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 #:	NDA 207154
Drug Name:	ACZONE (dapsone) gel 7.5%
Indication(s):	Acne Vulgaris
Applicant:	Allergan, Inc.
Date(s):	Letter Date: 4/28/2015
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Review Priority:	Standard
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Keywords: Acne vulgaris, superiority trial, multiple imputation

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1 EXECUTIVE SUMMARY

The applicant has developed ACZONE® (dapsone) gel, 7.5% for the topical treatment of acne vulgaris in patients 12 years of age and older. ACZONE® (dapsone) gel, 5% was approved on July 7, 2005 for the indication of topical treatment of acne vulgaris. It should be noted that the approved dose regimen for ACZONE® (dapsone) gel, 5% is twice daily and the proposed dose regimen for ACZONE® (dapsone) gel, 7.5% is once daily.

The applicant submitted data from two identically-designed, randomized, multicenter, vehicle-controlled, parallel-group, Phase 3 trials (Trials 006 and 007). For enrollment, the protocol specified the following key inclusion criteria: 12 years of age or older, a Global Acne Assessment Score (GAAS) of 3 (moderate), 20-50 inflammatory lesions (papules and pustules) on the face, and 30-100 non-inflammatory lesions (open comedones and closed comedones) on the face. The protocol-specified co-primary efficacy endpoints were the proportion of subjects achieving a GAAS score of 0 (none) or 1 (minimal) at Week 12 and the absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12. Secondary efficacy endpoints included percent change in inflammatory and non-inflammatory lesion counts from baseline to Week 12.

Table 1 presents the results of the co-primary efficacy endpoints and the secondary efficacy endpoints of percent change in inflammatory and inflammatory lesion counts from baseline to Week 12. In both trials, ACZONE gel, 7.5% was statistically superior (p-values ≤ 0.004) to vehicle gel for all endpoints presented in Table 1.

Table 1: Results for the Co-Primary and Secondary Efficacy Endpoints at Week 12

	Trial 006		Trial 007	
Endpoints	**ACZONE (N=1044)**	**Vehicle (N=1058)**	**ACZONE (N=1118)**	**Vehicle (N=1120)**
Co-Primary:				
GAAS (none or minimal): n (%)	30%	21%	30%	21%
Absolute Change in:				
Inflammatory Lesions: Mean	16.1	14.3	15.6	14.0
Non-Inflammatory Lesions: Mean	20.7	18.0	20.8	18.7
Secondary:				
Percent Change in:				
Inflammatory Lesions: Mean	56%	49%	54%	48%
Non-Inflammatory Lesions: Mean	45%	39%	46%	41%

Source: Reviewer's Analysis (same as Applicant's Analysis)

For the assessment of GAAS, the interpretation of a "few" or "no" lesions seemed to vary from investigator to investigator. Some subjects counted as successes under the GAAS seemed to have relatively high lesion counts for the definition of "none" (no evidence of facial acne vulgaris) or "minimal" (a few non-inflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) may be present). Subjects scored as 0 (none) had as many as 10 inflammatory lesions or 45 non-inflammatory lesions. Subjects scored as 1 (minimal) had as many as 57 inflammatory lesions or 102 non-inflammatory lesions.

2 INTRODUCTION

2.1 Overview

The applicant, Allergan, is developing ACZONE® (dapsone) gel, 7.5% for the topical treatment of acne vulgaris in patients 12 years of age and older. ACZONE® (dapsone) gel, 5% was approved on July 7, 2005 for the indication of topical treatment of acne vulgaris. It should be noted that the approved dose regimen for ACZONE® (dapsone) gel, 5% is twice daily and the proposed dose regimen for ACZONE® (dapsone) gel, 7.5% is once daily.

2.1.1 Regulatory History

On August 28, 2013, the Agency and the applicant met for an End-of-Phase 2 (EOP2) meeting to discuss the development plan for ACZONE (dapsone) gel, 7.5%. The applicant proposed to conduct two identically-designed Phase 3 trials (Trials 006 and 007) and submitted the protocol for these trials in the meeting package. The applicant proposed the co-primary efficacy endpoints of proportion of subjects with success on the GAAS (i.e., score of 0 or 1) at Week 12 and absolute change in lesion counts (inflammatory, non-inflammatory, and total) from baseline to Week 12. The Agency recommended that the co-primary endpoints regarding lesion counts be absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12 (i.e., not include total as a co-primary endpoint). The Agency also commented that several of the secondary endpoints are closely related and some of the secondary endpoints might not be clinically relevant for labeling. The Agency stated that the secondary endpoints of percent change in inflammatory and non-inflammatory lesion count from baseline to Week 12 are acceptable. In addition, the Agency stated that the proposed patient reported outcomes may have limited utility for eventual product labeling. The Agency also provided comments regarding the handling of missing data (i.e., recommended a more scientifically sound approach, such as multiple imputation or modeling approach, instead of the last observation carried forward (LOCF) approach).

On October 7, 2013, the applicant submitted amended protocols for the Phase 3 trials proposed during the EOP2 meeting. An advice letter was sent to the applicant on January 15, 2014. The Agency reiterated the comments from the EOP2 meeting regarding the absolute change in total lesion counts as a co-primary endpoint and the limited utility of the proposed patient reported outcomes (i.e., the Acne Symptom and Impact Scale (ASIS)).

On February 11, 2014, the applicant submitted their responses to the Agency's comments conveyed in the advice letter sent on January 15, 2014. In addition, on February 18, 2014, the applicant submitted their Patient Reported Outcomes (PRO) Questions Document, a new Acne Symptom and Impact Scale (ASIS) PRO Dossier and a draft statistical analysis plan (SAP) for their pivotal Phase 3 trials. An advice letter regarding these two submissions was sent to the applicant on June 13, 2014. The Agency provided extensive comments regarding the ASIS. For any PRO endpoints that are proposed to support labeling claims, the Agency recommended pre-specifying an appropriate responder definition, making appropriate adjustments for multiple endpoints, and discussing these considerations with the Agency.

On November 19, 2014, the applicant and the Agency met for a Pre-NDA meeting. The Agency provided general comments on how the data should be submitted (data tabulation datasets, data definition files, annotated case report forms, and analysis datasets). The applicant notified the Agency that a clinical center (16078; Dr. Ellen Marmur) did not follow Good Clinical Practice (GCP) procedures. The applicant noted the following instances of non-compliance:

- Numerous inconsistencies in documentation indicating that Dr. Marmur conducted patient assessments when it was confirmed she was not present in the office
- Consenting, screening, and enrolling patients into the study, as well as efficacy and safety assessments, conducted by a study coordinator who was not eligible to conduct the assessments, per protocol, and not listed on the Investigator's Form FDA 1572
- Lack of documentation for numerous patients who were randomized but who do not appear to have returned for any follow-up visits

Due to the above issues, the applicant terminated the center from the trial and all ongoing subjects at the center were discontinued. The Agency stated that given the potential seriousness of the violations described, data from this center should not be included in the primary efficacy analysis. In addition, the Agency commented that the statistical analysis should follow the randomization; therefore, as the randomization was stratified by gender and center, the Agency recommended the applicant conduct the analyses stratified by both factors with and without pooling.

2.1.2 Clinical Studies Overview

The applicant submitted data from a two pivotal Phase 3 trials (Trials 006 and 007). An overview of the trials is presented in Table 2.

Table 2: Clinical Study Overview

Trial	Location	Study Population	Treatment Arms	Number of Subjects	Dates
006	U.S. (96 centers) & Canada (9 centers)	Aged 12 years and older, GAAS of 3 (moderate), 20 to 50 inflammatory lesions, and 30 to 100 non-inflammatory lesions	ACZONE Gel, 7.5%	1044*	11/27/2013 – 10/28/2014
			Vehicle Gel	1058*	
007	U.S. (93 centers) & Canada (10 centers)		ACZONE Gel, 7.5%	1118	11/27/2013 – 10/21/2014
			Vehicle Gel	1120	

*Excluding subjects from center 16078 (25 on ACZONE gel, 7.5% and 26 on vehicle gel).

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 entirely electronic. The datasets in this review are archived at the following locations:
\\cdsesub1\evsprod\NDA207154\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 request for additional datasets were made to the applicant.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The applicant conducted two identically-designed Phase 3 trials (Trials 006 and 007). Both were randomized, double-blind, parallel-group, vehicle-controlled, 12-week trials investigating the safety and efficacy of ACZONE® (dapsone) gel, 7.5% compared to vehicle gel for the treatment of acne vulgaris. For enrollment, the protocol specified the following key inclusion criteria:

- Male or female 12 years of age or older
- Global Acne Assessment Score (GAAS) of 3 (moderate), see Table 3 for details on the GAAS
- 20-50 inflammatory lesions (papules and pustules) on the face
- 30-100 non-inflammatory lesions (open comedones and closed comedones) on the face

Each trial was designed to enroll and randomize approximately 2180 subjects in a 1:1 ratio to either ACZONE® gel, 7.5% or vehicle gel. Randomization was stratified by gender and center. Subjects applied study product once daily for 12 weeks. Subjects were evaluated at the following study visits: screening, baseline (Day 1) and Weeks 1, 2, 4, 8, and 12.

Table 3: Global Acne Assessment Score (GAAS)

Grade		Description
0	None	No evidence of facial acne vulgaris
1	Minimal	Few non-inflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) may be present
2	Mild	Several to many non-inflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) are present
3	Moderate	Many non-inflammatory (comedones) and inflammatory lesions (papules/pustules) are present; no nodulo-cystic lesions are allowed
4	Severe	Significant degree of inflammatory disease; papules/pustules are a predominant feature; a few nodulo-cystic lesions may be present; comedones may be present

The protocol specified the following co-primary efficacy endpoints:

- Proportion of subjects with a 0 (none) or 1 (minimal) on the GAAS at Week 12
- Absolute change in inflammatory lesion counts from baseline to Week 12
- Absolute change in non-inflammatory lesion counts from baseline to Week 12

The protocol specified the following secondary efficacy endpoints:

- Absolute change in total lesion counts from baseline to Week 12
- Percent change in total lesion counts from baseline to Week 12
- Percent change in inflammatory lesion counts from baseline to Week 12
- Percent change in non-inflammatory lesion counts from baseline to Week 12
- Proportion of subjects who report "very good" or "excellent" in Item 10 from the Acne Symptom and Impact Scale (ASIS) at Week 12, see Appendix for details on the ASIS
- Absolute change in ASIS Sign Domain Score (i.e., the average score over Items 1 through 9) from baseline to Week 12
- Proportion of subjects with at least a 1-grade improvement on Item 1 from the ASIS (subject's assessment of oiliness on the face) at Week 12
- Proportion of subjects with at least a 1-grade improvement on Item 8 from the ASIS (subject's assessment of redness on the face) at Week 12

However, as stated before, the Agency informed the applicant that some of secondary efficacy endpoints may not be relevant for labeling.

3.2.2 Statistical Methodologies

The primary analysis population specified in the protocol was the intent-to-treat (ITT) population, defined as all randomized subjects. The protocol also specified supportive analyses using the per-protocol (PP). The PP population was defined as all randomized subjects with no protocol deviations during the trial that might potentially affect the primary efficacy analyses.

The statistical analysis plan (SAP) specified a pooling algorithm for centers that enrolled less than 24 subjects. The pooling was conducted within 5 regional areas (i.e., Canada, northeastern states of U.S., southern states of U.S., west coast states of US, and all other states of the U.S.). Within each regional area, centers were ranked in descending order based on the total number of subjects enrolled. The first center with fewer than 24 subjects is combined with the next center, or with more centers if needed, until the total number in the pooled center reaches or exceeds 24 subjects. The algorithm continues down the list, and if the last pooled center has less than 24 subjects, then the last pooled center is combined with the previous pooled center.

The protocol-specified analysis method for the co-primary efficacy endpoint of GAAS success (i.e., none or minimal) at Week 12 was the Cochran-Mantel-Haenszel (CMH) test stratified by gender. The protocol specified investigating the treatment-by-gender interaction using the Breslow-Day test at $\alpha = 0.10$ level. The SAP (finalized after the protocol) specified investigating the treatment-by-center interaction using the Breslow-Day test at $\alpha = 0.10$ level.

For the co-primary efficacy endpoints of absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12, the protocol-specified analysis method was analysis of covariance (ANCOVA) with treatment, baseline lesion counts, and gender in the model. As a sensitivity analysis, the protocol specified including the treatment-by-center (pooled) interaction. If significant at the 0.10 level, the protocol specified that "data will be further explored by excluding those investigational centers with a large number of deviations."

For the analysis of the secondary efficacy endpoints of absolute change in total lesion counts and percent change in lesion counts (total, inflammatory, non-inflammatory) from baseline to Week 12, the protocol specified using the same method (i.e., ANCOVA model) used to analyze the co-primary efficacy endpoints of absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12. The protocol specified analyzing the binary secondary efficacy endpoints using the CMH test stratified by gender. For the secondary endpoint of absolute change in ASIS Sign Domain Score from baseline to Week 12, the protocol-specified analysis method was ANCOVA using rank data with treatment and gender in the model.

To control the Type I error rate for testing multiple secondary efficacy endpoints, the SAP specified using a sequential gatekeeping approach. The secondary efficacy endpoints were analyzed in the order specified in Section 3.2.1 of this review.

For co-primary efficacy endpoints (i.e., GAAS and lesion counts), the primary imputation method for the handling of missing data specified in the SAP was the multiple imputation (MI) approach. Missing data was imputed using regression models with treatment, age, gender, baseline lesion counts (only for inflammatory and non-inflammatory endpoints) and previous visits results (e.g., missing data for Week 4 was imputed using the data from Weeks 2 and 1). The SAP specified using the last observation carried forward (LOCF) as a sensitivity analysis for the handling of missing data. For the secondary endpoints based on the ASIS, the SAP specified imputing missing data using LOCF.

3.2.3 Patient Disposition, Demographics and Baseline Characteristics

Trial 006 enrolled and randomized a total (excluding center 16078) of 2102 subjects (1044 to ACZONE and 1058 to vehicle) from 105 centers (96 in U.S. and 9 in Canada). Trial 007 enrolled and randomized a total of 2238 subjects (1118 to ACZONE and 1120 to vehicle) from 103 centers (93 in U.S. and 10 in Canada). Table 4 presents the disposition of subjects in Trials 006 and 007. For Trial 006, the rate of discontinuation was slightly higher in the ACZONE arm comparted to the vehicle arm. For Trail 007, the rates of discontinuation were almost identical.

Table 4: Disposition of Subjects (ITT)

	Trial 006[1]		**Trial 007**	
	ACZONE (N=1044)	**Vehicle (N=1058)**	**ACZONE (N=1118)**	**Vehicle (N=1120)**
Discontinued	96 (9.2%)	82 (7.8%)	92 (8.2%)	93 (8.3%)
Adverse Event	4 (0.4%)	5 (0.5%)	2 (0.2%)	2 (0.2%)
Lack of Efficacy	0	1 (0.1%)	1 (0.1%)	1 (0.1%)
Lost to Follow-Up	38 (3.6%)	29 (2.7%)	45 (4.0%)	40 (3.6%)
Other	28 (2.7%)	18 (1.7%)	25 (2.2%)	28 (2.5%)
Personal Reasons	21 (2.0%)	20 (1.9%)	15 (1.3%)	19 (1.7%)
Pregnancy	3 (0.3%)	3 (0.3%)	2 (0.2%)	1 (0.1%)
Protocol Violations	2 (0.2%)	6 (0.6%)	2 (0.2%)	2 (0.2%)

Source: Reviewer's Analysis (same results as Applicant's Analysis)
(1) Excluding subjects from center 16078 (a total of 51 subjects).

Table 5 presents the demographic and baseline disease characteristics. The demographics and baseline disease characteristics were generally balanced across the treatment arms within each trial and similar between each trial. For enrollment, the protocol specified subjects to have a GAAS of 3 (moderate), 20 to 50 inflammatory lesions, and 30 to 100 non-inflammatory lesions. One subject in Trial 006 had a GAAS of 4 (severe). In Trial 006, one subject had a baseline non-inflammatory lesion count less than 30 (i.e., 5 lesions), one subject had a baseline non-inflammatory lesion count greater than 100 (i.e., 106 lesions), and one subject had a baseline inflammatory lesion count less than 20 and a baseline non-inflammatory lesion count less than 30 (i.e., 11 inflammatory lesions and 4 non-inflammatory lesions). In Trial 007, four subjects had a baseline inflammatory lesion count greater than 50 (i.e., 52, 53, 57), and 62 lesions, two subjects had a baseline non-inflammatory lesion count less than 30 (i.e., 21 and 28 lesions), and one subject had a baseline non-inflammatory lesion count greater than 100 (i.e., 112 lesions).

Table 5: Demographics and Baseline Disease Characteristics (ITT)

	Trial 006[(1)]		**Trial 007**	
	ACZONE (N=1044)	**Vehicle (N=1058)**	**ACZONE (N=1118)**	**Vehicle (N=1120)**
Age				
Mean (SD)	20.0 (7.4)	20.0 (7.5)	20.5 (8.2)	20.4 (7.4)
Median	17.0	17.0	18.0	18.0
Range	12 – 63	12 – 53	12 – 61	12 – 54
12-17	525 (50%)	554 (52%)	541 (48%)	530 (47%)
18+	519 (50%)	504 (48%)	577 (52%)	590 (53%)
Gender				
Male	453 (43%)	476 (45%)	500 (45%)	489 (44%)
Female	591 (57%)	582 (55%)	618 (55%)	631 (56%)
Race				
White	647 (62%)	623 (59%)	601 (54%)	619 (55%)
Black	173 (17%)	189 (18%)	230 (21%)	220 (20%)
Hispanic	135 (13%)	156 (15%)	212 (19%)	191 (17%)
Asian	44 (4%)	43 (4%)	37 (3%)	44 (4%)
Other	45 (4%)	47 (4%)	38 (3%)	46 (4%)
Country				
U.S.	984 (94%)	997 (94%)	1057 (95%)	1058 (94%)
Canada	60 (6%)	61 (6%)	61 (5%)	62 (6%)
GAAS				
3 – Moderate	1043	1058	1118	1119
4 - Severe	1	0	0	0
Inflammatory Lesion Counts				
Mean (SD)	28.8 (8.0)	29.3 (8.1)	29.6 (7.7)	30.0 (7.9)
Median	26.0	27.0	28.0	28.0
Range	11 – 50	20 – 50	20 – 62	20 – 57
Non-Inflammatory Lesion Counts				
Mean (SD)	46.9 (16.6)	48.6 (17.5)	46.7 (15.3)	46.7 (15.0)
Median	41.0	43.0	42.0	42.0
Range	4 – 100	30 – 106	21 – 112	30 – 100

Source: Reviewer's Analysis (same results as Applicant's Analysis)
SD: Standard Deviation
(1) Excluding subjects from center 16078 (a total of 51 subjects).

3.2.4 Primary Efficacy Results

ACZONE gel, 7.5% was statistically superior (p-values ≤ 0.004) to vehicle gel on all three co-primary efficacy endpoints in both trials. The results from the ITT and PP analyses were similar and are presented in Tables 6 and 7, respectively.

Table 6: Results for the Co-Primary Efficacy Endpoints at Week 12 (MI, ITT)

	Trial 006[1]			Trial 007		
Endpoint	**ACZONE (N=1044)**	**Vehicle (N=1058)**	**P-value**	**ACZONE (N=1118)**	**Vehicle (N=1120)**	**P-value**
GAAS: None or Minimal*	311.9 (30%)	224.2 (21%)	<0.001[2]	333.3 (30%)	234.1 (21%)	<0.001[2]
Absolute Change in Inflammatory Lesion Counts:						
Mean*	16.1	14.3		15.6	14.0	
LS Mean[3]	16.1	14.1	<0.001[3]	15.6	13.8	<0.001[3]
Absolute Change in Non-Inflammatory Lesion Counts:						
Mean*	20.7	18.0		20.8	18.7	
LS Mean[3]	20.8	17.6	<0.001[3]	20.7	18.5	0.004[3]

Source: Reviewer's Analysis (same results as Applicant's Analysis)
*The values displayed are the averages over the 20 imputed datasets (MI).
(1) Excluding subjects from center 16078 (a total of 51 subjects).
(2) P-value from a CMH test stratified by gender.
(3) LS means and p-values from an ANCOVA model with terms for treatment, gender, and baseline lesion counts.

Table 7: Results for the Co-Primary Efficacy Endpoints at Week 12 (PP)

	Trial 006[1]			Trial 007		
Endpoint	**ACZONE (N=880)**	**Vehicle (N=887)**	**P-value**	**ACZONE (N=950)**	**Vehicle (N=955)**	**P-value**
GAAS: None or Minimal	272 (31%)	199 (22%)	<0.001[2]	291 (31%)	203 (21%)	<0.001[2]
Absolute Change in Inflammatory Lesion Counts:						
Mean	16.2	14.6		15.8	14.4	
LS Mean	16.1	14.4	<0.001[3]	15.8	14.2	0.001
Absolute Change in Non-Inflammatory Lesion Counts:						
Mean	21.1	18.2		21.4	18.9	
LS Mean	21.0	17.9	<0.001[3]	21.1	18.7	<0.001[3]

Source: Reviewer's Analysis (same results as Applicant's Analysis)
(1) Excluding subjects from center 16078 (a total of 51 subjects).
(2) P-value from a CMH test stratified by gender.
(3) LS means and p-values from an ANCOVA model with terms for treatment, gender, and baseline lesion counts.

Table 8 provides the number of subjects with missing data for the co-primary efficacy endpoints by week and treatment arm for both trials. In both trials, the proportion of subjects with missing data at Week 12 was slightly higher (9% vs. 8%) in the ACZONE arm compared to the vehicle arm.

Table 8: Missing Data for the Co-Primary Efficacy Endpoints by Week (ITT)

	Trial 006		Trial 007	
	ACZONE (N=1044)	Vehicle (N=1058)	ACZONE (N=1118)	Vehicle (N=1120)
Baseline	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Week 1	68 (7%)	71 (7%)	67 (6%)	70 (6%)
Week 2	65 (6%)	61 (6%)	72 (6%)	63 (6%)
Week 4	38 (4%)	43 (4%)	50 (4%)	50 (4%)
Week 8	89 (9%)	72 (7%)	77 (7%)	85 (8%)
Week 12	95 (9%)	85 (8%)	96 (9%)	94 (8%)

Source: Reviewer's Analysis

For all three co-primary efficacy endpoints, the primary imputation method was the multiple imputation approach using a regression model with treatment, age, gender, baseline lesion counts (only for inflammatory and non-inflammatory lesion counts) and previous visits results in the model (MI-Reg). The SAP also specified using LOCF as a sensitivity analysis for the handling of missing data. For the co-primary efficacy endpoint of IGA success, this reviewer conducted a sensitivity analysis where missing data was imputed as failures. In addition, for all three co-primary efficacy endpoints, this reviewer conduct an additional sensitivity analysis where missing data was imputed using the multiple imputation Markov Chain Monte Carlo (MI-MCMC) approach.

Tables 9, 10, and 11 present the results for the co-primary efficacy endpoints in both trials by the various imputations methods. For both trials, the results were generally similar across the various methods for handling missing data.

Table 9: Comparison of Different Approaches for Handling Missing Data for GAAS Success[(1)] at Week 12 (ITT)

	Trial 006			Trial 007		
Imputation Method	ACZONE (N=1044)	Vehicle (N=1058)	P-value[(2)]	ACZONE (N=1118)	Vehicle (N=1120)	P-value[(2)]
MI-Reg[(3)] (Primary)	311.8 (30%)	222.6 (21%)	<0.001	333.3 (30%)	234.1 (21%)	<0.001
LOCF	288 (28%)	212 (20%)	<0.001	312 (28%)	218 (19%)	<0.001
Failure	284 (27%)	207 (20%)	<0.001	306 (27%)	215 (19%)	<0.001
MI-MCMC[(3)]	307.2 (29%)	222.7 (21%)	<0.001	330.5 (30%)	232.2 (21%)	<0.001

Source: Reviewer's Analysis
(1) Success is defined as achieving a GAAS of 0 (none) or 1 (minimal).
(2) P-value based on a CMH test stratified by gender.
(3) The rates displayed are the averages of the 20 imputed datasets.

Table 10: Comparison of Different Approaches for Handling Missing Data for Inflammatory Lesion Counts at Week 12 (ITT)

	Trial 006			Trial 007		
Imputation Method	**ACZONE (N=1044)**	**Vehicle (N=1058)**	**P-value[1]**	**ACZONE (N=1118)**	**Vehicle (N=1120)**	**P-value[1]**
MI-Reg[3] (Primary)	16.2	14.6	<0.001	15.8	14.4	0.001
LOCF	15.5	13.7	<0.001	14.9	13.4	<0.001
MI-MCMC[3]	16.0	14.1	<0.001	15.4	13.8	<0.001

Source: Reviewer's Analysis
(1) P-values from an ANCOVA model with terms for treatment, gender, and baseline lesion counts.
(2) The rates displayed are the averages of the 20 imputed datasets.

Table 11: Comparison of Different Approaches for Handling Missing Data for Non-Inflammatory Lesion Counts at Week 12 (ITT)

	Trial 006			Trial 007		
Imputation Method	**ACZONE (N=1044)**	**Vehicle (N=1058)**	**P-value[1]**	**ACZONE (N=1118)**	**Vehicle (N=1120)**	**P-value[1]**
MI-Reg[2] (Primary)	21.1	18.2	<0.001	21.4	18.9	0.004
LOCF	19.8	17.4	<0.001	19.9	17.8	0.010
MI-MCMC[2]	20.5	17.8	<0.001	20.5	18.4	0.007

Source: Reviewer's Analysis
(1) P-values from an ANCOVA model with terms for treatment, gender, and baseline lesion counts.
(2) The rates displayed are the averages of the 20 imputed datasets.

3.2.5 Secondary Efficacy Results

Table 12 presents the results for the secondary efficacy endpoints at Week 12 in both trials. For the secondary efficacy endpoints based on lesion counts (i.e., absolute change from baseline in total lesion counts and percent change in lesions counts (inflammatory, non-inflammatory, and total)), ACZONE gel, 7.5% was statistically superior (p-values ≤ 0.001) to vehicle gel in both trials. For the proportion of subjects with an ASIS score of "very good" or "excellent", ACZONE gel, 7.5% was statistically superior to vehicle gel (24% vs. 19%; p-value = 0.015) in Trial 006; however, ACZONE gel, 7.5% was not statistically superior to vehicle gel (24% vs. 22%; p-value = 0.252) in Trial 007. ACZONE gel, 7.5% was not statistically superior to vehicle gel for all other secondary efficacy endpoints based on the ASIS.

Table 12: Results for the Secondary Efficacy Endpoints at Week 12 (MI[1], LOCF[2], ITT)

	Trial 006[3]			Trial 007		
Endpoint	**ACZONE (N=1044)**	**Vehicle (N=1058)**	**P-value**	**ACZONE (N=1118)**	**Vehicle (N=1120)**	**P-value**
Absolute Change in Total Lesion Counts:						
Mean*	36.9	32.3		36.5	32.7	
LS Mean[4]	36.9	31.7	<0.001[4]	36.2	32.3	<0.001[4]
Percent Change in Total Lesion Counts:						
Mean*	49.4%	42.7%		49.2%	43.6%	
LS Mean[4]	48.7%	42.4%	<0.001[4]	48.9%	43.2%	<0.001[4]
Percent Change in Inflammatory Lesion Counts:						
Mean*	56.2%	49.5%		54.2%	47.6%	
LS Mean[4]	55.5%	49.0%	<0.001[4]	53.8%	47.3%	<0.001[4]
Percent Change in Non-Inflammatory Lesion Counts:						
Mean*	45.0%	38.9%		46.2%	40.8%	
LS Mean[4]	44.4%	38.4%	<0.001[4]	45.9%	40.4%	0.001[4]
ASIS Sign Domain[5]: Very Good or Excellent	217/910 (24%)	175/913 (19%)	0.015[6]	224/926 (24%)	211/961 (22%)	0.252[6]
Absolute Change in ASIS Sign Domain: Mean	0.73	0.69	0.145[7]	0.74	0.68	0.057[7]
ASIS Item 1: 1-grade improvement	477 (46%)	548 (52%)	0.005[6]	542 (48%)	552 (49%)	0.711[6]
ASIS Item 8: 1-grade improvement	580 (56%)	561 (53%)	0.244[6]	601 (54%)	592 (53%)	0.647[6]

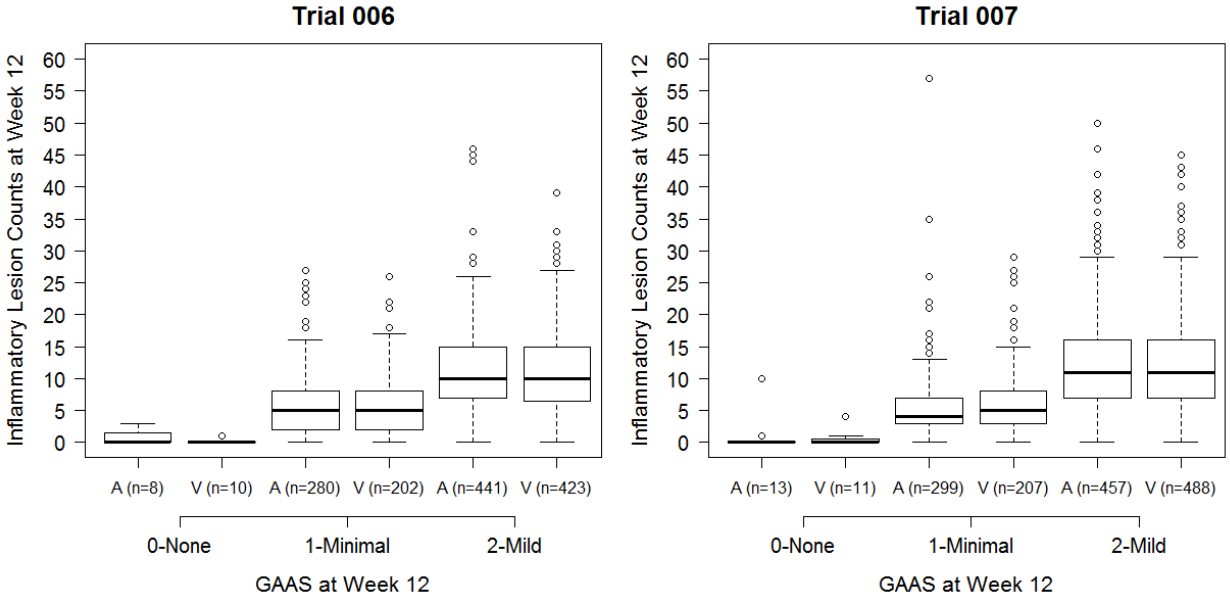
Source: Reviewer's Analysis (same results as Applicant's Analysis)
*The values displayed are the averages over the 20 imputed datasets (MI).
(1) Missing data for lesion count endpoints were imputed using multiple imputation (MI).
(2) Missing data for ASIS endpoints were imputed using last observation carried forward (LOCF).
(3) Excluding subjects from center 16078 (a total of 51 subjects).
(4) LS means and p-values from an ANCOVA model with terms for treatment, gender, and baseline lesion counts.
(5) Based on subjects who had an ASIS score of 4 (fair) or 5 (bad) at baseline.
(6) P-value based on a CMH test stratified by gender.
(7) P-value based on an ANCOVA model using rank data with terms for treatment and gender in the model.

3.2.6 Global Assessment of Acne Score (GAAS) vs. Lesion Counts at Week 12

Figures 1 and 2 present the inflammatory and non-inflammatory lesion counts at Week 12 for subjects who had a GAAS score of 0 (none), 1 (minimal) or 2 (mild) at Week 12 (note that subjects with a GAAS score of 3 (moderate) or 4 (severe) at Week 12 are not shown). Some subjects counted as successes under the GAAS seemed to have relatively high lesion counts for the definition of "none" (no evidence of facial acne vulgaris) or "minimal" (a few non-inflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) may be present). Subjects scored as 0 (none) had as many as 10 inflammatory lesions or 45 non-inflammatory lesions. Subjects scored as 1 (minimal) had as many as 57 inflammatory lesions and 102 non-inflammatory lesions. As can be seen from Figures 1 and 2, lesion counts do

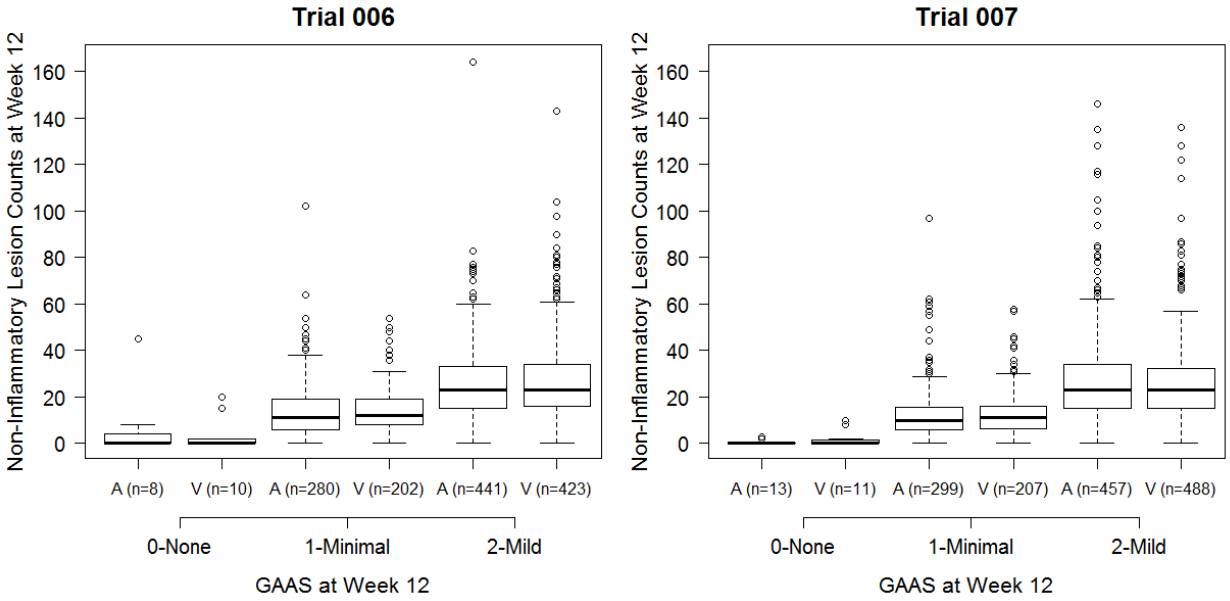
generally increase with increasing GAAS score; however, there is considerable overlap between the categories and the distributions are skewed. The success categories of "none" and "minimal" appear to contain many subjects with more than a "few" inflammatory and non-inflammatory lesions. For "minimal", the median number of inflammatory lesions was 5 and the median number of non-inflammatory lesions was 11.

Figure 1: Inflammatory Lesion Counts by GAAS at Week 12 (LOCF, ITT)



Source: Reviewer's Analysis
A=ACZONE gel, V=Vehicle gel

Figure 2: Non-Inflammatory Lesion Counts by GAAS at Week 12 (LOCF, ITT)



Source: Reviewer's Analysis
A=ACZONE gel, V=Vehicle gel

This reviewer conducted a sensitivity analysis where subjects with a GAAS score of 0 or 1 at Week 12 were imputed as failures if they had more than a certain number of inflammatory or non-inflammatory lesions. Specifically, this reviewer looked at the following three sets of values:

- Inclusion criteria for inflammatory and non-inflammatory lesion counts (i.e., 20 for inflammatory and 30 for non-inflammatory)
- Overall means for inflammatory and non-inflammatory lesion counts at Week 12 for subjects with a GAAS score of 2 (mild) at Week 12
- Overall means for inflammatory and non-inflammatory lesion counts at Week 12 for subjects with a GAAS score of 1 (minimal) at Week 12

Table 13 presents the results of this sensitivity analysis. While the response rates and treatment effect decreased with the stricter requirement for success, the treatment effect remained statistically significant (p-values ≤ 0.002) in both trials.

Table 13: GAAS Success Definition vs. A Definition based on Lesion Counts at Week 12 (LOCF)

	Trial 006		Trial 007	
	ACZONE (N=1044)	**Vehicle (N=1058)**	**ACZONE (N=1118)**	**Vehicle (N=1120)**
GAAS score of 0 or 1	288 (28%)	212 (20%)	312 (28%)	218 (19%)
Sensitivity Analysis[(1)]:				
Inflammatory ≥ 20 or Non-Inflammatory ≥ 30 [(2)]	264 (25%)	199 (19%)	292 (26%)	200 (18%)
Inflammatory ≥ 12 or Non-Inflammatory ≥ 27 [(3)]	235 (23%)	181 (17%)	267 (24%)	182 (16%)
Inflammatory ≥ 6 or Non-Inflammatory ≥ 14 [(4)]	127 (12%)	83 (8%)	149 (13%)	97 (9%)

Source: Reviewer's Analysis

(1) Subjects with GAAS score of 0 or 1 are imputed as failures if they have a certain number of inflammatory or non-inflammatory lesions at Week 12.

(2) Based on the inclusion criteria for inflammatory and non-inflammatory lesion counts.

(3) Based on the overall means (inflammatory and non-inflammatory lesions) for subjects with GAAS=2 at Week 12.

(4) Based on the overall means (inflammatory and non-inflammatory lesions) for subjects with GAAS=1 at Week 12.

3.3 Evaluation of Safety

3.3.1 Extent of Exposure

The extent of exposure to study product is presented in Table 14. The duration of exposure and average daily use of study product were similar between treatment arms within each trial and between each trial.

Table 14: Extent of Exposure (Safety Population)

	Trial 006		Trial 007	
	ACZONE (N=1044)	**Vehicle (N=1057)**	**ACZONE (N=1117)**	**Vehicle (N=1118)**
Duration of Exposure (Days)				
N	1044	1057	1117	1118
Mean (SD)	82.8 (14.4)	82.7 (12.7)	82.5 (12.8)	82.4 (12.9)
Median	85.0	85.0	85.0	85.0
Range	8 – 168	6 – 160	6 – 138	8 – 128
Average Daily Use (grams)				
N	1020	1037	1087	1095
Mean (SD)	0.64 (0.96)	0.64 (0.55)	0.65 (0.53)	0.66 (0.47)
Median	0.50	0.50	0.52	0.55
Range	0 – 21.2	0 – 8.0	0 – 5.39	0 – 4.11

Source: pg. 115 of Study Report for Trial 006 and pg. 113 of Study Report for Trial 007.

3.3.2 Adverse Events

Table 15 presents an overview of the adverse events reported during both trials. The treatment-related adverse events reported in both trials are presented in Table 16. These tables are also reproduced based on gender (Tables 17 and 18) and amount of product used (Tables 19 and 20).

Table 15: Overview of Adverse Events Reported (Safety Population)

	Trial 006		Trial 007		Pooled Trials	
Subjects With:	**ACZONE (N=1044)**	**Vehicle (N=1057)**	**ACZONE (N=1117)**	**Vehicle (N=1118)**	**ACZONE (N=2161)**	**Vehicle (N=2175)**
Any Treatment-Emergent AEs	199 (19%)	218 (21%)	197 (18%)	191 (17%)	396 (18%)	409 (19%)
Any Drug-Related(1) AEs	30 (3%)	35 (3%)	45 (4%)	38 (3%)	75 (3%)	73 (3%)
Any Serious AEs	3 (<1%)	5 (<1%)	4 (<1%)	4 (<1%)	7 (<1%)	9 (<1%)
Any Treatment-Emergent AEs Leading to Discontinuation	4 (<1%)	5 (<1%)	2 (<1%)	2 (<1%)	6 (<1%)	7 (<1%)

Source: pg. 117 of Study Report for Trial 006 and pg. 114 of Study Report for Trial 007.
(1) Assessed by investigator as possibly drug-related.

Table 16: Treatment-Related[(1)] Treatment-Emergent Adverse Events (Pooled Trials, Safety Population)

System Organ Class / Preferred Term	ACZONE (N=2161)	Vehicle (N=2175)
Eye disorders		
Eyelid rash	1 (<0.1%)	0
Lacrimation increased	1 (<0.1%)	0
Blepharitis	0	1 (<0.1%)
Gastrointestinal disorders		
Chapped lips	1 (<0.1%)	0
General disorders and administration site conditions		
Application site dryness	24 (1.1%)	21 (1.0%)
Application site pruritus	20 (0.9%)	11 (0.5%)
Application site erythema	14 (0.6%)	13 (0.6%)
Application site pain	9 (0.4%)	31 (1.4%)
Application site exfoliation	9 (0.4%)	14 (0.6%)
Application site paraesthesia	5 (0.2%)	7 (0.3%)
Application site irritation	3 (0.1%)	0
Application site acne	2 (0.1%)	2 (0.1%)
Application site dermatitis	1 (<0.1%)	1 (<0.1%)
Application site discomfort	1 (<0.1%)	0
Application site photosensitivity reaction	1 (<0.1%)	0
Application site reaction	1 (<0.1%)	0
Application site swelling	1 (<0.1%)	0
Application site vesicles	1 (<0.1%)	0
Application site papules	0	1 (<0.1%)
Application site warmth	0	1 (<0.1%)
Nervous system disorders		
Dizziness	1 (<0.1%)	0
Psychiatric disorders		
Depression	0	1 (<0.1%)
Skin and subcutaneous tissue disorders		
Skin tightness	3 (0.1%)	1 (<0.1%)
Seborrhoea	2 (0.1%)	1 (<0.1%)
Pruritis	1 (<0.1%)	0
Skin irritation	0	1 (<0.1%)
Sticky skin	0	1 (<0.1%)

Source: pg. 39 of Summary of Clinical Safety.
(1) Assessed by investigator as possibly drug-related.

Table 17: Overview of Adverse Events Reported by Gender (Pooled Trials; Safety Population)

	Males		Females	
Subjects With:	ACZONE (N=953)	Vehicle (N=965)	ACZONE (N=1208)	Vehicle (N=1210)
Any Treatment-Emergent AEs	166 (17%)	175 (18%)	230 (19%)	234 (19%)
Any Drug-Related[(1)] AEs	21 (2%)	30 (3%)	54 (4%)	43 (4%)
Any Serious AEs	4 (<1%)	3 (<1%)	3 (<1%)	6 (<1%)
Any Treatment-Emergent AEs Leading to Discontinuation	1 (<1%)	3 (<1%)	5 (<1%)	4 (<1%)

Source: Reviewer's Analysis.
(1) Assessed by investigator as possibly drug-related.

Table 18: Treatment-Related(1) Treatment-Emergent Adverse Events by Gender (Pooled Trials, Safety Population)

	Males		Females	
System Organ Class / Preferred Term	ACZONE (N=953)	Vehicle (N=965)	ACZONE (N=1208)	Vehicle (N=1210)
Eye disorders				
Eyelid rash	1 (0.1%)	0	0	0
Lacrimation increased	0	0	1 (0.1%)	0
Blepharitis	0	1 (0.1%)	0	0
Gastrointestinal disorders				
Chapped lips	0	0	1 (0.1%)	0
General disorders and administration site conditions				
Application site dryness	6 (0.6%)	10 (1.0%)	18 (1.5%)	11 (0.9%)
Application site pruritus	5 (0.5%)	5 (0.5%)	15 (1.2%)	6 (0.5%)
Application site erythema	3 (0.3%)	5 (0.5%)	11 (0.9%)	8 (0.7%)
Application site pain	4 (0.4%)	12 (1.5%)	5 (0.4%)	20 (1.7%)
Application site exfoliation	2 (0.2%)	6 (0.6%)	7 (0.6%)	8 (0.7%)
Application site paraesthesia	2 (0.2%)	3 (0.3%)	3 (0.2%)	4 (0.3%)
Application site irritation	0	0	3 (0.2%)	0
Application site acne	0	1 (0.1%)	2 (0.2%)	1 (0.1%)
Application site dermatitis	0	0	1 (0.1%)	1 (0.1%)
Application site discomfort	0	0	1 (0.1%)	0
Application site photosensitivity reaction	1 (0.1%)	0	0	0
Application site reaction	0	0	1 (0.1%)	0
Application site swelling	0	0	1 (0.1%)	0
Application site vesicles	0	0	1 (0.1%)	0
Application site papules	0	0	0	1 (0.1%)
Application site warmth	0	1 (0.1%)	0	0
Nervous system disorders				
Dizziness	0	0	1 (0.1%)	0
Psychiatric disorders				
Depression	0	0	0	1 (0.1%)
Skin and subcutaneous tissue disorders				
Skin tightness	0	0	3 (0.2%)	1 (0.1%)
Seborrhoea	0	0	2 (0.2%)	1 (0.1%)
Pruritis	0	0	1 (0.1%)	0
Skin irritation	0	1 (0.1%)	0	0
Sticky skin	0	0	0	1 (0.1%)

Source: Reviewer's Analysis.
(1) Assessed by investigator as possibly drug-related.

Table 19: Overview of Adverse Events Reported by Amount of Product Used (Pooled Trials; Safety Population)

	Averaged < 0.8 g/day		Averaged ≥ 0.8 g/day	
Subjects With:	ACZONE (N=1561)	Vehicle (N=1559)	ACZONE (N=546)	Vehicle (N=573)
Any Treatment-Emergent AEs	308 (20%)	314 (20%)	86 (16%)	92 (16%)
Any Drug-Related(1) AEs	52 (3%)	55 (4%)	22 (4%)	16 (3%)
Any Serious AEs	5 (<1%)	8 (<1%)	2 (<1%)	1 (<1%)
Any Treatment-Emergent AEs Leading to Discontinuation	5 (<1%)	6 (<1%)	1 (<1%)	1 (<1%)

Source: Reviewer's Analysis.
(1) Assessed by investigator as possibly drug-related.

Table 20: Treatment-Related[(1)] Treatment-Emergent Adverse Events by Amount of Product Used (Pooled Trials, Safety Population)

	Averaged < 0.8 g/day		Averaged ≥ 0.8 g/day	
System Organ Class / Preferred Term	**ACZONE (N=1561)**	**Vehicle (N=1559)**	**ACZONE (N=546)**	**Vehicle (N=573)**
Eye disorders				
Eyelid rash	1 (0.1%)	0	0	0
Lacrimation increased	0	0	1 (0.2%)	0
Blepharitis	0	1 (0.1%)	0	0
Gastrointestinal disorders				
Chapped lips	1 (0.1%)	0	0	0
General disorders and administration site conditions				
Application site dryness	16 (1.0%)	11 (0.7%)	8 (1.5%)	9 (1.6%)
Application site pruritus	14 (0.9%)	10 (0.6%)	5 (0.9%)	1 (0.2%)
Application site erythema	9 (0.6%)	10 (0.6%)	5 (0.9%)	3 (0.5%)
Application site pain	5 (0.3%)	25 (1.6%)	4 (0.7%)	5 (0.9%)
Application site exfoliation	8 (0.5%)	10 (0.6%)	1 (0.2%)	4 (0.7%)
Application site paraesthesia	4 (0.3%)	5 (0.3%)	1 (0.2%)	2 (0.3%)
Application site irritation	1 (0.1%)	0	2 (0.4%)	0
Application site acne	1 (0.1%)	2 (0.1%)	1 (0.2%)	0
Application site dermatitis	1 (0.1%)	1 (0.1%)	0	0
Application site discomfort	1 (0.1%)	0	0	0
Application site photosensitivity reaction	1 (0.1%)	0	0	0
Application site reaction	1 (0.1%)	0	0	0
Application site swelling	0	0	1 (0.2%)	0
Application site vesicles	0	0	1 (0.2%)	0
Application site papules	0	1 (0.1%)	0	0
Application site warmth	0	1 (0.1%)	0	0
Nervous system disorders				
Dizziness	1 (0.1%)	0	0	0
Psychiatric disorders				
Depression	0	1 (0.1%)	0	0
Skin and subcutaneous tissue disorders				
Skin tightness	2 (0.1%)	1 (0.1%)	1 (0.2%)	0
Seborrhoea	2 (0.1%)	0	0	1 (0.2%)
Pruritis	0	0	1 (0.2%)	0
Skin irritation	0	0	0	1 (0.2%)
Sticky skin	0	1 (0.1%)	0	0

Source: pg. 39 of Summary of Clinical Safety.

(1) Assessed by investigator as possibly drug-related.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Country

The results for the co-primary efficacy endpoints by gender, race, age (12-17 and 18+), and country (U.S. and Canada) are presented in Tables 21 and 22 for Trials 006 and 007, respectively.

For gender, the treatment effect was greater in females for all three co-primary endpoints in both trials. Results in the race subgroups are mixed in Trials 006 and 007. In Trial 006, the treatment effects for Whites and Blacks were generally similar across the co-primary endpoints; however, for Other (Hispanic, Asian and Other) the treatment effect on GAAS success was slightly smaller than the other two subgroups. In Trial 007, the treatment effects for Whites and Others were generally similar across the co-primary endpoints; however, the treatment effect on GAAS success was slightly smaller than the other two subgroups. In addition, the mean absolute change in inflammatory lesion counts for Blacks treated with vehicle gel was slightly higher than Blacks treated with ACZONE gel, 7.5%. For age, adult subjects had better results than adolescent subjects for ACZONE gel, 7.5% and vehicle gel in all three co-primary efficacy endpoints. In both trials, the treatment effect on GAAS success was greater in adult subjects than adolescent subjects; however, for change in inflammatory and non-inflammatory lesion counts, the treatment effect was equal or greater in adolescent subjects than adult subjects. The majority of the subjects enrolled in the trials were from the U.S. (approximately 96%); therefore, it would be difficult to detect any differences in efficacy for subjects from Canada.

Table 21: Co-Primary Efficacy Results at Week 12 by Gender, Race, Age, and Country for Trial 006 (MI, ITT)

	GAAS (none or minimal)		Absolute Change in Inflammatory Lesions		Absolute Change in Non-Inflammatory Lesions	
Subgroup (N_A, N_V)	ACZONE (N=1044)	Vehicle (N=1058)	ACZONE (N=1044)	Vehicle (N=1058)	ACZONE (N=1044)	Vehicle (N=1058)
Gender						
Male (453, 476)	24%	18%	15.0	13.4	18.7	16.5
Female (591, 582)	34%	24%	17.0	15.0	22.3	19.3
Race						
White (647, 623)	28%	19%	15.6	13.2	19.4	16.7
Black (173, 189)	31%	22%	16.5	15.8	21.3	18.4
Other(1) (224, 246)	33%	27%	17.6	16.0	24.4	21.1
Age						
12-17 (525, 554)	24%	17%	15.2	12.9	19.5	15.3
18+ (519, 504)	36%	26%	17.1	15.8	22.0	21.0
Country						
U.S. (984, 997)	30%	22%	16.2	14.3	20.9	18.2
Canada (60, 61)	26%	9%	15.2	15.0	18.4	15.6

Source: Reviewer's Analysis
*The values displayed are the averages over the 20 imputed datasets (MI).
(1) Other: Hispanic, Asian and Other.

Table 22: Co-Primary Efficacy Results at Week 12 by Gender, Race, Age, and Country for Trial 007 (MI, ITT)

	GAAS (none or minimal)		Absolute Change in Inflammatory Lesions		Absolute Change in Non-Inflammatory Lesions	
Subgroup (N_A, N_V)	ACZONE (N=1118)	Vehicle (N=1120)	ACZONE (N=1118)	Vehicle (N=1120)	ACZONE (N=1118)	Vehicle (N=1120)
Gender						
Male (500, 489)	25%	19%	14.6	13.3	18.2	18.1
Female (618, 631)	33%	22%	16.5	14.6	23.0	19.1
Race						
White (601, 619)	29%	19%	15.3	13.1	19.1	16.4
Black (230, 220)	34%	28%	16.9	17.0	23.4	22.4
Other(1) (287, 281)	30%	19%	15.3	13.8	22.4	20.7
Age						
12-17 (541, 530)	21%	16%	14.6	13.0	17.9	15.3
18+ (577, 590)	38%	26%	16.5	14.9	23.6	21.7
Country						
U.S. (1057, 1058)	30%	21%	15.8	14.5	21.5	19.0
Canada (61, 62)	25%	15%	12.2	7.0	10.1	13.1

Source: Reviewer's Analysis
*The values displayed are the averages over the 20 imputed datasets (MI).
(1) Other: Hispanic, Asian and Other.

4.2 Center

Trial 006 enrolled subjects from 105 centers (96 in U.S. and 9 in Canada) and Trial 007 enrolled subjects from 103 centers (93 in U.S. and 10 in Canada). The SAP specified pooling centers that enrolled less than 24 subjects. The applicant pooled centers based on 5 regional areas (i.e., Canada, northeastern states of U.S., southern states of U.S., west coast states of U.S., and all other states of the U.S.). For Trial 006, a total of 67 centers did not meet the minimum and the pooling process yielded 58 analysis centers (36 unpooled and 22 pooled). For Trial 007, a total of 72 centers did not meet the minimum and the pooling process yielded 54 analysis centers (28 unpooled and 26 pooled).

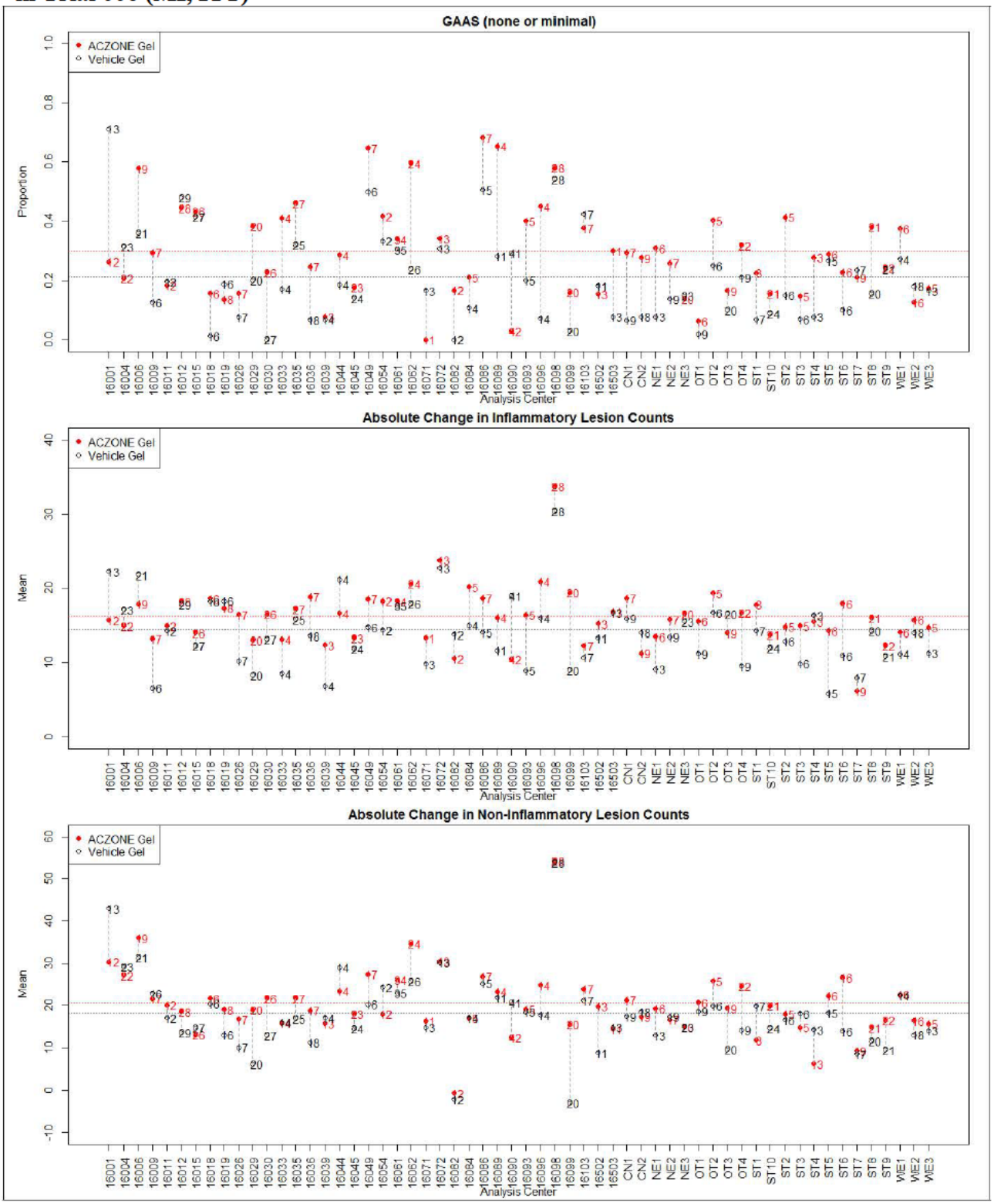
Figures 3 and 4 present the results for the co-primary efficacy endpoints at Week 12 by analysis centers for Trials 006 and 007, respectively. Efficacy results varied among centers. Some centers had higher efficacy with vehicle gel than with ACZONE gel, 7.5%. Per the protocol, the applicant conducted the Breslow-Day test for homogeneity of the odds ratio across strata at the $\alpha = 0.10$ level for the co-primary endpoint of GAAS success at Week 12. The p-value for the Breslow-Day test across analysis center was 0.100 for Trial 006 and 0.619 for Trial 007. For absolute change in inflammatory and non-inflammatory lesion counts, the protocol specified evaluating the treatment-by-analysis center interaction at the $\alpha = 0.10$ level. For Trial 006, the p-values for the interactions were 0.017 and 0.288 for absolute change in inflammatory and non-inflammatory lesion counts, respectively. For Trial 007, the p-values for the interactions were 0.102 and 0.209 for absolute change in inflammatory and non-inflammatory lesion counts, respectively.

For Trial 006, the applicant stated that additional sensitivity analysis was performed to investigate the potential source of the interaction (i.e., p-value = 0.017 for inflammatory lesion

counts) and center 16090 was identified. For this center, the vehicle arm had much better results than the ACZONE arm on all three co-primary efficacy endpoints. After removing this center, the p-value for the Breslow-Day test became 0.517 and the p-values for the treatment-by-analysis center for inflammatory lesion counts and non-inflammatory lesion counts became 0.526 and 0.691, respectively. For Trial 007, none of the p-values were less than 0.10, thus the applicant did not conduct any sensitivity analyses.

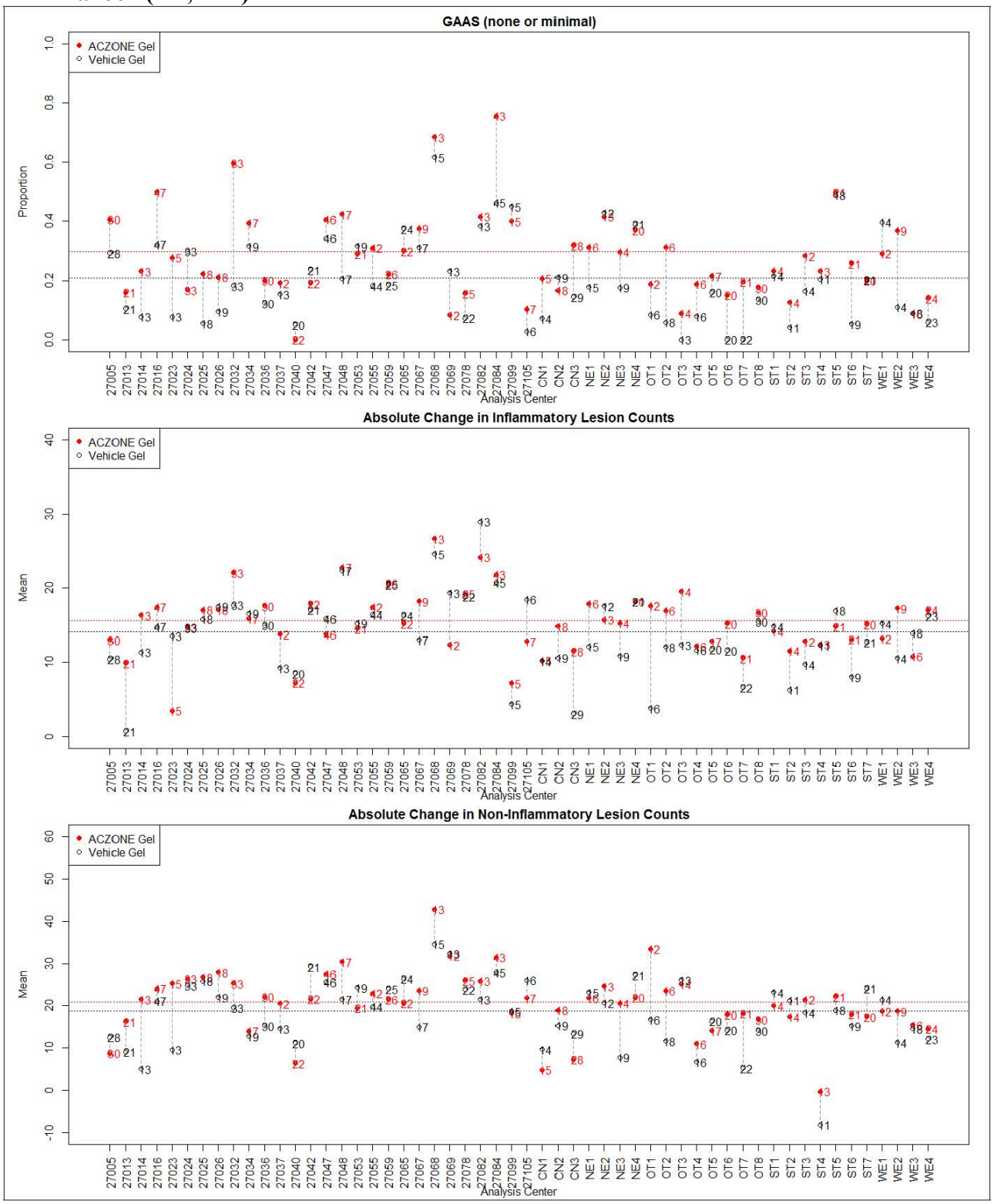
As the pooling process could mask center effects, this reviewer conducted a sensitivity analysis where each center (prior to pooling) was removed. The removal of any one center did not affect the overall conclusions in Trial 006 (p-values ≤ 0.001) and Trial 007 (p-values ≤ 0.01).

Figure 3: Results for the Co-Primary Efficacy Endpoints at Week 12 by Analysis Centers in Trial 006 (MI, ITT)



Source: Reviewer's Analysis

Figure 3: Results for the Co-Primary Efficacy Endpoints at Week 12 by Analysis Centers in Trial 007 (MI, ITT)



Source: Reviewer's Analysis

Two centers [redacted] in Trial 006 and three centers [redacted]) in Trial 007 had investigators with disclosable financial interests. Table 23 presents the co-primary efficacy results at Week 12 with and without the centers with financial disclosures. The results are very similar with and without these centers, and these centers did not affect the overall conclusion.

Table 23: Co-Primary Efficacy Results at Week 12 for All Centers and Centers with Financial Disclosures Removed (MI, ITT)

		GAAS (none or minimal)		Absolute Change in Inflammatory Lesions		Absolute Change in Non-Inflammatory Lesions	
		ACZONE	Vehicle	ACZONE	Vehicle	ACZONE	Vehicle
Trial 006[1]	**All Centers**	N=1044	N=1058	N=1044	N=1058	N=1044	N=1058
	Rate/Change	30%	21%	16.1	14.3	20.7	18.0
	P-value	<0.001[2]		<0.001[3]		<0.001[3]	
	Centers with Disclosures Removed	N=1027	N=1040	N=1027	N=1040	N=1027	N=1040
	Rate/Change	30%	21%	16.1	14.3	20.8	18.1
	P-value	<0.001[2]		<0.001[3]		<0.001[3]	
Trial 007	**All Centers**	N=1118	N=1120	N=1118	N=1120	N=1118	N=1120
	Rate/Change	30%	21%	15.6	14.0	20.8	18.7
	P-value	<0.001[2]		<0.001[3]		0.004[3]	
	Centers with Disclosures Removed	N=1108	N=1104	N=1108	N=1104	N=1108	N=1104
	Rate/Change	30%	21%	15.6	14.1	20.9	18.8
	P-value	<0.001[2]		<0.001[3]		0.006[3]	

Source: Reviewer's Analysis
*The values displayed are the averages over the 20 imputed datasets (MI).
(1) Excluding subjects from center 16078 (a total of 51 subjects).
(2) P-value based on a CMH test stratified by gender.
(3) P-value from an ANCOVA model with terms for treatment, gender, and baseline lesion counts.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The applicant submitted data from two identically-designed, randomized, multicenter, vehicle-controlled, parallel-group, Phase 3 trials (Trials 006 and 007). The protocol-specified co-primary efficacy endpoints were the proportion of subjects achieving a GAAS score of 0 (none) or 1 (minimal) at Week 12 and the absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12. Secondary efficacy endpoints included absolute change in total lesion counts from baseline to Week 12, percent change in lesion counts (total, inflammatory and non-inflammatory) from baseline to Week 12, proportion of subjects who report "very good" or "excellent" in Item 10 from the Acne Symptom and Impact Scale (ASIS) at Week 12, absolute change in ASIS Sign Domain Score from baseline to Week 12, proportion of subjects with at least a 1-grade improvement on Item 1 from the ASIS (subject's assessment of oiliness on the

face) at Week 12, and proportion of subjects with at least a 1-grade improvement on Item 8 from the ASIS (subject's assessment of redness on the face) at Week 12.

Table 24 presents the results of the co-primary efficacy endpoints and the secondary efficacy endpoints of percent change in inflammatory and inflammatory lesion counts from baseline to Week 12. In both trials, ACZONE gel, 7.5% was statistically superior (p-values ≤ 0.004) to vehicle gel for all endpoints presented in Table 24. Results for the other secondary efficacy endpoints are presented in Section 3.2.5.

Table 24: Results for the Co-Primary and Secondary Efficacy Endpoints at Week 12

	Trial 006		Trial 007	
Endpoints	**ACZONE (N=1044)**	**Vehicle (N=1058)**	**ACZONE (N=1118)**	**Vehicle (N=1120)**
Co-Primary:				
GAAS (none or minimal): n (%)	30%	21%	30%	21%
Absolute Change in:				
Inflammatory Lesions: Mean	16.1	14.3	15.6	14.0
Non-Inflammatory Lesions: Mean	20.7	18.0	20.8	18.7
Secondary:				
Percent Change in:				
Inflammatory Lesions: Mean	56%	49%	54%	48%
Non-Inflammatory Lesions: Mean	45%	39%	46%	41%

Source: Reviewer's Analysis (same as Applicant's Analysis)

For the assessment of GAAS, the interpretation of a "few" or "no" lesions seemed to vary from investigator to investigator. Some subjects counted as successes under the GAAS seemed to have relatively high lesion counts for the definition of "none" (no evidence of facial acne vulgaris) or "minimal" (a few non-inflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) may be present). Subjects scored as 0 (none) had as many as 10 inflammatory lesions or 45 non-inflammatory lesions. Subjects scored as 1 (minimal) had as many as 57 inflammatory lesions and 102 non-inflammatory lesions. This reviewer conducted a sensitivity analysis where subjects with a GAAS score of 0 or 1 were imputed as failures if they had a certain number of inflammatory or non-inflammatory lesion counts, see Section 3.2.6 for more detail. While the response rates and treatment effect decreased with the stricter requirement for success, the treatment effect remained statistically significant (p-values ≤ 0.002) in both trials.

For the handling of missing data, the results were similar between the primary imputation method (i.e., multiple imputation using a regression model) and the applicant's pre-specified sensitivity analyses. For the co-primary efficacy endpoint of IGA success, this reviewer conducted a sensitivity analysis where missing data was imputed as failures. In addition, for all three co-primary efficacy endpoints, this reviewer conduct an additional sensitivity analysis where missing data was imputed using the multiple imputation Markov Chain Monte Carlo (MI-MCMC) approach. For both trials, the results were generally similar across the various methods for handling missing data.

Efficacy rates varied among centers. Some centers had higher efficacy with vehicle gel than with ACZONE gel, 7.5%; however, this is not surprising given the modest treatment effect. The applicant's investigation of the treatment-by-center interaction focused on the effects after pooling. As the pooling process could mask center effects, this reviewer conducted a sensitivity analysis where each center (prior to pooling) was removed. The removal of any one center did not affect the overall conclusions in Trial 006 (p-values ≤ 0.001) and Trial 007 (p-values ≤ 0.01). Two centers ([redacted] (b) (6)) in Trial 006 and three centers ([redacted] (b) (6)) in Trial 007 had investigators with disclosable financial interests. The results with and without these centers were very similar, and these centers did not affect the overall conclusion, see Section 4.2 for more detail.

Examination of subgroups indicated that gender and age have an impact on efficacy results with females and adults generally having better outcomes than males and adolescents; however, the treatment differences across subgroups did not vary greatly (i.e., females and adults had better results on both the ACZONE and vehicle arms).

5.2 Conclusions and Recommendations

Efficacy findings from two pivotal Phase 3 trials (Trials 006 and 007) established the efficacy of ACZONE® (dapsone) gel, 7.5% for the topical treatment of acne vulgaris.

APPENDIX

A.1 Acne Symptom and Impact Scale (ASIS) [Items 1 to 10]

Instructions: Please read and answer each of the following questions. Before answering each question, **look in the mirror and think about the acne on your face**. Select one answer that best describes your experience with acne **right now**. There are no right or wrong answers. Please see the example below.

1. How oily is your face right now?
   - ☐0 Not at all
   - ☐1 A little
   - ☐2 Somewhat
   - ☐3 Quite a bit
   - ☐4 Very
2. How many pimples do you have on your face right now?
   - ☐0 None
   - ☐1 A few
   - ☐2 Some
   - ☐3 Quite a bit
   - ☐4 A lot
3. How many acne scars (holes or indents) do you have on your face right now?
   - ☐0 None
   - ☐1 A few
   - ☐2 Some
   - ☐3 Quite a bit
   - ☐4 A lot
4. How many scabs from acne do you have on your face right now?
   - ☐0 None
   - ☐1 A few
   - ☐2 Some
   - ☐3 Quite a bit
   - ☐4 A lot
5. How many dark marks from acne do you have on your face right now?
   - ☐0 None
   - ☐1 A few
   - ☐2 Some
   - ☐3 Quite a bit
   - ☐4 A lot

6. How many blackheads do you have on your face right now?

- ☐0 None
- ☐1 A few
- ☐2 Some
- ☐3 Quite a bit
- ☐4 A lot

7. How many whiteheads do you have on your face right now?

- ☐0 None
- ☐1 A few
- ☐2 Some
- ☐3 Quite a bit
- ☐4 A lot

8. How much redness do you have on your face right now?

- ☐0 None
- ☐1 A little
- ☐2 Some
- ☐3 Quite a bit
- ☐4 A lot

9. Overall, how is the acne on your face right now?

- ☐0 Clear
- ☐1 Almost clear
- ☐2 Mild
- ☐3 Moderate
- ☐4 Severe

Instructions: Please read and answer each of the following questions. Before answering each question, **look in the mirror and think about the acne on your face**. Select one answer that best describes your experience with acne in the **past 7 days**. There are no right or wrong answers.

10. Over the past 7 days, rate how your face looked because of your acne.

- ☐1 Excellent
- ☐2 Very good
- ☐3 Good
- ☐4 Fair
- ☐5 Bad

SIGNATURES/DISTRIBUTION LIST

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Date: January 14, 2016

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