

Telangiectasia

Telangiectasia ratings

Two (1%) patients in each of the 2 treatment groups had no telangiectasia at baseline. The majority of patients (62% each treatment group) had mild telangiectasia at baseline. Sites were queried about patients without telangiectasia at baseline. Patients who were confirmed to have no telangiectasia at baseline were allowed to continue in the study, if the investigator verified the diagnosis of stage 2 rosacea. These patients were excluded from the PP population.

Disposition of patients

One hundred thirty-three (81%) AzA 15% gel-treated patients and 150 (91%) vehicle-treated patients completed the study. Of the 46 patients who withdrew from the study prematurely, 12 discontinued for other reasons, 11 discontinued due to AEs, 8 patients discontinued due to lack of efficacy, 8 patients withdrew consent, and 7 patients discontinued because of protocol violations. The majority of patients discontinuing for other reasons were lost to follow-up (5 AzA 15% gel and 2 vehicle patients). Text Table 3 shows the disposition of patients by treatment group.

Text Table 3: Patient Disposition

	AzA 15% gel	Vehicle	Total
Randomized	164	165	329
Completed treatment	133 (81%)	150 (91%)	283 (86%)
Discontinued	31 (19%)	15 (9%)	46 (14%)
Reasons for discontinuation			
Adverse event	9	2	11
Lack of efficacy	1	7	8
Protocol deviation	6	1	7
Withdrawal of consent	6	2	8
Death	0	0	0
Other:	9	3	12
Lost to follow-up	5	2	7
Other	4	1	5

AzA = azelaic acid.

Reference: Section 14.1, Table 1 and Appendix 16.2.1.

Patient Evaluability

All 329 patients randomized were included in the ITT population. The per-protocol (PP) population consisted of all patients who finished the study fulfilling criteria detailed in the protocol, such as completion of 12 weeks of therapy, compliance, and no major protocol violations.

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Text Table 4 Patient Evaluability

	AzA 15% gel	Vehicle	Total
Randomized	164	165	329
Intent-to-treat population	164 (100%)	165 (100%)	329 (100%)
Per protocol population	114 (69.5%)	125 (75.8%)	239 (72.6%)
Violated any inclusion/exclusion criteria at screening	4	3	7
Did not complete Week 12 visit within window	30	23	53
Medication not used according to protocol	13	10	23
Used prohibited medications	3	4	7

AzA = azelaic acid

Reference: Section 14.1, Table 2.

According to the Sponsor, seven patients (4 AzA 15% gel and 3 vehicle) violated inclusion/exclusion criteria at screening. Two patients in the AzA 15% gel group did not have telangiectasia present at baseline. One AzA 15% gel-treated patient used chronic NSAIDs (naproxen 1100 mg), and 1 patient used ketoconazole shampoo daily. Of the 3 vehicle-treated patients that violated inclusion/exclusion criteria, 2 did not have telangiectasia present at baseline, and 1 did not observe the required washout period for amoxicillin/clavulanic acid.

A total of 53 patients (30 AzA 15% gel and 23 vehicle) did not complete the Week 12 visit within the allowed window (between 77 and 98 days post randomization). Medication was not used according to the protocol by 23 patients (13 AzA 15% gel and 10 vehicle). Prohibited medications were used during the study by 7 patients (3 AzA 15% gel and 4 vehicle). Thus, the total number of patients included in the PP population was 239 (114 AzA 15% gel and 125 vehicle).

Primary Efficacy Results

Inflammatory Lesion Counts

The FDA's statistical analysis Table 6 below displays Week-12 means for three patient populations (ITT, Completers, and Per Protocol), and the significance levels of the test for treatment differences from an ANCOVA model with classification effects for treatment, center, and interaction, and baseline lesion count as a covariate are presented.

FDA Statistical Table 6: Study A30125 Means and Tests of Treatment Differences in Inflammatory Lesion Counts

Response	Treat	ITT			Completers			Per Protocol		
		N	Mean	p-value	N	Mean	p-value	N	Mean	p-value
Change	Veh	165	7.1	0.0001	151	7.7	<0.0001	125	8.3	0.0010
	AzA	164	10.7		134	12.7		114	12.4	
% Change	Veh	165	39.9	0.0003	151	42.5	<0.0001	125	44.7	0.0016
	AzA	164	57.9		134	67.2		114	66.5	

Model: expected response = baseline + center + treatment + interaction

According to the FDA statistical reviewer, for all three populations, whether we use the change from baseline as specified in the protocol, or the percent change from baseline, differences are

statistically significant (all $p \leq 0.0016$). The ITT population is of primary interest; however for all three populations, differences are statistically significant (all $p \leq 0.0016$).

Sponsor's Efficacy Conclusion

The Sponsor's conclusion is that a statistically significant reduction ($p < 0.0001$) from baseline in mean inflammatory lesion counts for both the AzA 15% gel and vehicle groups was demonstrated. The difference between AzA 15% gel and vehicle for the mean nominal changes (treatment effect) was 3.63, with 95% confidence interval limits of 2.02 and 5.25. The p-value for the comparison of treatments was < 0.0001 , indicating a statistically significant advantage for the AzA 15% gel-treated patients. According to the Sponsor's analysis, there was no statistically significant ($p = 0.6391$) treatment-by-center interaction.

Investigator's Global Assessment

Reviewer's comments:

The FDA analysis for the determining "success" on the Investigator's Global Assessment differs from the advice given the Sponsor by the Division at the EP-2 meeting. At the EP-2 meeting the Division recommended that "success" be defined as the proportion of patients in the active group vs. the vehicle group who achieve a static global assessment score of 0 (clear) and 1 (minimal) at the end of study as described in the Investigator's Global Assessment Score.

Success was redefined for subjects with a baseline IGA score ≥ 3 (mild) were as follows:

- a patient who achieved an IGA of clear (i.e. score of 0) at the end of the study if they were mild at baseline (i.e. a score of 2) or*
- a patient who achieved a score of clear or minimal (i.e., 0 or 1) at the end of the study with a baseline score of 3-6 (i.e. "mild to moderate to severe").*

The rationale for redefining "success" was previously provided.

Investigator Global Evaluation

FDA Statistical Table 7: Study A30125 Investigator Global Evaluation at End of Study

Treat		ITT			Completers			Per Protocol		
		AzA	Veh	p-value	AzA	Veh	p-value	AzA	Veh	p-value
Success	N	50	20	0.001	49	19	0.001	39	17	0.001
	%	30.5%	12.1%		36.6%	12.6%		34.2%	13.6%	
0 (clear)	N	12	5	0.039	12	5	0.017	9	4	0.028
	%	7.3%	3.0%		9.0%	3.3%		7.9%	3.2%	
0,1 (≤Min)	N	60	32	0.001	57	31	0.001	45	24	0.001
	%	36.6%	19.4%		42.5%	20.5%		39.5%	19.2%	
0-2 (≤Mild)	N	100	67	0.001	93	62	0.001	76	51	0.001
	%	61.0%	40.6%		69.4%	41.1%		66.7%	40.8%	
3-6	N	64	98		41	89		38	74	
	%	39.0%	59.4%		30.6%	58.9%		33.3%	59.2%	
All	N	164	165		134	151		114	125	

According to the statistical reviewer, for all endpoints differences are statistically significant as depicted in Table 7. The conclusions are consistent with the Sponsor's conclusion in favor of AZA gel over vehicle.

Secondary Efficacy Endpoints

The Sponsor is making a labeling claim for _____ is one of the six secondary efficacy variables assessed. Three of the six secondary efficacy endpoints are of regulatory interest: Investigator Rating of Improvement, Change in Erythema at End of Study, and Change in Telangiectasia at End of Study.

For erythema, treatment success was redefined. "Success (1)" denotes the proportion of subjects who had a baseline score of moderate or severe and achieved a final score of none, while "success (1,2)" denotes the proportion of subjects who had a baseline score of moderate or severe and achieved a final score of none or mild. These post hoc definitions of response are somewhat more stringent since it was not noted at the original IND review that the scale provided by the Sponsor was not clear in that patients scored as "none" could actually have minimal residual erythema. The protocol specifies a comparison of mean change using modified ridit scores (see the first row of p-values).

FDA Statistical Table 8: Study A03125 Decrease From Baseline in Erythema Ratings at End of Study

Decrease †		ITT		Completers		Per Protocol	
		AzA	Veh	AzA	Veh	AzA	Veh
2	N	14	7	13	7	10	6
	%	8.5%	4.2%	9.7%	4.6%	8.8%	4.8%
1	N	58	41	55	38	48	28
	%	35.4%	24.9%	41.0%	25.2%	42.1%	22.4%
0	N	85	105	61	95	51	82
	%	51.8%	63.6%	45.5%	62.9%	44.7%	65.6%
-1	N	7	12	5	11	5	9
	%	4.3%	7.3%	3.7%	7.3%	4.4%	7.2%
p-value*		0.016		0.003		0.001	

*Significance level of CMH test of equality of mean proportions using modified ridit scores.

†Note that a negative decrease is an increase.

FDA Statistical Table 8 (cont.): Study A03125 Decrease From Baseline in Erythema Ratings at End of Study

Success (1)#	N	7	3	7	3	4	3
	%	4.3%	1.8%	5.2%	2.0%	3.5%	2.4%
p-value‡		0.166		0.114		0.433	
Success (1,2)#	N	56	40	52	37	45	30
	%	34.2 %	24.2%	38.8 %	24.5%	39.5 %	24.0%
p-value‡		0.041		0.011		0.007	
All	N	164	165	134	151	114	125

#Success(1) and Success(1,2) denote the proportion of subjects who have a baseline score of 3 or 4 and whose final erythema score is either 1 or is 1 or 2, respectively.

‡Significance level of MH test of equality of proportions in success in erythema using modified ridit scores.

According to the FDA statistical reviewer, results for Success(1) and Success(1,2) in the table above are given for the populations as randomized, i.e., including subjects who had a score of 2, i.e., "Mild", at baseline. It should be noted that by the definition of treatment success in erythema, these latter subjects are defined as failures in each population.

For Success (1) no treatment differences are statistically significant. For Success (1,2), for the ITT, Per Protocol, or the Completers populations there are statistically significant differences in treatment ($p \leq 0.041$, $p \leq 0.007$, and $p \leq 0.011$, respectively). The patient populations above could be modified to delete those subjects the subjects with a baseline score of 2.

Using the mean modified ridit score over the differences from baseline as implied by the protocol there are statistically significant differences in treatment ($p \leq 0.016$, $p \leq 0.001$, and $p \leq 0.003$ for the ITT, PP, and Completer populations respectively). The actual erythema scores are given in table 9 below.

Table 9: Study A03125 Erythema Ratings

Response		Baseline		End of Study					
				ITT		Completers		Per Protocol	
		AzA	Veh	AzA	Veh	AzA	Veh	AzA	Veh
1. None	N	0	0	17	7	17	7	11	4
	%	-	-	10.4%	4.2%	12.7%	4.6%	9.7%	3.2%
2. Mild	N	53	53	89	76	78	69	67	57
	%	32.3%	32.1%	54.3%	46.1%	58.2%	45.7%	58.8%	45.6%
3. Moderate	N	93	101	49	77	35	70	33	59
	%	56.7%	61.2%	29.9%	46.7%	26.1%	46.4%	29.0%	47.2%
4. Severe	N	18	11	9	5	4	5	3	5
	%	11.0%	6.7%	5.5%	3.0%	3.0%	3.3%	2.6%	4.0%
p-value*		0.345		0.002		0.001		0.004	
All	N	164	165	164	165	134	151	114	125

*Significance level of CMH test of equality of proportions using modified ridit scores.

According to the Sponsor's analysis of the ITT population (R-ITT, Text Table 18), 44% of patients in the AzA 15% gel-treated group vs. 29% in the vehicle-treated group showed improvement in Erythema Rating Change from Baseline. However, 52% of the patients showed no improvement of erythema in the AzA 15% gel treated group and 64% of the vehicle-treated group. In the AzA group, 4% worsened and with 7% worsening in the vehicle group. According to the Sponsor, statistical significance was demonstrated ($p=0.0017$) in favor of AzA.

Reviewer's comments:

Although statistical significance was demonstrated ($p=0.0017$) in favor of AzA in Erythema Rating Change from Baseline, the clinical relevance is not apparent with over half of the patients being treated showing no improvement and some worsening of erythema.

The Tables 10 and 11 gives change from baseline in telangiectasia:

FDA Statistical Table 10: Study A03125 Decrease From Baseline in Telangiectasia Ratings at End of Study

Decrease †		ITT		Completers		Per Protocol	
		AzA	Veh	AzA	Veh	AzA	Veh
2	N	2	3	2	3	1	2
	%	1.2%	1.8%	1.5%	2.0%	0.9%	1.6%
1	N	27	21	21	21	18	17
	%	16.5%	12.7%	15.7%	13.9%	15.8%	13.6%
0	N	127	132	105	119	91	100
	%	77.4%	80.0%	78.4%	78.8%	79.8%	80.0%
-1	N	8	8	6	7	4	6
	%	5.0%	4.9%	4.5%	4.6%	3.5%	4.8%
-2	N	0	1	0	1	0	0
	%	-	0.6%	-	0.7%	-	-
All	N	164	165	134	151	114	125
p-value*		0.756		0.884		0.745	

*Significance level of CMH test of equality of mean proportions using modified ridit scores.

†Note that a negative decrease is an increase.

FDA Statistical Table 11: Study A03125 Telangiectasia Ratings at End of Study

Response		ITT		Completers		Per Protocol	
		AzA	Veh	AzA	Veh	AzA	Veh
1. None	N	8	4	8	4	4	3
	%	4.9%	2.4%	6.0%	2.6%	4.9%	2.4%
2. Mild	N	110	111	90	102	77	83
	%	67.1%	67.3%	67.2%	67.6%	67.1%	66.4%
3. Moderate	N	45	48	36	43	33	38
	%	27.4%	29.1%	26.9%	28.5%	27.4%	30.4%
4. Severe	N	1	2		2		1
	%	0.6%	1.2%		1.3%		0.8%
All	N	164	165	134	151	114	125
p-value*		0.603		0.213		0.468	

*Significance level of CMH test of equality of mean proportions using modified ridit scores.

According to the FDA Statistical Review, there are no statistical significant differences between treatment groups in telangiectasia ratings at end of study. The Sponsor’s conclusion was also the same.

According to the Statistical Review, there are no statistically significant differences between azelaic acid and its vehicle in either study in terms of nodule counts between active and vehicle.

FDA Statistical Appendix Table 7: Study A03125 Distribution of Nodules

# Nodules	Visit 04		08		12		LOCF	
	AzA	Veh	AzA	Veh	AzA	Veh	AzA	Veh
0	151	153	130	138	132	138	157	147
1	8	4	10	5	2	10	3	10
2	1	1	1	7	0	2	0	4
3	1	2	0	0	0	1	1	1

FDA Statistical Table: Investigator Rating of Improvement

		Study A03125			
		ITT		Per Protocol	
Response		AzA	Veh	AzA	Veh
1. Complete Remission	n	18	5	13	4
	%	11.6%	3.1%	11.4%	3.2%
2. Marked Improvement	n	60	39	52	32
	%	38.7%	24.2%	45.6%	26.6%
3. Moderate Improvement	n	44	56	31	45
	%	28.4%	34.8%	27.2%	36.0%
4. No Improvement	n	29	53	17	41
	%	18.7%	32.9%	14.9%	32.8%
5. Deterioration	n	4	8	1	3
	%	2.6%	5.0%	0.9%	2.4%
All	n	155	161	114	125
p-value*		0.001		0.001	

Reviewer’s comment:

Although Investigator Rating of Improvement at end of study shows statistical significance over vehicle the secondary efficacy endpoint does not have regulatory utility for labeling. The assessment is made after 12 weeks of treatment, relying on memory of the patient’s condition at baseline.

Efficacy Conclusion (Study A03125)

For inflammatory lesions, the change from baseline as specified in the protocol or the percent change from baseline are statistically significant ($p \leq 0.0016$) in favor of Azelaic Acid 15% Gel over vehicle in treatment of patients with mild to moderate stage 2 papulopustular facial rosacea. For the Investigator Global Assessment at the end of study, statistical significance ($p \leq 0.001$) of

azelaic acid gel, 15% over vehicle was also demonstrated for “success” on the Investigator’s Assessment scale.

Statistical significance of AzA over vehicle was demonstrated for erythema (~~_____~~) in both decrease from baseline and end of study erythema ratings; however, the clinical relevance is not clear. There were no statistically differences between the active and vehicle treatment groups in telangiectasia and development of nodules.

Indication #1 Treatment of Moderate Papulopustular Facial Rosacea

Sponsor’s Protocol No. 304344 (Clinical Study Report A03126)

Title: “A 12-Week, Randomized, Double-Blind Multicenter Study Comparing The Clinical Efficacy And Safety Of Azelaic Acid 15% Gel (SH H 655 BA) With Its Vehicle in Patients With Moderate, Papulopustular Facial Rosacea”

(Study Dates: February 2, 2001 to June 29, 2001)

Protocol

Objective/Rationale

The objectives of this study were to evaluate the efficacy and safety of AzA 15% gel compared to its vehicle (gel base) in male and female patients with moderate, papulopustular, rosacea (stage 2 rosacea) during a 12-week treatment period.

Reviewer’s comments:

The Protocol No. 304344 is identical to Protocol No. 304342 except a pharmacokinetic evaluation was not performed.

Study Results Sponsor’s Protocol No. 304344 (Clinical Study Report A03126)

A total of 432 patients were screened for entry into the study, 335 patients (169 AzA 15% gel and 166 vehicle) were randomized and received study medication, and 97 were failures at screening.

The list of investigators, site numbers, and number of patients enrolled at each site follows:

List of investigators (Protocol 304344)

Site Number	Name of Principal Investigator	Number enrolled
01	Toni Funicella, MD	20
02	Michael Gold, MD	21
03	Jo Lynne Herzog, MD	20
04	Adelaide Hebert, MD	34
05	H. Irving Katz, MD	19
06	Steven Kempers, MD	18
07	J. Michael Maloney, MD	40
08	Robert Matheson, MD	20
09	David Pariser, MD	22
10	Elyse Rafal, MD	14
11	Toivo Rist, MD	20
12	Thomas Nigra, MD	40
14	Kimberly Stone, MD	10
15	Eduardo Tschen, MD	37

Demographics, Evaluability

Demographics and Baseline Characteristics (ITT Population) for Report A03126 follows:

Text Table 5: Demographic and Baseline Characteristics by Treatment Group (ITT Population)

	AZA 15% gel (N=169)	Vehicle (N=166)	p-value ^a
Mean age (years [range])	47.8(24.0-88.0)	47.0(23.0-78.0)	0.5913
Sex (n [%])			0.9038
Male	48 (28%)	46 (28%)	
Female	121 (72%)	120 (72%)	
Race (n [%])			0.3371
Caucasian	147 (87%)	153 (92%)	
Black	2 (1%)	2 (1%)	
Hispanic	19 (11%)	10 (6%)	
Asian	0 (0%)	0 (0%)	
Other	1 (1%)	1 (1%)	
Mean height (cm)	167.8	167.6	0.8460
Mean weight (kg)	82.1	81.1	0.6257
Body mass index	29.2	28.9	0.6861
Mean previous duration of rosacea (months)	100.8	103.0	0.8360
0-6 months	8 (5%)	3 (2%)	
> 6 months-2 years	28 (15%)	33 (20%)	
> 2 years-5 years	47 (28%)	54 (33%)	
> 5 years	88 (52%)	75 (45%)	

AZA = azelaic acid; ITT = Intent to treat; N = total number of patients; n = number of patients.

^aContinuous variables: t-test for independent groups; Categorical variables: Fisher's exact test; Ordinal variables: Wilcoxon rank-sum test.

Reference: Section 14.1, Table 3.

Baseline Investigator global assessment (n [%])

	<u>AZA 15% gel</u> (N = 169)	<u>Vehicle</u> (N = 166)
Clear	0 (0%)	0 (0%)
Minimal	2 (1%)	0 (0%)
Mild	19 (11%)	23 (14%)
Mild to moderate	75 (44%)	80 (48%)
Moderate	54 (32%)	42 (25%)
Moderate to severe	14 (8%)	16 (10%)
Severe	5 (3%)	5 (3%)
Missing	0 (0%)	0 (0%)

Reviewer's comment:

Based on the revised IGA efficacy criteria, the 2 patients classified as "minimal" at study entry were excluded from efficacy analysis.

Erythema

At baseline, all patients had some degree of erythema. The severity of erythema was similar between the 2 treatment groups, with about one third having mild erythema, and over half of patients having moderate erythema.

Telangiectasia ratings at baseline

At baseline, the majority of patients (53% AzA 15% gel patients and 58% vehicle patients) had mild telangiectasia. Nine (5%) patients in the AzA 15% gel group and 3 (2%) patients in the vehicle group had no telangiectasia at baseline. Sites were queried about patients without telangiectasia at baseline. Patients who were confirmed to have no telangiectasia at baseline were allowed to continue in the study, if the investigator verified the diagnosis of stage 2 rosacea.

Nodule counts

Nodule counts were not collected at baseline because the presence of nodules is a symptom of stage 3 rosacea and, thus was a study exclusion criterion. During the study, nodule counts were collected to account for a potential worsening of the disease.

The treatment groups were comparable with respect to demographic and baseline characteristics. The mean age was 47.6 years (24 to 86 years) for AzA 15% gel and 47.0 years (23 to 78 years) for vehicle patients. Females comprised approximately three-quarters of each treatment group; 72% for both AzA 15% gel and vehicle patients. Caucasians made up the majority of both treatment groups; 147 (87%) of AzA 15% gel patients and 153 (92%) of vehicle patients. In addition, height, weight, body mass index, and previous duration of rosacea were similar between treatment groups.

Disposition of Patients

A total of 44 patients (22 AzA 15% gel and 22 vehicle) did not complete the Week 12 visit within the allowed window (between 77 and 98 days post randomization). Medication was not used according to the protocol by 31 patients (16 AzA 15% gel and 15 vehicle). A patient was deemed non-compliant with study medication if the total number of missed doses exceeded 7 during the 12 weeks of treatment. Prohibited medications were used during the study by 8 patients (5 AzA 15% gel and 3 vehicle). Thus, the total number of patients included in the PP population was 233 (112 AzA 15% gel and 121 vehicle).

Text Table 4: Patient Evaluability

	AzA 15% gel	Vehicle	Total
Randomized	169	166	335
Intent-to-treat population	169 (100%)	166 (100%)	335 (100%)
Per-protocol population	112 (66.3%)	121 (73.0%)	233 (70.0%)
Violated any inclusion/exclusion criteria at screening	14	5	19
Did not complete Week 12 visit within window	22	22	44
Medication not used according to protocol	16	15	31
Used prohibited medications	5	3	8

AzA = azelaic acid.

Reference: Section 14.1, Table 2.

Efficacy Results Study A30126

Primary Efficacy

Results for the two primary efficacy endpoints (percent change in inflammatory lesion counts and success on the Investigator's Global Assessment follows.

Inflammatory Lesion Counts

FDA Statistical Table 10: Study A30126 Means and Tests of Treatment Differences in Inflammatory Lesion Counts

Response	Treat	ITT			Completers			Per Protocol		
		N	Mean	p-value	N	Mean	p-value	N	Mean	p-value
Change	Veh	166	6.4	0.0077	146	7.3	0.0012	121	6.6	0.0012
	AzA	167	9.0		148	10.2		110	10.2	
% Change	Veh	166	38.2	0.0172	146	42.8	0.0079	121	41.3	0.0124
	AzA	167	50.0		148	55.8		110	56.1	

Model: expected response = baseline + center + treatment + interaction

According to the FDA statistical reviewer, as in Study A03125, for all three populations differences, whether change from baseline as specified in the protocol or the percent change from baseline are used, treatment differences are statistically significant (all $p \leq 0.0172$). According to the statistical reviewer, the results are much less extreme than in Study A03125.

Sponsor’s results for inflammatory lesion counts

At the last visit (R-LOCF), the mean inflammatory lesion count was 8.9 for the AzA 15% gel group and 12.1 for the vehicle group. The nominal change in inflammatory lesion count from baseline was significantly higher in the AzA 15% gel group from Week 8 on. A statistically significant treatment-by-baseline lesion count interaction ($p=0.0018$) was noted. In both treatment groups the nominal change in inflammatory lesion count increased with increasing lesion counts at baseline. This was more pronounced in the AzA 15% gel group and thus the treatment effect (difference between AzA 15% gel and vehicle) increased with increasing baseline lesion counts, favoring AzA 15% gel.

Sponsor’s percent change in inflammatory lesion counts from baseline

The mean percent change in inflammatory lesion counts was -50.7% for the AzA 15% gel group and -38.7% for the vehicle group. Both treatment groups had statistically significant percent reductions ($p < 0.0001$) in inflammatory lesion counts from baseline (R-LOCF). The percent change in lesion count was significantly greater ($p=0.0208$) for AzA 15% gel patients than for vehicle patients, with a treatment effect of 12.0. There was no significant treatment-by-center interaction ($p=0.5607$).

Investigator’s Global Assessment (ITT Population, LOCF)

Sponsor’s assessment using the R-LOCF as previously defined finds that success rates were not statistically significantly ($p=0.8990$) different between the 2 treatment groups. The treatment-by-center interaction was not statistically significant ($p=0.4393$). However, when the revised IGA is used, the Sponsor’s results are found to be statistically significant as displayed in Table 11 below.

Investigator’s Global Assessment

FDA Statistical Table 11: Study A30126 Investigator Global Evaluation at End of Study

Treat		ITT			Completers			Per Protocol		
		AzA	Veh	p-value	AzA	Veh	p-value	AzA	Veh	p-value

Success	N	53	36	0.044	51	36	0.061	40	25	0.009
	%	31.7%	21.7%		34.5%	24.7%		36.4%	20.7%	
0 (clear)	N	11	10	0.889	11	10	0.819	9	5	0.164
	%	6.6%	6.0%		7.4%	6.8%		8.2%	4.1%	
0,1 (≤Min)	N	64	48	0.078	62	46	0.065	49	34	0.010
	%	38.3%	28.9%		41.9%	31.5%		44.5%	28.1%	
0-2 (≤Mild)	N	102	79	0.016	97	75	0.013	74	59	0.006
	%	61.1%	47.6%		65.5%	51.4%		67.3%	48.8%	
3-6	N	65	87		51	71		36	62	
	%	38.9%	52.4%		34.5%	48.6%		32.7%	51.2%	
All	N	167	166		148	146		110	121	

Statistical significance ($p = .044$) of AzA 15% gel over vehicle was demonstrated with "success" defined as: 1) a patient who achieved an IGA of clear (i.e. score of 0) at the point of measurement if they were mild at baseline (i.e. a score of 2) or 2) a patient who achieved a score of clear or minimal (i.e., 0 or 1) at the end of the study with a baseline score of 3-6 (i.e. "mild to moderate to severe").

Secondary Efficacy Endpoints

The scores in erythema, telangiectasia, investigator rating of improvement, and the nodule count were considered to be of clinical relevance. An analysis using variables denoting treatment success as follows was performed: "success (1)" and "success (1,2)" denote the proportions of subjects who had a baseline score of moderate or severe and achieved either a final score of none or a final score of none or mild, respectively.

FDA Statistical Table 14: Study A03126 Decrease From Baseline in Erythema Ratings at End of Study

Decrease †		ITT		Completers		Per Protocol	
		AzA	Veh	AzA	Veh	AzA	Veh
2	N	8	6	8	6	5	6
	%	4.8%	3.6%	5.4%	4.1%	4.6%	5.0%
1	N	69	40	65	37	52	27
	%	41.3%	24.1%	43.9%	25.3%	47.3%	22.3%
0	N	80	102	68	88	48	74
	%	47.9%	61.5%	46.0%	60.3%	43.6%	61.2%
-1	N	10	18	7	15	5	14
	%	6.0%	10.8%	4.7%	10.3%	4.6%	11.6%
p-value*		0.006		0.003		0.001	
Success(1)#	N	4	4	4	4	3	4
	%	2.4%	2.4%	2.7%	2.7%	2.7%	3.3%
p-value‡		0.936		0.950		0.783	
Success (1,2)#	N	61	31	57	30	46	26
	%	36.5 %	18.7%	38.5 %	20.6%	41.8 %	21.5%
p-value‡		0.001		0.001		0.001	
All	N	167	166	148	146	110	121

*Significance level of CMH test of equality of mean proportions using modified ridit scores.

†A negative decrease is an increase.

#Success(1) and Success(1,2) denote the proportion of subjects who have a baseline score of 3 or 4 AND whose final erythema score is either 1 or is 1 or 2, respectively.

‡Significance level of MH test of equality of proportions in success in erythema using modified ridit scores.

For Success(1) no treatment differences are statistically significant. However, for Success (1,2) in all three populations there are statistically significant differences in treatment (all $p \leq 0.001$). As in Study A30126, the populations were modified to delete the subjects with an erythema score of 2 at baseline we still have statistically significant differences from baseline (from results not presented here: $p \leq 0.003$, $p \leq 0.005$, and $p \leq 0.003$ for the ITT, PP, and completer populations respectively). Using the mean modified ridit score as given in the protocol there are also statistically significant differences in treatment ($p \leq 0.006$, $p \leq 0.001$, and $p \leq 0.003$ for the ITT, PP, and completer populations respectively).

Results for the actual erythema scores are given in table 15 below. Using the mean modified ridit score results are close to statistical significance ($p \leq 0.079$, $p \leq 0.055$, and $p \leq 0.069$ for the ITT, PP, and completer populations respectively).

FDA Statistical Table 15: Study A03126 Erythema Ratings

Response		Baseline		End of Study					
				ITT		Completers		Per Protocol	
		AzA	Veh	AzA	Veh	AzA	Veh	AzA	Veh
1. None	N	0	0	9	9	9	9	7	7
	%	-	-	5.4%	5.4%	6.1%	6.2%	6.4%	5.8%
2. Mild	N	43	57	90	67	85	63	63	50
	%	25.7%	34.3%	53.9%	40.4%	57.4%	43.2%	57.3%	41.3%
3. Moderate	N	100	85	54	72	42	58	30	51
	%	59.9%	51.2%	32.3%	43.4%	28.4%	39.7%	27.3%	42.2%
4. Severe	N	24	24	14	18	12	16	10	13
	%	14.4%	14.5%	8.4%	10.8%	8.1%	11.0%	9.1%	10.7%
p-value*		0.194		0.079		0.069		0.055	
All	N	167	166	167	166	148	146	110	121

*Significance level of CMH test of equality of proportions using modified ridit scores.

Reviewer’s comment:

No prior agreements were reached between the Sponsor and the Division regarding the efficacy endpoints. Results for the actual erythema scores given in Table 15 are close to statistical significance ($p \leq 0.079$) for the ITT population.

FDA Statistical Table 16: Study A03126 Telangiectasia Ratings at End of Study

Response		ITT		Completers		Per Protocol	
		AzA	Veh	AzA	Veh	AzA	Veh
1. None	N	8	9	7	8	4	6
	%	4.8%	5.4%	4.7%	5.5%	3.6%	5.0%
2. Mild	N	96	98	85	83	66	70
	%	57.5%	59.0%	57.4%	56.9%	60.0%	57.9%
3. Moderate	N	57	51	50	47	35	39

	%	34.1%	30.7%	33.8%	32.2%	31.8%	32.2%
4. Severe	N	6	8	6	8	5	6
	%	3.6%	4.8%	4.1%	5.5%	4.5%	5.0%
All	N	166	166	148	146	110	121
p-value		0.900		0.920		0.924	

*Significance level of CMH test of equality of proportions using modified ridit scores.

According to the statistical review, using the 0.0083 Bonferroni bound, in Study A03126, from Statistical Appendix 5, only the patient ratings of improvement, the investigators rating of improvement, and the change from baseline in erythema had statistically significant differences in favor of AzA 15% gel over its vehicle.

According to the Sponsor, for Erythema rating change from baseline (Text Table 18), 46% of AzA 15% gel-treated patients showed improvement of erythema than vehicle-treated patients (28%). While 82 (49%) of 169 AzA 15% gel-treated patients and 102 (61%) vehicle-treated patients remained unchanged in the degree of erythema present at baseline using a static scoring system. Worsening of erythema occurred in 10 (6%) AzA treated patients and 18 (11%) vehicle-treated patients. A statistically significant difference between treatment groups (p=0.005) in favor of AzA was found for the ITT population.

Reviewer’s comment:

Although statistical significance was demonstrated (p=0.0005) in favor of AzA in Erythema Rating Change from Baseline, the clinical relevance is not apparent with over half of the patients being treated showing no improvement and some worsening of erythema.

Telangiectasia ratings at last visit

At the last available visit (R-LOCF), these numbers were essentially unchanged, with no difference observed between treatment groups. Telangiectasia ratings at baseline and the last visit are summarized for the ITT population using both methods of LOCF in Text Table 19

Statistical Appendix Table 7: Study A03126 Distribution of Nodules

# Nodules	Visit 04		08		12		LOCF	
	AzA	Veh	AzA	Veh	AzA	Veh	AzA	Veh
0	152	141	144	139	140	134	150	146
1	4	11	7	10	7	6	7	7
2	3	3	1	3	1	2	2	2
3	1	1	2	0	0	2	0	2
4	0	1	0	0	0	1	0	0
>4	1	1	0	1	2	1	0	0

According to the statistical review, results would be similar at each time point for distribution of nodules.

Statistical Appendix Table A.8: Investigator Rating of Improvement

	Study A03126
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Response	ITT			Per Protocol	
		AzA	Veh	AzA	Veh
1. Complete Remission	n	11	13	8	6
	%	7.0%	8.3%	7.3%	5.0%
2. Marked Improvement	n	63	36	48	32
	%	39.9%	19.0%	44.0%	22.8%
3. Moderate Improvement	n	49	46	34	36
	%	31.0%	29.1%	31.2%	29.8%
4. No Improvement	n	24	45	14	37
	%	15.2%	28.5%	12.8%	30.6%
5. Deterioration	n	11	18	5	10
	%	7.0%	11.4%	4.6%	8.3%
All	n	159	158	110	121
p-value*		0.003		0.005	

*Significance level of CMH test of equality of proportions using modified ridit scores.

As in Study A03125, Investigator Rating of Improvement at end of study is not a static assessment and does not have regulatory utility for labeling

Reviewer's comments:

The following concern is under consideration by Division of Scientific Investigation. According to the FDA statistician, in terms of lesion counts, center 06 is apparently discrepant from the others. This center clearly drives part of the efficacy results, but again, at least among completers, the differences remain statistically significant even deleting this center. The apparent discrepancy from other centers is not apparent with the IGA, only with the lesion count above. DSI audit results are pending.

D. Efficacy Conclusions

Efficacy Conclusion (Study A03126)

For inflammatory lesions, the change from baseline as specified in the protocol or the percent change from baseline are statistically significant ($p \leq 0.0172$) in favor of Azelaic Acid 15% Gel over vehicle in treatment of patients with mainly mild to moderate stage 2 papulopustular facial rosacea. According to the statistical reviewer, there were statistically significant interactions between treatment and center. However, the statistical significance was largely due to one discrepant center, in the sense that deleting that center made the tests for interactions statistically non-significant. For the Investigator Global Assessment at the end of study, statistical significance ($p \leq 0.044$) of Azelaic Acid 15% Gel over vehicle was also demonstrated.

For treatment of erythema _____) a statistically significant difference was demonstrated over vehicle for decrease from baseline in erythema in the ITT population. However, results for the actual erythema scores are only close to statistical significance. Additionally, half of the patients being treated showed no improvement and some worsening of erythema. No differences in telangiectasia and development of nodules were noted.

Efficacy Conclusion (Study A03125)

For inflammatory lesions, the change from baseline as specified in the protocol or the percent change from baseline are statistically significant ($p \leq 0.0016$) in favor of Azelaic Acid 15% Gel over vehicle in treatment of patients with mild to moderate stage 2 papulopustular facial rosacea. For the Investigator Global Assessment at the end of study, statistical significance ($p \leq 0.001$) of azelaic acid gel, 15% over vehicle was also demonstrated for "success" on the Investigator's Assessment scale.

Statistical significance of AzA over vehicle was demonstrated for erythema in both decrease from baseline and end of study erythema ratings; however, the clinical relevance is not clear. There were no statistically differences between the active and vehicle treatment groups in telangiectasia and development of nodules.

VII. Integrated Review of Safety**A. Brief Statement of Conclusions**

Not unexpectedly, the clinical trials revealed the sponsor's product to be a potential irritant. Similarly, AzA 15% gel was found to have some irritation potential in both the cumulative irritancy study and the repeat insult patch test. There was no evidence of sensitization potential in the repeat insult patch test. There was no evidence of photosensitization or phototoxicity. No significant systemic safety concerns were raised.

B. Description of Patient Exposure**Exposure by treatment**

The data presented are for the intent-to-treat (ITT) populations. For the U.S. studies, the ITT population was defined as all subjects who were randomized and received study medication. For the European studies, the ITT population was defined as all subjects who were randomized, received study medication, and had at least one postbaseline assessment.

From the original submission, a total of 1009 subjects was exposed to AzA 15% gel. There were 716 AzA 15% gel-treated subjects in the rosacea and acne trials and 293 AzA 15% gel-treated subjects in the dermal safety studies.

An additional 124 subjects received AzA 15% gel in a trial in which AzA 15% gel was compared to Metronidazole 0.75% gel. The limited data pertaining to these subjects are separately discussed later in the review, as these data were received incomplete, late in the review cycle in the form of a "draft synopsis" of the clinical study report.

Number of subjects exposed by indication and treatment			
	AzA 15% gel (n=840*)	Vehicle gel (n=382)	AzA 20% cream
Rosacea	457*	331	-
Acne Vulgaris	383	51**	15

*includes the 124 subjects from the active-control trial (metronidazole 0.75% gel)

**most of the acne trials employed active controls, not vehicle

Number of subjects exposed in dermal safety studies		
	AzA 15% gel (n=293)	Vehicle gel (n=293)
Cumulative Irritancy	37	37
Repeat Insult Patch Study	220	220
Photosensitization	24	24
Phototoxicity	12	12

Duration of exposure

The rosacea trials were 12 weeks in duration; the acne trials ranged from eight weeks to four months in duration. In the rosacea studies, exposure was comparable for the 333 subjects who received AzA 15% gel and the 331 subjects who received vehicle. In the AzA 15% gel group, 266 subjects (86%) were exposed to treatment for >8 weeks, while 348 subjects (91%) in the vehicle group were exposed to treatment for >8 weeks. Of these, 205 subjects (62%) were exposed to AzA 15% gel and 213 (64%) were exposed to vehicle treatment for >12 to 16 weeks. The mean number of days of exposure for the AzA 15% gel group was 79.8 or 11.4 weeks (range: 2-106 days) and for the vehicle group was 82.3 days or 11.8 weeks (8-106 days).

Of the 383 subjects exposed to AzA 15% gel in the acne studies, 213 (56%) were exposed for >16 weeks. Of the 51 subjects exposed to vehicle in the acne studies, 46 (90%) were exposed for >12 to ≤ 16 weeks. Of the 15 subjects treated with AzA 20% cream, 14 (93%) were exposed for >8 to ≤ 12 weeks.

Disposition

Modified Sponsor Table 7

	Rosacea		Acne		
	AzA* 15% Gel n=333	Vehicle n=331	AzA 15% Gel n=383	Vehicle n=51	AzA 20% cream n=15
Completed Treatment	283 (85%)	296 (89%)	316 (83%)	48 (94%)	14 (93%)
Discontinued Treatment	50 (15%)	35 (11%)	67 (17%)	3 (6%)	1 (7%)
Prematurely discontinued for:					
Early complete Remission ^a	NA**	NA	1 (0%)	0 (0%)	0 (0%)
Adverse events	17 (5%)	6 (2%)	9 (2%)	0 (0%)	0 (0%)
Lack of efficacy	1 (0%)	12 (4%)	12 (3%)	0 (0%)	0 (0%)
Protocol deviation	7 (2%)	1 (0%)	2 (1%)	0 (0%)	0 (0%)
Withdrawal of Consent	6 (2%)	5 (2%)	12 (3%)	2 (4%)	0 (0%)
Other ^b reason	18 (5%)	11 (3%)	31 (8%)	1 (2%)	1 (7%)
Death	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

**AzA = azelaic acid

**not applicable

^a A discontinuation due to early complete remission was not allowed in the rosacea studies. ^b Other = lost to follow-up, cosmetically non-acceptable, worsening according to patient, study drug not given due to misunderstanding. In addition, lack of efficacy (3 subjects), protocol deviation (4 subjects), adverse events (3 subjects), and withdrawal of consent (1 subject) were erroneously included in the 'other' category

Demographics

Modified Sponsor Table 9

	Rosacea		Acne		
	AzA 15% Gel N=333	Vehicle n=331	AzA 15% Gel n=383	Vehicle n=51	AzA 20% cream n=15
Sex					
Male	88 (26%)	91 (27%)	156 (41%)	21 (41%)	4 (27%)
Female	245 (74%)	240 (73%)	227 (59%)	30 (59%)	11 (73%)
Race					
Caucasian	306 (92%)	308 (93%)	375 (98%)	51 (100%)	15 (100%)
Black	2 (1%)	4 (1%)	2 (1%)	0 (0%)	0 (0%)
Hispanic	23 (7%)	17 (5%)	2 (1%)	0 (0%)	0 (0%)
Asian	1 (0%)	0 (0%)	2 (1%)	0 (0%)	0 (0%)
Other	1 (0%)	2 (1%)	2 (1%)	0 (0%)	0 (0%)
Age (years)					
<12	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
12-16	0 (0%)	0 (0%)	88 (23%)	15 (29%)	1 (7%)
17-30	17 (5%)	13 (4%)	250 (65%)	31 (61%)	10 (67%)

31-65	283 (85%)	285 (86%)	45 (12%)	5 (10%)	4 (27%)
> 65	33 (10%)	33 (10%)	0 (0%)	0 (0%)	0 (0%)

The mean age of the AzA 15% gel-treated subjects was 33.7 years. For vehicle-treated subjects, the mean age was 45 years.

Concomittant medications

In the rosacea studies, a comparable proportion of subjects receiving AzA 15% gel (73%) and vehicle (76%) received at least one concomitant medication.

Selected concomitant medication groups with the potential to impact the safety and efficacy outcome, were reviewed with respect to their use by subjects in the rosacea studies. These groups were: antiacne preparations, antibacterials for systemic use, antibiotics and chemotherapeutics for dermatological use, antidiarrheals intestinal anti-inflammatory and anti-infective agents, antihistamines for systemic use, antifungal for dermatological use, anti-inflammatory and antirheumatic products, antimycotics for systemic use, corticosteroids for systemic use, corticosteroids (dermatologic preparations), diuretics (sulfonamides only), and gynecological anti-infectives and antiseptics. These selected concomitant medications were used by a small percentage of subjects in each treatment group and was similar between the treatment groups.

C. Methods and Specific Findings of Safety Review

Adverse events were classified by Hoechst Adverse Reactions Terminology System (HARTS) and preferred term. Most adverse events were local and associated with the skin and appendages body system. For purposes of the Integrated Summary of Safety, the sponsor referred to and presented these adverse events as "cutaneous" adverse events. Adverse events that originated in body systems other than skin and appendages, but were expressed as skin symptoms were also classified as cutaneous adverse events. These additional adverse events (reported terms) were:

- Paresthesia (stinging, tingling, facial stinging, facial tingling)
- Edema (edema)
- Photosensitivity (facial sunburn, sunburn, sunburn-forehead)
- Vasodilation (increased flushing, local sensation of heat)
- Neoplasia (laser treatment of paranasal angioma)
- Surgery (surgery of ingrown nails)
- Infection (plantar warts, common warts on hands, herpes simplex virus infections)

All adverse events that were not associated with the body system "skin and appendages", or were not expressed as skin symptoms were classified as systemic adverse events.

Cutaneous Adverse Events

Of the 716 AzA 15% gel-treated subjects in the rosacea and acne studies, 274 (38%) reported at least one cutaneous adverse event. The most frequently reported cutaneous adverse event for AzA 15% gel subjects was burning/stinging/tingling (148 subjects; 21%). Of the 382 subjects in the vehicle-treated subjects, 91 (24%) experienced at least one cutaneous adverse event. In the vehicle group, the most frequently reported cutaneous adverse event was scaling/dry skin/xerosis.

Intensity data were recorded for 272 of the 274 AzA 15% gel subjects who reported at least

one cutaneous adverse event. Most of these subjects (24%) of AzA 15% gel subjects had cutaneous adverse events rated by the investigator as mild, 11% had such events rated as moderate, while 23 (3%) subjects had cutaneous adverse events that were rated by the investigator as severe. For subjects who received vehicle, cutaneous adverse events were rated as follows: 15% mild, 8% moderate and 10% severe.

Of the 716 AzA 15% gel subjects, 254 (35%) had at least one cutaneous adverse event considered to be related to study medication. The sponsor assessed the maximum relatedness of the cutaneous adverse events to the study medication as: "definite" for 112 (16%), "probable" for 84 (12%), and "possible" for 58 (8%) subjects. "Unlikely" and "no relationship" to study medication were assessed as the maximum relatedness for five (1%) and 14 (2%) subjects, respectively. Of the 382 patients who received vehicle, 76 (20%) had at least one related cutaneous adverse event. In the vehicle group, the maximum relatedness to study treatment was reported as follows: 23 (6%) "definite," 27 (7%) "probable," and 26 (7%) "possible."

Most subjects were exposed to treatment for >four weeks: 645 of 716 AzA 15% gel-treated subjects (90%) and 359 of 382 vehicle-treated subjects (94%). Thus, the data pertaining to usage for ≤ four weeks are limited (31 AzA 15% gel-treated subjects and 11 vehicle-treated subjects). Data were missing for 40 AzA 15% gel-treated subjects and 12 vehicle-treated subjects. A higher proportion of AzA 15% gel subjects had at least one cutaneous adverse event when exposed to treatment for ≤ four weeks (68%) compared to treatment for >four weeks (38%). Burning/stinging/tingling was the most frequently reported cutaneous adverse event in the AzA 15% gel group and was reported by a higher proportion of subjects who had been treated for ≤ four weeks (39%) compared with > four weeks of treatment (20%). In the vehicle-treated group, burning/stinging/tingling was reported in the following proportions: in 27% treated for ≤ four weeks and in 4% treated for > four weeks.

Reviewer's comment: The data suggests that irritancy potentially decreases with continued use of the sponsor's product.

All Cutaneous Adverse Events* (taken from sponsor Tables 20 & 21)

	Rosacea		Acne	
	AzA 15% gel n=333	vehicle n=331	AzA 15% gel n=383	vehicle n=51
Subjects with at least one cutaneous adverse event(s):	151 (45%)	82 (25%)	123 (32%)	9 (18%)
preferred terms:				
Burning/stinging/tingling (1)	108 (32%)	16 (5%)	40 (10%)	3 (6%)
Pruritus	41 (12%)	15 (5%)	34 (9%)	3 (6%)
Scaling/dry skin/xerosis (2)	34 (10%)	47 (14%)	29 (8%)	2 (4%)
Erythema/irritation (3)	13 (4%)	3 (4%)	28 (7%)	4 (8%)
Edema	5 (2%)	3 (4%)	0 (0%)	0 (0%)
Derm contact	4 (1%)	1 (0%)	1 (0%)	0 (0%)
Acne	3 (1%)	1 (0%)	0 (0%)	0 (0%)
Eczema	2 (1%)	0 (0%)	2 (1%)	0 (0%)
Seborrhea	2 (1%)	0 (0%)	0 (0%)	0 (0%)
Herpes zoster	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Hirsutism	1 (0%)	1 (0%)	0 (0%)	0 (0%)
Neopl skin	1 (0%)	0 (0%)	4 (1%)	0 (0%)
Photosensitivity	1 (0%)	5 (2%)	0 (0%)	0 (0%)
Skin dis	1 (0%)	3 (1%)	2 (1%)	0 (0%)
Vasodilat	1 (0%)	0 (0%)	1 (0%)	0 (0%)
Derm fung	0 (0%)	1 (0%)	0 (0%)	0 (0%)
Hair dis	0 (0%)	1 (0%)	0 (0%)	0 (0%)
Herpes simplex	0 (0%)	1 (0%)	4 (1%)	0 (0%)

Urticaria	0 (0%)	1 (0%)	2 (1%)	0 (0%)
Infect	0 (0%)	0 (0%)	1 (0%)	0 (0%)
Nail dis	0 (0%)	0 (0%)	1 (0%)	0 (0%)
Skin discolor	0 (0%)	0 (0%)	1 (0%)	0 (0%)
Surgery	0 (0%)	0 (0%)	1 (0%)	0 (0%)

* In addition to all adverse events (AEs) coded under 'Skin and Appendages', the following AEs originated in other body systems, but were expressed by the sponsor as skin symptoms, and were classified as cutaneous AEs: paresthesia (nervous system), edema (metabolic and nutritional system), photosensitivity (body as a whole), vasodilation (cardiovascular), neoplasia (reported as laser treatment of paranasal angioma [body as a whole]), surgery (reported as surgery ingrown nails [body as a whole]), and infection (reported as plantar warts, common warts on hands, and herpes simplex virus infections [body as a whole]).

Reviewer's comment: The repeat insult patch study did not identify the sponsor's product as a sensitizer. The reported cases of contact dermatitis are therefore considered more likely to have been irritant in nature, rather than allergic. Similarly, the photosensitization study did not reveal the sponsor's product or its vehicle to be photosensitizers.

Cutaneous Adverse Events Occurring in ≥ 1% of Subjects in the Pivotal Rosacea Trials by Treatment Group and Maximum Intensity (Modified sponsor Table 26)*

	AzA 15% N=333 (100%)			Vehicle N=331 (100%)		
	Mild n=86 (26%)	Moderate n=44 (13%)	Severe n=20 (6%)	Mild n=49 (15%)	Moderate n=27 (8%)	Severe n=5 (2%)
Burning/stinging/tingling	66 (20%)	30 (9%)	12 (4%)	8 (2%)	6 (2%)	2 (1%)
Pruritus	24 (7%)	14 (4%)	3 (1%)	9 (3%)	6 (2%)	0 (0%)
Scaling/dry skin/xerosis	1 (0%)	21 (6%)	8 (2%)	33 (10%)	12 (4%)	1 (0%)
Erythema/irritation	0 (0%)	6 (2%)	6 (2%)	8 (2%)	4 (1%)	2 (1%)
Edema	3 (1%)	2 (1%)	0 (0%)	3 (1%)	0 (0%)	0 (0%)
Derm contact	2 (1%)	2 (1%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)
Acne	2 (1%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)
Seborrhea	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Photosensitivity	1 (0%)	0 (0%)	0 (0%)	3 (1%)	1 (0%)	1 (0%)
Skin dis	1 (0%)	0 (0%)	0 (0%)	1 (0%)	2 (1%)	0 (0%)

*subjects may have > 1 cutaneous adverse event; thus, the sum of the frequencies of preferred terms may exceed the number of subjects with at least 1 cutaneous adverse event

Related Cutaneous Adverse Events Occurring in the Pivotal Rosacea Trials by Treatment Group and Maximum Relatedness to Study Treatment (sponsor Table 33)*

	AzA 15% N=333 (100%)			Vehicle N=331 (100%)		
	Possible N=28 (8%)	Probable n=50 (15%)	Definite n=65 (20%)	Possible n=22 (7%)	Probable n=24 (7%)	Definite n=22 (7%)
Burning/stinging/tingling	19 (6%)	41 (12%)	46 (14%)	2 (1%)	6 (2%)	4 (1%)
Pruritus	8 (2%)	11 (3%)	22 (7%)	8 (2%)	3 (1%)	2 (1%)
Scaling/dry skin/xerosis	8 (2%)	14 (4%)	9 (3%)	13 (4%)	15 (5%)	14 (4%)
Erythema/irritation	1 (0%)	2 (1%)	9 (3%)	4 (1%)	3 (1%)	4 (1%)
Edema	0 (0%)	5 (2%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)
Acne	2 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)
Derm contact	1 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hirsutism	1 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)
Skin dis	1 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)	1 (0%)
Photosensitivity	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)
Urticaria	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)

*subjects may have > 1 cutaneous adverse event; thus, the sum of the frequencies of preferred terms may exceed the number of subjects with at least 1 cutaneous adverse event

Systemic Adverse Events

At least one systemic adverse event was reported by 117 (16%) AzA 15% gel patients. A greater proportion of the 382 patients who received the vehicle reported at least one systemic adverse event (91 patients; 24%). Ten subjects (67%) who received AzA 20% cream reported at least one systemic adverse event. Upper respiratory infection was the most

frequently reported systemic adverse event in all treatment groups except AzA 20% cream, where rhinitis was reported more often than upper respiratory infection. Most of these adverse events were rated by the investigator as mild or moderate.

Systemic adverse events were assessed by the sponsor as related to the study medication for four (<1%) of AzA 15% gel subjects: pain (“possibly” and “probably” related for one subject each), malaise and headache (“definitely” and “possibly” related, respectively, for one subject each). In the AzA 15% gel-treated group, “unlikely” and “no relationship” to study medication were assessed as the maximum relatedness for 14 (2%) and 96 (13%) subjects, respectively. Of the 15 patients who received AzA 20% cream, one (7%) subject had at least one related systemic adverse event (pain, considered “definitely” related). No systemic drug-related adverse events were reported by the 382 patients receiving vehicle.

A greater proportion of AzA 15% gel-treated subjects had at least one systemic adverse event when exposed to treatment for \leq four weeks compared to treatment for $>$ four weeks. A greater proportion of vehicle-treated subjects exposed for $>$ 4 weeks had at least one systemic adverse event compared with patients exposed for \leq 4 weeks. In the AzA 20% cream treatment group, only subjects treated for $>$ 4 weeks reported systemic adverse events. With respect to systemic adverse events, a higher proportion of subjects with $>$ four weeks of treatment with AzA 15% gel reported upper respiratory infection (4%) compared with those who had \leq four weeks of treatment (0%). Conversely, a higher proportion of subjects in the AzA 15% gel (6%) with \leq four weeks of treatment reported headache compared with those with $>$ four weeks of treatment (3%). However, the proportions of subjects in each treatment group were so small that comparisons between groups and treatment durations are not considered meaningful. In the rosacea studies, subjects treated with vehicle for \leq 4 weeks most often reported bronchitis and cystitis, respectively. For patients treated for $>$ 4 weeks, upper respiratory infection, was reported by the highest proportion of patients in the vehicle treatment group. In the AzA 20% cream treatment group, only patients treated for $>$ 4 weeks reported systemic adverse events. For AzA 20% cream-treated patients, rhinitis and upper respiratory infection and headache were the systemic adverse events that occurred in the highest proportion of patients treated for $>$ 4 weeks.

Laboratory evaluations were not conducted in the pivotal rosacea studies.

Discontinuations due to Adverse Events

The proportions of subjects who discontinued due to adverse events were similar between treatment groups. Of the 716 AzA 15% gel subjects, 25 (3%) discontinued the study due to cutaneous adverse events. Of these adverse events, burning/stinging/tingling; scaling/dry skin/xerosis, erythema/ irritation, and/or pruritus led to discontinuation most often. For vehicle-treated subjects, six (2%) of 382 patients discontinued the study due to cutaneous adverse events. Similarly, the highest proportion of vehicle-treated patients discontinued prematurely due to burning/stinging/tingling, scaling/dry skin/xerosis, and/or erythema/irritation.

Systemic adverse events led to discontinuation for five (1%) AzA 15% gel-treated subjects. Those events were facial edema, malaise, cerebral thrombosis, headache, and pneumonia. Of the subjects who received vehicle or AzA 20% cream, none reported systemic adverse events that led to discontinuation.

Adverse events that led to premature discontinuation in the rosacea studies are presented in the following table:

Discontinuations due to an adverse event rosacea studies (sponsor text tables 32 and 34 in the study reports)

Treatment group	Subject #	Adverse event	Intensity/severity	Relationship to study drug
Aza 15% gel	182	Itching of skin	Moderate	Definitely
		Rash	Moderate	Definitely
	273	Edema	Moderate	Probably
		Burning	"	"
		Stinging	"	"
	096	Intolerable burning	Severe	Probably
	126	Facial dryness	Moderate	Possibly
	041	Blood clot on brain	Severe	No relationship
	174	Itching	Moderate	Definitely
	224	Facial burning	Severe	Probably
	348	Facial dryness	Moderate	Probably
	032	Facial dryness	Unknown	Unknown
	196	Facial scaling/peeling	Severe	"
233				
	Headache	Mild	Possibly	
Burning				Moderate
	Pruritus	"	"	
Right eye edema				"
	Infected acne rosacea	Mild	Possibly	
Vehicle				125
	072	Worsening rosacea	Moderate	
	199	Burning	Moderate	Definitely
	164	Dryness	Unknown	Unknown
Burning	Moderate	Definitely		
			Erythema	Severe
Hives	Moderate	"		
			Pruritus	"

Deaths

There was one death reported in the rosacea and acne studies: Subject #41, treated with Aza 15% gel in trial A03126, died due to a cerebral thrombosis. The subject had begun study treatment on February 21, 2001. He presented to the emergency room on March 3, 2001 following an episode of loss of consciousness and was diagnosed with a "blood clot on the brain." He expired on March 4, 2001. The sponsor did not consider the death to be related to study medication; this appears to be a reasonable conclusion.

Serious Adverse Events

A total of eight subjects (five Aza 15% gel and three vehicle) experienced serious adverse events in the rosacea and acne studies. The serious adverse events experienced by Aza 15% gel subjects included cerebral thrombosis, exacerbation of asthma, pneumonia, uvulopalatopharyngealplasty, and hypoglycemia. Serious adverse events experienced by vehicle subjects were convulsion, urinary tract infection, and atrial fibrillation.

Seven of the serious adverse events were assessed as having no relation to study medication. The eighth, hypoglycemia in a subject treated with Aza 15% gel, was assessed by the sponsor as being unlikely related to study medication.

Reviewer's comment: According to the current Azelex® label, "worsening of asthma" has been reported rarely in patients using azelaic acid formulations. The subject who experienced an exacerbation of asthma during the rosacea pivotal trials had begun AzA 15% gel treatment on March 13, 2001. On _____ she began to experience shortness of breath for which she was treated in an emergency room, with release the same day, i.e. on _____. While on a flight on _____ the subject began to experience a recurrence of shortness of breath. She was admitted for treatment and discharged on _____. According to the patient, the treating physicians attributed the asthma exacerbation to "high outside temperature (108 degrees F) and air pollution." The assessment by the sponsor that the adverse event was not related to study treatment does not appear unreasonable.

Pregnancies

Pregnant and lactating women were not specifically excluded from the pivotal rosacea studies, nor were women required to practice a reliable method of contraception. However, a urine pregnancy test (β -HCG) was performed in female patients of childbearing potential at baseline and the last on-therapy visit. Two subjects in the rosacea trial A03126 became pregnant during the study (subjects 274 and 230) and completed the trial. Both were randomized to the AzA 15% gel treatment group. While a limited amount of information was provided regarding the pregnancy outcomes, neither infant was reported to have had any difficulties: the infant of subject 274 was reported as "fine" following a "healthy delivery;" the infant of subject 230 was reported as a "healthy baby girl" and born "at full term."

Number (%) of patients with systemic adverse events by treatment, body system and preferred term - all studies (ITT population - rosacea and acne (sponsor Table 22))

	AzA 15% gel	vehicle	AzA 20% cream
total number of patients:	716 (100%)	382 (100%)	15 (100%)
patients with at least one systemic adverse event(s):	117 (16%)	91 (24%)	10 (67%)
body system			
preferred terms			
BODY AS A WHOLE			
TOTAL	37 (5%)	23 (6%)	1 (7%)
Flu synd	13 (2%)	2 (1%)	0 (0%)
Allerg react	6 (1%)	7 (2%)	0 (0%)
Infect	6 (1%)	6 (2%)	0 (0%)
Injury accid	4 (1%)	3 (1%)	0 (0%)
Pain	4 (1%)	3 (1%)	1 (7%)
Malaise	2 (0%)	0 (0%)	0 (0%)
Abscess	1 (0%)	0 (0%)	0 (0%)
Edema face	1 (0%)	0 (0%)	0 (0%)
Fever	1 (0%)	0 (0%)	0 (0%)
Hernia	1 (0%)	0 (0%)	0 (0%)
Pain back	1 (0%)	2 (1%)	0 (0%)
Pain neck	1 (0%)	0 (0%)	0 (0%)
Cyst	0 (0%)	1 (0%)	0 (0%)
Surgery	0 (0%)	3 (1%)	0 (0%)
CARDIOVASCULAR SYSTEM			
TOTAL	3 (0%)	5 (1%)	2 (13%)
Heart fail	1 (0%)	0 (0%)	0 (0%)
Hypotens	1 (0%)	0 (0%)	1 (7%)

Pain chest	1 (0%)	0 (0%)	0 (0%)
Throm cerebr	1 (0%)	0 (0%)	0 (0%)
Cardiovasc dis	0 (0%)	0 (0%)	1 (7%)
Fibrillat atr	0 (0%)	1 (0%)	0 (0%)
Hypertens	0 (0%)	3 (1%)	0 (0%)
Vasc dis	0 (0%)	1 (0%)	0 (0%)
DIGESTIVE SYSTEM			
TOTAL	21 (3%)	11 (3%)	1 (7%)

Subjects may have more than one systemic adverse event and therefore the sum of the frequencies of preferred terms may exceed the number of subjects with at least one systemic adverse events.

Systemic adverse events are presented by descending frequencies within each body system according to AzA 15% gel.

**APPEARS THIS WAY
ON ORIGINAL**

	AzA 1 5% gel	vehicle	AzA 20% cream
Gastroenteritis	5 (1%)	2 (1%)	0 (0%)
Diarrhea	3 (0%)	1 (0%)	0 (0%)
Dyspepsia	2 (0%)	1 (0%)	0 (0%)
Enteritis	2 (0%)	0 (0%)	1 (7%)
Gastritis	2 (0%)	0 (0%)	0 (0%)
Gi dis	2 (0%)	0 (0%)	0 (0%)
Abscess periodont	1 (0%)	1 (0%)	0 (0%)
Cleft palate	1 (0%)	0 (0%)	0 (0%)
Esophagitis	1 (0%)	0 (0%)	0 (0%)
Gingivitis	1 (0%)	0 (0%)	0 (0%)
Nausea	1 (0%)	1 (0%)	0 (0%)
Vomit	1 (0%)	1 (0%)	0 (0%)
Constip	0 (0%)	1 (0%)	0 (0%)
Flatul	0 (0%)	1 (0%)	0 (0%)
Pain mouth	0 (0%)	1 (0%)	0 (0%)
Pain throat	0 (0%)	1 (0%)	0 (0%)
Tooth dis	0 (0%)	1 (0%)	0 (0%)
Ulcer mouth	0 (0%)	1 (0%)	0 (0%)
HEMIC AND LYMPHATIC SYSTEM			
TOTAL	0 (0%)	2 (1%)	0 (0%)
Anemia	0 (0%)	1 (0%)	0 (0%)
Anemia iron defic	0 (0%)	1 (0%)	0 (0%)
METABOLIC AND NUTRITIONAL SYSTEM			
TOTAL	1 (0%)	0 (0%)	0 (0%)
Hypoglycem	1 (0%)	0 (0%)	0 (0%)
MUSCULOSKELETAL SYSTEM			
TOTAL	3 (0%)	6 (2%)	0 (0%)
Arthrosis	1 (0%)	0 (0%)	0 (0%)
Cramps muscle	1 (0%)	0 (0%)	0 (0%)
Myalgia	1 (0%)	1 (0%)	0 (0%)
Arthralgia	0 (0%)	2 (1%)	0 (0%)
Bone fracture	0 (0%)	1 (0%)	0 (0%)
Tendon dis	0 (0%)	1 (0%)	0 (0%)
Twitch	0 (0%)	1 (0%)	0 (0%)
NERVOUS SYSTEM			
TOTAL	23 (3%)	17 (4%)	2 (13%)
Headache	22 (3%)	9 (2%)	2 (13%)

Subjects may have more than one systemic adverse event and therefore the sum of the frequencies of preferred terms may exceed the number of subjects with at least one systemic adverse events.

Systemic adverse events are presented by descending frequencies within each body system according to AzA 15% gel.

	AzA 1 5% gel	vehicle	AzA 20% cream
Insomnia	1 (0%)	2 (1%)	0 (0%)
	0 (0%)	2 (1%)	0 (0%)
Convuls	0 (0%)	1 (0%)	0 (0%)
Depression	0 (0%)	2 (1%)	0 (0%)
Emotion labil	0 (0%)	1 (0%)	0 (0%)
RESPIRATORY SYSTEM			
TOTAL	49 (7%)	40 (10%)	6 (40%)
Infect upper resp	26 (4%)	23 (6%)	2 (13%)
Bronchitis	6 (1%)	3 (1%)	0 (0%)
Rhinitis	6 (1%)	4 (1%)	3 (20%)
Sinusitis	6 (1%)	8 (2%)	1 (7%)
Cough inc	3 (0%)	1 (0%)	0 (0%)
Pneumonia	3 (0%)	1 (0%)	0 (0%)
Apnea	1 (0%)	0 (0%)	0 (0%)
Asthma	1 (0%)	0 (0%)	0 (0%)
Pharyngitis	0 (0%)	0 (0%)	0 (0%)
UROGENITAL SYSTEM			
TOTAL	10 (1%)	7 (2%)	0 (0%)

Cystitis	3 (0%)	3 (1%)	0 (0%)
Infect urin tract	3 (0%)	3 (1%)	0 (0%)
Dysmenorrhea	2 (0%)	0 (0%)	0 (0%)
Monilia vagina	1 (0%)	2 (1%)	0 (0%)
Prostat dis	1 (0%)	0 (0%)	0 (0%)
Cervix dis	0 (0%)	1 (0%)	0 (0%)

Subjects may have more than one systemic adverse event and therefore the sum of the frequencies of preferred terms may exceed the number of subjects with at least one systemic adverse events.

Systemic adverse events are presented by descending frequencies within each body system according to AzA 15% gel.

Study Report A08681: "A 15-week, randomized, double-blind multicenter study comparing the clinical efficacy and safety of Azelic Acid 15% gel (SH H 655 BA) with Metronidazole 0.75% gel in patients with papulo-pustular facial rosacea":

As was discussed, this trial is presented separately since the data were incomplete and were submitted late in the review cycle in the form of a "draft synopsis." The synopsis, however, was considered to have contained most of the pertinent safety data. In this trial, the sponsor's product was compared to Metronidazole 0.75% gel in the treatment of rosacea.

Two hundred fifty-one subjects were randomized and dispensed study medication: 124 subjects received AzA 15 % gel and 127 received Metronidazole 0.75% gel. Duration of treatment was 15 weeks. The following safety data were reported in the synopsis:

- Treatment-emergent adverse events were reported in 47.6% of AzA 15 % gel-treated subjects and 24.4% of Metronidazole 0.75% gel-treated subjects.
- Related-cutaneous adverse events were reported by the sponsor in 25.8% of AzA 15 % gel-treated subjects and 7.1% of Metronidazole 0.75% gel-treated subjects. Related events were burning sensation of the skin, pruritus, stinging/tingling, dry skin, rash, facial edema, and acne. The relationship of these events to treatment group assignment was not provided.
- Cutaneous adverse events were mostly mild to moderate intensity in both treatment groups, regardless of relatedness to study medication. Those of severe intensity were reported by 5.6% of subjects in the AzA 15 % gel group and none in the Metronidazole 0.75% gel group.
- Premature discontinuations occurred due to one or more adverse events with five subjects (4%) in the AzA 15 % gel group and none in the Metronidazole 0.75% gel group. Of the five AzA 15 % gel-treated subjects, the sponsor considered that four had at least one related-cutaneous adverse event that led to the premature discontinuation.
- Local tolerability was reported as "good" and "acceptable despite minor irritation" 96% in the Metronidazole 0.75% gel group and 89% in the AzA 15 % gel group.
- No systemic adverse events in either treatment group were considered to be related to study medication.
- There were no deaths of serious adverse events reported.

Reviewer's comment: This single study suggests that AzA gel 15% might be significantly more irritating than Metronidazole 0.75% gel.

Study Reports AE14, AE15 and AQ63:

These three studies did not employ the to-be-marketed formulation: two phase 3 studies (AE14 and AE15) studied a AzA 20% cream formulation, and a phase 1 scarification study (AQ63) studied two other AzA 15% gel formulations (SH H 655 A and SH H 655 B). Summary data were provided from these studies in the sponsor's Integrated Summary of Safety

Brief comments pertaining to these three studies follow, beyond which they will not be further discussed:

- Only cutaneous adverse events were observed in study AE14 (none serious).
- The majority of adverse events in study AE15 were cutaneous. However, systemic adverse events were reported for two subjects: one subject reported severe cough and throat infection, and the second subject reported moderate chest infection. The adverse events were not considered by the sponsor to be causally related to the study treatment, and no subjects were withdrawn from treatment due to adverse events. No serious adverse events or deaths were reported.
- Both experimental AzA 15% gel formulations had a mild to moderate irritant effect in the scarification study (AQ63).

Reviewer's comment: The methods for data recording and presentation for studies AE14 and AE15 did not permit incorporation into much of the safety review formatting (e.g extent of exposure). However, the data did not raise any systemic safety concerns.

DERMAL SAFETY STUDIES

Study (# of subjects)/Age in years (mean)/Sex/Race	Test articles	Methods	Findings/conclusions
A04832 <u>21-Day Cumulative Irritant Patch Study</u> (37 subjects) - 19-75 (44.7) - 8 males; 29 females - 33 Caucasians; 1 Black; 3 Hispanics	AzA 15% gel 0.1% sodium lauryl sulfate (SLS) vehicle gel	Five test sites: test articles applied under occlusion for 24 hrs (72 hrs for weekends) once daily on 5 consecutive days a week for 3 weeks; one site was occluded without treatment; one site left open untreated. Assessed visually by ordinal scoring system on removal of patch.	-AzA 15% gel and its vehicle may potentially elicit irritant reactions at the application site. -AzA gel caused significantly more irritation than its vehicle (p≤0.0001).
A04766 <u>Repeat Insult Patch Test</u> (220 subjects) - 18-75 (44.1) - 55 males; 165 females - 187 Caucasians; 1 Black; 22 Hispanics, 7 Asians, 3 Other	AzA 15% gel 0.1% SLS vehicle gel	Five test sites: test articles applied under occlusion to back 3 times weekly for 3 weeks; one site was occluded without treatment; one site left open untreated. Ten to 15 day rest period, then one challenge site. Assessed during induction, and at 48, 72 and 96 hours after challenge.	-AzA 15% gel and its vehicle elicited irritant reactions to a similar extent during induction. - AzA 15% gel and vehicle were significantly more irritating than the controls. - No reactions indicative of skin sensitization.
AZ00 <u>Photosensitization Study</u> (24 subjects) - 18-60 (36.1) - 3 males; 21 females - 24 Caucasians	AzA 15% gel vehicle gel	Epidermal barrier was pre-damaged by SLS. Three week induction phase where articles were applied twice weekly to both sides of back. After removal of articles, sites on one side of back irradiated with UVA; <i>contralateral sites were not</i> . After ten-days rest period, challenge treatment at a naïve site on back. Sites assessed immediately, at 24, 48 and 72 hours after UVA.	- AzA 15% gel and its vehicle caused minor irritation, but did not elicit photosensitization.
AZ01 <u>Phototoxicity Study</u> (12 subjects) - 26-62 (45.0) - 1 male; 11 females - 12 Caucasians	AzA 15% gel vehicle gel	Articles applied to back under occlusion for 24 hours. Sites were irradiated with 15 J/cm ² UVA. Assessed 24, 48, and 72 hours after irradiation.	Neither AzA 15% gel or its vehicle elicited phototoxic reactions.

21-Day Cumulative Irritant Patch Study (A04832)

Of the 37 subjects enrolled, three subjects discontinued due to withdrawal of consent. Of the remaining 34 subjects, discontinuation of patch application due to severe irritation occurred in three (8.8%) subjects at the AzA 15% gel patch sites. Discontinuation of patch application due

to severe irritation occurred in 12 (35.5%) of the 34 subjects in the second half of the 21-day study period at the vehicle patch sites. The reason for the higher rate of severe irritation at the sites patched with vehicle is not clear; however, the sponsor postulates that the vehicle may represent a "fatiguing substance", i.e. a mild irritant that causes more strongly positive reactions with successive skin exposures. The positive control sodium lauryl sulfate (SLS) caused less irritation than AzA15% gel and its vehicle. The sponsor considered this to be attributable to the relatively low SLS concentration (0.1%) used in this study.

A total of 11 (29.7%) of the 37 subjects enrolled in the study reported at least one adverse event. Of these adverse events, nine of 14 (64.3%) were cutaneous symptoms in the skin and skin appendages body system. All cutaneous symptoms were either mild or moderate in intensity, except for one case of severe burning (AzA 15% gel). A total of seven subjects had treatment-related adverse events, all of which were cutaneous in nature.

Repeat Insult Patch Test (A04766)

No skin reactions indicative of skin sensitization were observed in the challenge phase. During the challenge phase, 7.9% of the subjects experienced minimal irritation at the AzA 15% gel sites that quickly resolved. This reaction was regarded as irritation compatible with the irritation pattern observed in the induction phase. Both AzA 15% gel and gel vehicle elicited irritant reactions to a similar extent at the site of application, while no appreciable reactions were observed at the positive control site (SLS 0.1%), untreated occluded site, or untreated open sites. A pairwise comparison showed that AzA 15% gel was statistically significantly more irritating than each of the three control groups. The gel vehicle was also statistically significantly more irritating than each of the three control groups.

A total of 52 (24%) of the 220 subjects in the study reported at least one adverse event. The majority of adverse events were cutaneous symptoms within the skin and appendages body system. Two subjects discontinued the study prematurely due to adverse events. A total of 39 (18%) of the 220 subjects had treatment related adverse events, all of which were cutaneous symptoms. The most common related cutaneous adverse event was pruritus (36 subjects, 16%), while all other cutaneous adverse events were burning sensation (five subjects, 2%). All cutaneous adverse events were rated by the investigator as either mild or moderate intensity.

Photosensitization Study (AZ00)

AzA 15% gel and its vehicle caused minor irritation, but did not elicit any photosensitization reactions. No sensitization reactions were observed at the nonirradiated control sites. No other cutaneous adverse events were observed. There were no deaths or serious adverse events during the study.

Phototoxicity Study (AZ01)

Four subjects showed a cutaneous reaction on both the irradiated and non-irradiated sides with identical skin reaction scores. Therefore, it was concluded that neither AzA 15% gel nor its vehicle elicited any phototoxic reactions. No other cutaneous adverse events were observed.

adverse event reporting, and the published literature are consistent with the known safety profile of topical azelaic acid. There is no evidence of any new type of substance-related adverse drug reactions.

Safety information received from the post-marketing area for AzA 20% cream after data lock point for the PSUR

From January 1, 2002, to June 30, 2002, no serious adverse events were reported. For a total of five patients non-serious adverse reactions potentially associated with AzA 20% cream were reported. The reported events were: two subjects with cutaneous allergic reactions; one subject with dizziness, headache and allergy; one subject with a rash, and one subject with skin irritation including skin pustules and redness. Among these events only dizziness and headache are not included in the current labeling as known adverse drug reactions. Based on the given information the sponsor considers that dizziness and headache are unlikely related to AzA. As the review was being drafted, the sponsor saw no reason to alter the known risk/benefit profile for AzA.

Reviewer's comments: 1) One AzA 15% gel-treated subject was discontinued in the rosacea pivotal studies due to the adverse events of facial pruritus and headache ("definitely" and "possibly" related to study medication, respectively). It is unclear how much each of the two adverse events might have contributed to the discontinuation. No other reports of headache in the pivotal rosacea trials or acne trials were considered by the sponsor to have been study-medication related. There were no reports of dizziness in the rosacea or acne trials. Thus, the reviewer is in agreement with the sponsor's conclusion regarding dizziness and headache. Both adverse events were rated "mild." 2) Based on the information presented, there does not appear to be any reason to change the risk/benefit profile for AzA gel.

D. Adequacy of Safety Testing

The extent of safety testing is considered adequate as pertains to numbers of subjects exposed, duration of exposure, and safety assessments conducted. The appropriate topical safety studies were conducted, and an adequate number of subjects was enrolled in each of these studies.

E. Summary of Critical Safety Findings and Limitations of Data

AzA 15% gel and its vehicle were shown to be potential irritants in both the pivotal trials and in dermal safety studies. In the rosacea pivotal trials, the most commonly reported cutaneous adverse events in the AzA 15% gel group, in order of decreasing frequency, were burning/stinging/tingling, pruritus, scaling/dry skin/xerosis, erythema/irritation, and edema. While a similar pattern of reporting of cutaneous adverse events was seen in vehicle-treated subjects, the order of decreasing frequency differed: scaling/dry skin/xerosis, burning/stinging/tingling, pruritus, and erythema/irritation was reported as often as edema. Burning/stinging/tingling was the cutaneous adverse event that was most often considered to be drug-related in the AzA 15% gel group, while in the vehicle group it was scaling/dry skin/xerosis. Most cutaneous adverse events in both treatment groups were of mild severity.

A similar potential for irritancy has been shown with the drug substance marketed in a different vehicle (Azelex®). Additionally, hypopigmentation has been reported in patients with dark complexions following use of azelaic acid. Because the numbers of subjects in various ethnic and racial groups were few in the rosacea pivotal trials were few, meaningful conclusions pertaining to adverse events in these subgroups could not be drawn.

As with Azelex®, labeling for the sponsor's product should reflect the potential for irritancy. Additionally, the label should include the possibility of hypopigmentation following use of the product by subjects with dark complexions.

No significant systemic safety concerns were raised in the clinical trials.

VIII. Dosing, Regimen, and Administration Issues

Clinical dose-ranging studies were not conducted with AzA 15% gel. According to the Sponsor, the incorporation of 20% AzA in the gel base causes a _____ of the gel formulation. A twice-daily treatment regimen was used, consistent with the recommended use of topical AzA 20% cream.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The majority of subjects in the rosacea and acne studies were females. As pertains to rosacea, this is perhaps, at least in part, a function of the population more likely to be affected by this condition. However, there is no apparent reason to consider that there would be significant gender differences in the pharmacology, safety or effectiveness of the AzA 15% gel.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The majority of subjects in the rosacea and acne studies were Caucasians. Pertaining to rosacea, this is, again, perhaps partly a function of the population more likely to be affected by this condition. Pertaining to the acne studies, the racial/ethnic composition is likely a function of where the trials were conducted, i.e. in Europe. As discussed, hypopigmentation has been reported in patients with dark complexions following use of the drug substance in a different vehicle, and this should be reflected in the sponsor's label.

C. Evaluation of Pediatric Program

The sponsor requested a pediatric waiver. The request is reasonable and acceptable, as the indication sought is not typically seen in subjects younger than 18 years.

D. Comments on Data Available or Needed in Other Populations

As discussed, two subjects became pregnant during the rosacea trials, both of whom completed the study. Both were randomized to the AzA 15% gel treatment group, and both

completed the study. While a limited amount of information was provided regarding the pregnancy outcomes, neither baby was reported to have had any difficulties. However, the data are insufficient to speak to the safety of use of the sponsor's product during pregnancy.

X. Conclusions and Recommendations

A. Conclusions

While the sponsor did provide preliminary data from a single study in which their product was compared to metronidazole 0.75% gel in the treatment of rosacea, adequate data comparing the use of AzA 15% gel with other treatments for rosacea are not available.

B. Recommendations

Pending agreement by the Sponsor to labeling revisions, from a clinical perspective it is recommended that azelaic acid 15% gel be approved for treatment of the inflammatory papules and pustules in patients with mild to moderate papulopustular facial rosacea.

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/s/

Brenda Vaughan
12/9/02 11:44:56 AM
MEDICAL OFFICER

Markham Luke
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Dr. Brenda Vaughan is the primary NDA reviewer for efficacy. Dr. Brenda Carr is the primary NDA reviewer for safety. This MOR is a collaborative product.

Jonathan Wilkin
12/16/02 12:50:14 PM
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