CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-965

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

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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

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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 [redacted] 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.

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

	Whole Population (N=117)	Levulan (n=88)	Vehicle (n=29)	P-Value
Gender:				0.7
Female	19 (16.2%)	15 (17%)	4 (14%)	
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:				0.3
Face	93 (79.5%)	72 (82%)	21 (72%)	
Scalp	24 (20.5)	16 (18%)	8 (28%)	
SkinType:				0.4
1	28 (24%)	19 (22%)	9 (31%)	
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 ($p \geq 0.2$).

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