CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-184/001

Statistical Review(s)

Statistical Review and Evaluation

NDA #:	21-184/SE1-001
Applicant:	Allergan
Name of Drug:	Tazorac (tazarotene) cream 0.1%
Indication:	Topical treatment of acne vulgaris
Documents Reviewed:	Vol. 1, 32-42, submitted Dec. 8, 2000
Related NDAs:	NDA 20-600
Medical Reviewer:	Hon-Sum Ko, M.D., Ph.D. (HFD-540)
Statistical Reviewer:	Kathleen Fritsch, Ph.D. (HFD-725)

I. Introduction

Tazorac (tazarotene) cream in formulations 0.05% and 0.1% was approved in September 2000 for the treatment of stable plaque psoriasis (original filing of NDA 21-184.) In this supplement to NDA 21-184, the sponsor seeks approval for tazarotene cream 0.1% for the indication acne vulgaris. In a related submission (NDA 20-600) tazarotene gel was approved in June 1997 for both the treatment of stable plaque psoriasis (0.05% and 0.1% concentrations) and acne vulgaris (0.1% concentration). This review focuses on the two phase 3 trials submitted to support the efficacy and safety of tazarotene cream 0.1% in the treatment of acne vulgaris.

At a pre-NDA meeting held on September 11, 2000, the medical reviewer recommended that the sponsor analyze some additional efficacy endpoints, so that the endpoints would be more consistent with those generally recommended by the Division for acne trials. The differences between the endpoints planned by the sponsor in the protocol and those recommended by the Division at the pre-NDA meeting are discussed below.

II. Study Design and Statistical Methods

The two pivotal efficacy and safety studies (29C and 31C) are identical in design. Each study was randomized, double-blind, parallel-group, vehicle-controlled, and multi-center. Subjects aged 12 and higher were randomized in a 1:1 ratio to receive either tazarotene cream 0.1% or vehicle cream. The length of the study was 12 weeks with patients evaluated at baseline and Weeks 4, 8, and 12. The efficacy evaluation included the following measurements:

- Number of facial lesions (inflammatory, non-inflammatory, and total).
- Overall Acne Assessment (OAA), measured on a 6 point scale, where 0=none, 1=minimal, 2=mild, 3=moderate, 4=severe, 5=very severe.
- Global Response to Treatment measured on a 7 point scale where 0=completely cleared, 1=almost cleared (90% improvement), 2=marked response (75% improvement), 3=moderate response (50% improvement), 4=slight response (25% improvement), 5=condition unchanged, and 6=condition worsened.

The sponsor defined the following primary and secondary efficacy endpoints in the protocols for Studies 29C and 31C:
Primary: percent reduction in the total number of lesions from baseline to Week 12.
Secondary:

- percent reduction in non-inflammatory and inflammatory lesions (baseline to Week 12)
- clinical improvement (at least one grade improvement in Overall Acne Assessment, from baseline to Week 12)
- percent achieving a moderate response or better (≥ 50% improvement from baseline) on the Global Response to Treatment at Week 12)

All endpoints were also analyzed at Weeks 4 and 8 as secondary endpoints.

After discussions with the Agency at a pre-NDA meeting, the sponsor also included analyses for the following:

- proportion of subjects achieving either an Overall Acne Assessment (OAA) of none or minimal, or an OAA of none, minimal, or mild at Week 12
- actual change in number of lesions from baseline to Week 12, and actual lesion counts at Week 12 (inflammatory, non-inflammatory, and total)

Efficacy analyses were based on the intent-to-treat (ITT) population. The ITT population included all subjects randomized and dispensed medication. Subjects with missing Week 12 data had their last observation carried forward (LOCF). The sponsor did not include a definition of the per protocol population in the protocol, but was asked by the Agency at the pre-NDA meeting to include per protocol analyses in addition to the ITT analyses. After the meeting, the sponsor defined the per protocol population to exclude subjects who discontinued, had improper entry, used concomitant medication, became pregnant, missed two or more weeks of application, or had multiple visits within a time window.

In the protocol, the sponsor specified that the lesion count variables would be rank transformed and analyzed with two-way ANOVA with effects of treatment, investigator, and treatment-by-investigator interaction. The protocol stated that while the hypothesis tests would be conducted on the rank transformed data, the results would be presented using means from the original scale. However, because the distributions of the variables were observed to be skewed, the sponsor decided to summarize the variables with medians rather than means.

Categorical variables were analyzed with the Cochran-Mantel-Haenszel test, stratified by center.

III. Patient Disposition and Demographics

A total of 436 subjects were randomized into Study 29C, 218 to tazarotene and 218 to vehicle. A total of 411 subjects were randomized into Study 31C, 206 to tazarotene and 205 to vehicle. All randomized subjects were included in the ITT population. Table 1

summarizes the patient disposition data. Across both studies, 17 patients (2%) discontinued due to adverse events, and 17 (2%) discontinued due to lack of efficacy.

Table 1 – Patient Disposition in Pivotal Studies 29C and 31C

	Study 29C		Study 31C	
	Taz 0.1%	Vehicle	Taz 0.1%	Vehicle
Enrolled	218	218	206	205
Completed	182 (83.5%)	192 (88.1%)	167 (81.1%)	166 (81.1%)
Discontinued	36 (16.5%)	26 (11.9%)	39 (18.9%)	39 (19.0%)
Lack of Efficacy	3 (1.4%)	9 (4.1%)	2 (1.0%)	3 (1.5%)
Adverse Event	7 (3.2%)	0 (0.0%)	9 (4.4%)	1 (0.5%)
Lost to Follow-up	10 (4.6%)	12 (5.5%)	11 (5.3%)	17 (8.3%)
Non-Compliance	4 (1.8%)	3 (1.4%)	2 (1.0%)	2 (1.0%)
Pregnancy	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)
Other[a]	12 (5.5%)	2 (0.9%)	14 (6.8%)	15 (7.3%)

[a] "Other" category includes: personal reasons, relocation, and improper entry
Source: Sponsor's Table 1, Vol. 34, p. 74, and Vol. 38, p. 71.

Study 29C had 15 centers and Study 31C had 14 centers. Sites with fewer than 10 subjects per treatment arm were pooled with another site from a similar geographic region. According to the sponsor, decisions on pooling were made before breaking the treatment blind. In Study 29C, 2 sites remained unpooled and the remaining 13 sites were pooled into 6 groups. In Study 31C, 8 sites remained unpooled and the remaining 6 sites were pooled into 3 groups. Table A.1 in Appendix A lists the number of subjects per treatment center before and after pooling.

No significant differences in demographic variables were found between treatment groups at baseline. Approximately half of the subjects were male and half were female. The majority of subjects in both studies were white (≥67%). Table A.2 in Appendix A summarizes the age, race, and gender of the study participants. No significant differences between the treatment groups were found in terms of baseline severity of disease, as measured by the Overall Acne Assessment (Study 29C: p=0.292; Study 31C: p=0.075) [Sponsor's Analysis, Source: Table 7, Vol. 34, p. 84, and Vol. 38 p. 82. P-values based on CMH test].

IV. Primary Efficacy Results

The Division's recommendation for establishing efficacy in acne trials is to demonstrate (i) statistical significance for active versus vehicle in reducing lesions for two out of three types of lesions (inflammatory, non-inflammatory, and total lesions), and (ii) statistical significance in the "success rate" for the overall acne assessment. The sponsor has interpreted a "success" on the Overall Acne Assessment as an improvement of at least one grade from baseline to Week 12. However, the Division prefers defining "success" on the Overall Acne Assessment as achieving a score of none or minimal. At the Division's request, the sponsor included analyses of the percentage of subjects achieving

scores of none or minimal (and none, minimal, or mild) on the Overall Acne Assessment in addition to their analysis of the percentage of subjects improving at least one grade. The Division also requested that the sponsor include analyses of actual lesion counts and actual change in lesion counts in addition to the analyses of the percent change in lesion counts. This review will focus on the endpoints preferred by the Division for establishing efficacy in acne trials.

IV. A. *Analysis of Inflammatory, Non-Inflammatory, Total Lesions*

As part of their analysis for the percent change in inflammatory, non-inflammatory, and total lesions, the sponsor includes results from the Shapiro-Wilk test for normality. For both Studies 29C and 31C, the p-values for the Shapiro-Wilk test for all three types of lesions were all less than 0.001, providing evidence of non-normality. (Tables 50-52, Vol. 34, pp. 266-284, and Vol. 38, pp. 272-292.) Boxplots of the percent decrease in inflammatory, non-inflammatory, and total lesions by treatment group are given in Plots B.1 through B.3 in Appendix B. These plots demonstrate the skewness of the data, and how the mean is influenced by some subjects with large percentage increases in the number of lesions, particularly in Study 31C.

The sponsor specified in the protocol that the lesion count data would be rank-transformed for analysis, which is appropriate for skewed data. Their initial plan was to summarize their data with mean values on the original scale. However, because of the evidence of non-normality in the data, the sponsor proposed that medians would be more appropriate than means for summarizing the data. Because the data was skewed, and the fact that the analysis was performed on rank-transformed data, this reviewer concurs with the sponsor's decision to report medians rather than means. For completeness, both the medians and the means for the lesion count data will be presented in this review. In addition, for comparison purposes, this review also includes an analysis on the original unranked data, conducted by the reviewer. However, the sponsor's analysis of the ranked data and the corresponding medians should be considered the primary analysis.

The protocol stated that the analysis model would be ANOVA on the ranks with effects of treatment, center, and treatment by center interaction. Tables 2 and 3 present the data summaries and analysis results for the lesion count data for Studies 29C and 31C in the ITT population. Both means and medians are given for the baseline and Week 12 lesion counts, decrease (baseline – Week 12), and percent decrease ([baseline – Week 12]/baseline) variables. P-values for both the sponsor's analysis (ranked data) and the reviewer's analysis (unranked data) are included in Tables 2 and 3. Note that in the sponsor's submission, changes were calculated as (follow-up – baseline), and thus were predominately negative. In this review, changes are calculated as (baseline – follow-up), and thus are predominately positive.

Table 2 – Analysis of Lesion Count Data in Study 29C (Intent to Treat Population)

		Baseline Count		Week 12 Count		Decrease (BL-W12)		Percent Decrease	
		Taz.	Veh.	Taz.	Veh.	Taz.	Veh.	Taz.	Veh.
Inflam.	Mean	27.6	27.0	18.4	20.6	9.2	6.4	32.1%	21.4%
	Med	24.5	24.0	14.0	16.0	9.0	6.0	40.7%	27.4%
	p-value[a]	0.605		0.044		0.044		0.010	
	p-value[b]	0.665		0.130		0.030		0.015	
Non-Inf.	Mean	63.4	62.2	37.4	46.7	26.0	15.5	41.1%	24.8%
	Med	55.0	52.0	30.0	36.0	23.0	13.0	46.2%	26.7%
	p-value[a]	0.449		<0.001		<0.001		<0.001	
	p-value[b]	0.667		0.002		<0.001		<0.001	
Total	Mean	90.9	89.2	55.8	67.2	35.1	22.0	38.9%	24.8%
	Med	81.5	80.5	47.5	56.0	32.5	20.0	43.9%	24.0%
	p-value[a]	0.475		<0.001		<0.001		<0.001	
	p-value[b]	0.594		0.002		<0.001		<0.001	

[a] p-values based on ANOVA of rank transformed data (Sponsor Analysis)
Source: Sponsor's Tables 9 - 11, 55 - 60 (Vol. 34, pp. 86-88, 287-292)
[b] p-values based on ANOVA of original data (Reviewer Analysis)

Table 3 – Analysis of Lesion Count Data in Study 31C (Intent to Treat Population)

		Baseline Count		Week 12 Count		Decrease (BL-W12)		Percent Decrease	
		Taz.	Veh.	Taz.	Veh.	Taz.	Veh.	Taz.	Veh.
Inflam.	Mean	25.0	25.0	16.4	20.4	8.6	4.6	30.6%	18.9%
	Med	21.0	21.0	13.0	17.0	8.5	5.0	44.5%	25.0%
	p-value[a]	0.855		0.003		0.003		0.001	
	p-value[b]	0.783		0.002		0.002		0.025	
Non-Inf.	Mean	75.1	71.7	56.3	68.8	18.8	2.9	28.7%	6.4%
	Med	63.0	64.0	40.0	47.0	24.0	12.0	41.3%	20.8%
	p-value[a]	0.757		<0.001		<0.001		<0.001	
	p-value[b]	0.513		0.016		0.001		<0.001	
Total	Mean	100.1	96.7	72.7	89.2	27.4	7.5	30.1%	9.6%
	Med	86.5	88.0	53.0	67.0	33.0	18.0	41.8%	20.9%
	p-value[a]	0.946		<0.001		<0.001		<0.001	
	p-value[b]	0.611		0.004		<0.001		<0.001	

[a] p-values based on ANOVA of rank transformed data (Sponsor Analysis)
Source: Sponsor's Tables 9 - 11, 55 - 60 (Vol. 38, pp. 84-86, 295-300)
[b] p-values based on ANOVA of original data (Reviewer Analysis)

Both the sponsor's and reviewer's analyses meet the criteria of achieving significance for two out of three types of lesions for both Studies 29C and 31C. For the primary analysis of the percent decrease in lesions (ranked data), all three p-values are ≤0.010 in Study

29C and ≤0.001 in Study 31C. Similarly, for the sponsor's analyses on the Week 12 lesion counts and the decrease from baseline to Week 12 (ranked data), all p-values are significant with $p \leq 0.044$ in Study 29C, and $p \leq 0.003$ in Study 31C. The reviewer's analysis of the unranked data also meets the Division's requirements for significance in two of the three types of lesions. The inflammatory lesion count at Week 12 in Study 29C was not significant (p=0.13), but all other variables in Studies 29C and 31C did achieve significance (p≤0.030). Thus the analysis of the lesion counts is robust to the type of variable (count, decrease, or percent decrease) and transformation (rankings or original scale) as all meet the Division's criteria for significance.

A significance level of 0.10 was specified in the protocol to check for treatment-by-center interaction. For both studies, all p-values for the interaction term were greater than 0.10 in the sponsor's analysis of the percent decrease in lesions (ranked data) for all types of lesions. Thus, the sponsor did not perform any further investigation of interaction.

The reduction in total lesions for the ITT population can be summarized as follows. For Study 29C, the median decrease in total lesions on tazarotene is 32.5 lesions (43.9% reduction) versus a median decrease of 20 lesions (24.0% reduction) on vehicle. For Study 31C, the median decrease in total lesions on tazarotene is 33 lesions (41.8% reduction) versus a median decrease of 18 lesions (20.9% reduction) on vehicle.

Results from the per protocol population are similar to those in the ITT population. Tables 4 and 5 display the results of the analysis in the per protocol population (ranked data). The sponsor provided the analysis of the percent decrease in lesions. For completeness, this reviewer conducted the analyses for the Week 12 Count and Decrease data. The p-values from both studies for all types of lesions are significant (p≤0.027).

Table 4 – Analysis of Lesion Count Data in Study 29C (Per Protocol Population)

	Baseline Count		Week 12 Count		Decrease (BL-W12)		Percent Decrease	
	Taz.	Veh.	Taz.	Veh.	Taz.	Veh.	Taz.	Veh.
Inflam. (Med)	24.0	24.0	12.0	16.0	10.0	7.0	50.0%	34.5%
p-value[a]	0.959		0.013		0.027		0.002	
Non-Inf. (Med)	54.0	52.0	29.0	36.0	25.0	15.0	50.4%	30.0%
p-value[a]	0.794		<0.001		<0.001		<0.001	
Total (Med)	81.0	81.0	44.0	55.0	35.0	22.0	48.1%	29.7%
p-value[a]	0.793		<0.001		<0.001		<0.001	

[a] p-values based on ANOVA of rank transformed data
Source: *Percent Decrease Analysis* (Sponsor Analysis) – Sponsor's Tables 65-67 (Vol. 34, pp. 305-307); *Count and Decrease Analysis* (Reviewer Analysis)

Table 5 – Analysis of Lesion Count Data in Study 31C (Per Protocol Population)

	Baseline Count		Week 12 Count		Decrease (BL-W12)		Percent Decrease	
	Taz.	Veh.	Taz.	Veh.	Taz.	Veh.	Taz.	Veh.
Inflam. (Med)	21.0	21.5	12.0	17.0	10.0	7.0	53.2%	32.0%
p-value[a]	0.686		0.006		0.008		0.001	
Non-Inf. (Med)	63.0	63.0	40.0	46.0	24.5	14.0	46.2%	26.6%
p-value[a]	0.918		0.001		<0.001		<0.001	
Total (Med)	87.0	87.5	50.5	65.0	35.5	21.5	45.1%	28.5%
p-value[a]	0.812		<0.001		<0.001		<0.001	

[a] p-values based on ANOVA of rank transformed data
Source: *Percent Decrease Analysis* (Sponsor Analysis) – Sponsor's Tables 65-67 (Vol. 38, pp. 297-299); *Count and Decrease Analysis* (Reviewer Analysis)

Thus, the results of the per protocol analysis for the lesion counts are consistent with the results for the ITT analysis. Both analyses show a significant treatment effect in favor of tazarotene in reducing the number of lesions.

IV. B. *Analysis of the Overall Acne Assessment*

Subjects were rated by the investigator on the Overall Acne Assessment at both baseline and Week 12. The assessment is measured on a 6-point scale from 0 = none to 5 = severe. The analysis planned by the sponsor in the protocol was to compare the percentage of subjects achieving at least one grade improvement from baseline to Week 12. However, the Division prefers to compare the percentage of patients achieving a certain level of clearing. The sponsor also includes analyses of the percentage of subjects with final acne assessments of none or minimal, and none, minimal or mild, following a Division request at the pre-NDA meeting. Both the results of the FDA-requested analysis, and the sponsor's planned analysis are presented below.

Table 6 compares the percentage of patients categorized by the investigator with acne assessment of none or minimal (or none, minimal, or mild) at study endpoint. The success rate on tazarotene (both cut-off points) is significantly higher than with vehicle ($p \leq 0.039$). In study 29C, 18.4% of subjects on tazarotene had a final assessment of none or minimal, versus 11.5% on vehicle. In Study 31C, 19.9% of subjects on tazarotene had a final assessment of none or minimal, versus 6.3% on vehicle.

Table 6 - Number/Percentage of Subjects with Overall Acne Assessment Scores of None or Minimal, and None, Minimal, or Mild at Week 12 (Intent-to-Treat Population)

	Study 29C			Study 31C		
	Taz. 0.1%	Vehicle	p-value[a]	Taz. 0.1%	Vehicle	p-value[a]
None or Minimal	40/218 (18.4%)	25/218 (11.5%)	0.039	41/206 (19.9%)	13/205 (6.3%)	<0.001
None, Minimal, or Mild	119/218 (54.6%)	79/218 (36.2%)	<0.001	110/206 (53.4%)	74/205 (36.1%)	<0.001

Source: Sponsor's Tables 53, 54; Vol. 34, pp. 285-286 and Vol. 38, pp. 293-294
[a] p-values based on Cochran-Mantel-Haenszel Test

The sponsor specified a significance level of 0.10 to test for treatment by center interaction. For success/failure data, the Breslow-Day test was used to check for treatment by center interaction. All p-values for the interaction in the sponsor's analysis of the percentage of subjects classified as none or minimal, and none, minimal, or mild, were greater than 0.10 in both studies.

Results from the per protocol analysis are given in Table 7. The results in the per protocol population were similar to those in the ITT population, except that one non-significant result was obtained. In Study 29C, statistical significance was not achieved for the proportion of subjects with none or minimal acne at study endpoint ($p=0.079$), though the numerical trend was similar to that observed in the ITT population. Statistical significance was achieved for the proportion of subjects with none, minimal or mild acne in Study 29C ($p<0.001$). In Study 31C, both definitions of success led to the statistical significance of tazarotene versus vehicle. ($p\leq 0.002$).

Table 7 - Number/Percentage of Subjects with Overall Acne Assessment Scores of None or Minimal, and None, Minimal, or Mild at Week 12 (Per Protocol Population)

	Study 29C			Study 31C		
	Taz. 0.1%	Vehicle	p-value[a]	Taz. 0.1%	Vehicle	p-value[a]
None or Minimal	33/174 (19.0%)	25/192 (13.0%)	0.079	38/164 (23.2%)	12/165 (7.3%)	<0.001
None, Minimal, or Mild	103/174 (59.2%)	76/192 (39.6%)	<0.001	94/164 (57.3%)	67/165 (40.6%)	0.002

Source: Sponsor's Tables 63, 64, Vol. 34, pp. 295-296 and Vol. 38, pp. 303-304
[a] p-values based on Cochran-Mantel-Haenszel Test

Since the sponsor's planned analysis of the overall acne assessment was on the incidence of improvement of at least one grade from baseline, the sponsor's results are included in Table 8 for completeness. This analysis also shows a significant treatment effect for tazarotene.

Table 8 – Number/Percentage of Subjects with at Least One Grade Improvement on the Overall Acne Assessment (Baseline to Week 12) (Intent to Treat Population)

	Study 29C			Study 31C		
	Taz. 0.1%	Vehicle	p-value[a]	Taz. 0.1%	Vehicle	p-value[a]
Number/Total (Percent)	107/218 (49.1%)	73/218 (33.5%)	0.001	99/206 (48.1%)	67/205 (32.7%)	0.001

Source: Sponsor's Table 8; Vol. 34, pp. 85 and Vol. 38, pp. 83
[a] p-values based on the Cochran-Mantel-Haenszel Test

Both the sponsor's planned analysis of the proportion showing improvement on the Overall Acne Assessment, and the Division-requested analysis of the proportion achieving scores of none or minimal at Week 12 support the superiority of tazarotene to its vehicle in terms of the Overall Acne Assessment.

IV. C. *Global Response to Treatment*

The sponsor's protocol also included a secondary analysis of the Global Response to Treatment, where the investigator assessed the subject's condition at Week 12 relative to baseline. "Treatment success" was defined as a moderate response or better (≥50% improvement). The results of this analysis are presented in Table 9.

Table 9 – Number/Percentage of Subjects with a Moderate Response or Better (≥ 50% Improvement) on the Global Response to Treatment (Intent to Treat Population)

	Study 29C			Study 31C		
	Taz. 0.1%	Vehicle	p-value[a]	Taz. 0.1%	Vehicle	p-value[a]
Number/Total (Percent)	129/218 (59.2%)	74/218 (33.9%)	<0.001	100/206 (48.5%)	55/205 (26.8%)	<0.001

Source: Sponsor's Table 13; Vol. 34, pp. 90 and Vol. 38, pp. 88
[a] p-values based on the Cochran-Mantel-Haenszel Test

A significantly higher percentage of tazarotene subjects achieved success on the Global Response to Treatment, and the results are consistent with the primary analyses of lesion count reduction and the Overall Acne Assessment and support the superiority of tazarotene to its vehicle.

IV. D. *Subgroup Analyses*

Combined data from Studies 29C and 31C was analyzed by age, gender, and race subgroups. Results in the subgroups are similar to the overall results. Table A.3 in Appendix A summarizes the median percent decrease in lesions by subgroup. Although the study was not designed to test for significance within subgroups, small p-values (<0.05) for comparing tazarotene to vehicle were observed in most moderate sized

subgroups (at least 46 subjects per arm), with the exceptions of inflammatory lesions in Hispanic patients, and inflammatory lesions in those over 30 years old.

V. Safety Assessment

Safety of tazarotene cream 0.1% was assessed through incidences of adverse events and length of treatment exposure. Patients exposed to tazarotene cream had a significantly higher incidence of adverse events and treatment related adverse events (those rated as possibly, probably, or definitely treatment related). Table 10 compares the incidences of total, treatment related, and treatment unrelated adverse events (as classified by investigator). Overall, 66% of tazarotene patients and 31% of vehicle patients across both studies reported adverse events. Adverse events in both treatment arms were reported at higher rates in Study 31C than in Study 29C. Across both studies, 53% of patients in the tazarotene group experienced treatment related adverse events, while 8% of vehicle patients had treatment related adverse events.

Table 10 – Number/Percentage of Patients with Adverse Events

	Study 29C			Study 31C		
	Taz. 0.1%	Vehicle	p-value[a]	Taz. 0.1%	Vehicle	p-value[a]
All Adverse Events	123/218 (56.4%)	52/218 (23.9%)	<0.001	157/206 (76.2%)	79/205 (38.5%)	<0.001
Treatment Related	91/218 (41.7%)	9/218 (4.1%)	<0.001	134/206 (65.0%)	26/205 (12.7%)	<0.001
Treatment Unrelated	51/218 (23.4%)	47/218 (21.6%)	0.646	69/206 (33.5%)	69/205 (33.7%)	0.972

Source: Sponsor's Table 16; Vol. 34, p. 93 and Vol. 38, p. 91

[a] p-values based on Pearson's chi-square (Sponsor's Analysis)

Table 11 lists the adverse events reported by more than 2% of subjects in either treatment group, as reported by the sponsor. Adverse events from the skin and appendages body system were observed at significantly higher rates in the tazarotene group than in the vehicle group. Adverse events from the skin and appendages system that were reported by more than 2% of tazarotene patients include desquamation, dry skin, erythema, burning sensation, pruritis, and irritation.

For the two studies combined, the average drug exposure for tazarotene patients was 75.6 days (range: 1 to 114), and the average exposure for vehicle patients was 78 days (range: 1 to 128). Ninety-two percent of tazarotene patients, and 93% of vehicle patients were exposed for at least 4 weeks. Seventy-two percent of tazarotene and 75% of vehicle patients were exposed to treatment for at least 12 weeks. (Source: Sponsor's Tables 14, 15; Vol. 34, pp. 91-92 and Vol. 38, pp. 89-90.)

Table 11 – Number/Percentage of Subjects with Adverse Events in Studies 29C and 31C with Incidence >2% from either Treatment Group.

	Taz. 0.1% N=424	Vehicle N=423	p-value[a]
Body as a Whole			
Headache	21 (5.0%)	13 (3.1%)	0.164
Respiratory			
Infection	31 (7.3%)	34 (8.0%)	0.691
Pharyngitis	14 (3.3%)	9 (2.1%)	0.293
Skin & Appendages			
Desquamation	124 (29.2%)	12 (2.8%)	<0.001
Dry Skin	114 (26.9%)	11 (2.6%)	<0.001
Erythema	88 (20.8%)	9 (2.1%)	<0.001
Burning Sensation	60 (14.2%)	3 (0.7%)	<0.001
Pruritis	20 (4.7%)	6 (1.4%)	0.005
Irritation	18 (4.2%)	1 (0.2%)	<0.001

Source: Sponsor's Table 8.8.5.2, Vol. 32, p. 126 (Sponsor's Analysis)
[a] p-values based on Pearson's chi-square

Thus, similar numbers of subjects on tazarotene and vehicle were exposed to at least 12 weeks of treatment, 72% on tazarotene and 75% on vehicle. The incidence of adverse events classified by the investigator as treatment unrelated was similar in both groups, while the incidence of treatment related adverse events was higher in the tazarotene group, particularly for those events in the skin and appendages system.

VI. Overall Summary

Tazarotene 0.1% has been shown to be statistically superior to its vehicle in reducing the number of inflammatory, non-inflammatory, and total lesions. In Study 29C, the median percent reduction in total lesions was 44% on tazarotene versus 24% on vehicle. In Study 31C, the median percent reduction in total lesions was 42% on tazarotene, versus 21% on vehicle. The median reduction in total lesions in Study 29C was 32.5 lesions on tazarotene versus 20 lesions on vehicle. The median reduction in total lesions in Study 31C was 33 lesions on tazarotene versus 18 lesions on vehicle. Per protocol analyses, and analyses based on unranked data were consistent with the sponsor's primary analyses.

The tazarotene treatment also has a significantly higher incidence of patients achieving an acne assessment of none or minimal (or none, minimal, or mild) at study endpoint. With the more stringent definition of success, 18% of tazarotene subjects were rated with none or minimal acne versus 11.5% on vehicle in Study 29C. In Study 31C, 20% of tazarotene subjects were rated with none or minimal acne versus 6% of vehicle subjects. With the more relaxed definition of success (none, minimal or mild), in Study 29C 54% were rated successful on tazarotene versus 36% on vehicle, while in Study 31C 53% were rated successful on tazarotene versus 36% on vehicle. Per protocol analyses were consistent with ITT analyses with the exception that incidence of none or minimal endpoint

assessment was not statistically significant for the comparison of the two treatment arms in Study 29C (p=0.079).

Tazarotene is associated with a higher incidence of skin related adverse events such as skin irritation, pruritis, burning sensation on skin, desquamation, dry skin, and erythema than vehicle, with 53% of tazarotene patients experiencing treatment related adverse events versus 8% of vehicle patients.

VII. Conclusion/Recommendations

The results of the analyses for Studies 29C and 31C support the sponsor's claim of efficacy of tazarotene cream 0.1% in the treatment of acne vulgaris. Each study has demonstrated that (i) tazarotene can reduce significantly more lesions (inflammatory, non-inflammatory, and total lesions) over a 12 week period than its vehicle, and (ii) a significantly higher percentage of tazarotene patients than vehicle patients are classified as having no acne or minimal acne at Week 12. Thus the sponsor has met the Division's usual requirements for establishing efficacy in acne trials.

/S/ 6/7/01

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This review contains 17 pages.

APPENDIX A– Additional Tables

Table A.1 – Number of Subjects for each Center Before and After Pooling

Study 29C					Study 31C				
Center	Tazarotene		Vehicle		Center	Tazarotene		Vehicle	
	Bef.	Aft.	Bef.	Aft.		Bef.	Aft.	Bef.	Aft.
0084	8		8		2137	3		2	
2148	16	(24)	16	(24)	2925	18	(21)	19	(21)
2912	16		17		3218	6		7	
3256	12	(28)	11	(28)	2679	17	(23)	16	(23)
0626	20		19		2677	7		7	
2927	12	(32)	14	(33)	2187	13	(20)	13	(20)
1185	4		4		1900		(20)		(20)
2168	24		24		1962		(19)		(19)
3285	2	(30)	2	(30)	1967		(20)		(20)
1104	24		24		2181		(14)		(15)
1593	11	(35)	10	(34)	2427		(19)		(18)
1562	8		7		2990		(15)		(15)
2926	13	(21)	13	(20)	2995		(15)		(14)
3197		(26)		(26)	3278		(20)		(20)
3257		(22)		(22)					

Source: Sponsor's Submission Vol. 34, pp. 41, 154, and Vol. 38, pp. 40, 164.

Table A.2 – Demographic Data for Pivotal Studies 29C and 31C

	Study 29C		Study 31C	
	Taz 0.1% N=218	Vehicle N=218	Taz 0.1% N=206	Vehicle N=205
Age (Mean ± SD)	20.3 ± 8.1	19.5 ± 7.2	17.9 ± 6.7	19.3 ± 8.1
p-value[a]	p=0.284		p=0.058	
Race				
Caucasian	151 (69.3%)	142 (65.1%)	164 (79.6%)	157 (76.6%)
Black	22 (10.1%)	17 (7.8%)	21 (10.2%)	20 (9.8%)
Asian	6 (2.8%)	4 (1.8%)	4 (1.9%)	5 (2.4%)
Hispanic	37 (17.0%)	53 (24.3%)	16 (7.8%)	22 (10.7%)
Other	2 (0.9%)	2 (0.9%)	1 (0.5%)	1 (0.5%)
p-value[b]	p=0.359		p=0.458	
Gender				
Male	113 (51.8%)	112 (51.4%)	108 (52.4%)	97 (47.3%)
Female	105 (48.2%)	106 (48.6%)	98 (47.6%)	108 (52.7%)
p-value[c]	p=0.924		p=0.300	

Source: Sponsor's Table 3, Vol. 34 p. 78, and Vol. 38, p. 76

[a] p-values based on one-way ANOVA

[b] p-values based on Pearson's chi-square for Caucasian vs. non-Caucasian

[c] p-values based on Pearson's chi-square

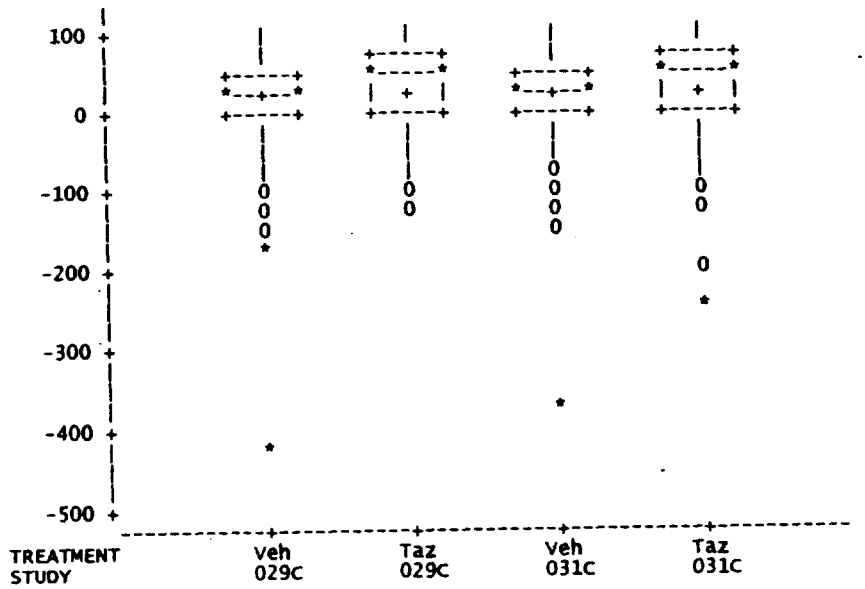
Table A.3 – Subgroup Analysis: Median Percent Decrease in Lesions (Baseline to Week 12), Combined Studies 29C and 31C, (Intent-to-Treat)

	Inflammatory		Non-Inflammatory		Total	
	Taz	Veh	Taz	Veh	Taz	Veh
	Med % (N)	Med % (N)	Med % (N)	Med % (N)	Med % (N)	Med % (N)
Age						
≤17	38.7 (250)	23.5 (245)	40.5 (250)	20.7 (245)	37.8 (250)	19.1 (245)
18-29	50.0 (123)	27.2 (132)	43.1 (123)	25.0 (132)	42.2 (123)	25.6 (132)
≥30	47.8 (51)	42.5 (46)	61.1 (51)	41.1 (46)	54.7 (51)	39.4 (46)
Gender						
Male	45.1 (221)	23.5 (209)	39.3 (221)	25.6 (209)	40.0 (221)	23.0 (209)
Female	41.7 (203)	27.7 (214)	49.5 (203)	23.3 (214)	45.6 (203)	22.6 (214)
Race						
Caucasian	39.3 (315)	21.2 (299)	42.7 (315)	23.1 (299)	41.4 (315)	20.3 (299)
Black	54.6 (43)	42.9 (37)	48.8 (43)	30.0 (37)	47.9 (43)	33.3 (37)
Asian	46.4 (10)	9.1 (9)	58.9 (10)	0.0 (9)	49.6 (10)	0.0 (9)
Hispanic	49.3 (53)	36.4 (75)	48.2 (53)	24.5 (75)	43.8 (53)	26.6 (75)
Other	64.3 (3)	40.0 (3)	65.5 (3)	57.1 (3)	58.6 (3)	58.5 (3)

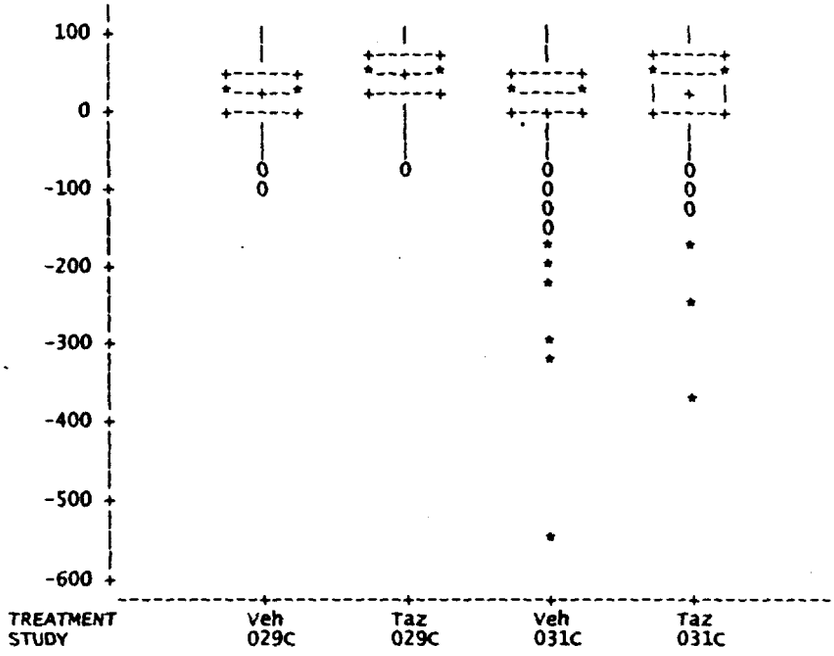
Source: Sponsor's Tables 13-21; Vol. 32, pp. 98-109.

APPENDIX B – Plots

Plot B.1 – Percent Decrease in Inflammatory Lesions (Baseline to Week 12) (Reviewer Analysis)



Plot B.2 – Percent Decrease in Non-Inflammatory Lesions (Baseline to Week 12) (Reviewer Analysis)



Plot B.3 – Percent Decrease in Total Lesions (Baseline to Week 12) (Reviewer Analysis)