

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Indication(s): Psoriasis
Applicant: Ferndale Laboratories
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1 Executive Summary

Halobetasol propionate lotion 0.05% was superior to vehicle lotion in the treatment of psoriasis in two studies. Studies 304 and 305 enrolled subjects age 18 and older with stable plaque psoriasis involving 2-12% body surface area (BSA), excluding the face, scalp, groin, axillae, and other intertriginous areas, and an investigator's global assessment (IGA) of moderate or severe. Subjects applied treatment twice daily for two weeks. The primary efficacy endpoint was treatment success, defined as clear or almost clear on the IGA with at least 2 grades reduction at Day 15. The secondary endpoints were treatment success for scaling, erythema, and plaque elevation at Day 15. The primary and secondary endpoints were all statistically significant ($p < 0.001$). See Table 1.

Table 1 – Efficacy Results at Day 15 in Studies 304 and 305

	Study 304		Study 305	
	Halobetasol N=110	Vehicle N=111	Halobetasol N=110	Vehicle N=112
Primary^a				
Clear or Almost Clear on the IGA	49 (44.5%)	7 (6.3%) $p < 0.001$	49 (44.5%)	8 (7.1%) $p < 0.001$
Secondary^b				
Clear or Almost Clear for Scaling	61 (55.5%)	12 (10.8%)	65 (59.1%)	11 (9.8%)
Clear or Almost Clear for Erythema	40 (36.4%)	8 (7.2%)	48 (43.6%)	12 (10.7%)
Clear or Almost Clear for Plaque Elevation	50 (45.5%)	9 (8.1%)	48 (43.6%)	9 (8.0%)

^a Logistic regression imputation

^b Missing as failure imputation. The secondary endpoints were statistically significant using Hochberg's method to control for multiplicity.

The protocols stated that multiple imputation would be used to handle missing data for the primary endpoint. However, neither the protocol nor the statistical analysis plan contained sufficient details regarding how to implement the proposed multiple imputation. In particular, details such as the number of planned imputations, the randomization seed, and the procedure for combining the multiple imputed datasets into a single analysis were not included protocol of statistical analysis plan. The applicant's datasets and SAS programs indicate that the applicant used only a single imputation for each missing value and thus did not use any method for combining results from multiple imputations. Even though the applicant did not implement a true multiple imputation procedure, the amount of missing data in Studies 304 and 305 is small (2.7%) and the treatment effects are around 38%, so the conclusions of the study are not impacted by the handling of missing data. Although the imputation method used by the applicant did not use multiple imputations, the single imputation used by the applicant is consistent with the model specified in the protocol and is reasonable for labeling purposes. The protocol did not specify a method of imputation for the secondary endpoints, and the applicant presented an observed-case analysis. This reviewer recommends using the missing as failure imputation for the secondary endpoints (the applicant's first sensitivity analysis for the primary endpoint) as a reasonable imputation for the secondary endpoints, because it is not clear that the same logistic regression imputation model used by the

applicant for IGA treatment success (with terms for treatment, baseline IGA, and baseline plaque elevation) would be appropriate for the individual signs of psoriasis.

2 Introduction

2.1 Overview

2.1.1 Clinical Studies

The applicant, Ferndale, is developing halobetasol propionate lotion 0.05% for the treatment of psoriasis under the 505(b)(1) pathway. Another applicant, Ranbaxy, currently markets two formulations of halobetasol propionate 0.05% (cream and ointment) for the treatment of corticosteroid-responsive dermatoses under the tradename Ultravate. These two products were approved in 1990. Ferndale has secured a right of reference to the NDAs for Ultravate cream and Ultravate ointment. In addition, Ferndale has received a letter of authorization from Ranbaxy to use the tradename Ultravate for the lotion product.

Halobetasol lotion was evaluated in an exploratory Phase 2 study (Study 207) and two Phase 3 studies (Study 304 and Study 305). The basic design details for the three studies are summarized in Table 2. All studies were conducted in the United States. This review will focus on the two Phase 3 studies (Study 304 and Study 305).

Table 2 – Clinical Studies Overview

Study numbers	207 (Phase 2), 304 and 305 (Phase 3)		
Study design	Randomized, double-blind, vehicle-controlled		
Inclusion criteria	Age 18 and older with psoriasis (2-12% BSA ^a , moderate to severe on IGA)		
Treatment regimen	Twice daily for 2 weeks		
Primary endpoint	Treatment success on the IGA defined as clear or almost clear with at least 2 grades reduction at Week 2		
Treatment arms and sample size		Halobetasol 0.05%	Vehicle
	Study 207	36	35
	Study 304	110	111
	Study 305	110	112
Study location	US		
Study dates	Study 207 – Nov. 2011 – Feb. 2012		
	Study 304 – May 2013 – Dec. 2013		
	Study 305 – June 2013 – Feb. 2014		

^a Subjects in Study 207 were to have a maximum of 10% BSA.

2.1.2 Regulatory History

The IND for halobetasol lotion was opened in October 2008 with a Phase 1 vasoconstriction assay study. The following meetings were held with the sponsor:

- End-of Phase 2 Meeting (7/25/2012)
- Pre-NDA Meeting (10/27/2014)

Studies 304 and 305 were evaluated under Special Protocol Assessments (SPA) and an Agreement letter for the two protocols was issued on 12/5/2012. Agreement was reached with regard to the overall study design and primary endpoint. The applicant was initially planning to pursue a 505(b)(2) application with Ultravate cream as the listed drug. Study 305 was originally designed as a 4-arm study which included Ultravate cream and vehicle cream arms. In 2013 the applicant notified the Agency that they intended to pursue a 505(b)(1) pathway and that Study 305 would be of identical design (halobetasol lotion vs. vehicle) as Study 304. The Agency responded that the SPA agreements reached with regard to Study 304 could be applied to Study 305.

2.2 Data Sources

This reviewer evaluated the applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. This 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\nda208183\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 and no requests for additional datasets were made to the applicant.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Statistical Analysis

Studies 304 and 305 were identically designed, randomized, double-blind, vehicle-controlled studies of the efficacy and safety of halobetasol propionate lotion, 0.05% in the treatment of psoriasis. The studies enrolled subjects age 18 and older with stable plaque psoriasis involving 2-12% body surface area (BSA), excluding the face, scalp, groin, axillae, and other intertriginous areas, and an investigator's global assessment of moderate or severe. Subjects were randomized in a 1:1 ratio to halobetasol or vehicle. Treatment was applied twice daily for 2 weeks. Subjects were evaluated at screening, baseline, Day 8, and Day 15. The screening and baseline visits could be combined if the subject did not require medication washout.

Efficacy was assessed using the investigator's global assessment (IGA). The IGA was defined as follows:

Investigator's Global Assessment

Clear (0)	
Scaling	No evidence of scaling.
Erythema	No erythema (hyperpigmentation may be present).
Plaque elevation	No evidence of plaque elevation above normal skin level.
Almost Clear (1)	
Scaling	No more than a limited amount of very fine scales partially covers some of the plaques.
Erythema	No more than faint red coloration.
Plaque elevation	No more than a very slight elevation above normal skin level, easier felt than seen.
Mild (2)	
Scaling	No more than mainly fine scales; some plaques are partially covered.
Erythema	No more than light red coloration.
Plaque elevation	No more than a slight but definite elevation above normal skin level, typically with edges that are indistinct or sloped, on some of the plaques.
Moderate (3)	
Scaling	No more than somewhat coarser scales predominate; most plaques are partially covered.
Erythema	No more than moderate red coloration.
Plaque elevation	No more than a moderate elevation with rounded or sloped edges on most of the plaques.
Severe/Very Severe (4)	
Scaling	Coarse, thick tenacious scales predominate; virtually all or all plaques are covered; rough surface.
Erythema	Dusky to deep red coloration.
Plaque elevation	Marked to very marked elevation, with hard to very hard sharp edges on virtually all or all of the plaques.

The individual clinical signs of psoriasis (scaling, erythema, and plaque elevation) were also assessed on comparable 5-point scales (clear, almost clear, mild, moderate, severe). The primary efficacy endpoint was treatment success at Day 15, where treatment success was defined as clear or almost clear on the IGA with at least 2 grades reduction. The secondary endpoints were treatment success at Day 15 for scaling, erythema, and plaque elevation. Other efficacy endpoints included the proportion of subjects with treatment success at Day 8 on the IGA and the individual signs of psoriasis, change from baseline in pruritus score at Day 15, and the change in percent BSA at Days 8 and 15.

The treatment success for the IGA and individual signs was analyzed with the Cochran-Mantel-Haenszel test stratified on analysis center. Multiplicity among the three secondary endpoints for the individual signs of psoriasis was controlled using Hochberg's procedure.

The ITT population was defined as all subjects randomized and dispensed test medication. The per protocol population excluded subjects who did not meet key inclusion criteria (stable plaque psoriasis with 2-12% BSA, IGA 3 or 4), took interfering

concomitant medications, did not complete Day 15 procedures within ± 3 days, or did not apply at least 80% of expected applications. Subjects who discontinued the study prematurely due to treatment failure were included in the per protocol population.

Small centers were combined into analysis centers for the CMH analyses. Sites that enrolled fewer than 8 subjects per treatment arm were pooled. Within the centers that did not enroll at least 8 subjects per treatment arm, the smallest such center was pooled with the largest such 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. Consistency across analysis centers was analyzed using a Breslow-Day test at significance level 0.10. If the Breslow-Day test was significant, sensitivity analyses were conducted to assess the impact of extreme centers.

The primary method of handling missing data was specified as multiple imputation. The protocol and statistical analysis plan provided only limited details regarding the imputation plan, stating only that missing IGA outcomes would be imputed using logistic regression with terms for treatment and plaque elevation. Key details regarding the number of planned imputations, the randomization seed, and the procedure for combining the multiply imputed datasets into a single analysis were not included protocol or statistical analysis plan. In the study report under ‘Changes in the Planned Analyses’ section, the applicant notes that baseline IGA score was also added to the imputation model, because baseline IGA was also a possible interacting variable. Although the protocol did not specifically say that only baseline plaque elevation scores would be used in the imputation model, the SAS programs provided by the applicant use only the baseline observations (plaque elevation and IGA). Day 8 data is not used, even if available. Note however, that the baseline IGA and baseline plaque elevation scores are highly correlated, with 91% of subjects having moderate IGA at baseline and 87% of subjects having moderate plaque elevation at baseline (see Table 5).

Although the applicant claims that they used multiple imputation, they actually only used a single run of the logistic regression imputation model to impute missing observations. The following is the applicant’s SAS code for the imputation, using logistic regression with terms for treatment, baseline IGA, and baseline plaque values to impute missing values for IGA at Day 15:

```
proc mi data = iga seed = 131 out = est;
  class iga15;
  monotone logistic (iga15 = trtpn biga bplaque / details);
  var trtpn biga bplaque iga15;
run;

data est;
  set est (where=( _Imputation_=1));
...
```

The PROC MI statement uses the SAS default of 5 imputations, as no value of NIMPUTE has been specified. However, in the next statement, the applicant selects only the values associated with the first imputation (where=(_Imputation_=1)), discarding the

other four imputations. The applicant proceeds with analyzing the data from the first imputation with CMH as otherwise specified in the protocol.

As sensitivity analyses, the protocol also stated that missing values would be imputed treating all subjects with missing data as (1) IGA treatment failures, and (2) IGA treatment successes.

Reviewer Comment

As the applicant's 'multiple imputation' procedure involved using only a single imputation from the output, this reviewer will refer to the applicant's missing data procedure as 'logistic regression imputation', rather than as multiple imputation, which is the term the applicant uses.

3.2.2 Subject Disposition

Study 304 randomized 110 subjects to halobetasol and 111 subjects to vehicle. Study 305 randomized 110 subjects to halobetasol and 112 subjects to vehicle. More subjects on the vehicle arm (3-5%) discontinued the study than on the halobetasol arm (1-2%). The most common reason for study discontinuation was lost to follow-up and withdrawal by subject. See Table 3.

Table 3 – Disposition of Subjects in Studies 304 and 305

	Study 304		Study 305	
	Halobetasol	Vehicle	Halobetasol	Vehicle
Subjects Randomized	110	111	110	112
Discontinued	1 (1%)	3 (3%)	2 (2%)	6 (5%)
Lost to follow-up	1 (1%)	--	2 (2%)	2 (2%)
Withdrawal by subject	--	2 (2%)	--	4 (4%)
Noncompliance	--	1 (1%)	--	--

Source: pg 64 of study-000-0551-304-study-report-body and 66 of study-000-0551-305-study-report-body and reviewer analysis.

3.2.3 Baseline Characteristics

Baseline demographics were generally balanced across the treatment groups in the two studies, except that in Study 305 on the halobetasol arm 55% of subjects were male while on the vehicle arm 46% of subjects were male. The mean age was about 51 years, with approximately 18% of subjects age 65 and older. Approximately 58% of subjects in Study 304 and 50% of subjects in Study 305 were male. The majority of subjects were white (79% in Study 304 and 92% in Study 305) and non-Hispanic (91% in Study 304 and 82% in Study 305). See Table 4.

Table 4 – Demographics in Studies 304 and 305

	Study 304		Study 305	
	Halobetasol N=110	Vehicle N=111	Halobetasol N=110	Vehicle N=112
<i>Age (years)</i>				
Mean	52.9	50.8	50.8	50.8
Range	21 - 86	21 - 76	18 - 81	19 - 89
18 to 64 years	94 (85%)	90 (81%)	87 (79%)	93 (83%)
65 + years	16 (15%)	21 (19%)	23 (21%)	19 (17%)
<i>Gender</i>				
Female	47 (43%)	46 (41%)	50 (45%)	60 (54%)
Male	63 (57%)	65 (59%)	60 (55%)	52 (46%)
<i>Race</i>				
White	88 (80%)	87 (78%)	102 (93%)	102 (91%)
Black or Afric.-Amer.	11 (10%)	10 (9%)	4 (4%)	9 (9%)
Amer. Ind./AK Native	1 (1%)	3 (3%)	--	1 (1%)
Asian	5 (5%)	7 (6%)	4 (4%)	--
Native HI/Pac. Islander	1 (1%)	1 (1%)	--	--
Other	4 (4%)	3 (3%)	--	--
<i>Ethnicity</i>				
Hispanic or Latino	5 (5%)	15 (14%)	19 (17%)	21 (19%)
Not Hispanic or Latino	105 (95%)	96 (86%)	91 (83%)	91 (81%)

Source: pg 70 of study-000-0551-304-study-report-body and 72 of study-000-0551-305-study-report-body and reviewer analysis.

To be enrolled in the study, subjects were to have an IGA of moderate to severe and a percent BSA of 2-12%. All subjects met the disease characteristic inclusion criteria. The vast majority of subjects had moderate IGA at baseline and the mean percent BSA was about 5.4%. The baseline disease characteristics were balanced across treatment arms. See Table 5.

Table 5 – Baseline Disease Characteristics in Studies 304 and 305

	Study 304		Study 305	
	Halobetasol N=110	Vehicle N=111	Halobetasol N=110	Vehicle N=112
<i>IGA</i>				
Moderate	102 (93%)	101 (91%)	101 (92%)	98 (88%)
Severe	8 (7%)	10 (9%)	9 (8%)	14 (12%)
<i>Scaling</i>				
Mild	7 (6%)	10 (9%)	4 (4%)	4 (4%)
Moderate	90 (82%)	86 (77%)	97 (88%)	92 (82%)
Severe	13 (12%)	15 (14%)	9 (8%)	16 (14%)
<i>Erythema</i>				
Mild	6 (5%)	11 (10%)	2 (2%)	0 (0%)
Moderate	92 (84%)	90 (81%)	99 (90%)	94 (84%)
Severe	12 (11%)	10 (9%)	9 (8%)	18 (16%)
<i>Plaque Elevation</i>				
Mild	6 (5%)	5 (5%)	1 (1%)	1 (1%)
Moderate	96 (87%)	93 (84%)	97 (88%)	99 (88%)
Severe	8 (7%)	13 (12%)	12 (11%)	12 (11%)
<i>BSA</i>				
Mean	5.0	5.4	5.4	5.8
Standard deviation	2.97	3.12	3.08	3.19

Source: pg 77 of study-000-0551-304-study-report-body and 79 of study-000-0551-305-study-report-body.

3.2.4 Primary Efficacy Endpoint

Halobetasol lotion was superior to vehicle lotion on the primary efficacy endpoint of treatment success at Day 15, defined as clear or almost clear on the IGA with at least 2 grades reduction from baseline. Treatment success was analyzed with a CMH test stratified on analysis center. Although the protocol stated that the primary method of handling missing data was to be multiple imputation, the applicant did not provide sufficient details in the protocol or SAP about how to implement multiple imputation for this analysis. According to the submitted SAS programs, the applicant actually used a single imputation from PROC MI using a logistic regression model with terms for treatment, baseline IGA, and baseline plaque elevation to impute missing treatment success values at Day 15. The imputed dataset was then analyzed with the CMH test. With only a single imputation analyzed, the applicant did not need to use PROC MIANALYZE to combine the results of multiple analyses.

For Study 304, using this method and the given seed (131), the first imputation imputed 0 out of 1 halobetasol subjects and 0 out of 3 vehicle subjects with missing Day 15 data as successes. For Study 305, using this method and the same seed, the first imputation imputed 1 out of 2 halobetasol subjects and 1 out of 6 vehicle subjects with missing Day 15 data as successes. The p-values for the applicant's primary analyses using these imputed values were <0.001 in both studies. See Table 6.

This reviewer analyzed the five datasets created by the applicant's PROC MI statement and completed the steps for multiple imputation as follows. Each imputed dataset was analyzed with the CMH test stratified on analysis center. The relative risks from each CMH analysis were transformed using the log transformation so that the distribution would be closer to normal. The transformed statistics were then submitted to PROC MIANALYZE. The p-value using this analysis is also <0.001 in both studies. The average response rates for the five imputed datasets are also presented in Table 6.

The protocol specified two sensitivity analyses for handling missing data—treating all subjects with missing data as failures and treating all subjects with missing data as successes. Because of the low rates of missing data in these studies, the results of these sensitivity analyses are similar. Even doing a conservative imputation where all subjects with missing data on the halobetasol arm are imputed as failures and all subjects with missing data on the vehicle arm are imputed as successes leads to a large observed treatment effect and a statistically significant outcome ($p < 0.001$). The primary efficacy endpoint under various imputation methods are presented in Table 6.

Table 6 – Treatment Success at Day 15 under Various Missing Data Imputations

	Study 304		Study 305	
	Halobetasol N=110	Vehicle N=111	Halobetasol N=110	Vehicle N=112
Logistic Regression Imputation (Applicant's Primary Analysis)	49 (44.5%) $p < 0.001$	7 (6.3%)	49 (44.5%) $p < 0.001$	8 (7.1%)
Missing as failure (Applicant's Sensitivity Analysis)	49 (44.5%) $p < 0.001$	7 (6.3%)	48 (43.6%) $p < 0.001$	7 (6.3%)
Missing as success (Applicant's Sensitivity Analysis)	50 (45.5%) $p < 0.001$	10 (9.0%)	50 (45.5%) $p < 0.001$	13 (11.6%)
Active as failure/Vehicle as success (Reviewer's Sensitivity Analysis)	49 (44.5%) $p < 0.001$	10 (9.0%)	48 (43.6%) $p < 0.001$	13 (11.6%)
Multiple Imputation (Reviewer's Sensitivity Analysis) ^a	49.6 (45.1%) $p < 0.001$	7.6 (6.8%)	49.8 (45.3%) $p < 0.001$	7.6 (6.8%)

^a 5 imputations, imputation model: logistic regression with terms for treatment, baseline IGA, and baseline plaque elevation, CMH test stratified on analysis site, log transform of relative risk.

Source: pg 79 of study-000-0551-304-study-report-body and 81 of study-000-0551-305-study-report-body and reviewer analysis.

Subjects were evaluated at one interim visit at Day 8. Treatment success rates on the IGA increased from Day 8 to Day 15. Approximately 11-16% of halobetasol subjects and 2-3% of vehicle subjects achieved treatment success by Day 8. For consistency with the Day 15 results, missing data at Day 8 was imputed using the same logistic regression model and seed on the Day 8 data as had been done in the applicant's Day 15 analysis. See Table 7.

Table 7 – Treatment Success Rates over Time in Studies 304 and 305 (Logistic Regression Imputation)

	Study 304		Study 305	
	Halobetasol N=110	Vehicle N=111	Halobetasol N=110	Vehicle N=112
Day 8	18 (16.4%)	2 (1.8%)	13 (11.8%)	3 (2.7%)
Day 15	49 (44.5%)	7 (6.3%)	49 (44.5%)	8 (7.1%)

Source: reviewer analysis.

3.2.5 Secondary Efficacy Analyses

The secondary endpoints were treatment success at Day 15 on the individual signs of psoriasis: scaling, erythema, and plaque elevation. To control Type I error, the secondary endpoints were analyzed using Hochberg’s method. The applicant did not specify a method of handling missing data for the secondary endpoints in the protocol or SAP. In the study reports, the applicant reported the results for observed cases only. Because it is not clear that the same logistic regression imputation model used by the applicant for IGA treatment success (with terms for treatment, baseline IGA, and baseline plaque elevation) would be appropriate for the individual signs of psoriasis, this reviewer recommends using ‘missing as failure’ imputation to accommodate an ITT analysis. Missing as failure was the applicant’s first sensitivity analysis proposed for the primary endpoint. Due to the relatively few cases of missing data, the results are very similar using observed cases and missing as failure. All secondary endpoints are statistically significant (nominal $p < 0.001$) under Hochberg’s method. See Table 8.

Table 8 – Secondary Efficacy Endpoints at Day 15 in Studies 304 and 305

	Study 304		Study 305	
Observed Cases (Applicant’s Analysis)	Halobetasol N=109	Vehicle N=110	Halobetasol N=108	Vehicle N=106
Clear or Almost Clear for Scaling	61 (56.0%)	12 (11.1%)	65 (60.2%)	11 (10.4%)
Clear or Almost Clear for Erythema	40 (36.7%)	8 (7.4%)	48 (44.4%)	12 (11.3%)
Clear or Almost Clear for Plaque Elevation	50 (45.9%)	9 (8.3%)	48 (44.4%)	9 (8.5%)
Missing As Failure (Reviewer’s Analysis)	Halobetasol N=110	Vehicle N=111	Halobetasol N=110	Vehicle N=112
Clear or Almost Clear for Scaling	61 (55.5%)	12 (10.8%)	65 (59.1%)	11 (9.8%)
Clear or Almost Clear for Erythema	40 (36.4%)	8 (7.2%)	48 (43.6%)	12 (10.7%)
Clear or Almost Clear for Plaque Elevation	50 (45.5%)	9 (8.1%)	48 (43.6%)	9 (8.0%)

Note: all nominal p-values are < 0.001 and significant under Hochberg’s method for either the observed case analysis or missing as failure.

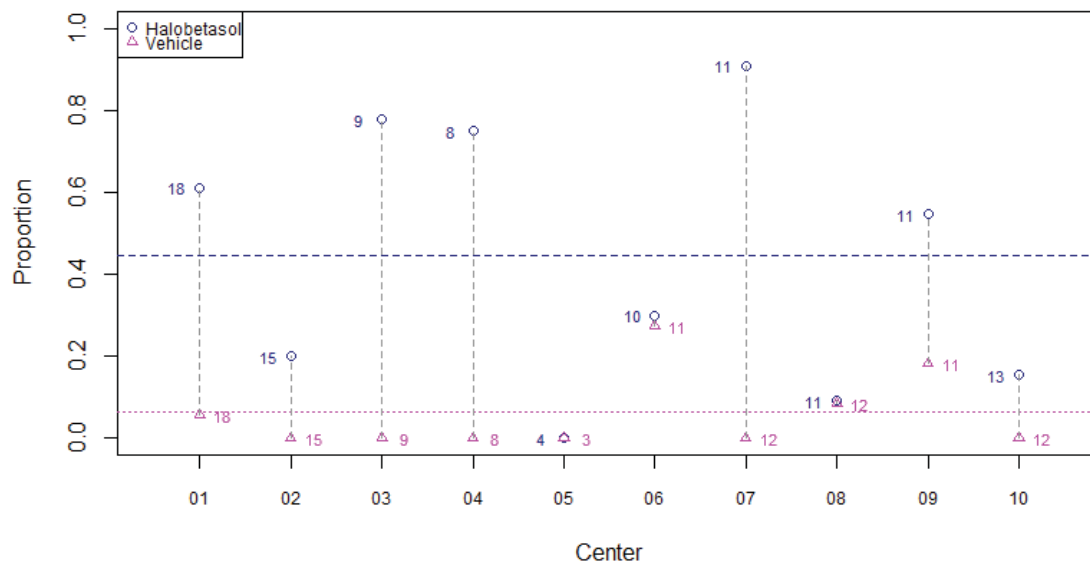
Source: pg 105 of study-000-0551-304-study-report-body and 109 of study-000-0551-305-study-report-body and reviewer analysis.

3.2.6 Efficacy by Center

Study 304 was conducted at 10 centers and Study 305 was conducted at 11 centers. All centers were in the United States. Response rates varied somewhat across centers, but the response rate on the halobetasol arm was higher than the response rate on the vehicle arm

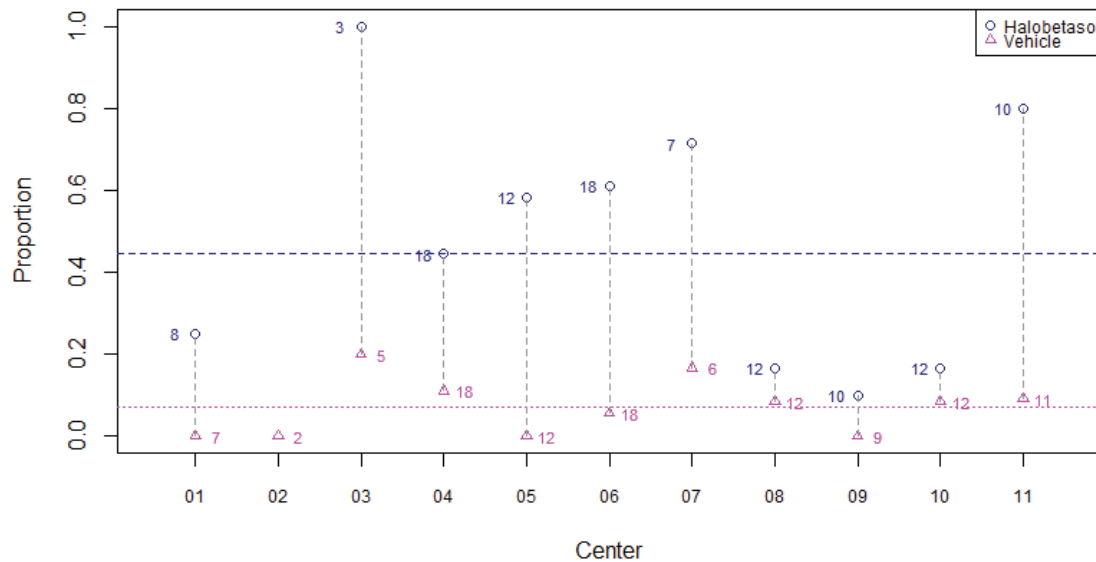
at all centers except for two small centers with no responses on either arm. See Figure 1 and Figure 2. The p-values from the Breslow-Day test were 0.113 in Study 304 and 0.445 in Study 305. Thus, the studies were not able to detect a significant lack of homogeneity for the treatment success endpoint ($p > 0.10$), though the p-value in Study 304 approached significance. In Study 304, Centers 3, 4, 5, and 6 were pooled into a single analysis center, while the remaining centers were left separate. In Study 305, centers 1 and 2 were pooled into an analysis center and centers 3 and 7 were pooled into another analysis center.

Figure 1 – IGA Treatment Success by Center (Study 304)



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

Figure 2 – IGA Treatment Success by Center (Study 305)



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

3.3 Evaluation of Safety

3.3.1 Extent of Exposure

Subjects on the halobetasol and vehicle arms used similar amounts of study treatment in Studies 304 and 305. The planned number of days of treatment was 14 days, and the mean in the studies was approximately 14 on each arm. In addition, the mean amount of study product (grams) used in the two studies was similar for the two arms with a mean of around 70 g in the halobetasol arms and 65-69 g in the vehicle arms. See Table 9.

Table 9 – Extent of Exposure in Studies 304 and 305 (Safety Population)

	Study 304		Study 305	
	Halobetasol N=110	Vehicle N=111	Halobetasol N=110	Vehicle N=112
<i>Days</i>	<i>N=110</i>	<i>N=111</i>	<i>N=110</i>	<i>N=112</i>
Mean (SD)	14.5	14.2	14.6	13.9
Range	1-18	1-18	1-20	1-19
<i>Amount used (g)</i>	<i>N=109</i>	<i>N=111</i>	<i>N=108</i>	<i>N=109</i>
Mean (SD)	70.7 (45.0)	69.2 (44.8)	70.1 (41.0)	65.3 (39.3)
Range	8-167	1-167	4-172	2-156

Source: pg 123 of study-000-0551-304-study-report-body and 127 of study-000-0551-305-study-report-body.

3.3.2 Adverse Events

Telangiectasia, skin atrophy, folliculitis, and burning/stinging were actively monitored at each visit with scores of none, mild, moderate, or severe. These events were relatively uncommon except for burning/stinging at Day 8 and Day 15. Results were generally similar on the halobetasol and vehicle arms. Table 10 presents the number of subjects reporting mild, moderate or severe outcomes for the signs and symptoms at each visit.

Table 10 – Subjects Actively Assessed Local Skin Reactions

		Study 304		Study 305	
	Day	Halobetasol N=110	Vehicle N=111	Halobetasol N=110	Vehicle N=112
Telangiectasia	1	--	--	2 (2%)	--
	8	1 (1%)	--	1 (1%)	2 (2%)
	15	--	--	2 (2%)	--
Skin Atrophy	1	--	--	4 (4%)	3 (3%)
	8	3 (3%)	--	2 (2%)	4 (4%)
	15	1 (1%)	2 (2%)	2 (2%)	3 (3%)
Folliculitis	1	--	--	2 (2%)	--
	8	--	--	--	--
	15	--	--	--	1 (1%)
Burning/Stinging	1	1 (1%)	3 (3%)	8 (7%)	3 (3%)
	8	8 (7%)	7 (6%)	12 (11%)	10 (9%)
	15	3 (3%)	8 (7%)	4 (4%)	12 (11%)

Source: pg 141-142 of study-000-0551-304-study-report-body and 151-152 of study-000-0551-305-study-report-body

Fewer than 10% of subjects on either arm reported adverse events during the studies. The administration site conditions were more common on the vehicle arm. Application site pain was the most commonly reported administration site condition. Table 11 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 11- Total Adverse Events and Administration Site Conditions

	Study 304		Study 305	
	Halobetasol N=110	Vehicle N=111	Halobetasol N=110	Vehicle N=112
Any adverse event	2 (2%)	7 (6%)	10 (9%)	5 (5%)
Administration site conditions	--	5 (5%)	2 (2%)	2 (2%)
Application site erythema	--	1 (1%)	--	--
Application site atrophy	--	--	--	1 (1%)
Application site pain	--	4 (4%)	2 (2%)	1 (1%)
Application site telangiectasia	--	--	--	1 (1%)

Source: pg 137 of study-000-0551-304-study-report-body and 144 of study-000-0551-305-study-report-body

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. All subjects were enrolled in the United States. See Table 12.

Table 12 – IGA Treatment Success Rates by Subgroup (Logistic Regression Imputation)

	Study 304		Study 305	
	Halobetasol N=110	Vehicle N=111	Halobetasol N=110	Vehicle N=112
<i>Age (years)</i>				
< 65	38/94 (40.4%)	6/90 (6.7%)	33/87 (37.9%)	6/93 (6.5%)
≥ 65	11/16 (68.8%)	1/21 (4.8%)	16/23 (69.6%)	2/19 (10.5%)
<i>Gender</i>				
Male	28/63 (44.4%)	2/65 (3.1%)	30/60 (50.0%)	5/52 (9.6%)
Female	21/47 (44.7%)	5/46 (10.9%)	19/50 (38.0%)	3/60 (5.0%)
<i>Race</i>				
White	38/88 (43.2%)	5/87 (5.7%)	46/102 (45.1%)	7/102 (6.9%)
Not white	11/22 (50.0%)	4/24 (16.7%)	3/8 (37.5%)	1/10 (10.0%)

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 halobetasol propionate lotion 0.05% in two vehicle-controlled studies for the treatment of psoriasis. The Agency provided agreement regarding the overall design and primary endpoints for Studies 304 and 305 under a Special Protocol Assessment. Both studies had statistically significant results for the primary efficacy endpoint of IGA treatment success (clear or minimal on the IGA with at least two grades reduction from baseline) at Day 15 ($p < 0.001$). The secondary endpoints of the individual signs of psoriasis (scaling, erythema, and plaque elevation) were consistent with the results of the IGA. Treatment success at Day 15 for each of the individual signs was statistically significant using Hochberg's method to control for multiplicity.

The protocols stated that multiple imputation would be used to handle missing data. However, neither the protocol nor the statistical analysis plan contained sufficient details regarding how to implement the proposed multiple imputation. In particular details such as the number of planned imputations, the randomization seed, and the procedure for combining the multiple imputed datasets into a single analysis were not included protocol of statistical analysis plan. The applicant's datasets and SAS programs indicate that the applicant used only a single imputation for each missing value and thus did not use any

method for combining results from multiple imputations. Even though the applicant did not implement a true multiple imputation procedure, the amount of missing data in Studies 304 and 305 is small (2.7%) and the treatment effects are around 38%, so the conclusions of the study are not impacted by the handling of missing data. Although the imputation method used by the applicant did not use multiple imputations, the single imputation used by the applicant is consistent with the model specified in the protocol and is reasonable for labeling purposes. The protocol did not specify a method of imputation for the secondary endpoints, and the applicant presented an observed-case analysis. This reviewer recommends using the missing as failure imputation for the secondary endpoints (the applicant's first sensitivity analysis for the primary endpoint) as a reasonable imputation for the secondary endpoints, because it is not clear that the same logistic regression imputation model used by the applicant for IGA treatment success (with terms for treatment, baseline IGA, and baseline plaque elevation) would be appropriate for the individual signs of psoriasis.

5.2 Conclusions and Recommendations

Halobetasol propionate lotion 0.05% was superior to vehicle lotion in the treatment of psoriasis in two studies. Studies 304 and 305 enrolled subjects age 18 and older with stable plaque psoriasis involving 2-12% body surface area (BSA), excluding the face, scalp, groin, axillae, and other intertriginous areas, and an investigator's global assessment of moderate or severe. Subjects applied treatment twice daily for two weeks. The primary efficacy endpoint was treatment success, defined as clear or almost clear on the IGA with at least 2 grades reduction at Day 15. The secondary endpoints were treatment success for scaling, erythema, and plaque elevation at Day 15. The primary and secondary endpoints were all statistically significant ($p < 0.001$). See Table 13.

Table 13 – Efficacy Results at Day 15 in Studies 304 and 305

	Study 304		Study 305	
	Halobetasol N=110	Vehicle N=111	Halobetasol N=110	Vehicle N=112
Primary^a				
Clear or Almost Clear on the IGA	49 (44.5%)	7 (6.3%) $p < 0.001$	49 (44.5%)	8 (7.1%) $p < 0.001$
Secondary^b				
Clear or Almost Clear for Scaling	61 (55.5%)	12 (10.8%)	65 (59.1%)	11 (9.8%)
Clear or Almost Clear for Erythema	40 (36.4%)	8 (7.2%)	48 (43.6%)	12 (10.7%)
Clear or Almost Clear for Plaque Elevation	50 (45.5%)	9 (8.1%)	48 (43.6%)	9 (8.0%)

^a Logistic regression imputation

^b Missing as failure imputation. The secondary endpoints were statistically significant using Hochberg's method to control for multiplicity.

Signatures/Distribution List

Primary Statistical Reviewer: Kathleen Fritsch, Ph.D.
Date: 9/3/2015

Statistical Team Leader: Mohamed Alosch, Ph.D.

cc:

DDDP/Marcus

DDDP/Lindstrom

DDDP/Carr

DDDP/Attinello

OBIO/Patrician

DBIII/Wilson

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/s/

KATHLEEN S FRITSCH
09/03/2015

MOHAMED A ALOSH
09/03/2015

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 208183

Applicant: Ferndale

Stamp Date: 1/8/2015

Drug Name: Halobetasol
Lotion, 0.05%

NDA/BLA Type: 505(b)(1)

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			

74-DAY LETTER REQUESTS TO THE APPLICANT

None.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

SUBMISSION SUMMARY

This submission contains a Phase 2 study and two Phase 3 studies of halobetasol lotion 0.05% versus vehicle for the treatment of psoriasis.

Studies 304 and 305 enrolled subjects age 18 and older with plaque psoriasis (2-12% BSA, IGA of moderate or severe). Subjects applied treatment twice daily for 2 weeks. The primary efficacy endpoint was treatment success, defined as a score of clear or almost clear (with at least 2 grades reduction from baseline) on the IGA at Day 15. The secondary endpoints were treatment success on Day 15 for the individual signs plaque elevation, erythema, and scaling.

Efficacy Results at Day 15 in Studies 304 and 305

	Study 304		Study 305	
	Halobetasol N=110	Vehicle N=111	Halobetasol N=110	Vehicle N=112
Primary				
Clear or Almost Clear on the IGA (Multiple Imputation)	49 (44.5%)	7 (6.2%) p<0.001	49 (44.5%)	8 (7.1%) p<0.001
Secondary				
Clear or Almost Clear for Scaling	61 (55.5%)	12 (10.8%)	65 (59.1%)	11 (9.8%)
Clear or Almost Clear for Erythema	40 (36.4%)	8 (7.2%)	48 (43.6%)	12 (10.7%)
Clear or Almost Clear for Plaque Elevation	50 (45.5%)	9 (8.1%)	48 (43.6%)	9 (8.0%)

ASSOCIATED IND: (b) (4)

WERE PROTOCOLS REVIEWED UNDER A SPA? Yes.

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

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

cc:
NDA 208183 / 000
DDDP/Marcus
DDDP/Lindstrom
DDDP/Carr
DDDP/Attinello
OBIO/Patrician
DBIII/Wilson
DBIII/Alosch
DBIII/Fritsch

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

/s/

KATHLEEN S FRITSCH
02/20/2015

MOHAMED A ALOSH
02/20/2015