (2.7%)	30.1/152 (19.8%)	6/81 (7.5%)
≥ 65	5/27 (18.5%)	0/12 (0%)	9/30 (30.0%)	1/14 (7.1%)
Gender				
Male	18/111 (16.2%)	0/51 (0%)	27/114 (23.7%)	5/58 (8.7%)
Female	15/63 (23.8%)	2/36 (5.6%)	12.1/68 (17.8%)	2/37 (5.4%)
Race				
White	26.5/146 (18.2%)	2/76 (2.6%)	34.1/147 (23.2%)	7/86 (8.2%)
Black	2.5/14 (17.8%)	0/3 (0%)	0/13 (0%)	0/8 (0%)
Asian	3/10 (30.0%)	0/5 (0%)	3/11 (27.3%)	--
Other	1/4 (25.0%)	0/3 (0%)	2/11 (18.2%)	0/1 (0%)

Missing data handled with multiple imputation.
Source: reviewer analysis.

4.2 Other Special/Subgroup Populations

Not applicable.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The applicant evaluated the efficacy of betamethasone spray 0.05% in two vehicle-controlled studies for the treatment of psoriasis. One of the studies also included a treatment arm for the listed drug for this 505(b)(2) application, betamethasone lotion, and a treatment arm for vehicle lotion. Both studies had statistically significant results for the primary efficacy endpoint of treatment success (clear or almost clear (0 or 1) on the IGA with at least 2 grades reduction from baseline) at Day 15 for betamethasone spray versus vehicle spray ($p \leq 0.002$). The first ranked secondary endpoint of treatment success at Day 29 was also statistically significant in both studies ($p < 0.001$). However, the second ranked secondary endpoint of treatment success at Day 8 was only significant in Study 1205 ($p=0.003$), but was not significant in Study 1206 ($p=0.156$). Consequently the final ranked secondary endpoint of at least a 50% reduction in the total symptom score at Day 4 was not evaluated in Study 1206. Thus, the applicant has demonstrated efficacy in terms of the primary endpoint of treatment success at Day 15 and the secondary endpoint of treatment success at Day 29. The efficacy results were consistent across the proposed sensitivity analyses for handling missing data.

5.2 Conclusions and Recommendations

Betamethasone dipropionate spray, 0.05% was superior to vehicle spray in the treatment of psoriasis in two studies. Studies 1205 and 1206 enrolled subjects age 18 and older with stable plaque psoriasis involving 10-20% body surface area not including the face, scalp, groin, axillae, and other intertriginous areas, and an investigator's global assessment of moderate. Subjects applied treatment twice daily for 28 days. The primary and first ranked secondary endpoint of treatment success at Days 15 and 29 were statistically significant in both studies. The secondary assessments at Days 8 and 4 were only statistically significant in one of the studies, and thus efficacy has not been established for these endpoints. See Table 11.

Table 11 – Efficacy Results in Studies 1205 and 1206

	Beta Spray	Vehicle Spray	Beta / Veh Lotion	Vehicle Lotion	Beta Spray	Vehicle Spray
Primary	N=174	N=87	N=90	N=43	N=182	N=95
Trt Succ. at Day 15	19.0%	2.3%	18.9%	9.3%	21.5%	7.4%
	p<0.001				p=0.002	
Secondary						
Trt Succ. at Day 29	34.5%	13.6%	21.1%	9.3%	42.7%	11.7%
	p<0.001				p<0.001	
Trt Succ. at Day 8	10.0%	1.2%	6.7%	2.3%	12.7%	7.4%
	p=0.003				p=0.156	
TSS50 at Day 4	12.1%	2.3%	5.6%	2.3%	14.3%	10.5%
	p=0.004				Not tested	

Signatures/Distribution List

Primary Statistical Reviewer: Kathleen Fritsch, Ph.D.
Date: 12/9/2015

Statistical Team Leader: Mohamed Alosh, Ph.D.

cc:
DDDP/Marcus
DDDP/Ko
DDDP/Williams
OBIO/Patrician
DBIII/Wilson
DBIII/Alosh
DBIII/Fritsch

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/s/

KATHLEEN S FRITSCH
12/09/2015

MOHAMED A ALOSH
12/09/2015

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 208079 **Applicant:** Promius **Stamp Date:** 4/6/2015

Drug Name: Betamethasone propionate spray 0.05% **NDA Type:** 505(b)(2) **Indication:** Psoriasis

I. On **initial** overview of the NDA/BLA application identify and list any potential Refuse to File issues:

	Content Parameter for RTF	Yes	No	NA	Comments
1	Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?

Yes

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

74-DAY LETTER REQUESTS TO THE APPLICANT

None.

SUBMISSION SUMMARY

This submission contains two Phase 3 studies in subjects with psoriasis. One study is a 4-arm study comparing betamethasone spray, vehicle spray, betamethasone lotion (Diprolene), and vehicle lotion. The other study evaluates betamethasone spray versus vehicle spray. Studies 1205 and 1206 enrolled subjects age 18 and older with stable plaque psoriasis (10-20% BSA (not including the face, scalp, groin, axillae, or other intertriginous areas), and a IGA of moderate). Subjects applied treatment twice daily for 4 weeks (subjects on the Diprolene arm in Study 1205 applied treatment twice daily for 2 weeks followed by vehicle lotion twice daily for 2 weeks). The primary efficacy endpoint was treatment success at Day 15 defined as an IGA or clear or almost clear with at least 2 grades reduction from baseline. The secondary endpoints were treatment success at Day 29, treatment success at Day 8, and TSS50 at Day 4, where TSS50 is defined as at least a 50% reduction from baseline in the total symptom score (sum of erythema, scaling, and plaque elevation scores).

Efficacy Results in Study 1205

Primary	Betamethasone Spray N=174	Vehicle Spray N=87	Betamethasone Lotion/Vehicle Lotion N=90	Vehicle Lotion N=43
Trt Success at Day 15	19%	2%	19%	9%
	p<0.001			
Secondary				
Trt Success at Day 29	35%	14%	21%	9%
	p<0.001			
Trt Success at Day 8	10%	1%	7%	2%
	p=0.003			
TSS50 at Day 4	12%	2%	6%	2%
	p=0.004			

P-values are for bethamethasone spray vs. vehicle spray

Efficacy Results in Study 1206

Primary	Betamethasone Spray N=182	Vehicle Spray N=95
Trt Success at Day 15	22%	7%
	P=0.002	
Secondary		
Trt Success at Day 29	43%	12%
	p<0.001	
Trt Success at Day 8	13%	7%
	0.156	
TSS50 at Day 4	14%	11%
	Not tested	

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

ASSOCIATED IND: 104853
WERE PROTOCOLS REVIEWED UNDER A SPA? No.

Reviewing Statistician: Kathleen Fritsch, Ph.D.
Mathematical Statistician, Biometrics III

Supervisor/Team Leader: Mohamed Alosh, Ph.D.
Team Leader, Biometrics III

cc:
NDA 208079 / 000
DDDP/Marcus
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05/22/2015

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