CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-184

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

(ADDENDUM)

JUL 17

NDA #: 21–184
Applicant: Allergan, Inc.
Name of Drug: Tazorac (tazarotene)
Indication: Treatment of plaque psoriasis
Document reviewed: Volumes 1.82–1.147, submitted on September 30, 1999
Statistical Reviewer: John Lawrence, Ph.D. (HFD–710)
Medical Reviewer: Hon–Sum Ko, M.D. (HFD–540)

1) The definition used in determining the number of dropouts in Table 6.1 of the review is different from the definition used by the sponsor. Therefore, the number of dropouts in this table differs from the number presented by the sponsors. The FDA review defined a patient as a dropout if the overall lesional assessment at the end of the 12-week treatment period was missing in the data set. The reason for this definition is that for those patients, the primary efficacy variable would have to be imputed. The sponsor defined a patient as a dropout if they did not complete the study. The number of dropouts in each arm for both trials using the sponsor's definition and the definition used in the FDA review are presented in Table A.1.

Table A.1 Number of patients not completing study and number of patients missing overall lesional assessment at week 12.

Treatment Arm	n	# patients not completing study	# patients missing overall lesional assessment end of treatment period
Vehicle	229	74	74
0.05% tazarotene	218	93	90
0.1% tazarotene	221	76	74
Vehicle	214	51	48
0.05% tazarotene	210	66	65
0.1% tazarotene	211	51	49

Source: FDA analysis, Study Report –016C, Section 14.1, Table 1 and Study Report –017C, Section 14.1, Table 1.

In some cases, a patient completed the treatment period, but did not have an overall lesional assessment at week 12. In other cases, a patient had an overall lesional assessment at week 12, but did not complete the study according to the sponsor. Table A.2 lists the identification codes for these patients.

Table A.2 Patient IDs for those patients who are missing overall lesional assessment at week 12 (OLA12) or did not completed study, but are not in both categories.

Treatment Arm	patients not completing study with observed OLA12			patients missing OLA12 who completed study		
	ID	# days exposure	# days to OLA12	ID	# days exposure	# days to OLA12
[redacted]						
Vehicle						
0.05% tazarotene	E07	80	80			
	K05	72	72			
	P11	73	73			
	P22	45	143			
	R02	77	77			
				C21	84	62
				P28	57	57
0.1% tazarotene	C23	85	85			
	N27	57	142			
[redacted]						
Vehicle	F43	77	77			
	T05	71	71			
	T10	78	78			
0.05% tazarotene	B11	78	78			
0.1% tazarotene	F39	78	78			
	L18	98	98			

Source: FDA analysis.

2) In the discussion following Table 9.2 the review states that among those patients with less than 20% body surface area involved, the higher dose was significantly more effective. The p-value in the table for the comparison of the two doses within this subgroup is 0.09. Since this was an exploratory analysis, some judgement can be used in deciding that a p-value of a certain magnitude is persuasive or not. However, the FDA usually accepts a two-sided p-value less than 0.05 as significant.

3) The protocol states that Hochberg's step-up procedure will be used to adjust for multiplicity, but Fisher's LSD is used in the FDA statistical review.

/S/

John Lawrence, Ph.D.
Mathematical Statistician

This review consists of 3 pages of text, tables, and figures.

Concur: Mohamed Al–Osh, Ph.D. /S/ 7/12/00
Acting Team Leader, Biometrics III

cc: NDA #21–184
HFD–540/Dr. Walker
HFD–540/Dr. Wilkin
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LAWRENCEJ/594–5375/addendum.doc/07/06/00

STATISTICAL REVIEW AND EVALUATION

MAY 15 2000

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1. Introduction

Psoriasis is a chronic skin disorder that usually is identified clinically by plaques on the surface of the elbows, knees, back, buttocks and/or scalp. A gel formulation of tazarotene was approved for marketing in the United States in June 1997. The NDA under review here is for a tazarotene cream formulation.

2. Study Design

The sponsor conducted two multicenter, double–blind, vehicle–controlled trials (190168–016C–03 and 190168–017C–03). In both trials, there were three arms: 0.05% tazarotene cream applied once daily, 0.1% tazarotene cream applied once daily, and vehicle applied once daily. Both trials had a 12-week treatment period. Lesions were evaluated at baseline and at the end of weeks 1, 2, 4, 8, and 12. No analysis was planned based on the repeated measurements. However, the intermediate results may be used to impute data on patients that dropped out of the study before the end. One of the trials (–016C) included an additional 12 week post–treatment follow–up. In this follow–up period, the lesions were evaluated every four weeks. The goal of both studies was to assess the safety and efficacy of both the 0.05% dose and the 0.1% dose.

In both trials, male and female patients 18 years and older with psoriasis were enrolled. Overall lesion assessment was graded on a 6–point scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe, 5=very severe). According to protocol, only those patients with a minimum psoriasis involvement of at least 2% of the total body surface area and overall assessment of at least 3 were admitted to the study.

All patients were equally likely to be randomized to any one of the three treatment arms. Within each site, patients were randomly assigned to one of the three groups in a 2:2:2 ratio, based on a blocking factor of 6.

In trial –016C, there were 21 investigators and 668 patients enrolled. In trial –017C, there were 17 investigators and 635 patients enrolled.

3. Primary Efficacy Variable

The primary efficacy variable in both studies was the proportion of clinical successes after 12 weeks of treatment. Clinical success was defined as an overall lesional assessment of none, minimal, or mild (the lowest three grades on the 6–point scale).

4. Secondary Efficacy Variables

Secondary analyses were done to detect differences in specific aspects of the disease (plaque elevation, scaling, and erythema) and the effect on different areas of the body (all, knees/elbows, trunk/limbs). These were all measured on a 5–point scale. In order to determine if the treatment effect persisted, clinical success rates were compared at all post–treatment visits in trial –016C.

5. Protocol Specified Planned Statistical Analysis

All analyses were based on the Cochran–Mantel–Haenszel test statistic stratified by investigator. For the intent–to–treat (ITT) analysis, the last observation was carried forward to impute missing data. A per–protocol analysis was also planned.

Since there were two active treatment arms, an adjustment was necessary for multiple comparisons versus the control arm. This adjustment was made using Fisher's protected least significant difference test; a pairwise comparison p–value of 0.05 or less was declared significant only if the among–group comparison p–value was 0.05 or less.

6. Statistical Issues

There were a significant number of patients that dropped out of the study before the end of the trial. In general, when there are a large number of dropouts, any specific approach toward handling the missing data can work in favor or against the treatment. For example, the LOCF can make the treatment effect look greater than it is in reality. On the other hand, it can make the treatment effect look smaller than it is in reality, depending on the reasons that the patients drop out in each treatment arm. It is also important to make sure that patients in the treatment arm are not systematically being counted as a "clinical success" while dropping out before the end of the trial due to adverse events.

In both trials, approximately one fourth of the patients dropped out of the trial before the end of the 12-week treatment period. Table 6.1 summarizes the number of patients in each arm who dropped out and the number of these dropouts that were counted as treatment successes using LOCF analysis. Although roughly the same number of patients dropped out of the trial in each treatment arm, there were more dropouts who were clinical successes in the active treatment arms.

Table 6.1 Proportion of dropouts counted as clinical successes in LOCF analysis, and the number with adverse events.

Treatment Arm	n	Fraction of successful dropouts	Number with adverse event
Vehicle	229	4/74	1
0.05% tazarotene	218	21/90	3
0.1% tazarotene	221	14/74	6
Vehicle	214	1/48	1
0.05% tazarotene	210	8/65	3
0.1% tazarotene	211	7/49	3

Source: FDA analysis.

Upon discussion with the medical reviewer, Dr. Ko, it was decided that the intent–to–treat analysis would be used as the primary analysis. The per–protocol analysis of the primary efficacy variable that was provided by the sponsor is also presented in this review.

7. Analysis of Efficacy During 12 Week Treatment Period

The primary efficacy variable in both trials was the clinical success rate after 12 weeks of treatment. Clinical success was defined by a global assessment of 0, 1, or 2 on the 6–point scale. This variable was analyzed using the CMH test statistic adjusting for investigator. All results in this review, unless specifically stated otherwise, are from the FDA's analysis. The results from the FDA analysis are the same as those presented by the sponsor unless stated otherwise. The FDA analysis used the intent–to–treat population and missing values were imputed by carrying the last observation forward. The result of this analysis appears in Table 7.1.

Table 7.1 Results of analysis of primary efficacy variable (clinical success rates).

Variable	Trial –016C			Trial –017C		
	n	Confidence interval	P–value	n	Confidence interval	P–value
Vehicle	229	0.245 ± 0.056		214	0.262 ± 0.059	
0.05% tazarotene	218	0.417 ± 0.066		210	0.405 ± 0.067	
0.1% tazarotene	221	0.394 ± 0.065		211	0.507 ± 0.068	
Among group	668		0.001	635		0.001
0.05% vs. vehicle	447		0.001	424		0.001
0.1% vs. vehicle	450		0.001	425		0.001
0.1% vs. 0.05%	439		0.671	421		0.025

Source: FDA analysis.

In this table, the p–values are calculated using the CMH statistic adjusting for investigator. The results are identical to the results from the sponsor's ITT analysis with the exception of the p–value for the comparison of the two active treatments in trial –016C [*Source: Study Report –016C, Section 14.2, Table 11 and Study Report –017C, Section 14.2, Table 10*]. The FDA p–value is 0.671 and the sponsor's p–value is 0.648. A possible explanation for the difference in this p–value is the way that missing values for investigator were handled in the analysis.

These results show that in both trials, the active treatments were statistically better than vehicle. In one trial (–016C), the lower dose actually had a numerically higher clinical success rate, although this was not statistically significant. In the other trial (–017C), there was a moderately significant difference between the two active treatments; the higher dose had a clinical success rate about 10% higher than the low dose. If all data from both trials are combined together, the estimated clinical success rate is about 41% for the low dose and 45% for the high dose.

The sponsor's per–protocol analysis gives similar differences between the two active treatment arms and vehicle. The point estimates for the primary efficacy variable in trial –016C using the per–protocol analysis are roughly 49% for both treatment arms and 30% for vehicle. The estimates are 59% and 50% for the two active treatment arms versus 31% for vehicle in trial –017C [*Source: Study Report –016C, Section 14.2, Table 29 and Study Report –017C, Section 14.2, Table 28*].

All lesions were also rated by severity of plaque elevation, scaling, and erythema on a 5–point scale. Furthermore, the lesions in specific areas were rated on a 6–point scale. These variables were each individually analyzed using the CMH statistic adjusting for investigator using modified ridit scores. The results of these analyses appear in Table 7.2.

Table 7.2 Results of analysis of secondary endpoints (differences between active treatment arms in severity of symptoms after 12-week treatment period).

Variable	Trial –016C		Trial –017C	
	Among Group P–value	0.1% vs. 0.05% P–value	Among Group P–value	0.1% vs. 0.05% P–value
All lesions plaque elevation	0.001	0.310	0.001	0.026
All lesions scaling	0.001	0.812	0.001	0.025
All lesions erythema	0.279	0.544	0.001	0.066
Knees/elbows global	0.001	0.065	0.001	0.014
Trunk/limbs global	0.011	0.087	0.001	0.003

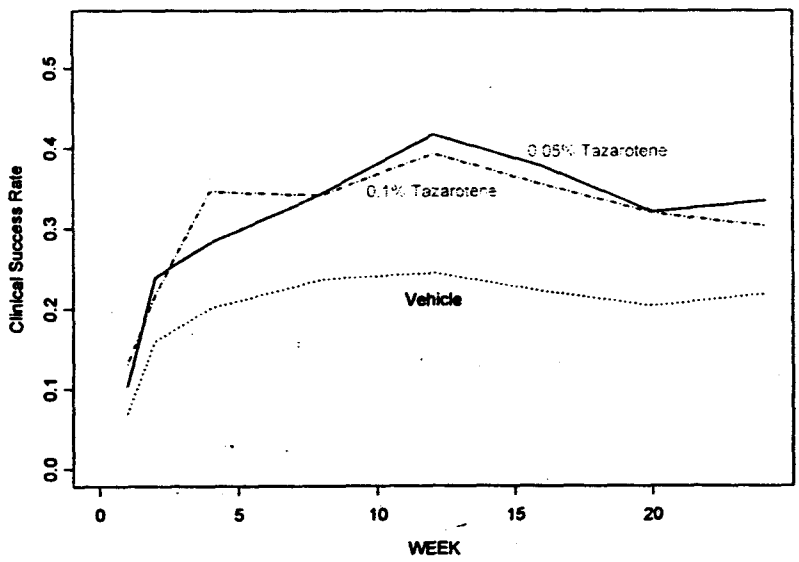
Source: FDA analysis

The p–values in this table are found using the aforementioned CMH statistic. These results agree with the results reported by the sponsor [*Source: Study Report –016C, Section 14.2, Tables 12, 13, 14, 21, and 26 and Study Report –017C, Section 14.2, Tables 11, 12, 13, 20, and 25*]. In trial –016C, there was no statistically significant difference between the two active treatments in the severity of any of the symptoms measured. In trial –017C, there was a statistically significant difference in plaque elevation, scaling, and the global measurement at the two target areas.

8. Analysis of Changes in Global Assessment Over Time

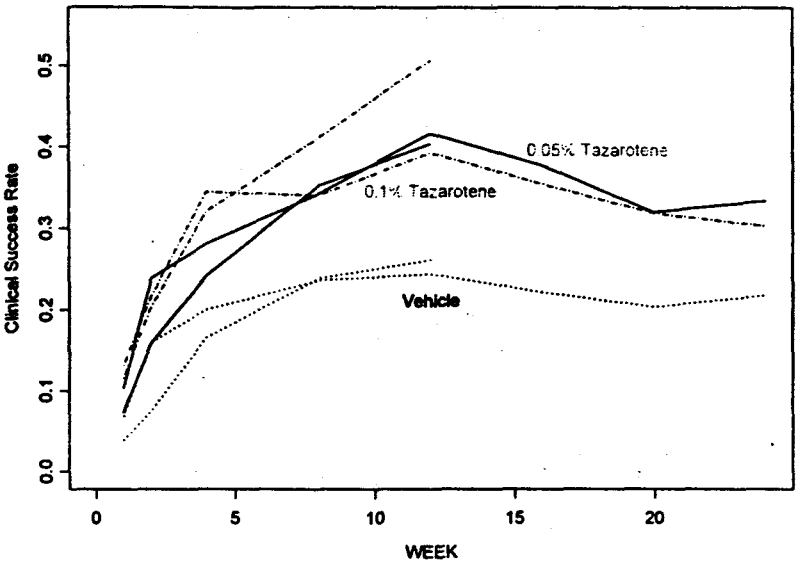
There was no analysis planned that looks at the clinical success rate over time. However, since we have the data, it may give us some information about the efficacy of the two doses. The clinical success rates in the three treatment arms as a function of time are shown in Figures 8.1a and 8.1b. Figure 8.1a shows the data from trial –016C. Figure 8.1b shows the data from both studies.

Figure 8.1a Clinical success rates over time in trial –016C.



Source: FDA analysis.

Figure 8.1b Clinical success rates over time in trials –016C and –017C.



Source: FDA analysis.

There is visually very little difference between the success rates over time in the two active treatment groups. Also, the success rate drops to about 30% from 40% 12 weeks after the treatment is stopped. Figure 1b shows the data from both studies. In trial –017C there was no post–treatment follow–up so the curves stop after the 12-week treatment period. In trial –017C, the curves for the active treatment arms appear to diverge after about 5 weeks.

9. Exploratory Subgroup Analysis

Table 9.1 shows the clinical success rates in the two trials for subgroups based on age, race, gender, and weight. Sample sizes for each subgroup appear next to each estimate. The p–value in the last column represents the significance of the difference between the 0.05% tazarotene arm and the 0.1% tazarotene arm for that subgroup.

Table 9.1 Estimates of clinical success rates after 12-week treatment period for various subgroups.

Subgroup	Vehicle	0.05% tazarotene	0.1% tazarotene	P–value
[redacted]				
Males	0.20 (n=151)	0.38 (n=146)	0.35 (n=135)	0.54
Females	0.33 (n=78)	0.49 (n=72)	0.47 (n=86)	0.79
Age 18–40	0.25 (n=71)	0.42 (n=65)	0.37 (n=51)	0.64
Age 41–60	0.20 (n=101)	0.40 (n=90)	0.34 (n=99)	0.42
Age >60	0.32 (n=57)	0.44 (n=63)	0.48 (n=71)	0.69
Race White	0.25 (n=199)	0.40 (n=193)	0.38 (n=189)	0.72
Race Black	0.22 (n=9)	1.0 (n=1)	0.5 (n=8)	N/A
Race Other	0.24 (n=21)	0.54 (n=24)	0.46 (n=24)	0.57
Weight 0–200	0.26 (n=139)	0.45 (n=150)	0.38 (n=141)	0.23
Weight >200	0.22 (n=89)	0.34 (n=68)	0.41 (n=80)	0.36
[redacted]				
Males	0.23 (n=116)	0.34 (n=132)	0.50 (n=136)	0.008
Females	0.30 (n=98)	0.51 (n=78)	0.52 (n=75)	0.93
Age 18–40	0.31 (n=72)	0.29 (n=62)	0.51 (n=67)	0.01
Age 41–60	0.23 (n=94)	0.46 (n=93)	0.48 (n=88)	0.84
Age >60	0.25 (n=48)	0.44 (n=55)	0.55 (n=56)	0.22
Race White	0.28 (n=181)	0.41 (n=182)	0.50 (n=183)	0.08
Race Black	0.25 (n=8)	0.44 (n=9)	0.40 (n=5)	0.88
Race Other	0.16 (n=25)	0.32 (n=19)	0.57 (n=23)	0.11
Weight 0–200	0.29 (n=143)	0.44 (n=144)	0.52 (n=141)	0.22
Weight >200	0.20 (n=71)	0.32 (n=66)	0.48 (n=69)	0.06

Source: FDA analysis.

There does not appear to be any important differences between the treatment effect in these different subgroups. It is interesting that females had a higher clinical success rate across all treatment groups. Nonetheless, the difference between the tazarotene groups and vehicle remains about the same for each gender.

At the request of the FDA medical officer, the efficacy stratified by baseline extent of disease was also investigated. The results of these analyses appear in Table 9.2. In this table, the results are stratified by baseline overall lesional assessment score and by the percent of body surface area psoriasis involvement. Results are given for each trial separately as well as the results from both studies combined. The average overall score and the proportion of patients with a score less than 3 is shown in the table. The p–values represent the "asymptotic p–values" using the normal approximation for the difference between the proportion of clinical successes in the two active treatment arms in that subgroup.

Table 9.2 Estimates of clinical success rates after 12-week treatment period stratified by baseline extent of disease (overall lesional assessment score or percent of body area psoriasis involvement).

Disease Extent at Baseline	Treatment arm	Mean Score After 12 Weeks	Proportion of Clinical Successes	P–value
[redacted]				
Score=3	Vehicle	2.70	44/139 = 0.317	
	0.05% tazarotene	2.47	73/141= 0.518	0.88
	0.1% tazarotene	2.43	62/122 = 0.508	
Score=4	Vehicle	3.37	12/81 = 0.148	
	0.05% tazarotene	3.09	18/69 = 0.261	0.84
	0.1% tazarotene	3.03	25/91 = 0.275	
Score=5	Vehicle	3.67	0/9 = 0	
	0.05% tazarotene	4.00	0/8 = 0	1.0
	0.1% tazarotene	3.62	0/8 = 0	
<20% Baseline Body Area Involvement	Vehicle	2.97	49/203 = 0.241	
	0.05% tazarotene	2.71	78/188 = 0.415	0.80
	0.1% tazarotene	2.71	76/189 = 0.402	
≥20% Baseline Body Area Involvement	Vehicle	3.04	7/26 = 0.27	
	0.05% tazarotene	2.77	13/30 = 0.433	0.47
	0.1% tazarotene	2.78	11/32 = 0.344	
[redacted]				
Score=3	Vehicle	2.70	34/97 = 0.351	
	0.05% tazarotene	2.51	47/100 = 0.470	0.0007
	0.1% tazarotene	2.16	68/96 = 0.70	
Score=4	Vehicle	3.22	20/93 = 0.215	
	0.05% tazarotene	2.99	28/80 = 0.350	0.89
	0.1% tazarotene	2.93	31/86 = 0.360	
Score=5	Vehicle	3.88	2/24 = 0.083	
	0.05% tazarotene	3.67	10/30 = 0.333	0.63
	0.1% tazarotene	3.41	8/29 = 0.276	
<20% Baseline Body Area Involvement	Vehicle	2.95	53/177 = 0.299	
	0.05% tazarotene	2.78	74/170 = 0.435	0.09
	0.1% tazarotene	2.65	94/179 = 0.525	
≥20% Baseline Body Area Involvement	Vehicle	3.54	3/37 = 0.081	
	0.05% tazarotene	3.17	11/40 = 0.275	0.24
	0.1% tazarotene	2.59	13/32 = 0.406	

Source: FDA analysis.

Table 9.2 (continued)

Disease Extent at Baseline	Treatment arm	Mean Score After 12 Weeks	Proportion of Clinical Successes	P–value
[redacted]				
Score=3	Vehicle	2.70	78/236 = 0.331	
	0.05% tazarotene	2.49	120/241 = 0.498	0.035
	0.1% tazarotene	2.32	130/218 = 0.596	
Score=4	Vehicle	3.29	32/174 = 0.184	
	0.05% tazarotene	3.03	46/149 = 0.309	0.88
	0.1% tazarotene	2.98	56/177 = 0.316	
Score=5	Vehicle	3.82	2/33 = 0.061	
	0.05% tazarotene	3.74	10/38 = 0.263	0.63
	0.1% tazarotene	3.46	8/37 = 0.216	
<20% Baseline Body Area Involvement	Vehicle	2.96	102/380 = 0.268	
	0.05% tazarotene	2.75	152/358 = 0.425	0.31
	0.1% tazarotene	2.68	170/368 = 0.462	
≥20% Baseline Body Area Involvement	Vehicle	3.33	10/63 = 0.159	
	0.05% tazarotene	3.00	24/70 = 0.343	0.70
	0.1% tazarotene	2.69	24/64 = 0.375	

Source: FDA analysis.

In trial –016C, there was no significant difference between the two tazarotene arms in any of the subgroups. In trial –017C, the higher dose was significantly more effective on those patients with a less severe extent of disease. In this trial, only among those patients with a baseline score of 3 and among those patients with less than 20% body surface area involved was the higher dose significantly more effective. When the data from both trials were combined, there was a moderately significant difference between the two doses only among those patients with baseline score of 3. The exact p–values using "Fisher's exact test" were also calculated, but do not appear in the table because the results were very similar to the asymptotic p–values.

10. Adverse events

According to the sponsor's report for trial –017C, significantly more tazarotene patients reported adverse events than did vehicle patients. The number of adverse events in each treatment arm and the p-values comparing the rates in the two tazarotene arms are in Table 10.1. The p-values are based on Fisher's exact test.

Table 10.1 Rates of adverse events and p-values comparing two doses of tazarotene.

Adverse Event	Vehicle	0.05% tazarotene	0.1% tazarotene	P–value
[redacted]				
Burning skin	13/229=5.7%	35/218=16.1%	39/221=17.7%	0.703
Erythema	3/229=1.3%	39/218=17.9%	38/221=17.2%	0.9
Pruruitis	32/229=14%	53/218=24.3%	66/221=29.9%	0.199
Rash	2/229=0.9%	10/218=4.6%	12/221=5.4%	0.828
Skin Irritation	2/229=0.9%	16/218=7.3%	20/221=9.1%	0.603
Stinging skin	2/229=0.9%	5/218=2.3%	10/221=4.5%	0.293
[redacted]				
Burning skin	8/214=3.7%	16/210=7.6%	22/211=10.4%	0.395
Dermatitis	1/214=0.5%	6/210=2.9%	12/211=5.7%	0.228
Eczema	0/214=0%	3/210=1.4%	11/211=5.2%	0.053
Erythema	7/214=3.3%	19/210=9.1%	35/211=16.6%	0.028
Pruritis	19/214=8.9%	30/210=14.4%	35/211=16.6%	0.590
Skin Irritation	6/214=2.8%	15/210=7.1%	22/211=10.4%	0.302

Source: Study Report –016C, Section 14.3.1, Table 49 and Study Report –017C, Section 14.3.1, Table 46.

Accoring to the sponsor, the majority of these events were considered by the investigators to be possibly, probably, or definitely related to study medication. Patients receiving tazarotene 0.1% reported significantly more incidences of burning skin, rash, erythema, skin irritation, stinging skin, and pruritis relative to vehicle. Patients receiving tazarotene 0.05% reported significantly more incidences of burning skin, rash, erythema, skin irritation, and pruritis relative to vehicle. The comparison of the two tazarotene groups does not show a statititically significant difference, but an increasing trend is evident.

Similar results were reported for study –017C. There was a statistically significant dose–response pattern in the incidence of burning skin, dermatitis, eczema, erythema, skin irritation, and pruritis in trial –017C. Adverse events in the "skin and appendages" body system were reported by 49.8% of patients in the tazarotene 0.1% group, 41.4% of patients in the tazarotene 0.05% group, and 22.0% in the vehicle group.

11. Conclusions

In both trials, both doses of tazarotene cream were shown to be more effective than vehicle. In the trial that had a 12–week post–treatment follow–up period (trial –016C), the benefit of the treatment was shown to persist throughout this period. This reviewer was not convinced that there is a difference in efficacy between the two doses based on these two trials. In the two trials, the p–values for the comparison of the two active treatments were 0.67 and 0.025. However, the trials were not powered to detect a

difference between the two treatments. Moreover, both doses appeared to work equally well in the demographic subgroups analyzed on an exploratory basis. Since there was a dose–response pattern in the incidence of treatment related adverse events in both trials (specifically burning skin, erythema, and skin irritation), the 0.05% dose may be the better dose when balancing risk and benefit.

/S/

John Lawrence, Ph.D.
Mathematical Statistician

This review consists of 11 pages of text, tables, and figures.

Concur: For Mohamed Al–Osh, Ph.D. /S/ 5.15.2000
Acting Team Leader, Biometrics III

cc:
NDA #21–184
HFD–540/Dr. Walker
HFD–540/Dr. Wilkin
HFD–540/Dr. Bhatt
HFD–540/Dr. Ko
HFD–725/ Dr. Huque
HFD–725/ Dr. Al–Osh
HFD–725/chron

LAWRENCEJ/594–5375/report.doc/05/04/00

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Dr. Jim Hung/Dr. John Lawrence HFD-710
Thru HFD-110 Document Room

FROM: HFD-540 (Division of Dermatologic and Dental Drug Products)
Mohammed Al-Osh, Ph.D.

IND NO.	NDA NO. 21-184	TYPE OF DOCUMENT : New NDA	DATE OF DOCUMENT 9-30-99

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Tazorac		3S	4-15-00

NAME OF FIRM: Allergan Inc

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*: New NDA Submission

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW): New NDA Submission

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS:
Please review the Statistical Section of this New NDA application.

If you have any questions , Kalyani Bhatt 301-827-2049

cc: Original NDA 21-184
HFD-540/Div. Files

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER