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/BLA Serial Number:	022320 / S-4
Drug Name:	Epiduo® (adapalene 0.1% / benzoyl peroxide 2.5%) Gel
Indication(s):	Treatment of acne vulgaris in patients 9 years of age and older
Applicant:	Galderma
Date(s):	Letter Date: 4/3/2012
	PDUFA Date: 2/4/2013
Review Priority:	Standard review
Biometrics Division:	Division of Biometrics III
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Keywords: Acne vulgaris, single pivotal trial, superiority trial, combination product

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1 EXECUTIVE SUMMARY

Epiduo® gel was approved for the indication of topical treatment of acne vulgaris in patients 12 years of age and older. The sponsor, Galderma, is seeking approval to extend the patient population to patients 9 years of age and older. The sponsor conducted a multi-center, randomized, double-blind, vehicle-controlled trial (SRE.18155) comparing Epiduo® gel to vehicle gel. A total of 285 subjects were enrolled from 25 centers (US and Canada). The trial enrolled subjects aged 9 to 11 years, who had an Investigator's Global Assessment (IGA) score of 3 (Moderate), and 20 to 100 total lesions (inflammatory and/or non-inflammatory). The sponsor assessed efficacy at Week 12 with treatment success defined as the proportion of subjects with an IGA of 0 (Clear) or 1 (Almost Clear) and change in total lesion counts. The sponsor evaluated change in inflammatory and non-inflammatory lesion counts as secondary efficacy endpoints. This reviewer assessed efficacy based on inflammatory and non-inflammatory lesion counts instead of total lesion counts to be consistent with the co-primary endpoints used in the original NDA submission. The results are presented in Table 1 and show that Epiduo® gel is statistically ($\alpha = 0.05$) superior to vehicle gel.

Table 1: Efficacy Endpoints at Week 12 (ITT, LOCF)

Endpoints	Epiduo® Gel (N=142)	Vehicle Gel (N=143)	p-value
IGA Success(1), n (%)	67 (47.2%)	22 (15.4%)	<0.001(2)
Change in Inflammatory Lesion Count: Mean Absolute (%)	7.4 (36.0%)	0.7 (-13.2%)	<0.001(3)
Change in Non-Inflammatory Lesion Count: Mean Absolute (%)	20.2 (54.7%)	2.9 (2.3%)	<0.001(3)

(1) Success is defined as achieving an IGA score of 0 (Clear) or 1 (Almost Clear)
(2) p-value calculated from CMH test stratified by analysis centers
(3) p-value calculated based on an ANCOVA model using rank data with baseline, treatment, and analysis center as factor
ITT: Intent-to-treat, defined as all randomized subjects.
LOCF: Last observation carried forward
Source: Reviewer's Analysis

2 INTRODUCTION

2.1 Overview

Epiduo® gel is a combination of adapalene (0.1%), a retinoid, and benzoyl peroxide (2.5%). Epiduo® gel was approved on December 8, 2008 for the indication of topical treatment of acne vulgaris in patients 12 years of age and older. The sponsor, Galderma, is seeking to extend the indication to patients 9 years of age and older.

In the approval letter dated December 8, 2008, the Agency waived the pediatric study requirement for subjects less than 9 years of age, because necessary studies are impossible or highly impractical in that age group. In addition, the Agency deferred submission of pediatric studies for ages 9 to 11 years because the product was ready for approval for use in patients 12 years and older. The Agency listed the following required post-marketing study:

> "A multi-center, randomized, placebo-controlled double blind study to evaluate the safety and efficacy of Epiduo Gel administered once daily for the treatment of subject 9 to 11 years of age with acne vulgaris."

On April 24, 2009, the sponsor submitted the post-marketing commitment pediatric study protocol (IND 67801, SDN 73) for Agency review. The sponsor proposed a multi-center, randomized, double-blind study of Epiduo® gel versus vehicle gel in subjects 9 to 11 years of age with acne vulgaris. The primary efficacy endpoint was the change from baseline in total lesion count at Week 12. In the Advice Letter dated November 6, 2009, the Agency conveyed the following comments and recommendations:

1. Include an appropriate Investigator Global Assessment (IGA). The inclusion criteria should define an appropriate severity on the IGA for enrollment.
2. Define the primary efficacy endpoints as success on IGA (clear or almost clear with at least 2 grade reduction from baseline), and absolute change in lesions.
3. Include sensitivity analyses for handling missing data to ensure that the conclusions are not driven by the method of handling missing data.
4. Exclude subjects with an acne nodule (even one) from the study. Nodular acne may require more aggressive treatment than topical alone to prevent scarring.
5. Identify the principal investigator and the Institutional Review Board before the study begins.

2.2 Clinical Study Program

The sponsor submitted data from a single trial (Study SRE.18115). An overview of the study is presented in Table 2.

Table 2: Clinical Study Overview

Location	Study Population	Treatment Arms	Number of Subjects	Dates
US (20 centers) and Canada (5 centers)	Age 9-11, IGA of 3 (Moderate), and 20-100 total lesions (inflammatory and non-inflammatory)	Epiduo® Gel	142	6/21/2010 — 8/2/2011
		Vehicle Gel	143	

2.3 Data Sources

This reviewer evaluated the sponsor's clinical study reports, datasets, clinical summaries, and proposed labeling. This submission was submitted in eCTD format and entirely electronic. The datasets in this review are archived at the following location: \\cdsesub1\evsprod\NDA022320\0040\m5\datasets\rd-06-spr-18155\.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data submitted on April 4, 2012 was not in an accessible format. Therefore, the Agency requested that the data be submitted following the guidelines specified by the CDISC Analysis Data Model (ADaM) Team. The sponsor submitted the data in the requested format on May 22, 2012. The databases required minimal data management prior to performing analyses and no request for additional datasets were made to the sponsor.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study SRE.18155 was a randomized, multi-center, vehicle-controlled, double-blind, study evaluating the safety and efficacy of Epiduo® (adapalene 0.1% and benzoyl peroxide 2.5%) gel in the treatment of acne vulgaris. The study randomized a total of 285 subjects (142 to Epiduo® gel and 143 to vehicle gel) from 25 centers (20 in the United States and 5 in Canada). The sponsor used a balanced block randomization with a block size of 4. The study enrolled subjects 9 to 11 years of age with an Investigator's Global Assessment (IGA) score of 3 (moderate) and 20 to 100 total lesions (non-inflammatory and/or inflammatory). The IGA scale is presented in Table 3. Subjects applied study product to the face and trunk, as applicable, once daily in the evening for 12 weeks. Subjects were evaluated at baseline and Weeks 1, 2, 4, 8, and 12.

Table 3: Investigator's Global Assessment (IGA) Scale

Grade	Description	
0	Clear	No comedones, papules or pustules. Residual hyperpigmentation and erythema may be present.
1	Almost Clear	Rare comedones. No more than a few small papules and pustules might be present.
2	Mild	Easily recognizable comedones in limited numbers, with or without the presence of some small papules or pustules.
3	Moderate	Many comedones. Easily recognizable small and medium sized papules or pustules may be present. No nodules or cysts.
4	Severe	Widespread and numerous comedones with may small, medium sized and large papules and pustules. Nodules or cysts may or may not be present.

The protocol defined the co-primary endpoints as follows:

1. IGA Success rate, defined as the proportion of subjects with an IGA score of 0 (Clear) or 1 (Almost Clear), at Week 12
2. Absolute change from baseline in total lesion count (inflammatory and non-inflammatory) at Week 12

The protocol defined the secondary endpoints as follows:

1. Percent change from baseline in total lesion count (inflammatory and non-inflammatory)
2. Absolute change from baseline in inflammatory lesion count at Week 12
3. Absolute change from baseline in non-inflammatory lesion count at Week 12

While the above co-primary and secondary endpoints were pre-specified in the protocol and evaluated by the sponsor, this review focused on the following co-primary endpoints used in the original NDA submission:

1. IGA Success rate, defined as the proportion of subjects with an IGA score of 0 (Clear) or 1 (Almost Clear), at Week 12
2. Absolute change from baseline in inflammatory lesion count at Week 12
3. Absolute change from baseline in non-inflammatory lesion count at Week 12

In the original NDA submission, percent change in inflammatory and non-inflammatory lesion counts were included in label for descriptive purposes.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 25 randomized subjects prematurely discontinued from the study. The vehicle gel arm had a higher rate of discontinuation (11.9%) compared to the Epiduo® gel arm (5.6%). The disposition of subjects is presented in Table 4.

Table 4: Disposition of Subjects (ITT)

	Epiduo® Gel (N=142)	**Vehicle Gel (N=143)**
Completed	134 (94.4%)	126 (88.1%)
Discontinued	8 (5.6%)	17 (11.9%)
Adverse Event	2 (1.4%)	0
Subject's Request	3 (2.1%)	7 (4.9%)
Lost to Follow-Up	3 (2.1%)	9 (6.3%)
Other	0	1 (0.7%)

Source: Reviewer's Analysis

The demographics were generally balanced across the treatment arms and are summarized in Table 5.

Table 5: Demographics

	Epiduo® Gel (N=142)	Vehicle Gel (N=143)
Age		
Mean (SD)	10.3 (0.76)	10.4 (0.68)
9 years	25 (17.6%)	15 (10.5%)
10 years	45 (31.7%)	49 (34.3%)
11 years	72 (50.7%)	79 (55.2%)
Gender		
Male	33 (23.2%)	35 (24.5%)
Female	109 (76.8%)	108 (75.5%)
Race		
Caucasian	81 (57.0%)	87 (60.8%)
Black	36 (25.4%)	32 (22.4%)
Asian	2 (1.4%)	1 (0.7%)
Hispanic	6 (4.2%)	5 (3.5%)
Other	17 (12.0%)	18 (12.6%)

SD: Standard Deviation
Source: Reviewer's Analysis

The baseline disease characteristics are summarized in Table 6. For enrollment, all subjects must have had an IGA score of 3 (moderate). There was a slight imbalance in lesion counts, with the vehicle arm having on average more lesions. This imbalance was taken into account in the statistical analyses for change in lesion counts by including baseline lesion count as a covariate in the model. This inclusion was pre-specified in the protocol.

Table 6: Baseline Disease Characteristics (ITT)

	Epiduo® Gel (N=142)	Vehicle Gel (N=143)
IGA		
3 – Moderate	142 (100%)	143 (100%)
Mean Lesion Count (SD)		
Total Lesions	50.5 (20.9)	56.4 (21.8)
Inflammatory Lesions	13.8 (11.7)	16.6 (16.3)
Non-Inflammatory Lesions	36.7 (17.6)	39.9 (19.6)

SD: Standard Deviation
Source: Reviewer's Analysis

3.2.3 Statistical Methodologies

The intent-to-treat (ITT) population was defined as all subjects who were randomized and dispensed medication. The per-protocol (PP) population was defined as the ITT subjects who met all major protocol criteria. The major protocol deviations include:

- Entrance criteria deviations: subjects who did not meet one or more major inclusion/exclusion criteria such as: out of range for IGA at baseline, out of range for total lesion counts at baseline, and insufficient washouts for prohibited therapies usage prior to baseline

- Non-compliance: subjects who had dosing deviations more than 30% of the planned 84 doses (<59 or >109 doses)
- Prohibited medications: subjects who had taken interfering concomitant therapies during post-baseline period
- Administrative error: subjects who had administrative errors, such as unblinding or medication dispensing errors

The protocol specified that analysis of the ITT population will be primary and analysis of the PP population will be supportive.

The protocol specified a pooling strategy for centers that enrolled less than 16 subjects. These centers were pooled by ordering and combining the smallest with the largest. The process repeated until all pooled centers had at least 16 subjects. For this trial, 19 of the 25 centers enrolled less than 16 subjects and the pooling strategy yielded a total of 14 pooled analysis centers.

For the analysis of IGA success at Week 12, the protocol-specified analysis method was the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center with a two-sided 0.05 significance level. The Breslow-Day test was to be performed to test for homogeneity across analysis centers at $\alpha = 0.10$ level. If the test was significant, the protocol specified sensitivity analyses where centers would be systematically removed to explore the possible source of the interaction effect.

For the analyses of absolute change in inflammatory and non-inflammatory lesion counts, the protocol-specified method was a two-way Analysis of Covariance (ANCOVA) model including the respective baseline lesion count as a covariate with treatment, analysis center, and treatment-by-baseline interaction as factors. Treatment-by-center interaction was included in the model if the interaction is significant at $\alpha = 0.10$ level. The normality assumption was tested using the Shaprio-Wilks test on the residuals from the ANCOVA model at $\alpha = 0.10$ level. If the normality assumption was not met, the ranked change in lesion count will be analyzed using a two-way ANCOVA model with respective ranked baseline lesion count as a covariate and treatment and analysis center as factors.

For missing data, the primary imputation method was the LOCF with two sensitivity analyses for each co-primary endpoint. For IGA success at Week 12, the two sensitivity analyses were (1) impute missing data as failures and (2) impute missing data as successes. For change in total lesion count at Week 12, the two sensitivity analyses were (1) impute missing data as the median change (from baseline) from the Week 12 IGA failures for each treatment group and (2) impute missing data as the median change (from baseline) from the Week 12 IGA successes for each treatment group. This reviewer conducted these sensitivity analyses for both inflammatory and non-inflammatory lesions instead of total lesions.

3.2.4 Primary Efficacy Endpoints Results

Table 7 provides the analysis results for the co-primary efficacy endpoints at Week 12 in the ITT population and PP population. For the ITT population, Epiduo® gel was statistically ($\alpha = 0.05$) superior to vehicle gel for all co-primary endpoints. Note that the analyses for change in inflammatory and non-inflammatory lesion counts were based on ranked changes because the Shapiro-Wilk's test on the residuals was highly significant ($p < 0.001$) for all models fitted using the unranked data, indicating the violation of the normality assumption for the unranked data. The Shapiro-Wilk's test for the main effects model using ranked data was non-significant ($p = 0.151$) for inflammatory lesions and significant ($p = 0.049$) for non-inflammatory lesions.

For the PP population, approximately 15% of the subjects in the Epiduo® gel arm were excluded, while approximately 21% of the subjects in the vehicle arm were excluded. The analysis results in the PP population were very similar to those in the ITT population.

Table 7: Co-Primary Efficacy Endpoints at Week 12 (LOCF)

	Endpoints	**Epiduo® Gel (N=142)**	**Vehicle Gel (N=143)**	**p-value**
ITT	IGA Success[(1)], n (%)	67 (47.2%)	22 (15.4%)	<0.001[(2)]
	Change in Inflammatory Lesion Count: Mean Absolute (%)	7.4 (36.0%)	0.7 (-13.2%)	<0.001[(3)]
	Change in Non-Inflammatory Lesion Count: Mean Absolute (%)	20.2 (54.7%)	2.9 (2.3%)	<0.001[(3)]
	Endpoints	**Epiduo® Gel (N=121)**	**Vehicle Gel (N=113)**	**p-value**
PP	IGA Success[(1)], n (%)	60 (49.6%)	19 (16.8%)	<0.001[(2)]
	Change in Inflammatory Lesion Count: Mean Absolute (%)	7.3 (37.9%)	1.3 (-9.9%)	<0.001[(3)]
	Change in Non-Inflammatory Lesion Count: Mean Absolute (%)	20.8 (56.8%)	3.0 (0.3%)	<0.001[(3)]

(1) Success is defined as achieving an IGA score of 0 (Clear) or 1 (Almost Clear)
(2) p-value calculated from CMH test stratified by analysis centers
(3) p-value calculated based on an ANCOVA model using rank data with baseline, treatment, and analysis centers as factors
ITT: Intent-to-treat, defined as all randomized subjects.
PP: Per-Protocol
LOCF: Last observation carried forward
Source: Reviewer's Analysis

3.2.5 Missing Data Sensitivity Analyses

The vehicle gel arm had a higher rate of dropout (11.9%) compared to the Epiduo® gel arm (5.6%), which might suggest dropout can be attributed to lack of efficacy. For IGA success at Week 12, the two pre-specified sensitivity analyses for missing data were (1) impute missing data as failures and (2) impute missing data as successes. The results are presented in Table 8. Epiduo® was statistically ($\alpha = 0.05$) superior to vehicle in both sensitivity analyses. This reviewer also conducted an additional sensitivity analysis where missing data for Epiduo® was imputed as failures and missing data for vehicle was imputed as successes. In this extreme case, Epiduo® was still significantly superior to vehicle (46.5% vs. 25.9%; $p < 0.001$).

Table 8: Missing Data Sensitivity Analysis for IGA Success[(1)] at Week 12 (ITT)

Imputation Method	Epiduo® Gel (N=142)	Vehicle Gel (N=143)	p-value[(2)]
LOCF (primary)	67 (47.2%)	22 (15.4%)	<0.001
Impute as Failures	66 (46.5%)	20 (14.0%)	<0.001
Impute as Successes	74 (52.1%)	37 (25.9%)	<0.001

(1) Success is defined as achieving an IGA score of 0 (Clear) or 1 (Almost Clear)
(2) p-value calculated from CMH test stratified by analysis centers
Source: Reviewer's Analysis

For change in lesion count, the sponsor only conducted sensitivity analyses for total lesion count. The two sensitivity analyses for total lesion count were (1) imputing missing data as the median change in total count from the Week 12 IGA failures in each treatment group, and (2) imputing missing data as the median change in lesion count from the Week 12 IGA successes in each treatment group. This reviewer conducted these sensitivity analyses for both inflammatory and non-inflammatory lesions instead of total lesions. The results are presented in Table 9. For both sensitivity analyses and lesion types, Epiduo® was statistically ($\alpha = 0.05$) superior to vehicle and the results were similar to those using LOCF. This reviewer also performed an additional sensitivity analysis using multiple imputation for both lesion types, assuming monotone missingness and a regression model with treatment, analysis center, last observed lesion count, and the interaction between last observed and treatment as covariates. For each lesion type, ten imputed datasets were generated and analyzed. For both lesion types, all ten datasets had Epiduo® as statistically ($\alpha = 0.05$) superior to vehicle with p-values < 0.001. These results support that the method for handling missing data is not driving the efficacy results.

Table 9: Missing Data Sensitivity Analysis for Change in Lesion Count at Week 12 (ITT)

	Imputation Method	Epiduo® Gel (N=142)	Vehicle Gel (N=143)	p-value[(1)]
Change in Inflammatory Lesion Count	LOCF (primary), Mean (SD)	-7.4 (12.5)	-0.7 (12.5)	<0.001
	Impute from IGA Failures, Mean (SD)	-7.4 (12.2)	-0.5 (12.2)	<0.001
	Impute from IGA Successes, Mean (SD)	-7.7 (12.2)	-1.1 (12.3)	<0.001
Change in Non-Inflammatory Lesion Count	LOCF (primary), Mean (SD)	-20.2 (18.2)	-2.9 (19.6)	<0.001
	Impute from IGA Failures, Mean (SD)	-20.3 (17.9)	-3.5 (18.9)	<0.001
	Impute from IGA Successes, Mean (SD)	-20.8 (17.8)	-5.2 (19.4)	<0.001

(1) p-value calculated based on an ANCOVA model using rank data with baseline, treatment, and analysis centers as factors
SD: Standard Deviation
Source: Reviewer's Analysis

3.3 Evaluation of Safety

A total of 184 adverse events (AE) were reported by 112 subjects: 120 AEs by 67 subjects (47.2%) in the Epiduo® gel arm and 64 AEs by 45 subjects (31.5%) in the vehicle gel arm. The AE rates for events occurring in at least 1% of subjects per treatment arm are presented in Table 10. In the Epiduo® gel arm, 36 AEs were considered to be related to the product, while only 1 AE was considered to be related to vehicle gel arm. The summary of drug related AEs by treatment arm is presented in Table 11. The summary of the incidence of cutaneous irritation is presented in Table 12.

Table 10: Adverse Events by System Organ Class and Preferred Term

	Epiduo® Gel (N=142)	Vehicle Gel (N=143)
Gastrointestinal disorders		
Abdominal pain upper	2 (1.4%)	1 (0.7%)
Vomiting	2 (1.4%)	2 (1.4%)
Infections and infestations		
Gastroenteristis	0	2 (1.4%)
Gastroenteristis viral	5 (3.5%)	0
Influenza	2 (1.4%)	1 (0.7%)
Nasopharyngitis	8 (5.6%)	13 (9.1%)
Otitis media	2 (1.4%)	2 (1.4%)
Pharyngitis streptococcal	3 (2.1%)	0
Sinusitis	1 (0.7%)	2 (1.4%)
Upper respiratory tract infection	10 (7.0%)	5 (3.5%)
Musculoskeletal and connective tissue disorders		
Arthralgia	2 (1.4%)	0
Nervous System Disorders		
Headache	2 (1.4%)	2 (1.4%)
Respiratory, thoracic and mediastinal disorders		
Cough	2 (1.4%)	1 (0.7%)
Nasal congestion	2 (1.4%)	0
Pharyngolaryngeal pain	0	2 (1.4%)
Skin and subcutaneous tissue disorders		
Dermatitis	2 (1.4%)	0
Dermatitis contact	1 (0.7%)	2 (1.4%)
Dry skin	4 (2.8%)	0
Erythema	3 (2.1%)	0
Skin burning sensation	14 (9.9%)	0
Skin discomfort	5 (3.5%)	0
Skin irritation	8 (5.6%)	0
Sunburn	4 (2.8%)	1 (0.7%)

Source: Reviewer's Analysis

Table 11: Drug Related Adverse Events

Age (Years)		Epiduo® Gel (N=142)	Vehicle Gel (N=143)
9-11[(1)]	**Subjects with AE(s)**	20%	1%
	Skin burning sensation	9%	0
	Skin irritation	6%	0
	Skin discomfort	4%	0
	Dry skin	3%	0
	Erythema	2%	0
	Skin hypopigmentation	1%	0
	Dermatitis	1%	0
	Sunburn	1%	1%
		Epiduo® Gel (N=564)	**Vehicle Gel (N=489)**
≥12[(2)]	**Subjects with AE(s)**	14%	4%
	Dry Skin	7%	2%
	Contact dermatitis	3%	<1%
	Application site burning	2%	<1%
	Application site irritation	1%	<1%
	Skin irritation	1%	0

(1) Source: Reviewer's Analysis
(2) Source: Section 6.1 of Epiduo® label approved on 12/14/2011

Table 12: Incidence of Local Cutaneous Irritation

Age		Maximum Severity During Treatment			Final Treatment Severity		
		Mild	Moderate	Severe	Mild	Moderate	Severe
9-11[(1)] (N=140)	Erythema	29%	13%	1%	9%	5%	0
	Scaling	42%	13%	1%	8%	2%	0
	Dryness	44%	10%	2%	11%	1%	0
	Stinging/burning	39%	18%	6%	9%	1%	0
≥12[(2)] (N=553)	Erythema	27%	13%	1%	8%	2%	1%
	Scaling	35%	11%	1%	9%	1%	<1%
	Dryness	41%	13%	1%	10%	2%	<1%
	Stinging/burning	41%	15%	3%	7%	2%	1%

(1) Source: Reviewer's Analysis
(2) Source: Section 6.1 of Epiduo® label approved on 12/14/2011

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender, and Race

Table 13 contains the IGA success rates at Week 12 by age, sex, and race. The IGA success rates were similar between 10 and 11 year old subjects and higher for 9 year old subjects; however, the sample size was smaller in the 9 year old group. In terms of sex, there does not appear to be a differential treatment effect between males and females. Black and Caucasian subjects had similar IGA success rates, while Other subjects had a higher rate; however, the sample size was smaller in the Other group.

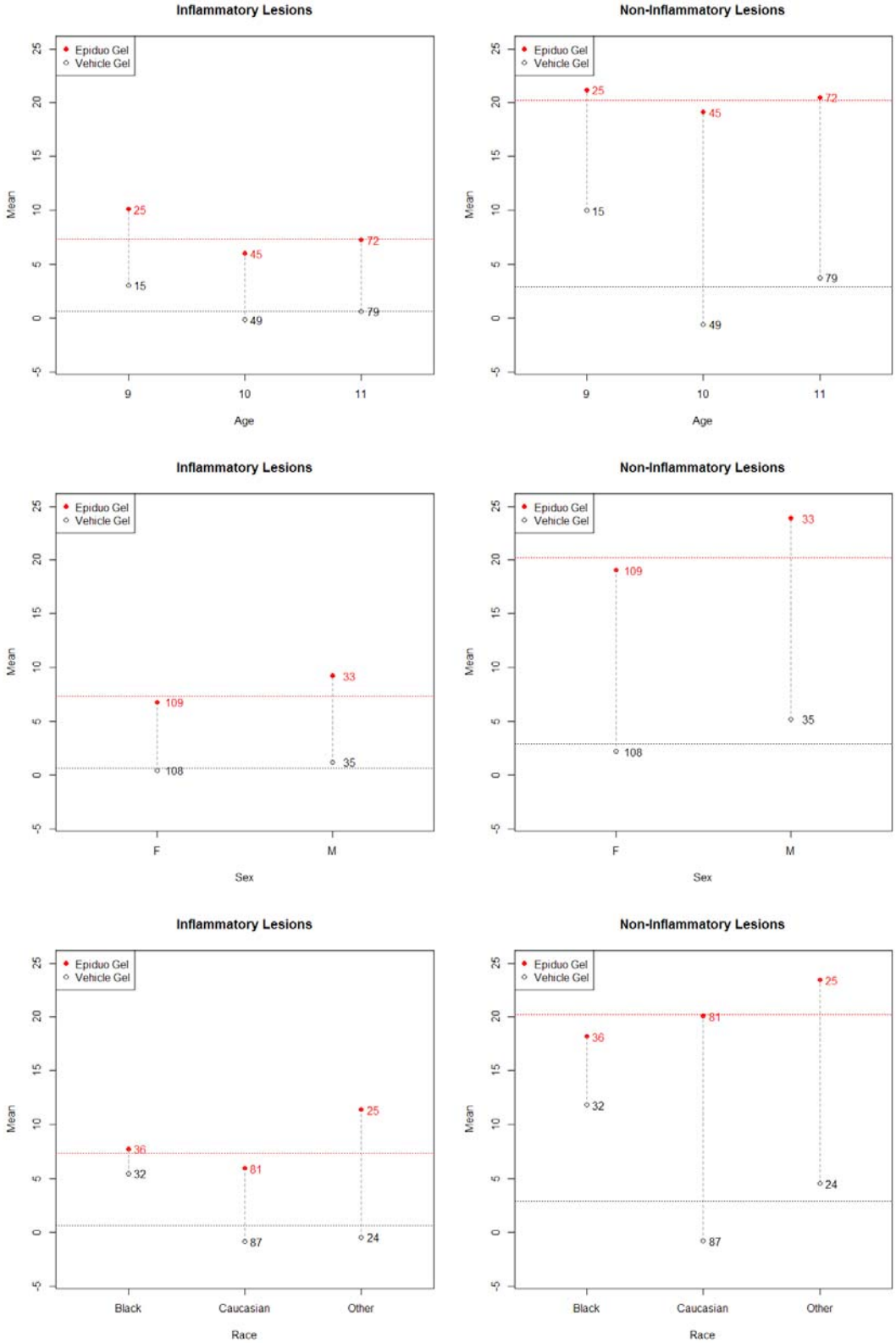
Table 13: IGA Success Rates by Age, Sex, and Race at Week 12 (ITT, LOCF)

	Epiduo® Gel (N=142)	Vehicle Gel (N=143)
Age (year)		
9	14/25 (56.0%)	5/15 (33.3%)
10	21/45 (46.7%)	7/49 (14.3%)
11	32/72 (44.4%)	10/79 (12.7%)
Sex		
Male	15/33 (45.5%)	7/35 (20.0%)
Female	52/109 (47.7%)	15/108 (13.9%)
Race		
Black	17/36 (47.2%)	8/32 (25.0%)
Caucasian	35/81 (43.2%)	14/87 (16.1%)
Other	15/25 (60%)	0/24 (0%)

Source: Reviewer's Analysis

The results for the absolute change in lesion counts are presented in Figure 1. The treatment effects were generally consistent across age, sex, and race.

Figure 1: Absolute Change in Lesions by Age, Sex, and Race at Week 12 (ITT, LOCF)



Source: Reviewer's Analysis

4.2 Efficacy by Center

Table 14 contains the IGA success rates at Week 12 by analysis centers. The IGA success rates were higher in the Epiduo® arm compared to vehicle in all but one analysis center ("Analysis Center 5"). The Breslow-Day test for homogeneity across analysis centers had a p-value of 0.08; therefore, this reviewer conducted a sensitivity analysis where each analysis center was systematically removed to explore the possible source of the interaction effect. The removal of either "Analysis Center 2" or "Analysis Center 5" produced a non-significant (α =0.10) Breslow-Day test. While "Analysis Center 2" had the largest treatment effect (87.5% vs. 0%) and largest sample size, the removal of this analysis center still produced a significant CMH test (p-value <0.001).

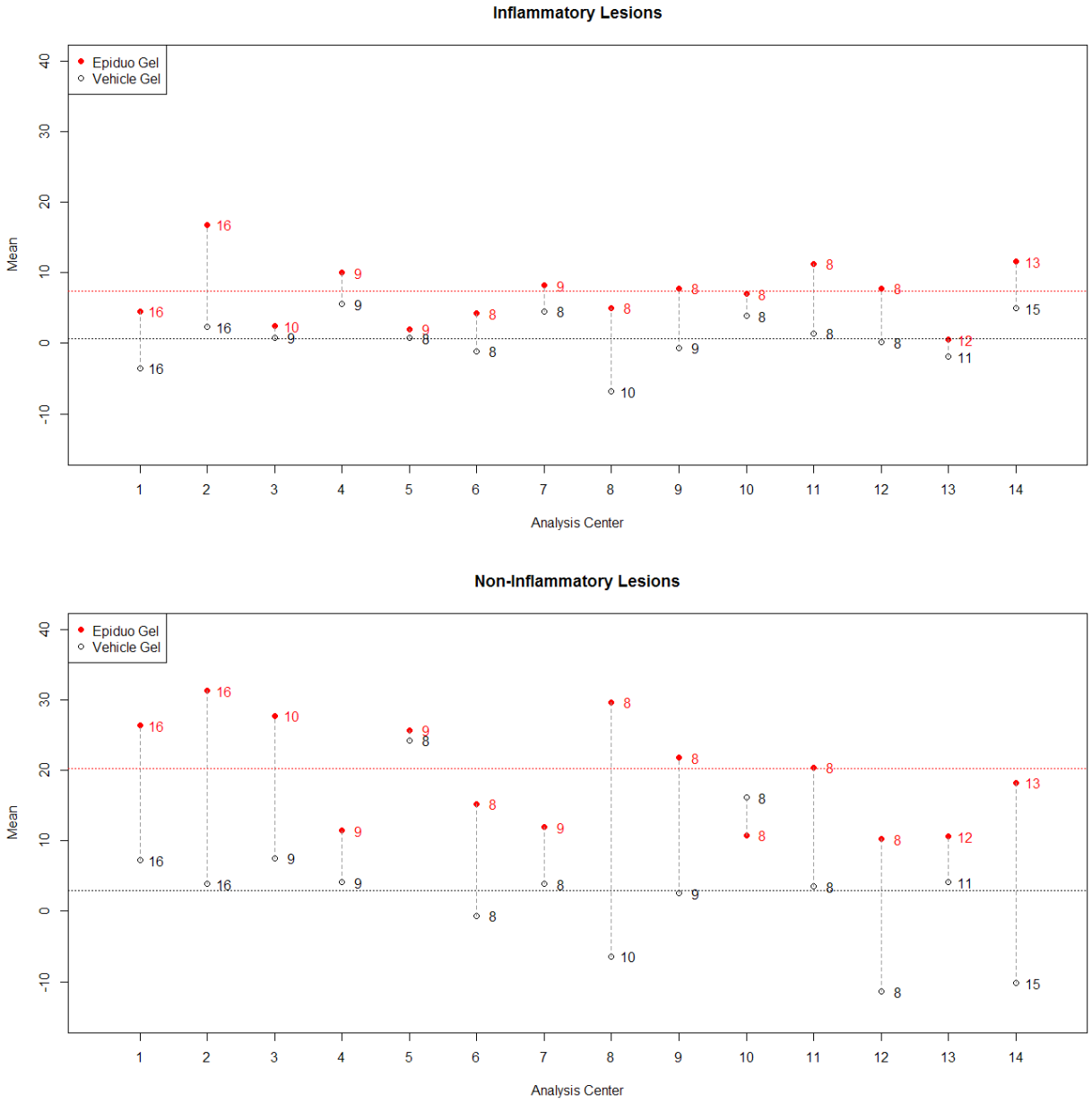
Table 14: IGA Success Rates by Analysis Centers at Week 12 (ITT, LOCF)

Analysis Center	Centers	Number of Subjects	Epiduo® Gel (N=142)	Vehicle Gel (N=95)
1	8008	32	3/16 (18.8%)	1/16 (6.3%)
2	8259	32	14/16 (87.5%)	0/16 (0%)
3	8195	19	4/10 (40%)	3/9 (33.3%)
4	8110	18	4/9 (44.4%)	2/9 (22.2%)
5	8039	17	4/9 (44.4%)	4/8 (50%)
6	8186	16	6/8 (75%)	1/8 (12.5%)
7	8056/8132	17	2/9 (22.2%)	1/8 (12.5%)
8	8135/8140	18	5/8 (62.5%)	1/10 (10%)
9	8147/8188	17	3/8 (37.5%)	0/9 (0%)
10	8026/8299	16	6/8 (75%)	3/8 (37.5%)
11	8069/8183	16	3/8 (37.5%)	2/8 (25%)
12	8155/8297	16	2/8 (25%)	1/8 (12.5%)
13	8048/8094/8294	23	4/12 (33.3%)	1/11 (9.1%)
14	8005/8161/8187/8198	28	7/13 (53.9%)	2/15 (13.3%)

Source: Reviewer's Analysis

The results for the absolute change in lesion counts by analysis centers at Week 12 are presented in Figure 2. For inflammatory lesions, the mean change for the Epiduo® arm was greater than the vehicle arm in all analysis centers and the treatment effect was generally consistent across analysis centers. For non-inflammatory lesions, the mean change for the Epiduo® arm was greater than the vehicle arm in all but one analysis center ("Analysis Center 10").

Figure 2: Absolute Change in Inflammatory Lesions by Analysis Centers at Week 12 (ITT, LOCF)



Source: Reviewer's Analysis

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Epiduo® gel was approved for the indication of topical treatment of acne vulgaris in patients 12 years of age and older. To extend the treatment population to patients 9 years of age and older, the sponsor submitted efficacy and safety results from a multi-center, randomized, double-blind, vehicle-controlled trial (SRE.18155) comparing Epiduo® gel to vehicle. The trial enrolled 285 subjects 9 to 11 years of age with moderate acne. The sponsor assessed efficacy at Week 12 with treatment success defined as the proportion of subjects with an IGA of 0 (Clear) or 1 (Almost Clear) and change in total lesion counts. Instead of total lesion counts, this reviewer assessed efficacy based on inflammatory and non-inflammatory lesion counts to be consistent with the co-primary endpoints used in the original NDA submission. The results are presented in Table 15 and show that Epiduo® gel is statistically ($\alpha = 0.05$) superior to vehicle gel in all endpoints.

Table 15: Efficacy Endpoints at Week 12 (ITT, LOCF)

Endpoints	Epiduo® Gel (N=142)	Vehicle Gel (N=143)	p-value
IGA Success(1), n (%)	67 (47.2%)	22 (15.4%)	<0.001(2)
Change in Inflammatory Lesion Count: Mean Absolute (%)	7.4 (36.0%)	0.7 (-13.2%)	<0.001(3)
Change in Non-Inflammatory Lesion Count: Mean Absolute (%)	20.2 (54.7%)	2.9 (2.3%)	<0.001(3)

(1) Success is defined as achieving an IGA score of 0 (Clear) or 1 (Almost Clear)
(2) p-value calculated from CMH test stratified by analysis centers
(3) p-value calculated based on an ANCOVA model using rank data with baseline, treatment, and analysis center as factor
ITT: Intent-to-treat, defined as all randomized subjects.
LOCF: Last observation carried forward
Source: Reviewer's Analysis

5.2 Conclusions

Efficacy findings from the single pivotal trial (SRE.18155) established the superiority of Epiduo® gel over vehicle gel in the treatment of acne after 12 weeks of treatment in subjects 9 to 11 years of age.

5.3 Labeling Recommendations

The sponsor's proposed label contains Table 16 in Section 14 (Clinical Studies). The values for change in lesion counts (total, inflammatory, and non-inflammatory) are based on only subjects with Week 12 evaluations (completers) which is why they differ from those found in Table 15. To be consistent with the results from the two trials from the original NDA contained in the label, this reviewer recommends removing change in total lesion count from the table and including subjects without Week 12 evaluations using the pre-specified imputation method for missing data (i.e. LOCF).

Table 16: Efficacy Table in the Sponsor's Proposed Label

	Epiduo Gel N=142	Vehicle Gel N=143
IGA: Two Grade Improvement and Clear or Almost Clear	67 (47.2%)	22 (15.4%)
		(b) (4)
Inflammatory Lesions: Mean Absolute (Percent) Change		(b) (4)
Non-inflammatory Lesions: Mean Absolute (Percent) Change		

Source: The sponsor's proposed label

6 SIGNATURES/DISTRIBUTION LIST

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