

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-070

STATISTICAL REVIEW(S)



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

STATISTICAL REVIEW AND EVALUATION

NEW DRUG APPLICATION

CLINICAL STUDIES

NDA/Serial Number: 22-070 / N-000
Drug Name: Atralin (tretinoin) gel
Indication(s): Acne vulgaris
Applicant: Coria Laboratories
Dates: Submitted: September 29, 2006
PDUFA: July 29, 2007

Review Priority: Standard review

Biometrics Division: Division of Biometrics III
Statistics Reviewer: Kathleen Fritsch, Ph.D.
Concurring Reviewer: Mohamed Alish, Ph.D.

Medical Division: Division of Dermatology and Dental Products
Clinical Team: David Kettl, M.D. / Markham Luke, M.D., Ph.D.
Project Manager: Melinda Bauerlien

Keywords: 505 (b) 2

Table of Contents

1	EXECUTIVE SUMMARY	3
1.1	Conclusions and Recommendations.....	3
1.2	Brief Overview of Clinical Studies	3
1.3	Statistical Issues and Findings	4
2	INTRODUCTION.....	4
2.1	Overview	4
2.2	Data Sources	5
3	STATISTICAL EVALUATION.....	5
3.1	Evaluation of Efficacy.....	5
3.1.1	Study Design.....	5
3.1.1.1	Study 009	5
3.1.1.2	Study 0418	7
3.1.2	Subject Disposition and Demographics	9
3.1.3	Demographic and Baseline Data.....	10
3.1.4	Efficacy Results	12
3.1.5	Efficacy by Center	16
3.1.6	Impact of Changes to Global Severity Score Analyses between Studies ..	18
3.2	Evaluation of Safety	19
3.2.1	Extent of Exposure.....	19
3.2.2	Adverse Events	19
4	FINDINGS IN SPECIAL/SUBGROUP POPULATIONS.....	22
4.1	Gender, Race, and Age	22
4.2	Other Special/Subgroup Populations.....	24
5	SUMMARY AND CONCLUSIONS.....	25
5.1	Statistical Issues and Collective Evidence.....	25
5.2	Conclusions and Recommendations.....	26
	APPENDIX – ADDITIONAL FIGURES.....	26
	SIGNATURES/DISTRIBUTION LIST	28

1 Executive Summary

1.1 Conclusions and Recommendations

Studies 009 and 0418 demonstrate that tretinoin gel 0.05% is superior to vehicle gel in the treatment of acne vulgaris. Study 009 was a three-arm study designed to demonstrate that tretinoin gel 0.05% was superior to vehicle gel and non-inferior to Retin-A Micro 0.1%. Although tretinoin gel was superior to vehicle for all of the pre-specified efficacy endpoints ($p < 0.0022$), the 0.05% tretinoin gel was not able to demonstrate non-inferiority to the 0.1% Retin-A Micro (lower 97.5% confidence bounds $\leq -13\%$ with a 10% non-inferiority margin). Since the sponsor was unable to build an efficacy bridge to the listed product for this 505(b)2 application, the sponsor conducted a second two-arm study (0418) to demonstrate that tretinoin gel was superior to vehicle. Tretinoin gel was superior to vehicle in Study 0418 on all pre-specified endpoints ($p < 0.0021$).

1.2 Brief Overview of Clinical Studies

The sponsor's original development plan for tretinoin gel 0.05% in the treatment of acne vulgaris was to conduct one three-arm study to support a 505(b)2 application with listed drug Retin-A Micro (tretinoin) 0.1% (Study 009). The study demonstrated that tretinoin gel was superior to vehicle but could not demonstrate that tretinoin gel was non-inferior to Retin-A Micro. After meeting with the Agency (December 2, 2004), the sponsor agreed to revise their development plan and conduct a second study so that the efficacy assessment could be based on two studies with vehicle control arms with the Retin-A Micro arm of the first study providing a bridge to the Agency's findings of safety for the listed product. Features of the clinical studies are presented in Table 1.

Table 1 – Clinical Study Program for Tretinoin Gel

Study	Treatment Arms	No. of Subjects	Study Dates
735.126.CL009	Tretinoin Gel 0.05%	375	November 2002 – December 2003
	Retin-A Micro 0.1%	376	
	Vehicle Gel	185	
20.CLN.126.0418	Tretinoin Gel 0.05%	299	June 2005 – February 2006
	Vehicle Gel	302	

The two studies differed slightly in their inclusion criteria and primary endpoints. In Study 009, the sponsor did not include lesions on the nose in the lesion counts. During the protocol review, the Agency requested that the sponsor record nasal lesion counts. The original protocol called for the collection of nasal lesion counts at Week 12 but not at baseline, and the primary analyses were not designed to incorporate nasal lesion counts. During the study the sponsor modified the protocol to include the recording of baseline nasal lesion counts, however approximately 50% of subjects were enrolled in the study before the amendment took effect and did not have nasal lesion counts at baseline. Another difference in inclusion criteria between the two studies was the acceptable range of baseline global severity scale scores. In Study 009 subjects were to have a baseline

global score of mild (2), mildly-moderate (3), or moderate (4). In Study 0418 subjects were limited to baseline global score of mildly-moderate (3) or moderate (4).

The pre-specified primary endpoints also differed slightly in the two studies, reflecting changes in the Agency's recommendations for acne endpoints over the study period. The first study (009) was designed to demonstrate statistical significance for the *percent* reduction in two out of three lesion counts from baseline to Week 12 (inflammatory, non-inflammatory, and total) as well as for the proportion of subjects achieving scores of 0 (clear) or 1 (very mild) on the global scale at Week 12. Study 0418 was designed to demonstrate statistical significance for the *absolute* reduction in inflammatory and non-inflammatory lesions from baseline to Week 12, as well as for the proportion of subjects achieving scores of 0 or 1 on the global scale with at least 2 grades reduction at Week 12. Note that Study 0418 required at least a 2 grade reduction on the global scale for success while Study 009 did not. However, Study 0418 also required a baseline score of at least 3 so that by default all subjects would need at least a 2 grade reduction to achieve a score of 0 or 1. The protocol for Study 009 permitted subjects with baseline scores of 2 to have Week 12 scores of 1 and be considered global successes.

1.3 Statistical Issues and Findings

In Study 009, tretinoin gel was superior to vehicle for all pre-specified endpoints (percent reductions in lesion counts and clear (0) or very mild (1) on the global). Tretinoin gel was also superior to vehicle in Study 009 when using the same endpoints that were pre-specified for Study 0418 (absolute reduction in lesion counts and clear (0) or very mild (1) with at least 2 grades reduction on the global). Tretinoin gel was not non-inferior to Retin-A Micro. Tretinoin gel was also superior to vehicle for all pre-specified endpoints (absolute reduction in lesion counts and clear (0) or very mild (1) with at least 2 grades reduction on the global) in Study 0418. Efficacy results for all primary endpoints are presented in Table 10 and Table 12 on page 13.

The most common adverse events were skin-related and included dry skin, skin exfoliation, erythema, and skin burning. The incidence of these events appears to be related to the dose of tretinoin with Retin-A Micro 0.1% having the highest rates, with tretinoin gel 0.05% in the middle, followed by vehicle with low incidence rates.

2 Introduction

2.1 Overview

Tretinoin in concentrations from 0.01% to 0.1% has been marketed for the treatment of acne in various topical dosage forms (solutions, creams, and gels) since 1971. In this application, the sponsor has evaluated a gel formulation of tretinoin at a concentration of 0.05%. Tretinoin at a 0.05% concentration has been approved as a cream and solution (Retin-A cream and solution 0.05%, plus generics). Available gel formulations of tretinoin include Retin-A gel 0.01% and 0.025% (plus generics) and Retin-A Micro 0.04% and 0.1%. This application is a 505 (b) 2 application with Retin-A Micro 0.1% as the reference listed drug.

The sponsor conducted two Phase 3 studies for this application. The first study (Study 735.126.CL009) was a three-arm study comparing tretinoin gel 0.05% to vehicle and Retin-A Micro 0.1%. The study was conducted from November 2002 to December 2003 and enrolled 936 subjects. This study demonstrated the superiority of tretinoin gel 0.05% to its vehicle, but failed to demonstrate that tretinoin gel 0.05% was non-inferior to Retin-A Micro 0.1%. Since Retin-A Micro 0.1% has twice the amount of tretinoin as the tretinoin gel 0.05%, the failure to demonstrate non-inferiority is not too surprising. Because the study was unable to build a bridge to the Agency's findings of efficacy for Retin-A Micro 0.1%, the Agency and sponsor agreed at a guidance meeting held December 2, 2004 that a second study demonstrating the superiority of tretinoin gel to vehicle would be needed to establish efficacy. The second study (Study 20.CLN.126.0418) was a two-arm study comparing tretinoin gel to its vehicle. The study was conducted from June 2005 to February 2006 and enrolled 601 subjects. Study 0418 was evaluated under a special protocol assessment (letter date March 29, 2005).

2.2 Data Sources

This reviewer evaluated the sponsor's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was submitted in eCTD format and was entirely electronic. The datasets used in this review are archived at [\\cdsesub1\evsprod\NDA022070\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\acne-vulgaris\5351-stud-rep-contr.](#)

3 Statistical Evaluation

3.1 Evaluation of Efficacy

This application for tretinoin gel 0.05% has been submitted as a 505 (b) 2 application with Retin-A Micro (tretinoin) gel 0.1% as the reference listed drug. The sponsor's original development plan was to establish efficacy by conducting one three-arm study (Study 009) demonstrating that tretinoin gel was superior to vehicle gel and non-inferior to Retin-A Micro. Although the study demonstrated that tretinoin gel was superior to its vehicle, it failed to demonstrate that tretinoin gel was non-inferior to Retin-A Micro. Consequently, the sponsor conducted a second study (Study 0418) to demonstrate the superiority of tretinoin gel over its vehicle. Thus, the sponsor is relying on comparisons to vehicle from two studies to establish the efficacy of tretinoin gel in the treatment of acne. The Retin-A Micro arm will be used to establish a clinical bridge to the Agency's findings of safety only for Retin-A Micro.

3.1.1 Study Design

3.1.1.1 Study 009

Study 735.126.CL009 is a randomized, investigator-blind, three-arm study comparing tretinoin gel 0.05% to vehicle and Retin-A Micro 0.1% in subjects age 10 and older. At baseline, subjects were to have mild (2), mildly moderate (3), or moderate (4) scores on the acne global severity scale, 30 to 125 facial (excluding the nose) non-inflammatory lesions, and 15 to 40 facial (excluding the nose) inflammatory lesions. Subjects were

allowed to have up to 3 non-inflamed nodules/cysts that were counted separately. The study enrolled 936 subjects (375 tretinoin gel 0.05%, 376 Retin-A Micro 0.1%, and 185 vehicle gel) at 22 U.S. centers. Subjects applied treatment once per day at bedtime. Subjects were evaluated at baseline and Weeks 1, 2, 4, 8, 12.

The primary efficacy endpoints were the percent reduction in lesion counts in two out of three lesion groups (inflammatory, non-inflammatory, and total), and success on the global severity score (clear or very mild). The global severity scale is presented in Table 2. The study was designed to demonstrate the superiority of tretinoin gel 0.05% to its vehicle and to demonstrate the non-inferiority of tretinoin gel 0.05% to Retin-A Micro 0.1% on both the lesion count and global severity scale endpoints. The pre-specified non-inferiority margin for all endpoints was 10%.

Table 2 – Global Severity Scale

GRADE	DESCRIPTION	
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Very Mild	Skin almost clear; rare non-inflammatory lesions present, with rare non-inflamed papules (papules may be hyperpigmented, though not pink-red, less than 4 lesions)
2	Mild	Some non-inflammatory lesions present, with few inflammatory lesions (papules/pustules only, no nodulo-cystic lesions) Less than half of the face involved.*
3	Mildly Moderate	Non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules only, and there may or may not be 1 small nodulo-cystic lesion. More than half of the face involved.*
4	Moderate	Inflammatory lesions are more apparent: many comedones and papules/pustules, there may or may not be a few nodulo-cystic lesions. Entire face involved.*
5	Severe	Highly inflammatory lesions predominate: variable number of comedones, many papules/pustules and nodulo-cystic lesions.

* The global severity scale used in Study 0418 was identical to the scale used in Study 009, except that it did not include the descriptions “less than half of the face involved” (for grade 2), “more than half of the face involved” (for grade 3), or “entire face involved” (for grade 4).

The superiority analyses were based on the ITT population. Success on the global severity score was to be analyzed with a Cochran-Mantel-Haenszel test stratified on investigator. The percent change in lesion count variables were to be analyzed with an ANOVA (restricted to the tretinoin 0.05% and vehicle arms) with factors for treatment and investigator. According to the statistical analysis plan, if the test for skewness (not otherwise specified) is significant at 0.01 then the analysis would be based on analysis of variance applied to the ranks. No additional details about the test for skewness are provided in the analysis plan or study report (including the observed p-value), however, the primary analyses presented in the study report are based on ranked data.

The non-inferiority analyses were based on both the ITT and per protocol populations. For success on the global severity score, the non-inferiority of tretinoin 0.05% to Retin-A Micro was evaluated with a 10% non-inferiority margin and a 97.5% one-sided confidence interval based on the following formula (Wald's formula with Yates continuity correction, where T =test and R =reference):

$$P_T - P_R - z_{\alpha/2} \sqrt{P_T(1-P_T)/n_T + P_R(1-P_R)/n_R - (1/n_T + 1/n_R)/2}$$

For the percent reduction in lesion counts, the sponsor used an iterative procedure to identify the value of delta such that, when delta is subtracted from each observation in the tretinoin 0.05% arm, the test procedure (ANOVA on the ranks) yields a two-sided p-value of 0.05. In the parametric case (ANOVA on the original values) the delta identified through iteration is equivalent to the 97.5% lower confidence bound. This procedure introduces the ranking step and posits that the identified delta can still be considered a 97.5% lower confidence bound. The procedure is limited to the tretinoin 0.05% and Retin-A micro arms.

The ITT population was defined as all subjects randomized and dispensed study medication. Subjects included in the per protocol population: met the inclusion criteria for lesion counts and global severity, did not take interfering concomitant medications, attended the Week 12 visit (± 3 days) or discontinued due an adverse event related to treatment, did not miss more than one study visit before Week 12, and were compliant with the dosing regimen (did not miss more than 5 consecutive days of dosing and applied 80-120% of expected dosing applications).

In the ITT population, missing lesion count data was imputed using LOCF. For the global evaluation, subjects with missing Week 12 global scores were imputed as failures.

3.1.1.2 Study 0418

Study 0418 was a randomized, investigator-blind, two-arm study comparing tretinoin 0.05% to vehicle in subjects age 10 and older. At baseline, subjects were to have mildly moderate (3), or moderate (4) scores on the acne global severity scale, 30 to 125 facial (including the nose) non-inflammatory lesions, and 15 to 40 facial (including the nose) inflammatory lesions. Subjects were allowed to have up to 3 non-inflamed nodules/cysts that were counted separately. The study enrolled 601 subjects (299 tretinoin gel 0.05% and 302 vehicle gel) at 23 U.S. centers. Subjects applied treatment once per day at bedtime. Subjects were evaluated at baseline and Weeks 1, 2, 4, 8, 12.

The primary efficacy endpoints were the absolute reduction in inflammatory and non-inflammatory lesion counts, and success on the global severity score (clear or very mild with at least 2 grades reduction). The global severity scale is the same as was used in Study 009 except the descriptions of the amount of facial area involved ("less than half of the face involved", "more than half of the face involved", or "entire face involved") were removed. The version of the scale used in Study 009 is presented in Table 2. The study was designed to demonstrate the superiority of tretinoin gel 0.05% to its vehicle. The baseline entry criteria and endpoints in Studies 009 and 0418 had a number of minor

differences, some of which were based on recommendations by the Agency during the review of Protocol 0418. These differences are highlighted in Table 3.

Table 3 – Baseline and Endpoint Differences between Study 009 and Study 0418

	Study 009	Study 0418
Global Severity Scale	Included descriptions of facial area involvement	Did not include descriptions of facial are involvement
Baseline Global Score	Mild (2), mildly moderate (3), or moderate (4)	Mildly moderate (3) or moderate (4)
Treatment success	Clear (0) or very mild (1)	Clear (0) or very mild (1) with at least 2 grades reduction
Lesion Counts	Excluded counts on the nose	Included counts on the nose
Baseline lesion counts	30-125 non-inflammatory (excluding the nose) 15-40 inflammatory (excluding the nose)	30-125 non-inflammatory (including the nose) 15-40 inflammatory (including the nose)
Lesion Count Endpoints	Percent reduction in 2 out of 3 counts (inflammatory, non-inflammatory, total)	Absolute reduction in inflammatory and non-inflammatory lesions

The superiority analyses were based on the ITT population. The primary method of handling missing data was LOCF (for both lesion counts and global success). Success on the global severity score was to be analyzed with a Cochran-Mantel-Haenszel test stratified on investigator. The absolute change in lesion count variables were to be analyzed with an ANOVA with factors for treatment and investigator. If the Wilk-Shapiro test on the residuals was significant at 0.01 then the primary analysis would be based on analysis of variance applied to the ranks with factors of treatment and investigator. The protocol stated that if the ranked ANOVA analysis was selected that the analysis on the original data would be presented as a secondary analysis. The protocol also stated that the percent reduction in lesion counts would be presented as a secondary analysis.

The ITT population was defined as all subjects randomized and dispensed study medication. Subjects included in the per protocol population met the inclusion criteria for lesion counts and global severity, did not take interfering concomitant medications, attended the Week 12 visit (\pm 3 days) or discontinued due an adverse event related to treatment, did not miss more than one study visit before Week 12, and were compliant with the dosing regimen (did not miss more than 5 consecutive days of dosing and applied 80-120% of expected dosing applications).

3.1.2 Subject Disposition and Demographics

Approximately 14% of subjects in Study 009 discontinued early. The discontinuation rate was higher in the tretinoin and vehicle arms than in the Retin-A arm. The most common reason for discontinuation was loss to follow-up, and the loss to follow-up rate was twice as high in the tretinoin gel arm (8%) as it was in either the Retin-A arm or the vehicle arm (3-4%). The next most common reason for discontinuation was 'subject request unrelated to an AE' (4%) and the rate was similar among all three arms. The subject disposition in Study 009 is presented in Table 4.

Table 4 – Subject Disposition (Study 009)

	Tretinoin Gel, 0.05%	RETIN-A Micro, 0.1%	Gel Vehicle
Number of Subjects	375	376	185
Subjects with Normal Study Completion	311 (83%)	338 (90%)	156 (84%)
Reasons for Study Discontinuation			
Adverse Reaction or Event	4 (1%)	3 (1%)	0 (0%)
Lost to Follow-Up	30 (8%)	12 (3%)	8 (4%)
Subject Request Unrelated to an AE	15 (4%)	11 (3%)	8 (4%)
Interfering Therapy	5 (1%)	4 (1%)	5 (3%)
Treatment Failure	1 (<1%)	0 (0%)	2 (1%)
Noncompliance	8 (2%)	8 (2%)	4 (2%)
Incl/Excl Discrepancy/Violation	0 (0%)	0 (0%)	1 (<1%)
Other	1 ^a (<1%)	0 (0%)	1 ^b (<1%)

^a Subject dropped in error

^b Subject wanted to try other treatment

Approximately 13% of subjects in Study 0418 discontinued early. The discontinuation rate was slightly higher in the tretinoin than the vehicle arm. The most common reason for discontinuation was 'subject request unrelated to an AE', and the rate was higher in the tretinoin gel arm (8%) than it was in the vehicle arm (5%). The next most common reason for discontinuation was 'lost to follow-up' and the rate was slightly higher on the tretinoin arm than the vehicle arm (5% vs. 3%). The subject disposition for Study 0418 is presented in Table 5.

Table 5 – Subject Disposition (Study 0418)

	Tretinoin Gel, 0.05%	Gel Vehicle
Number of Subjects	299	302
Subjects with Normal Study Completion	253 (85%)	269 (89%)
Reasons for Study Discontinuation		
Adverse Reaction or Event	4 ^a (1%)	0 (0%)
Lost to Follow-Up	15 (5%)	9 (3%)
Subject Request Unrelated to an AE	23 (8%)	16 (5%)
Interfering Therapy	0 (0%)	0 (0%)
Treatment Failure	0 (0%)	4 (1%)
Noncompliance	4 (1%)	2 (<1%)
Inclusion/Exclusion Discrepancy/Violation	0 (0%)	1 (<1%)
Other	0 (0%)	1 ^b (<1%)

^a One tretinoin subject who discontinued due to an adverse reaction (facial burning and peeling) was found to be pregnant at the exit visit.

^b Investigator's decision

3.1.3 Demographic and Baseline Data

Both studies were fairly balanced across treatment arms for all demographic variables. The average age was 18 to 19 in all arms, with over half of subjects under age 17, including about 3% of subjects aged 10 to 11. About half the subjects were male and half female. Study subjects were predominately Caucasian/white (68% in Study 009; 83% in Study 0418) followed by black (17% in 009 and 13% in 0418). In Study 0418 ethnicity was collected separately from race. In Study 0418, 19% of subjects were Hispanic. The baseline demographic data for the two studies is presented in Table 6 and Table 7.

Table 6 – Demographic Data (Study 009)

		Tretinoin Gel, 0.05% N=375	RETIN-A Micro, 0.1% N=376	Gel Vehicle N=185
Age (years)	Mean	18.2	18.4	19
	Range	10-53	10-45	10-49
	10 - 11	12 (3%)	15 (4%)	5 (3%)
	12 - 16	202 (54%)	190 (51%)	102 (55%)
	≥ 17	161 (43%)	171 (45%)	78 (42%)
Gender	Male	178 (47%)	167 (44%)	88 (48%)
	Female	197 (53%)	209 (56%)	97 (52%)
Race	Caucasian	258 (69%)	262 (70%)	121 (65%)
	Black	57 (15%)	69 (18%)	36 (19%)
	Asian	12 (3%)	10 (3%)	5 (3%)
	Other	48 (13%)	35 (9%)	23 (12%)

Table 7 – Demographic Data (Study 0418)

	Tretinoin Gel, 0.05% N=299	Gel Vehicle N=302
Age (years)		
Mean (Std)	18.7 (6.9)	19.1 (7.8)
Range	10-52	10-65
10 - 11	7 (2%)	7 (2%)
12 - 16	160 (54%)	164 (54%)
≥ 17	132 (44%)	131 (43%)
Gender		
Male	149 (50%)	149 (49%)
Female	150 (50%)	153 (51%)
Ethnicity		
Hispanic/Latino	56 (19%)	57 (19%)
Not Hispanic/Latino	243 (81%)	245 (81%)
Race		
White	250 (84%)	248 (82%)
Black or African American	37 (12%)	41 (14%)
Asian	8 (3%)	7 (2%)
American Indian or Alaska Native	0 (0%)	1 (<1%)
Native Hawaiian or other Pacific Islander	1 (<1%)	0 (0%)
Other	5 (2%)	7 (2%)

In both studies baseline severity measures were fairly balanced across treatment arms. In Study 009, subjects were enrolled with global scores of 2, 3 or 4. Just over half of the subjects were classified as mildly-moderate (3). In Study 0418, subjects were to have global scores of 3 or 4 at baseline, and 61% of subjects were classified as mildly-moderate (3). Subjects in both studies had similar numbers of baseline lesions. Subjects in both studies had an average of 50-52 non-inflammatory lesions, and 23 inflammatory lesions. Of note, the baseline counts for subjects in Study 009 excluded the nose, while the counts in Study 0418 included the nose. Only a subset (approximately 50%) of subjects in Study 009, those enrolled after a protocol amendment, had baseline nasal counts recorded. Among the subset of subjects with baseline nasal lesion counts, subjects averaged about 9 non-inflammatory nasal lesions and 1.7 inflammatory nasal lesions. The baseline severity data is presented in Table 8 and Table 9.

Table 8 – Baseline Severity (Study 009)

	Tretinoin Gel, 0.05%	RETIN-A Micro, 0.1%	Gel Vehicle
Number of Subjects	375	376	185
Global Severity Score			
Mild (2)	97 (26%)	90 (24%)	49 (26%)
Mildly-Moderate (3)	211 (56%)	203 (54%)	98 (53%)
Moderate (4)	67 (18%)	82 (22%)	38 (21%)
Non-Inflammatory Lesion Count ¹			
Mean (Std)	50.7 (21.9)	48.2 (19.6)	52.4 (22.5)
Range	30-122	30 -129	30-122
Non-Inflammatory Nasal Count ²			
Mean (Std)	8.4 (10.7)	8.8 (8.5)	9.8 (9.5)
Range	0 - 100	0 - 39	0 - 45
Inflammatory Lesion Count ¹			
Mean (Std)	23.4 (7.2)	23.6 (7)	23.9 (7.2)
Range	15-43	15-46	15-40
Inflammatory Nasal Count ²			
Mean (Std)	1.5 (1.7)	1.7 (2.3)	1.7 (1.9)
Range	0 - 9	0 - 16	0 - 8

¹ Lesion counts excluded lesions on the nose.

² Baseline nasal lesion counts were collected on a subset of enrolled subjects after a protocol amendment. Baseline nasal lesion counts were collected on 192 tretinoin, 189 Retin-A Micro, and 94 vehicle subjects.

Table 9 – Baseline Severity (Study 0418)

	Tretinoin Gel, 0.05%	Gel Vehicle
Number of Subjects	299	302
Global Severity Score		
Mild (2)	0 (0%)	0 (0%)
Mildly Moderate (3)	189 (63%)	178 (59%)
Moderate (4)	110 (37%)	124 (41%)
Non-Inflammatory Lesion Count ¹		
Mean (Std)	51.9 (21.9)	52.7 (23.3)
Range	25-123	30-186
Inflammatory Lesion Count ¹		
Mean (Std)	22.9 (8)	23.4 (7.3)
Range	15-64	15-40

¹ Lesion counts included the nose.

3.1.4 Efficacy Results

Both studies evaluated inflammatory lesions, non-inflammatory lesions, and global severity, however, the primary analyses differed slightly between the two studies. In Study 009, subjects had scores of 2, 3, or 4 at baseline and success on the global was defined as a score of 0 or 1. In Study 0418, success on the global was defined as a score

of 0 or 1 with at least 2 grades reduction. However, a higher baseline global score was required (3 or 4), so all subjects achieving a score of 0 or 1 would automatically have at least 2 grades reduction. Global success results from Study 009 are presented both as defined in the protocol (0 or 1) and as 0 or 1 with at least 2 grades reduction for consistency with Study 0418. Both studies demonstrated statistical significance for their protocol-specified global success endpoint. Study 009 is also significant if 2 grades reduction is required for the definition of success. Efficacy results are presented in Table 10 and Table 12.

For lesions counts, the primary endpoints for Study 009 were the percent reduction in lesions from baseline to Week 12. For a successful study, two out of inflammatory, non-inflammatory, and total were to have been significant. The percent reductions in both inflammatory and non-inflammatory lesions were significant (as well as for total lesions – results not displayed). Lesion counts in Study 009 excluded the nose. Efficacy results for lesion counts in Study 009 are also presented in Table 10. To see if the exclusion of nasal lesion counts had any impact on the analysis, the lesion count analyses including nasal counts for those subjects with baseline nasal counts were conducted by this reviewer. The results are presented in Table 11. All of the analyses had p-values less than 0.05 except for the absolute reduction in inflammatory lesions (p=0.0687). However the magnitude of the treatment effect for this analysis is not that different from the analysis excluding nasal lesions (3.6 vs. 3.9) and the fact that the analysis including nasal lesions is based on about half of the subjects clearly is an important factor.

In Study 0418, the primary endpoints for lesion counts were the absolute reduction in inflammatory and non-inflammatory lesions. Percent reductions in lesions were secondary endpoints. Tretinoin was superior to vehicle for all lesion analyses in both studies. Lesion counts in Study 0418 included the nose. Efficacy results for lesion counts in Study 0418 are also presented in Table 12.

Table 10 – Efficacy Results at Week 12 - ITT (Study 009)

	Tretinoin Gel 0.05% N=375	RETIN-A Micro, 0.1% N=376	Gel Vehicle N=185	p-value (Tret. vs. Veh.)	LCB (Tret. – Ret.-A)
Non-Inflammatory Lesions¹					
Mean Baseline	50.7	48.2	52.4		
Mean Absolute Reduction	21.8	24.7	10.3	<0.0001 ³	
Mean Percent Reduction ²	43.3%	51.9%	21.2%	<0.0001 ³	-12.5% ³
Inflammatory Facial Lesions¹					
Mean Baseline	23.4	23.6	23.9		
Mean Absolute Reduction	9.7	11.8	5.8	0.0004 ³	
Mean Percent Reduction ²	40.8%	50.5%	25.6%	<0.0001 ³	-13.1% ³

¹ Excluding the nose

² Primary endpoints

³ P-value and LCB based on ANOVA on the ranks with terms for treatment, pooled investigator, and treatment-by-pooled investigator interaction. Non-inferiority margin was 10%.

<Table continues next page>

Table 10 <Continued> – Efficacy Results at Week 12 - ITT (Study 009)

	Tretinoin Gel 0.05% N=375	RETIN-A Micro, 0.1% N=376	Gel Vehicle N=185	p-value (Tret. vs. Veh.)	LCB (Tret. – Ret.-A)
Global Severity Scale					
Clear or Very Mild ²	78 (20.8%)	120 (31.2%)	23 (12.4%)	0.0022 ⁴	-17.6% ⁵
Clear or Very Mild with at least 2 grades reduction	45 (12%)	71 (18.9%)	6 (3.2%)	0.0002 ⁴	

² Primary endpoints⁴ P-value for CMH stratified on pooled investigator⁵ 97.5% lower confidence bound based on Wald's interval with Yates continuity correction. Non-inferiority margin was 10%.**Table 11 – Lesion Analysis Including Nasal Lesions among Subjects with Nasal Lesion Counts at Baseline (Study 009)**

	Tretinoin Gel 0.05% N=192	RETIN-A Micro, 0.1% N=189	Gel Vehicle N=94	p-value (Tret. vs. Veh.)
Non-Inflammatory Lesions ¹				
Mean Baseline	61.6	57.9	66.6	
Mean Absolute Reduction	22.9	28.3	13.2	0.0025
Mean Percent Reduction	36.2%	50.2%	20.1%	0.0002
Inflammatory Facial Lesions ¹				
Mean Baseline	25.0	23.9	24.5	
Mean Absolute Reduction	9.5	12.0	5.9	0.0687
Mean Percent Reduction	37.8%	49.7%	24.9%	0.0168

¹ Includes nasal lesions.**Table 12 – Efficacy Results - ITT (Study 0418)**

	Tretinoin Gel 0.05% N=299	Gel Vehicle N=302	p-value
Non-Inflammatory Lesions ¹			
Mean Baseline	51.9	52.7	
Mean Absolute Reduction to Week 12 ²	18.7	10.8	<0.0001 ³
Mean Percent Reduction to Week 12	37.2%	20.4%	<0.0001 ³
Inflammatory Facial Lesions ¹			
Mean Baseline	22.9	23.4	
Mean Absolute Reduction to Week 12 ²	7.0	4.0	0.0015 ³
Mean Percent Reduction to Week 12	29.7%	17.0%	0.0006 ³
Global Severity Scale			
Clear or Very Mild with at least 2 grades reduction ²	69 (23.1%)	42 (13.9%)	0.0021 ⁴

¹ Including the nose² Primary endpoints³ P-value for ANOVA on the ranks with terms for treatment, pooled investigator, and treatment-by-pooled investigator interaction⁴ P-value for CMH stratified on pooled investigator

In addition to demonstrating superiority to vehicle, Study 009 had the goal of demonstrating that tretinoin gel was non-inferior to Retin-A Micro. For each endpoint, the sponsor specified a non-inferiority margin of 10%. The sponsor failed to meet the non-inferiority criteria for all of the endpoints. In fact, Retin-A Micro was superior to tretinoin gel for each endpoint. The fact that Retin-A Micro is superior to tretinoin gel is not overly surprising since Retin-A has twice the concentration of tretinoin. To compute the lower confidence bounds for the lesion analyses, the sponsor identified the value of delta which when subtracted from all of the observations on the tretinoin gel arms just led to statistical significance in the analysis of the ranked data. Since the sponsor was unable to demonstrate that tretinoin gel was non-inferior to Retin-A Micro, the sponsor conducted the second study to get two studies that could demonstrate that tretinoin gel was superior to vehicle.

Results in the per protocol population were similar to the ITT population. All of the global success and lesion count analyses for tretinoin versus vehicle were significant in the per protocol population as well in both studies. Per protocol efficacy results are presented in Table 13 and Table 14.

Table 13 – Efficacy Results at Week 12 -PP (Study 009)

	Tretinoin Gel 0.05% N=257	RETIN-A Micro, 0.1% N=285	Gel Vehicle N=143	p-value (Tret. vs. Veh.)	LCB (Tret. – Ret.-A)
Non-Inflammatory Lesions¹					
Mean Baseline	51.2	48.7	53.5		
Mean Absolute Reduction	24.3	26.5	11.7	<0.0001	
Mean Percent Reduction ²	47.4%	54.9%	23.1%	<0.0001	-11.2%
Inflammatory Facial Lesions¹					
Mean Baseline	23.5	23.9	24.4		
Mean Absolute Reduction	10.4	12.9	5.1	<0.0001	
Mean Percent Reduction ²	43.6	54.7	22.4	<0.0001	-12.7%
Global Severity Scale					
Clear or Very Mild ²	63 (24.5%)	101 (35.4%)	20 (14.0%)	0.0188	-18.9%
Clear or Very Mild with at least 2 grades reduction	39 (15.2%)	64 (22.5%)	5 (3.5%)	0.0078	

¹ Excluding the nose

² Primary endpoints

³ P-value for ANOVA on the ranks with terms for treatment, pooled investigator, and treatment-by-pooled investigator interaction

⁴ P-value for CMH stratified on pooled investigator

⁵ 97.5% lower confidence bound based on an analysis of the ranks for lesion endpoints and Wald's interval with Yates continuity correction for GSS. Non-inferiority margin was 10%.

Table 14 – Efficacy Results - PP (Study 0418)

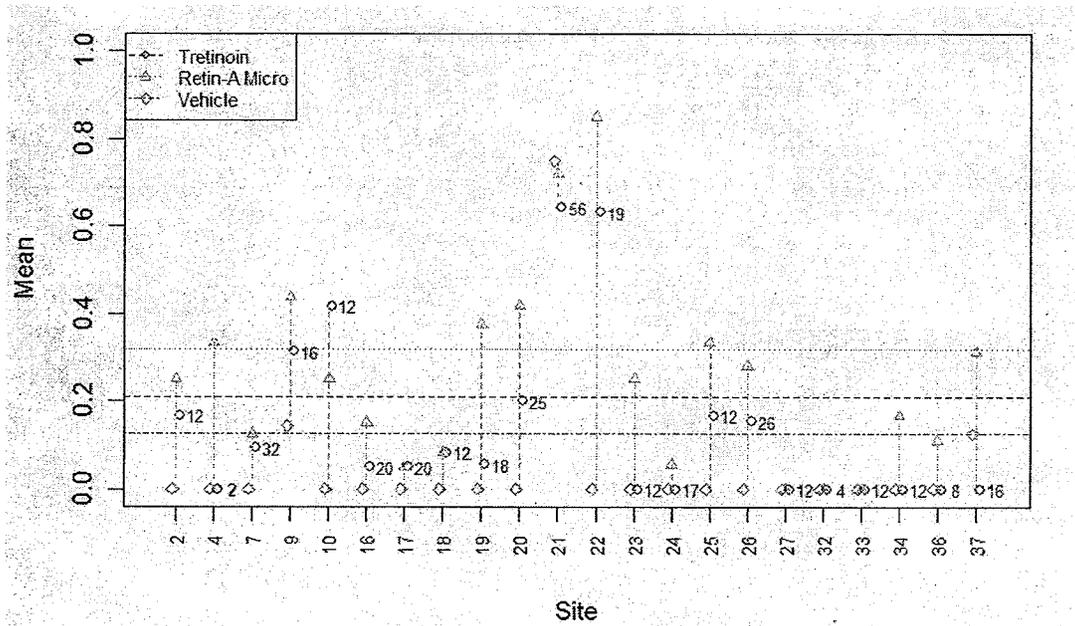
	Tretinoin Gel 0.05% N=197	Gel Vehicle N=226	p-value
Non-Inflammatory Lesions¹			
Mean Baseline	51.4	51.6	
Mean Absolute Reduction to Week 12 ²	20.0	10.6	<0.0001 ³
Mean Percent Reduction to Week 12	38.7%	21.4%	<0.0001 ³
Inflammatory Facial Lesions¹			
Mean Baseline	22.2	23.6	
Mean Absolute Reduction to Week 12 ²	7.5	4.0	0.0041 ³
Mean Percent Reduction to Week 12	31.0%	18.1%	0.0062 ³
Global Severity Scale			
Clear or Very Mild with at least 2 grades reduction ²	50 (25.4%)	34 (15.0%)	0.0120 ⁴

¹ Including the nose² Primary endpoints³ P-value for ANOVA on the ranks with terms for treatment, pooled investigator, and treatment-by-pooled investigator interaction⁴ P-value for CMH stratified on pooled investigator

3.1.5 Efficacy by Center

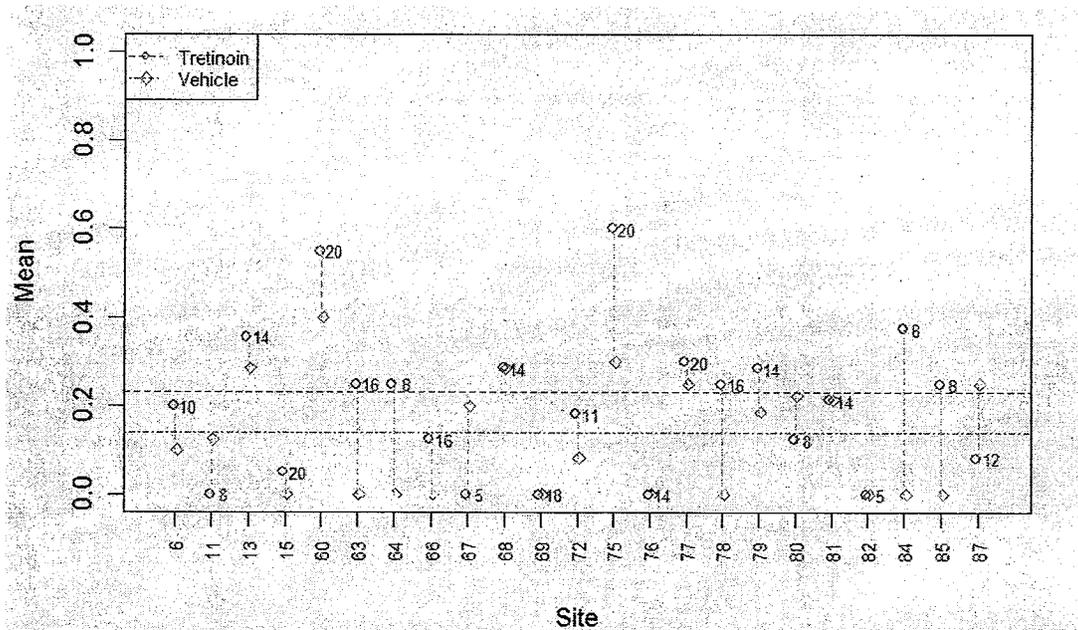
Study 009 involved 22 centers that were pooled into 14 analysis centers. Subjects with less than 10 subjects per treatment arm were pooled such that the smallest of the small centers was pooled with largest of the small centers, and so forth, until all pooled centers had at least 10 subjects per treatment arm. The global success rates by center are displayed in Figure 1 and Figure 2. Center 21 is the most notable center in Study 009. Besides enrolling the most subjects (141), Center 21 had high success rates on all arms, but especially the vehicle arm which had a higher success rate than either tretinoin or Retin-A Micro. In fact, 21 out of the 23 global successes on the vehicle arm for the whole study were from subjects at Center 21. This center contributed to a significant result on the Breslow-Day test for tretinoin versus vehicle ($p=0.0561$). However, without Center 21, due to the high vehicle success rate the observed difference between tretinoin and vehicle would have been even larger, and the unusual results from Center 21 make the overall results less significant than they would be otherwise. Center 22 is also an influential center with the largest differences between the tretinoin and vehicle arms. For Study 0418, the Breslow-Day test was non-significant ($p=0.2663$). By center results for the percent reduction in lesions are presented in the appendix.

Figure 1 – Success Rate by Center (Study 009)



Note: Numbers represent the tretinoin sample sizes. Randomization was 2:2:1 for tretinoin gel: Retin-A Micro: vehicle. The horizontal lines represent the overall treatment means.

Figure 2 – Success Rate by Center (Study 0418)



Note: Numbers represent the tretinoin sample sizes. Randomization was 1:1 for tretinoin gel: vehicle. The horizontal lines represent the overall treatment means.

3.1.6 Impact of Changes to Global Severity Score Analyses between Studies

In Study 009 subjects were required to have baseline global scores of 2, 3, or 4, and treatment success at Week 12 was defined as achieving a score of 0 or 1. However, due to evolving Agency recommendations, in Study 0418, the Agency recommended that a treatment success should involve achieving a score of 0 or 1 with at least 2 grades reduction from baseline. Additionally, the sponsor also raised the entry criteria to a global score of 3 or 4 only. One rationale for requiring a 2 grade reduction is to ensure that subjects classified as global successes truly had clinically meaningful improvement. Since the inclusion criteria for Studies 009 and 0418 were different, and evaluation of results across studies needs to take the baseline global into account. The following figures (Figure 3 and Figure 4) graphically display the global score (symbol), inflammatory count (horizontal axis), and non-inflammatory count (vertical axis) for both baseline (light blue) and Week 12 (dark blue). Baseline and Week 12 results for the same subject are connected by lines. Only tretinoin subjects classified as Week 12 successes on the global scale are displayed on the graphs. In particular, the graphs show that subjects in Study 009 with a baseline global score of 2 and Week 12 global score of 1 have Week 12 lesion counts generally separated from their baseline values. In fact the cases where subjects were classified as global successes yet the lesion count scores did not improve substantially from baseline generally occurred in subjects moving from 3 to 1 on the global scale. One 'successful' subject in Study 0418 actually had more inflammatory lesions at Week 12 than at baseline.

Figure 3 – Baseline and Week 12 Lesion Counts and Global Score for Tretinoin Subjects Classified as Global Successes at Week 12 (Study 009)

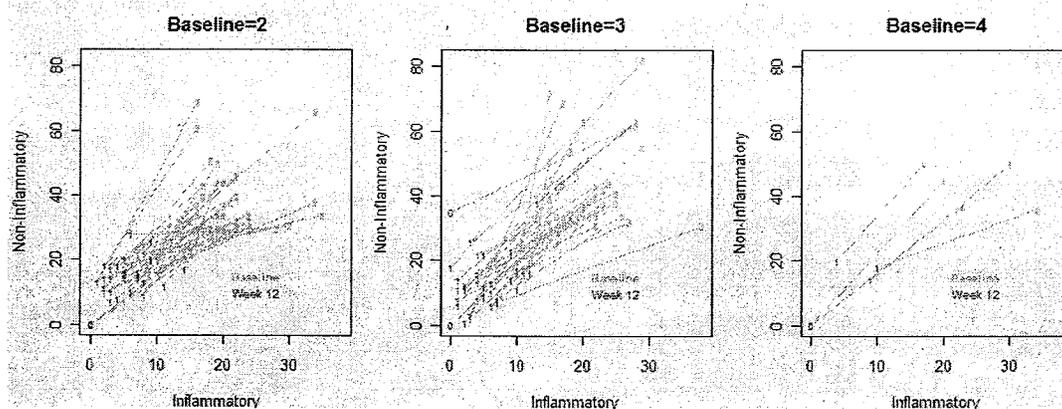
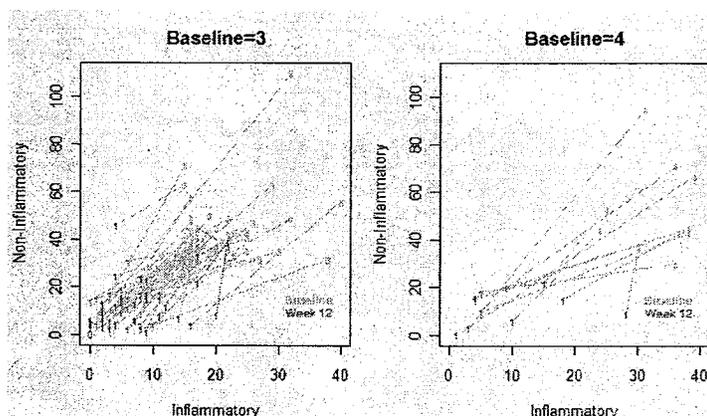


Figure 4 - Baseline and Week 12 Lesion Counts and Global Score for Tretinoin Subjects Classified as Global Successes at Week 12 (Study 0418)



3.2 Evaluation of Safety

3.2.1 Extent of Exposure

The data regarding the extent of exposure from Studies 009 and 0418 are limited. The study report for Study 009 notes only that the mean daily usage for all arms was 0.5 grams per day for subjects treating only the face and 0.6 grams per day for subjects with face plus chest, back, or neck involvement. The sponsor did not provide information on the distribution of the number of treatment days for this study.

The study report for Study 009 refers to a supplemental report (Annex II) for information on drug usage, but this supplemental report appears to be missing a substantial number of pages (pages 15 to 46). In addition, the database for drug usage was separate from the primary database and this supplemental database was not submitted to the NDA. Due to the lack of raw data and the missing pages from Annex II, it was not possible for this reviewer to verify any of the sponsor's calculation on drug use levels.

For Study 0418, the study report provides information on the distribution of the number of days of treatment, but does not provide any information on the amount of grams of drug product used per day. In terms usage days, tretinoin gel subjects applied a mean of 78.4 doses and vehicle subjects applied a mean of 79.1 doses. The full 12-week treatment course involved 84 doses. In the tretinoin arm 82% of subjects were 'dose-compliant' compared with 88% of vehicle subjects. Dose compliance was defined as applying 80-120% of expected doses and not missing more than 5 consecutive doses.

3.2.2 Adverse Events

The most common adverse events in Studies 009 and 0418 were dry skin, skin exfoliation, erythema, and burning. All of these events appear to be related to the dose of tretinoin with Retin-A Micro 0.1% having the highest rates followed by tretinoin gel 0.05% and then by vehicle. The adverse events reported by at least 3% of subjects are presented in Table 15 and Table 16. Of note, the coding differed between Studies 009

and 0418. In particular, investigator verbatim terms for ‘peeling’, ‘scaling’, and ‘flaking’ were coded differently for the two studies. In Study 009 verbatim terms including ‘peeling’ were coded as ‘dermatitis exfoliative’, verbatim terms including ‘scaling’ were coded as ‘rash scaly’, and verbatim terms including ‘flaking’ were coded as ‘skin desquamation’. In Study 0418, the verbatim terms for ‘peeling’, ‘scaling’, and ‘flaking’ were all coded as ‘skin exfoliation’.

Table 15 – Adverse Events Reported by $\geq 3\%$ of Subjects (Study 009)

	Tretinoin Gel 0.05% N=375	RETIN-A Micro, 0.1% N=376	Gel Vehicle N=185
Subjects Reporting AEs	199 (53%)	245 (65%)	69 (37%)
Skin Events			
Dry Skin	73 (19%)	112 (30%)	5 (3%)
Dermatitis Exfoliative	37 (10%)	80 (21%)	4 (2%)
Erythema	35 (9%)	67 (18%)	0 (0%)
Skin Burning Sensation	35 (9%)	57 (15%)	6 (3%)
Rash Scaly	14 (4%)	29 (8%)	1 (1%)
Pruritus	10 (3%)	11 (3%)	2 (1%)
Other Events			
Headache	20 (5%)	22 (6%)	9 (5%)
Nasopharyngitis	18 (5%)	29 (8%)	14 (8%)
Pharyngolaryngeal pain	14 (4%)	5 (1%)	4 (2%)

Source: file 735126c.00901-report-body-2.pdf, pg 157-162.

Table 16 – Adverse Events Reported by $\geq 3\%$ of Subjects (Study 0418)

	Tretinoin Gel 0.05% N=299	Gel Vehicle N=302
Subjects Reporting AEs	137 (46%)	72 (24%)
Skin Events		
Dry Skin	36 (12%)	3 (1%)
Skin Exfoliation	25 (8%)	2 (1%)
Skin Burning Sensation	18 (6%)	2 (1%)
Erythema	12 (4%)	1 (<1%)
Other Events		
Nasopharyngitis	17 (6%)	9 (3%)
Upper Resp. Tract Inf.	10 (3%)	9 (3%)
Headache	9 (3%)	7 (2%)

Source: file 20clin1260418-report-body.pdf, pg 239 – 244.

The sponsor did not actively collect data on local skin reactions at study visits. However, it is still of interest to understand the time course of the spontaneously reported skin reaction events. The adverse event information includes start and stop dates for each event. To evaluate the time course of skin-related adverse events, all events in the ‘skin and subcutaneous tissue disorders’ were pooled together. Time was categorized into one-week intervals. Subjects were counted as having a skin event for a particular week if any

skin-related adverse event had been reported as starting before or during the given week and stopping during or after the given week (7-day interval). Many events did not list stopping dates and were marked as 'continuing'. In these cases, the event was considered to have continued until the subject left the trial (date of last visit). The skin events were most common during the first three weeks of the studies, however, many subjects had events that continued throughout the course of the trial, and the incidence rate of subjects experiencing an event declined only slightly over time. The incidence of skin-related adverse events was higher on Retin-A Micro than tretinoin, and the vehicle rate was very low. The event rates over time are presented in Figure 5 and Figure 6.

Figure 5 – Proportion of Subjects Experiencing a New or Continuing Skin-Related Adverse Event by Study Week (Study 009)

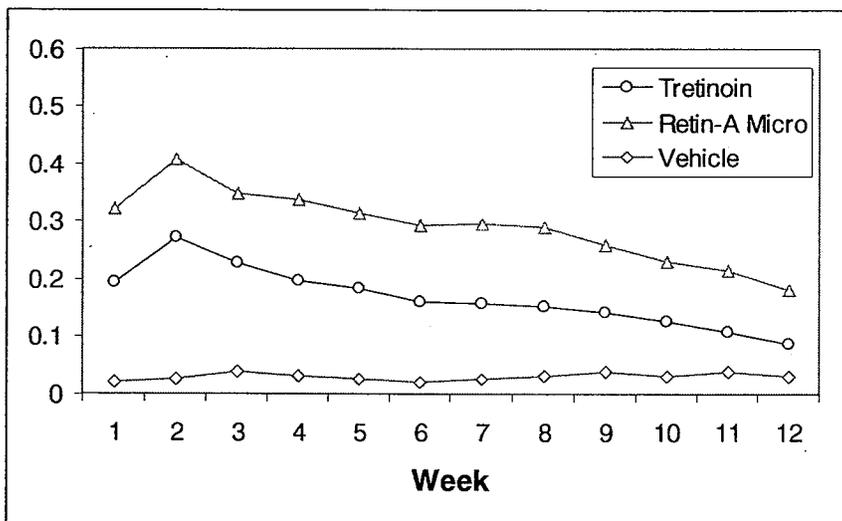
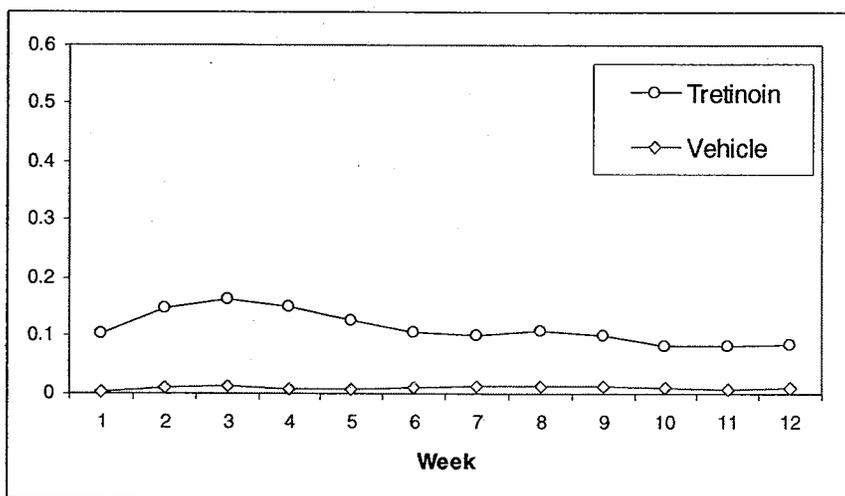


Figure 6 - Proportion of Subjects Experiencing a New or Continuing Skin-Related Adverse Event by Study Week (Study 0418)



4 Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

The efficacy results in Studies 009 and 0418 were generally consistent across race groups, at least among race groups with moderate sample sizes. Most subjects in both studies were Caucasian. Although treatment effects were generally similar, female subjects tended to have slightly better overall results than males. Similarly, adult subjects (18 and older) generally had slightly better results than adolescent subjects (age 10 – 17), although again, the treatment effects were generally similar. One difference between the two studies was that in Study 0418 adult tretinoin subjects demonstrated almost no treatment effect of vehicle, whereas in Study 009 the treatment effect in adult subjects was greater than in adolescent subjects. Subgroup analysis results by gender, race, and age are presented in Figure 7 through Figure 12.

Figure 7 – Global Success by Subgroups (Study 009)

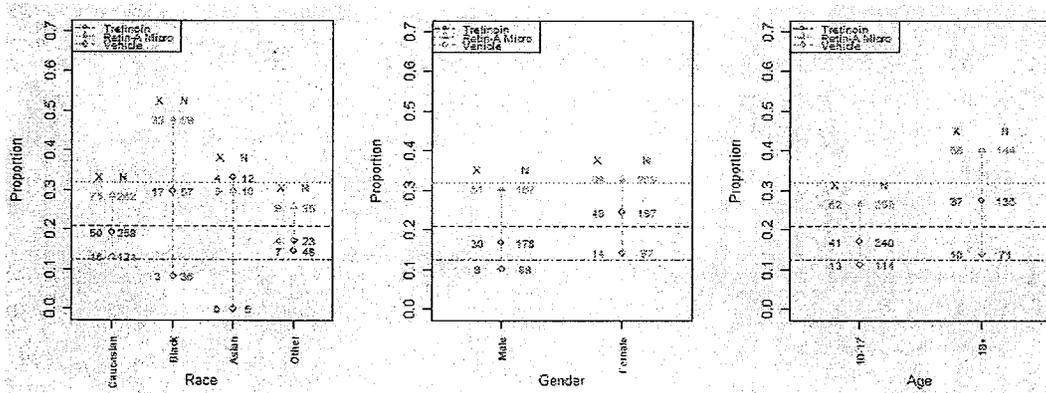


Figure 8 – Percent Reduction in Non-Inflammatory Lesions by Subgroups (Study 009)

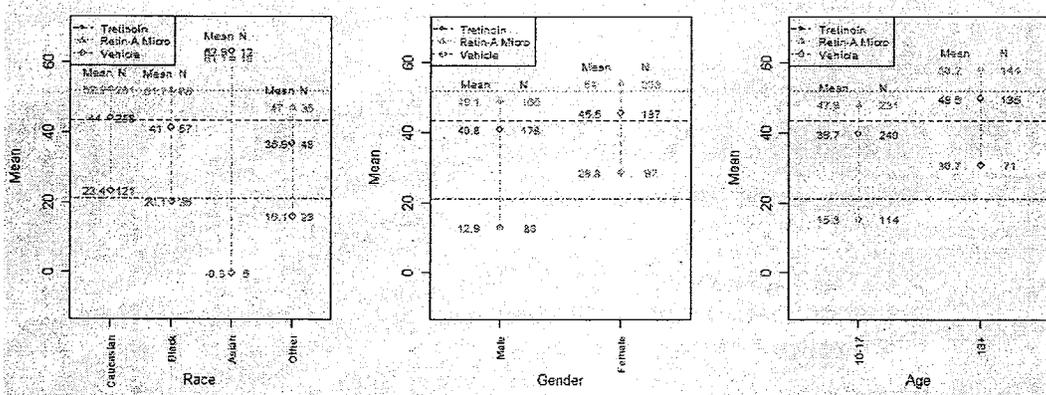


Figure 9 – Percent Reduction in Inflammatory Lesions by Subgroups (Study 009)

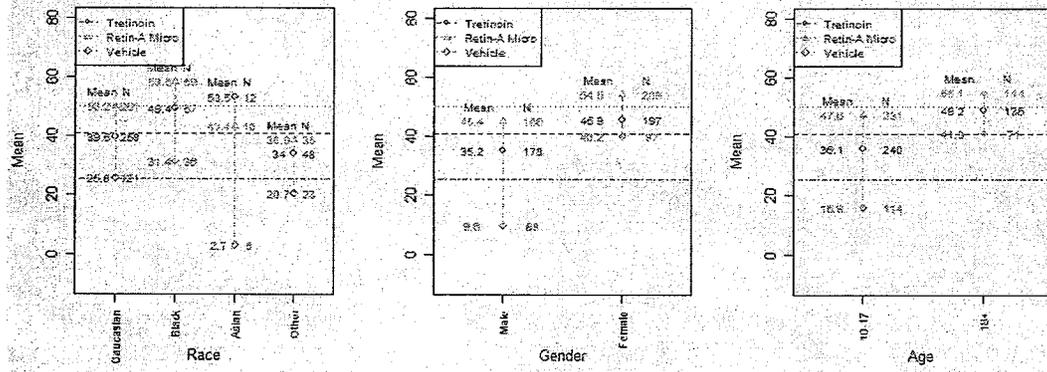


Figure 10 – Global Success by Subgroups (Study 0418)

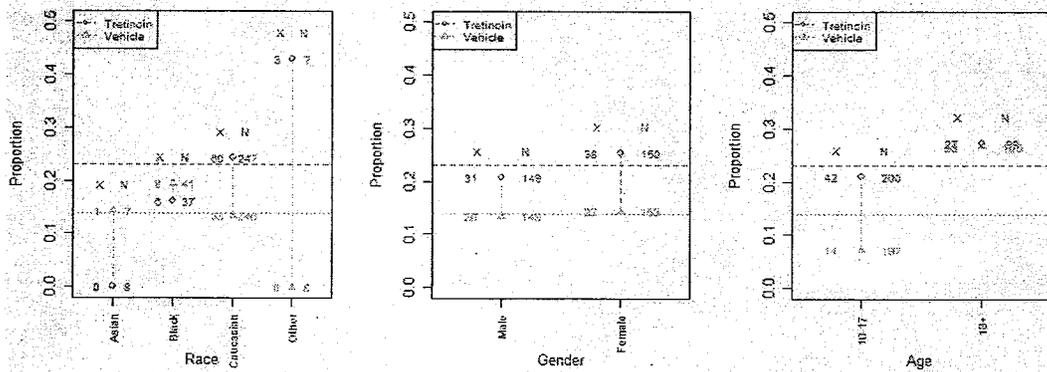


Figure 11 – Percent Reduction in Non-Inflammatory Lesions by Subgroups (Study 0418)

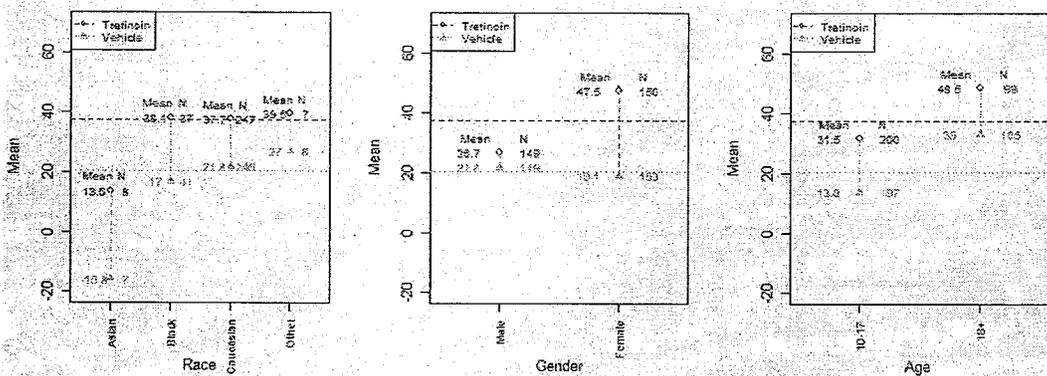
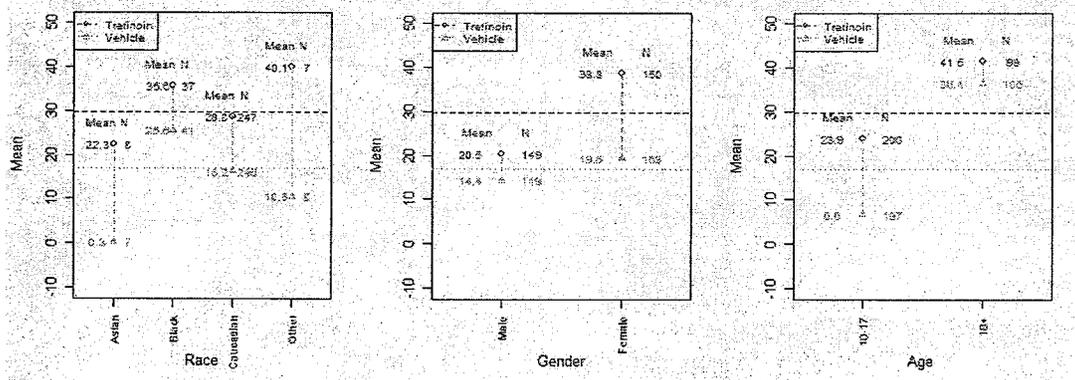


Figure 12 – Percent Reduction in Inflammatory Lesions by Subgroups (Study 0418)



4.2 Other Special/Subgroup Populations

Baseline severity, as measured by the global scale, does not appear to have much impact on the percent reduction in lesions by Week 12, though there may be a slight trend that subjects with higher baseline global scores have lower percent reductions in inflammatory lesions on average than subjects with lower baseline global scores. The baseline global score however, has a larger impact on the global success rate, as might be expected since the baseline global score impacts how many grades a subject must improve to achieve success (subjects with baseline 2 must improve at least 1 grade, subjects with baseline 3 must improve at least 2 grades, and subjects with baseline of 4 must improve at least 3 grades). Most of the efficacy in Study 009 from subjects with baseline scores of 2 would disappear if the requirement of at least 2 grades reduction were applied. Efficacy results by baseline global are presented in Figure 13 and Figure 14.

Figure 13 – Efficacy Results by Baseline Global (Study 009)

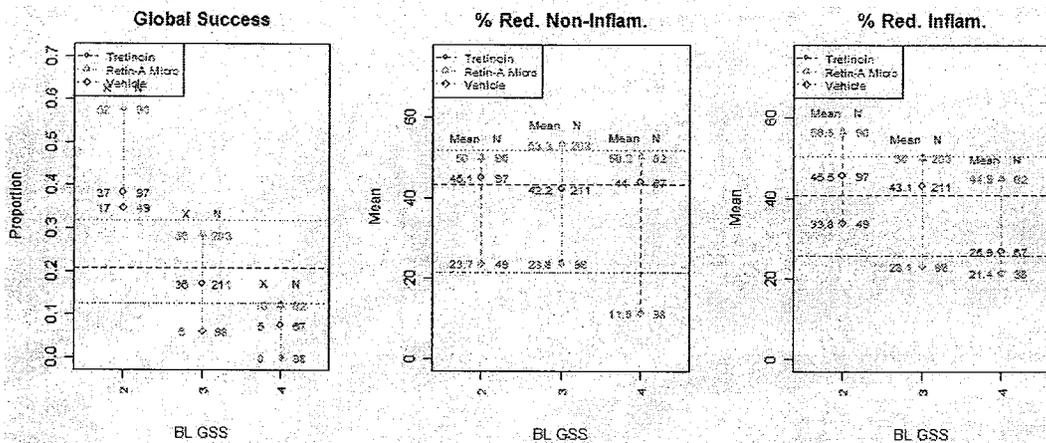
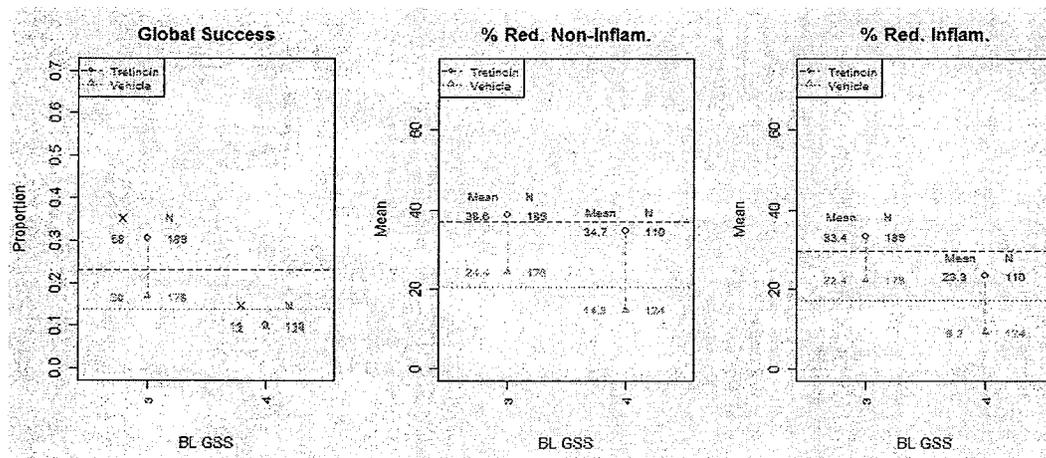


Figure 14 – Efficacy Results by Baseline Global (Study 0418)



5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

Studies 009 and 0418 demonstrate that tretinoin gel is superior to vehicle gel in the treatment of acne. All of the pre-specified primary endpoints in each study were statistically significant (percent reduction in lesions and clear/very mild on the global scale for Study 009, and absolute reduction in lesions and clear/very mild with at least two grades reduction on the global for Study 0418). Study 009 also demonstrates statistical significance for the absolute reduction in lesions and the stricter definition of success on the global scale. Study 009 also had the goal of demonstrating that tretinoin gel 0.05% was non-inferior to Retin-A Micro 0.1%. However, the study was unable to demonstrate the non-inferiority. The efficacy results are summarized in Table 17. All of the p-values for tretinoin gel versus vehicle were ≤ 0.0022 .

Table 17 – Summary of Efficacy Results

	Study 009			Study 0418	
	Tretinoin Gel N=375	Retin-A Micro N=376	Vehicle N=185	Tretinoin Gel N=299	Vehicle N=302
Global Success					
Clear/Very Mild	45 (12%)	120 (31%)	6 (3%)	69 (23%)	42 (14%)
Clear/Very Mild (2 grd red)	39 (15%)	64 (23%)	5 (4%)	69 (23%)	42 (14%)
Non-Inflammatory Lesions					
Mean Baseline Count	50.7	48.2	52.4	51.9	52.7
Mean Absolute Reduction	21.8	24.7	10.3	18.7	10.8
Mean Percent Reduction	43%	52%	21%	37%	20%
Inflammatory Facial Lesions					
Mean Baseline	23.4	23.6	23.9	22.9	23.4
Mean Absolute Reduction	9.7	11.8	5.8	7.0	4.0
Mean Percent Reduction	41%	51%	26%	30%	17%

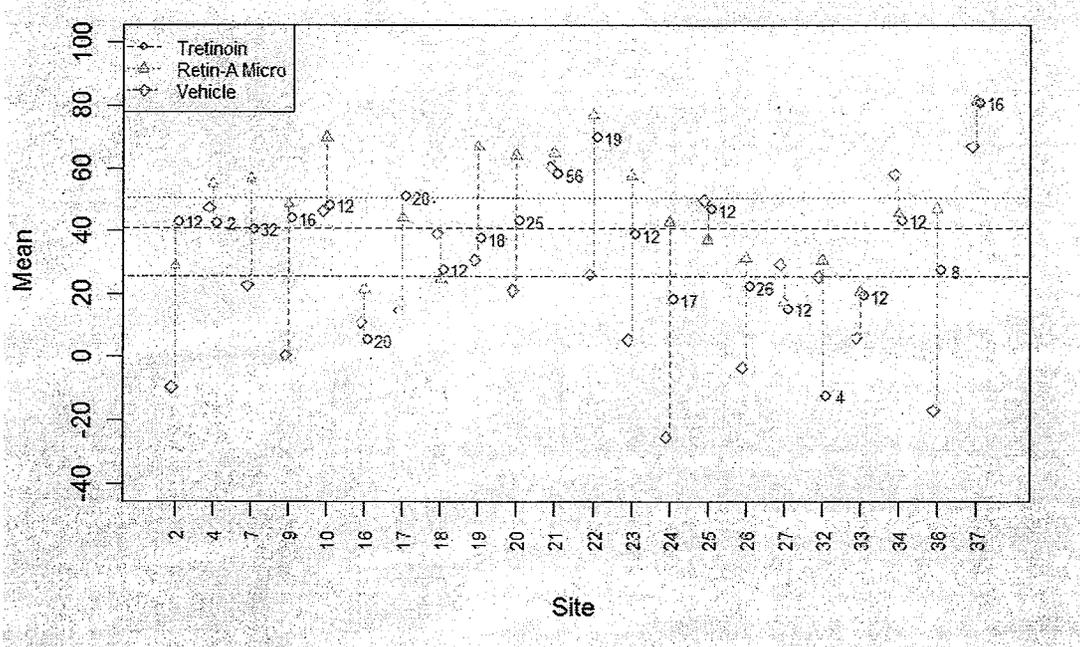
5.2 Conclusions and Recommendations

The efficacy of tretinoin gel 0.05% over its vehicle in the treatment of acne vulgaris is supported by two studies. Both studies met all of their pre-specified endpoints for demonstrating superiority over vehicle for inflammatory lesions, non-inflammatory lesions, and global severity. Study 009 originally had the goal of demonstrating that tretinoin gel 0.05% was non-inferior to Retin-A Micro 0.1%, however, non-inferiority could not be established for any of the endpoints. Consequently the sponsor conducted the second study to obtain two studies demonstrating superiority to vehicle.

The most common adverse events were skin-related: dry skin, skin exfoliation, burning, and erythema. The incidence rate of these events appears to be related to the tretinoin concentration with higher doses leading to higher incidences of events.

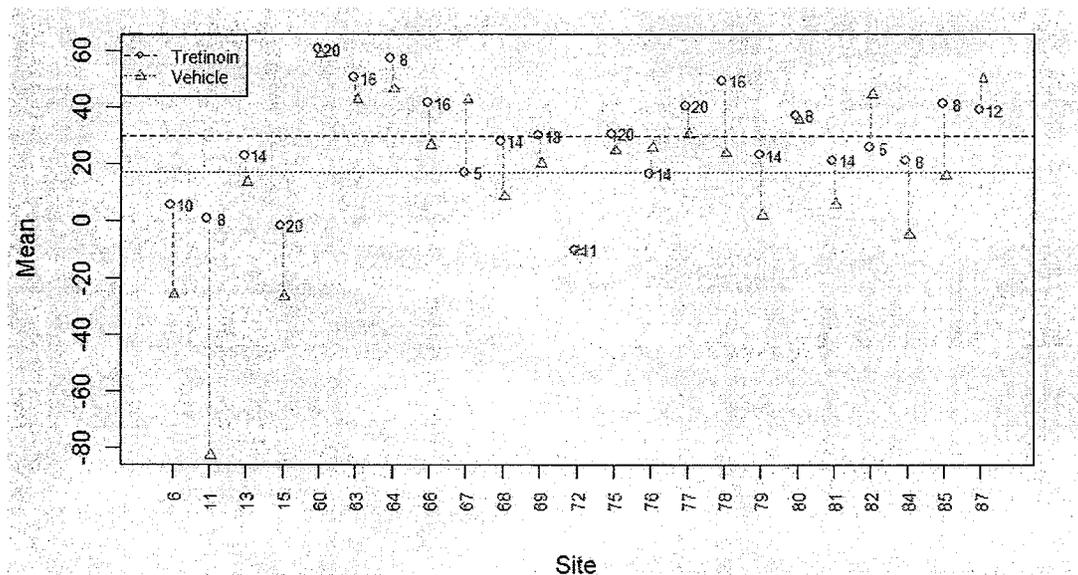
Appendix – Additional Figures

Figure 15 – Percent Change in Inflammatory Lesions (Study 009)



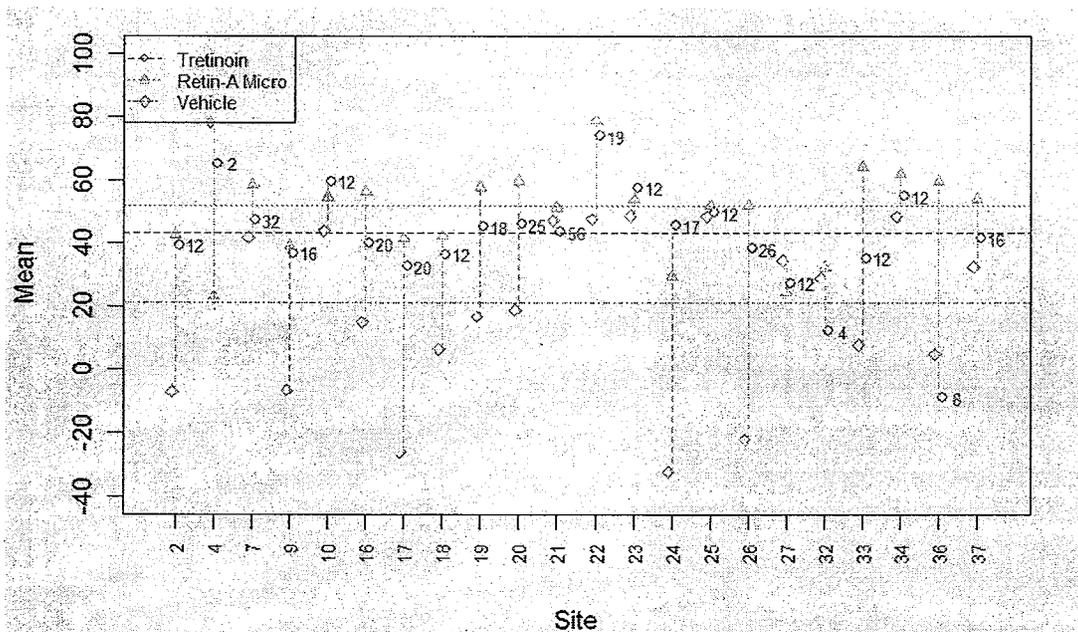
Note: Numbers represent the tretinoin sample sizes. Randomization was 2:2:1 for tretinoin gel: Retin-A Micro: vehicle. The horizontal lines represent the overall treatment means.

Figure 16 – Percent Reduction in Inflammatory Lesions (Study 0418)



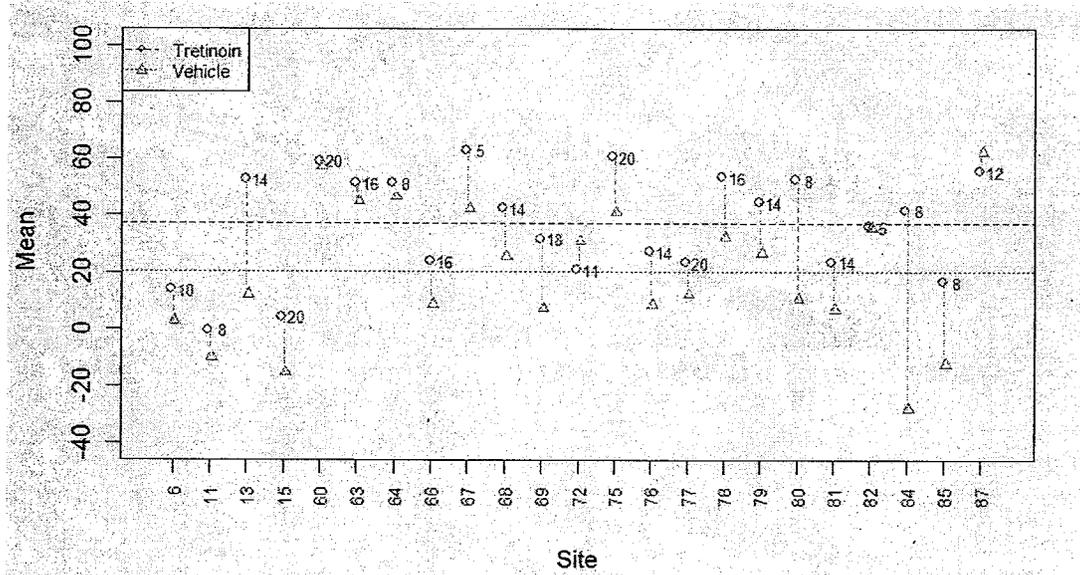
Note: Numbers represent the tretinoin sample sizes. Randomization was 2:2:1 for tretinoin gel: Retin-A Micro: vehicle. The horizontal lines represent the overall treatment means.

Figure 17 – Percent Change in Non-Inflammatory Lesions (Study 009)



Note: Numbers represent the tretinoin sample sizes. Randomization was 2:2:1 for tretinoin gel: Retin-A Micro: vehicle. The horizontal lines represent the overall treatment means.

Figure 18 – Percent Reduction in Non-Inflammatory Lesions (Study 0418)



Note: Numbers represent the tretinoin sample sizes. Randomization was 2:2:1 for tretinoin gel: Retin-A Micro: vehicle. The horizontal lines represent the overall treatment means.

Signatures/Distribution List

Primary Statistical Reviewer: Kathleen Fritsch, Ph.D.
 Date: June 15, 2007

Statistical Team Leader: Mohamed Alosch, Ph.D.

- cc:
 DDDP/Walker
 DDDP/Luke
 DDDP/Kettl
 DDDP/Bauerlien
 OBIO/O'Neill
 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 Fritsch
6/18/2007 03:34:22 PM
BIOMETRICS

Mohamed Alosch
6/19/2007 03:45:42 PM
BIOMETRICS
Concur with review