CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-965

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

MAR 22 1999

NDA/DRUG CLASS: 20-965/1S

NAME OF DRUG: Levulan Kerastick (Aminolevulinic Acid HCl) Topical Solution 20%

APPLICANT: DUSA Pharmaceuticals, Inc.

INDICATION(S): [redacted] Actinic Keratoses of the Face & Scalp

TYPE OF REVIEW: Statistical

DOCUMENTS REVIEWED: Two Controlled Studies: ALA-018 & ALA-019, Dated July 1, 1998

MEDICAL REVIEWER: Martin Okun, M.D./HFD-540

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I. INTRODUCTION:

The sponsor has submitted two identically designed (multicenter, investigator-blind, randomized, unbalanced, parallel group, Vehicle and blue light controlled) pivotal studies in patients with multiple actinic keratoses of the face and scalp. (Studies ALA-018 & ALA-019).

Table I lists the two pivotal trials:

Table I
Summary of the Pivotal Studies

Study # (# of Centers)	Study Design, (Duration)	Treatment Arm (n)	N	Endpoint
ALA-018 (8)	Randomized, Multicenter, Investigator-Blind, Parallel, Vehicle-Controlled (8 Weeks)	Levulan (88) Vehicle (29)	117	Subjects' Complete Cure Rate
ALA-019 (8)	Randomized, Multicenter, Investigator-Blind, Parallel, Vehicle-Controlled (8 Weeks)	Levulan (93) Vehicle (33)	126	Subject's Complete Cure Rate

II. REVIEW:

Objective & Design:

To evaluate the safety and efficacy of Levulan 20% solution and 10 J/cm^2 of blue light delivered at 10mW/ cm^2 in treatment of [redacted] actinic keratoses of the face and scalp.

Eight centers in the United States participated in each of these studies. After qualifying for the study, subjects were randomized in 3:1 ratio to receive a pre-numbered kit containing either Levulan or Vehicle Kerastick applicators, respectively. Four to 15 target lesions on either the face or scalp were selected. The subjects were directed to apply the study medication or the vehicle to individual Actinic Keratoses (AK) lesions of the face or scalp. Blue light from the 4170 light device was delivered at a power density of 10mW/cm^2 to a total light dose of 10 J/cm^2 14-18 hours after Levulan Topical Solution application.

Patients returned for follow up visits 24 hours after light treatment and at Weeks 1, 4 and 8. If re-treatment was necessary at Week 8, either the study drug or vehicle (according to the original randomization) and light were re-administered and the patients returned 24 hours later and Week 9. All patients returned at Week 12 for a final visit. The blinded investigator performed efficacy and cosmetic evaluations at Weeks 4, 8 and 12.

Patient Population, Primary Endpoint Variables, Sample Size & Statistical Methods:
Men and non-pregnant women, over the age of 18, who had a minimum of 4 discrete non-hyperkeratotic lesions on either the face or scalp participated in these trials. Patients could have up to 15 discrete target regions treated as long as they were confined to either the face or the scalp.

The primary measure of efficacy was the clinical response based on the complete clearing of lesions at Visit 5 (week 8). The secondary measures were the cosmetic response of the lesions to treatment, which was evaluated by the blinded investigator at Visits 4, 5, and 9 (Week 4, 8 and 12) respectively, and by the patient at Visit 9 (Week 12).

Based on the sponsor's submission, the efficacy results were analyzed as the percent reduction in lesion count (CR rate) and the percentage of patients with at least a 75% reduction in lesion counts. The treatment groups were compared with respect to each parameter with the data stratified by center. The primary time point was Week 8. Treatment differences with respect to the patient's cosmetic evaluations were assessed at Week 12 using ridit analysis. Treatment differences with respect to the proportions of lesions with pigmentary changes relative to baseline were evaluated using a Mantel-Haenszel test. The studies sought to show a statistically significant difference between Levulan solution and Vehicle with respect to the proportions of patients with a CR at Week 8 based on ***per-protocol population***.

However, in this review the primary endpoint parameter is based on the percent of subjects who were completely cleared of all targeted lesions at Week-8 based on ***Intent-to-Treat population.***

In order to calculate the sample size, the sponsor is assuming CR rates of 80% in the Levulan group and 20% in the Vehicle group at a 1% significance level and 95% power, requiring a sample size of 24 lesions per treatment group. Assuming 4 lesions per patient, 6 patients were needed per treatment group. The total sample size chosen was 100 patients. The patients were to be randomized in a 3 to 1 ratio (active to vehicle) so that 75 patients would receive active drug and 25 patients would receive vehicle. Since each patient was required by the protocol to

have a minimum of 4 target lesions, the active treatment group would have at least 300 lesions and the vehicle group would have at least 100 lesions.

The sponsor is basing the sample size calculations on the percentage of lesions cured and not on the percentage of subjects who were completely cured. The method of sample size calculation is not acceptable by this reviewer.

Comparability of the two treatment groups with respect to demographic and baseline characteristics was assessed using a univariate analysis of variance (ANOVA), with treatment effect for continuous variables and the Cochran-Mantel-Haenszel (CMH) test for discrete variables.

For the purpose of investigating the differences between the age groups, the variable age was categorized between two groups: younger than 60 or 60 and older.

Per-Subject Analysis:

Study ALA-018:

Demographics:

A total of 117 subjects from eight centers were enrolled into this study, where 88 subjects were randomized into the Levulan and 29 into the Vehicle arm.

Two centers had less than 10 subjects enrolled (Piacquadio, n=7 and Scher, n=4). For the purpose of the analyses, these two centers were combined.

Three (3%) subjects in the Levulan arm and one (3%) in the vehicle group dropped out.

Table II summarizes the demographics of these subjects.

Table II
Demographics & Baseline Characteristics
All Randomized Subjects
Study ALA-018

	Whole Population (N=117)	Levulan (n=88)	Vehicle (n=29)	P-Value
Gender:				
Female	19 (16.2%)	15 (17%)	4 (14%)	0.7
Male	98 (83.8%)	73 (83%)	25 (86%)	
Race:				
White	117 (100%)	88 (100%)	29 (100%)	
Age (Mean ± Std)	66.4 ± 10.4	67.1 ± 9.7	64.2 ± 12.4	0.2
Weight (Mean ± Std)	180.4 ± 37.2	179.7 ± 35	182.6 ± 43.8	0.7
Location of Lesions:				
Face	93 (79.5%)	72 (82%)	21 (72%)	0.3
Scalp	24 (20.5)	16 (18%)	8 (28%)	
SkinType:				
1	28 (24%)	19 (22%)	9 (31%)	0.4
2	56 (48%)	46 (52%)	10 (34%)	
3	30 (26%)	21 (24%)	9 (31%)	
4	3 (3%)	2 (2%)	1 (3%)	
Total # of Lesions per Subject:				0.6
4	27 (23%)	17 (19%)	10 (34%)	
5	32 (27%)	29 (33%)	3 (10%)	
6	12 (10%)	9 (10%)	3 (10%)	
7	4 (3%)	3 (3%)	1 (3%)	
8	8 (7%)	5 (6%)	3 (10%)	
9	3 (3%)	2 (2%)	1 (3%)	
10	14 (12%)	10 (11%)	4 (14%)	
11	3 (3%)	2 (2%)	1 (3%)	
12	6 (5%)	4 (5%)	2 (7%)	
13	3 (3%)	3 (3%)	0 (0%)	
14	0 (0%)	0 (0%)	0 (0%)	
15	5 (4%)	4 (5%)	1 (3%)	
Lesions (Mean ± Std)	7 ± 3	7 ± 3	7 ± 3	0.99
Investigator:				
Farber	10 (8.5%)	7 (8%)	3 (10%)	
Glazer	24 (20.5%)	18 (20%)	6 (21%)	
Goodman	18 (15.4%)	13 (15%)	5 (17%)	
Ling	24 (20.5%)	18 (20%)	6 (21%)	
Piacquadio + Scher	11 (9.4%)	9 (10%)	2 (7%)	
Taylor	20 (17.1%)	15 (17%)	5 (17%)	
Whitmore	10 (8.5%)	8 (9%)	2 (7%)	

As it is shown in Table II, no statistical differences were found between the two treatment arms in regards to the demographics and baseline characteristics of the subjects ($p \geq 0.2$).

Clinical Efficacy Analysis & Results:

Table III summarizes the results of the analysis for the primary endpoint variable:

Table III
Rate of Complete Clearance of the Actinic Keratosis Lesions
Intent-To-Treat Population
Study ALA-018

	Levulan (n=88)	Vehicle (n=29)	P-Value
Week-4 Cure Not-Cure	 34/88=39% 54/88=61%	 1/29=3% 28/29=97%	0.001
Week-8 **Cure** **Not-Cure**	 **59/88=67%** **29/88=33%**	 **4/29=14%** **25/29=86%**	**0.001**
Week-12 Cure Not-Cure	 70/88=80% 18/88=20%	 3/29=10% 26/29=90%	0.001

As it is seen in Table III, highly significant results (p=0.001) were observed when Levulan was compared to the Vehicle arm relative to rate of complete clearance at Week-8.

Analysis controlling for center effect, age category (younger than 60, 60 and older), sex, skin type and the location of the lesions (face or scalp) showed the same highly significant results (p=0.001).

Study ALA-019:

Demographics:
A total of 126 subjects from eight centers were enrolled into this study, where 93 subjects were randomized into the Levulan and 33 into the Vehicle arm.

Four (4%) subjects in the Levulan arm dropped out and two (6%) in the vehicle group.

Table IV summarizes the demographics of these subjects.

Table IV
Demographics & Baseline Characteristics
All Randomized Subjects
Study ALA-019

	Whole Population (N=126)	Levulan (n=93)	Vehicle (n=33)	P-Value
Gender:				0.06
Female	21 (17%)	19 (20%)	2 (6%)	
Male	105 (83%)	74 (80%)	31 (94%)	
Race:				
White	126 (100%)	93 (100%)	33 (100%)	
Age (Mean ± Std)	66.5 ± 10.9	67.1 ± 11.8	64.7 ± 12.1	0.3
Weight (Mean ± Std)	179.2 ± 31.1	177 ± 31	184 ± 30.9	0.3
Location of Lesions:				0.2
Face	87 (69%)	67 (72%)	20 (61%)	
Scalp	39 (31%)	26 (28%)	13 (39%)	
SkinType:				0.6
1	44 (35%)	33 (35%)	11 (33%)	
2	57 (45%)	44 (47%)	13 (39%)	
3	23 (18%)	15 (16%)	8 (24%)	
4	2 (2%)	1 (1%)	1 (3%)	
Total # of Lesions per Subject:				0.7
4	9 (7%)	6 (6%)	3 (9%)	
5	13 (10%)	11 (12%)	2 (6%)	
6	22 (17%)	17 (18%)	5 (15%)	
7	11 (9%)	9 (10%)	2 (6%)	
8	17 (13%)	13 (14%)	4 (12%)	
9	7 (6%)	5 (5%)	2 (6%)	
10	11 (9%)	9 (10%)	2 (6%)	
11	6 (5%)	4 (4%)	2 (6%)	
12	10 (8%)	6 (6%)	4 (12%)	
13	5 (4%)	2 (2%)	3 (9%)	
14	4 (3%)	2 (2%)	2 (6%)	
15	11 (9%)	9 (10%)	2 (6%)	
Lesions (Mean ± Std)	9 ± 3	8 ± 3	9 ± 3	0.3
Investigator:				
Chen	12 (9.5%)	8 (9%)	4 (12%)	
Fowler	16 (12.7%)	12 (13%)	4 (12%)	
Hruza	20 (15.9%)	15 (16%)	5 (15%)	
Phillips	16 (12.7%)	12 (13%)	4 (12%)	
Rallis	16 (12.7%)	12 (13%)	4 (12%)	
Tashjian	14 (11.1%)	10 (11%)	4 (12%)	
Taylor	16 (12.7%)	12 (13%)	4 (12%)	
Weinstein	16 (12.7%)	12 (13%)	4 (12%)	

As it is shown in Table IV, no statistical differences were found between the two treatment arms in regards to the demographics and baseline characteristics of the subjects ($p \geq 0.06$).

Clinical Efficacy Analysis & Results:

Table V summarizes the results of the analysis for the primary endpoint variable, rate of complete clearance of lesions:

Table V
Rate of Complete Clearance of the Actinic Keratosis Lesions
Intent-To-Treat Population
Study ALA-019

	Levulan (n=93)	Vehicle (n=33)	P-Value
Week-4			0.001
Cure	52/93=56%	3/33=9%	
Not-Cure	41/93=44%	30/33=91%	
Week-8			**0.001**
Cure	**58/93=62%**	**4/33=12%**	
Not-Cure	**35/93=38%**	**29/33=88%**	
Week-12			0.001
Cure	54/93=58%	4/33=12%	
Not-Cure	39/93=42%	29/33=88%	

As it is seen in Table V, highly significant results (p=0.001) were observed when Levulan was compared to the Vehicle arm.

Analysis controlling for center effect, age category (younger than 60, 60 and older), sex, skin type and the location of the lesions (face or scalp) showed the same highly significant results (p=0.001).

Subset Analysis:

The two data sets were merged and subset analysis was done based on gender, age category (younger than 60, 60 and older), skin type and the location of the lesions (face or scalp). The highly significant results was observed in each sub-category (p=0.001).

Among all the subjects in the two studies, twenty subjects who were completely cured on Week-8 had recurrence by Week-12. Of these, 17 had been treated by Levulan and three subjects with the Vehicle.

Per-Lesion Analysis:

Study ALA-018:

A total of 803 lesions were under the study. Of these, the data was available for only 784 at Week-8. Table VI gives the cure rate for these lesions.

Table VI
Rate of Complete Clearance of the Actinic Keratosis Lesions
Per-Lesion Analysis
Study ALA-018

	Levulan	Vehicle	P-Value
Week-4			0.001
Cure	438/574=76%	48/203=24%	
Not-Cure	136/574=24%	155/203=76%	
Week-8			**0.001**
Cure	**498/585=85%**	**69/199=35%**	
Not-Cure	**87/585=15%**	**130/199=65%**	
Week-12			0.001
Cure	545/580=94%	68/199=34%	
Not-Cure	35/580=6%	131/199=66%	

As it is seen in Table VI, highly significant results (p=0.001) were observed when Levulan was compared to the Vehicle arm, relative to rate of complete clearance at Week-8.

All investigators followed the same pattern of significance, except the investigator "Taylor". The success and failure rates for this center were different from the rest of the centers.

Cure Rate for Investigator Taylor

	Levulan	Vehicle	P-Value
Week-8			0.9
Cure	104/136=76%	44/57=77%	
Not-Cure	32/136=24%	13/57=23%	

Removing this center from the analysis did not change the statistically significant results.

Analysis controlling for center effect, age category (younger than 60, 60 and older), sex, skin type, grade and the location of the lesions (face or scalp) showed the same highly significant results (p=0.001).

Subset Analysis:

Subset analysis was done for gender, age category (younger than 60, 60 and older), skin type, grade and the location of the lesions (face or scalp). The highly significant results were observed in each sub-category (p=0.001).

Among all the lesions in the study, twenty-eight lesions that were completely cured on Week-8 had recurrence by Week-12. Of these, 19 had been treated with Levulan and nine lesions with the Vehicle.

Study ALA-019:

A total of 1086 lesions were under the study. Of these, the data was available for 1066 at Week-8. Table VII gives the cure rate for these lesions.

Table VII
Rate of Complete Clearance of the Actinic Keratosis Lesions
Per-Lesion Analysis
Study ALA-019

	Levulan	Vehicle	P-Value
Week-4			0.001
Cure	646/780=83%	77/298=26%	
Not-Cure	134/780=17%	221/298=74%	
Week-8			**0.001**
Cure	**630/768=82%**	**105/298=35%**	
Not-Cure	**138/768=18%**	**193/298=65%**	
Week-12			0.001
Cure	664/760=87%	85/284=30%	
Not-Cure	96/760=13%	199/284=70%	

As it is seen in Table VII, highly significant results (p=0.001) were observed when Levulan was compared to the Vehicle arm relative to the rate of complete clearance at Week-8.

All investigators followed the same pattern of significance, except the investigator "Tashjian". The success and failure rates for this center were different from the rest of the centers.

Cure Rate for Investigator Tashjian

	Levulan	Vehicle	P-Value
Week-8			0.5
Cure	35/91=38%	12/38=32%	
Not-Cure	56/91=62%	26/38=68%	

Removing investigator Tashjian from the analysis did not change the statistically significant results.

Analysis controlling for center effect, age category (younger than 60, 60 and older), sex, skin type, grade and the location of the lesions (face or scalp) showed the same highly significant results (p=0.001).

Subset Analysis:

Subset analysis was done for gender, age category (younger than 60, 60 and older), skin type, grade and the location of the lesions (face or scalp). Highly significant results were observed in each sub-category (p=0.001).

Among all the lesions in the study, one hundred and one lesions that were completely cured on Week-8 had recurrence by Week-12. Of these, sixty-four had been treated with Levulan and thirty-seven lesions with the Vehicle.

III. Conclusions:

The results of the analyses of efficacy of the two studies (Study ALA-018 & ALA-019) demonstrate that Levulan Kerastick Topical Solution 20% is statistically significantly better than Vehicle in the treatment of [redacted] Actinic Keratoses of the face & scalp.

The subset analyses relative to gender, age category (<60, ≥60), skin type and location of lesions also demonstrated similar statistically significantly results favoring Levulan over Vehicle.

According to the reviewing medical officer, the data presented by the sponsor did not raise any safety issues to be analyzed and addressed by the statistical reviewer.

/S/ 3/22/99

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APPEARS THIS WAY
ON ORIGINAL

This review contains 10 pages.