CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-985

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

AUG 14 2000

NDA/Drug Class: 20-985/3S

Name of Drug: ——————(fluorouracil) Cream, 0.5%

Applicant: Dermik Laboratories, Inc.

Indication(s): Treatment of Multiple Actinic or Solar Keratoses of Face and Scalp

Documents Reviewed: Two Phase 3 Studies, Volumes 1, 17-33, dated 10/28/99

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I. INTRODUCTION:

The sponsor has submitted this NDA, primarily, based on two Phase 3 trials (Studies DL6025-9721 and DL6025-9722) to demonstrate the safety and efficacy of 5-Fluorouracil 0.5% (5-FU) cream in the treatment of Actinic Keratoses (AK) of the face and anterior scalp.

The study goal was to compare efficacy of treatment durations.

II. STUDY DESCRPITION:

Design, Randomization, Sample Size, Patient Population, Primary Endpoint Variables and Statistical Methods:

Both studies are adequate and well-controlled and follow similar study designs and subject inclusion criteria. For enrollment in the study, the protocols required each subject to have a minimum of 5 AK measuring $\geq$ 4 mm in size. Subjects were randomly assigned to one of six treatment groups:

1) 5-FU cream for 1 week.
2) 5-FU cream for 2 weeks.
3) 5-FU cream for 4 weeks.
4) Vehicle for 1 week.
5) Vehicle for 2 weeks.
6) Vehicle for 4 weeks.

Each treatment was applied once daily to the affected areas of the face and/or anterior scalp. The studies consisted of a screening visit, a treatment phase continuing for a total of one, two or four weeks according to treatment group randomization, and a follow-up phase which included a final evaluation 4 weeks after completing the treatment phase or 4 weeks after discontinuing treatment for any reason. The study goal was to compare the efficacy of 3 treatment durations.

Table I lists the two Phase 3 trials:

Table I: Summary of the Phase III Studies

Study # (# of Centers)	Study Design	Treatment Arm (n)	N	Endpoint
DL6025-9721 (9)	Randomized, Multicenter, Double-Blind, Parallel, Vehicle-Controlled	5-FU 0.5% Cream (47, 46, 45): QD (1, 2 or 4 Wks) Vehicle (69 combined): QD (1, 2 or 4 Wks)	207	AK Lesion Counts Total AK Clearance
DL6025-9722 (9)	Randomized, Multicenter, Double-Blind, Parallel, Vehicle-Controlled	5-FU 0.5% Cream (38, 41, 40): QD (1, 2 or 4 Wks) Vehicle (58 Combined): QD (1, 2 or 4 Wks)	177	AK Lesion Counts Total AK Clearance

The randomization was based on 2:1, active vs. vehicle. The supplies were sent to the investigators in blocks of nine. Each center was given two or three blocks, depending on the number of subjects in each center. All patients enrolling in the study were assigned a unique allocation number corresponding to the number on the patient's drug supply package. Allocation numbers were assigned in sequential order. Each patient treatment number corresponded to a randomized treatment group assignment.

The treatment regimens were supplied in boxes, each box containing 1 tube of 0.5% 5-FU cream or vehicle cream. Patients assigned to the one and two week treatment regimens received one tube of 0.5% 5-FU cream or vehicle cream and patients assigned to the four week treatment regimen received 2 tubes of 0.5% 5-FU cream or vehicle cream.

One box which included 1 tube of the 5-FU or vehicle was given to patients assigned to the one and two week regimen, and patients in the 4-week arms received two boxes. This system of dispensing the medication can cause un-blinding of the study.

As it was agreed between the sponsor and the Division, the comparability of the three vehicle arms was tested. In both studies the comparability of the three vehicle arms were tested in regards to Final Cure Rate. In study 9721, all the Vehicle arms had 0 success rate and in study 9722 only 2/21=9.5% in One-Week Vehicle arm were cured. No statistically significant results were observed among these arms ($p \geq 0.05$). Therefore, the vehicle arms were pooled and were considered as one arm in each study.

According to the sponsor, the primary efficacy parameter in both studies was:

"Reduction from baseline in regional count of visible and palpable AK lesions". However in a meeting with the sponsor (dated July 26, 1999), the Division recommended using "The proportion of subjects with 100% clearance of their AK" as the primary endpoint variable.

In this review, the primary endpoint variable is: The proportion of subjects with 100% clearance of their AK 4 weeks after their treatment termination (based on agreement between the sponsor and the Division), in an ITT population. Subjects with missing end of treatment value were considered failure. The secondary endpoint parameter is the rate of subjects with 75% clearance of their AK. In addition, a per-lesion analysis was conducted to show the percent change of the total number of lesions from baseline. These last two endpoints were analyzed in this review based on the medical reviewer's request.

The sponsor had calculated their sample sizes based on Mean Reduction of AK Lesions. For this reason, the results of the FDA's analyses might be under powered to demonstrate statistically significant results in the differences of the proportion of subjects with 100% clearance, among the different treatment arms.

In this review, the demographics and baseline characteristics were compared using Chi-Squared test for categorical data and an analysis of variance (ANOVA) test for continuous variables. The primary endpoint parameters were compared using Cochran Mantel Haenszel (CMH) test (controlling for centers) for categorical data, and for continuous variables an ANOVA test with center and treatment by center interaction as effects in the model was performed.

In the protocol, the sponsor had intended to make adjustments for multiplicity of the comparisons among the four treatment arms (six comparisons). In other words, the statistical significance of the pair-wise treatment differences would be evaluated:

- 4 weeks vs. 2 weeks
- 4 weeks vs. 1 week
- 2 weeks vs. 1 week
- 4 weeks vs. combined vehicle
- 2 weeks vs. combined vehicle
- 1 week vs. combined vehicle

A Dunnett adjustment may be applied if the contrasts against vehicle have comparison-wise significance levels greater than p=0.03. The interpretation of contrasts 1, 2 and 3 will be conditional upon finding each of the active treatments significantly more effective than the vehicle. However, in a meeting held with the sponsor (dated July 26, 1999), it was agreed that since the sponsor desires to demonstrate the superiority of any or all three duration of treatments vs. vehicle, these constitute three separate possibilities for a win. Hence, the sponsor needs to adjust the level using Bonferroni or any other appropriate multiple adjustment procedure. Therefore, the adjustment for multiplicity should only be done between the active treatment arms and the combined vehicle arm (three comparisons).

In order to adjust for the three multiple comparisons among the active treatment arms and the vehicle arm (One-Week vs. Vehicle, Two-Week vs. Vehicle and Four-Week vs. Vehicle), in this reviewer Holm procedure was applied; If none of the three p-values in the test is ≤ 0.017 (0.05/3), then the procedure will be stopped without a significant result. If the smallest p-value is ≤ 0.017, then the second smallest p-value will be compared to the alpha level of 0.025 (0.05/2), and the third p-value will be compared to 0.05 (0.05/1).

For the purpose of the analysis small centers with 10 or less subjects were combined.

To investigate the differences between the age groups, the variable age was categorized between two groups: 60 and younger and older than 60.

In order for this drug product to prove efficacy, the sponsor should demonstrate the superiority of any of the ——Cream 0.5% treatment regimens to the vehicle arm (after adjustment for multiplicity) in both of the pivotal studies.

Study DL6025-9721:

Demographics:

A total of 207 subjects from nine centers were enrolled into this study.
Two subjects (4%) in the one-week group, one subject (2%) in the two-week arm and one patient (2%) in the four-week arm had dropped out of the study.

Table II summarizes the demographics and baseline characteristics of all randomized subjects.

Table II: Demographics & Baseline Characteristics
All Randomized Subjects, Study 9721

	Whole Population (N=207)	One-Week (n=47)	Two-Week (n=46)	Four-Week (n=45)	Vehicle (n=69)	P-Value
Gender:						0.6
Female	41 (20%)	9 (19%)	8 (17%)	7 (16%)	17 (25%)	
Male	166 (80%)	38 (81%)	38 (83%)	38 (84%)	52 (75%)	
Race:						0.2
Caucasian	201 (97%)	46 (98%)	43 (93%)	43 (96%)	69 (100%)	
Hispanic	6 (3%)	1 (2%)	3 (7%)	2 (4%)	0 (0%)	
Age (Mean ± Std)	65 ± 10	64 ± 11	65 ± 11	67 ± 10	64 ± 10	0.6
Skin Type:						0.4
1	80 (39%)	21 (45%)	15 (33%)	15 (33%)	29 (42%)	
2	99 (48%)	23 (49%)	27 (59%)	22 (49%)	27 (39%)	
3	27 (13%)	3 (6%)	4 (9%)	8 (18%)	12 (17%)	
4	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	
Baseline Overall Severity:						0.8
Mild	54 (26%)	12 (26%)	13 (28%)	11 (24%)	18 (26%)	
Moderate	118 (57%)	26 (55%)	23 (50%)	26 (58%)	43 (62%)	
Severe	35 (17%)	9 (19%)	10 (22%)	8 (18%)	8 (12%)	
Baseline Erythema:						0.6
No	120 (58%)	30 (64%)	26 (57%)	28 (62%)	36 (52%)	
Yes	87 (42%)	17 (36%)	20 (43%)	17 (38%)	33 (48%)	
Baseline Dryness:						0.5
No	132 (64%)	33 (70%)	27 (59%)	31 (69%)	41 (59%)	
Yes	75 (36%)	14 (30%)	19 (41%)	14 (31%)	28 (41%)	
Baseline Burning:						0.05
No	201 (97%)	43 (91%)	46 (100%)	45 (100%)	67 (97%)	
Yes	6 (3%)	4 (9%)	0 (0%)	0 (0%)	2 (3%)	
Baseline Total Lesion (Mean ± Std)	15 ± 10	15 ± 8	16 ± 10	15 ± 8	16 ± 12	0.9
Investigators:						
101	23 (11%)	5 (11%)	4 (9%)	9 (13%)	8 (12%)	
102	36 (17%)	8 (17%)	8 (17%)	8 (18%)	12 (17%)	
103	18 (9%)	4 (9%)	4 (9%)	4 (9%)	6 (9%)	
104	18 (9%)	4 (9%)	4 (9%)	4 (9%)	6 (9%)	
105	25 (12%)	6 (13%)	6 (13%)	6 (13%)	7 (10%)	
106	15 (7%)	4 (9%)	4 (9%)	2 (4%)	5 (7%)	
107	22 (11%)	6 (13%)	4 (9%)	5 (11%)	7 (10%)	
108	34 (16%)	7 (15%)	8 (17%)	7 (16%)	12 (17%)	
109	16 (8%)	3 (6%)	4 (9%)	3 (7%)	6 (9%)	

As shown in Table II, no statistically significant differences were found among the four treatment arms in regards to the demographics and baseline characteristics of the subjects ($p \geq 0.05$).

Clinical Efficacy Analysis & Results:

The primary efficacy endpoint is the proportion of subjects with 100% clearance of their AK, 4 weeks after their treatment termination, in the ITT population. According to the reviewing medical officer, subjects who were dropped out of the study for any reason or had protocol violations were considered failure. As a result one subject in the two-week arm was set to failure, in this review. A total of 207 subjects were included in these analyses.

Table III: FDA's Intent-To-Treat (ITT) Population Proportion of Subjects With 100% Clearance, Study 9721

	Cure Rate	P-Values*			
		One-Week	Two-Week	Four-Week	Vehicle
One-Week (n=47)	7 (15%)		0.03	0.001	0.001
Two-Week (n=46)	16 (35%)			0.02	0.001
Four-Week (n=45)	26 (58%)				0.001
Vehicle (n=69)	0 (0%)				

*P-values based on the CMH test, controlling for Center.

As seen in Table III, highly significant results (p=0.001) were observed when ——Cream was compared to the Vehicle arm relative to cure rate at the end of treatment period. None of the subjects who were treated with Vehicle were 100% cleared. As it was mentioned before in this review, Holm procedure was applied for adjustment for the multiplicity of comparisons among the active treatment arms vs. Vehicle. If the smallest p-value is $\leq$0.017, then the second smallest p-value will be compared to the alpha level of 0.025 (0.05/2), and the third p-value will be compared to 0.05 (0.05/1). As it is seen in the above table, all the p-values for comparing active treatment arms against the vehicle are smaller than 0.017. Therefore, all the different dosage regimens are statistically significantly superior to the vehicle arm (p=0.001). In addition, a clear dose-response was observed in this study, indicating the superiority of the Four-Week regimen to one and two week regimens.

Table IV lists the sponsor's results for the same endpoint.

Table IV: Sponsor's (ITT) Population Proportion of Subjects With 100% Clearance, Study 9721

	Cure Rate	P-Values*			
		One-Week	Two-Week	Four-Week	Vehicle
One-Week (n=47)	7 (15%)		0.014	0.001	0.001
Two-Week (n=46)	17 (37%)+			0.029	0.001
Four-Week (n=45)	26 (58%)				0.001
Vehicle (n=69)	0 (0%)				

Source: Study Report DL6025-0721, Table 14
* P-values based on generalized linear model
+The discrepancy between the FDA's data and the Sponsor data is due to one subject with protocol violation.

The secondary endpoint parameter is the rate of subjects with 75% clearance of their AK.

Table V: FDA's Intent-To-Treat (ITT) Population Proportion of Subjects With at Least 75% Clearance, Study 9721

	Cure Rate	P-Values*			
		One-Week	Two-Week	Four-Week	Vehicle
One-Week (n=47)	18 (38%)		0.001	0.001	0.001
Two-Week (n=46)	33 (72%)			0.5	0.001
Four-Week (n=45)	35 (78%)				0.001
Vehicle (n=69)	4 (6%)				

*P-values based on the CMH test, controlling for Center.

As it is observed in Table V, highly statistically significant results were observed when the three treatment regimens were compared to Vehicle, and also when One-Week treatment was compared to Two-Week and Four-Week treatment arms (p=0.001). However, no statistically significant result was achieved when Two-Week treatment was compared to Four-Week (p=0.5).

In addition to per-person analysis, a per-lesion analysis was conducted to show the percent change of the total number of lesions from baseline. The results of these analyses are shown in Table VI.

Table VI: FDA's Intent-To-Treat (ITT) Population Percent Change from Baseline, Study 9721

	Mean ± Std %	P-Values*			
		One-Week	Two-Week	Four-Week	Vehicle
One-Week	52 ± 40		0.001	0.001	0.001
Two-Week	78 ± 32			0.6	0.001
Four-Week	84 ± 28				0.001
Vehicle	19 ± 31				

*P-values based on ANOVA test

Highly statistically significant results were observed when the three treatment regimens were compared to vehicle, and also when One-Week treatment was compared to Two-Week and Four-Week treatment arms (p=0.001). However, no statistically significant result was achieved when Two-Week treatment was compared to Four-Week (p≥0.6).

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Study DL6025-9722:

Demographics:

A total of 177 subjects from nine centers were enrolled into this study. Centers 2619, 2985 and 4146 had only 3, 9 and 7 subjects respectively. For the purpose of the analyses, we combined these centers.

A total of seven subjects did not complete the study. One subject (3%) in the one-week group, one subject (3%) in the four-week arm and one patient (2%) in the vehicle arm left the study voluntarily. In addition, one subject (2%) in the two-week arm and 2 subjects (5%) in the four-week arm did not complete the study because of adverse events, and one patient (3%) in the four-week arm had dropped out of the study for non-compliance. In this review, subjects who were dropped out of the study for any reason or had protocol violations were considered failure.

Table VII summarizes the demographics of all randomized subjects.

Table VII: Demographics & Baseline Characteristics
All Randomized Subjects, Study 9722

	Whole Population (N=177)	One-Week (n=38)	Two-Week (n=41)	Four-Week (n=40)	Vehicle (n=58)	P-Valu[redacted]
Gender:						0.05
Female	25 (14%)	6 (16%)	6 (15%)	10 (25%)	3 (5%)	
Male	152 (86%)	32 (84%)	35 (85%)	30 (75%)	55 (95%)	
Race:						
Caucasian	177 (100%)	38 (100%)	41 (100%)	40 (100%)	58 (100%)	
Age (Mean ± Std)	63 ± 11	63 ± 11	63 ± 11	63 ± 11	64 ± 11	>0.9
Skin Type:						0.5
1	69 (39%)	13 (34%)	14 (34%)	18 (45%)	24 (41%)	
2	81 (46%)	16 (42%)	19 (46%)	17 (43%)	29 (50%)	
3	27 (15%)	9 (24%)	8 (20%)	5 (13%)	5 (9%)	
Baseline Overall Severity:						0.03
Mild	26 (15%)	8 (21%)	6 (15%)	9 (23%)	3 (5%)	
Moderate	127 (72%)	22 (58%)	32 (78%)	29 (73%)	44 (76%)	
Severe	24 (14%)	8 (21%)	3 (7%)	2 (5%)	11 (19%)	
Baseline Erythema:						0.9
No	47 (27%)	10 (26%)	12 (29%)	9 (22.5%)	16 (28%)	
Yes	130 (73%)	28 (74%)	29 (71%)	31 (77.5%)	42 (72%)	
Baseline Dryness:						>0.9
No	[redacted] (42%)	17 (45%)	16 (39%)	17 (42.5%)	25 (43%)	
Yes	[redacted] (58%)	21 (55%)	25 (61%)	23 (57.5%)	33 (57%)	
Baseline Burning:						0.5
No	[redacted] (89%)	32 (84%)	36 (88%)	38 (95%)	52 (90%)	
Yes	[redacted] (11%)	6 (16%)	5 (12%)	2 (5%)	6 (10%)	
Baseline Total Lesion (Mean ± Std)	15 ± 10	13 ± 7	15 ± 12	14 ± 8	16 ± 11	0.3
Investigators (small centers were pooled):						
1	39 (22%)	9 (24%)	8 (20%)	9 (23%)	13 (22%)	
2	19 (11%)	2 (5%)	5 (12%)	5 (13%)	7 (12%)	
4	31 (18%)	7 (18%)	8 (20%)	7 (18%)	9 (16%)	
5	25 (14%)	6 (16%)	6 (15%)	5 (13%)	8 (14%)	
6	18 (10%)	4 (11%)	4 (10%)	4 (10%)	6 (10%)	
7	18 (10%)	4 (11%)	4 (10%)	4 (10%)	6 (10%)	
9	27 (15%)	6 (16%)	4 (10%)	6 (15%)	9 (16%)	

As shown in Table VII, no statistically significant differences were found among the four treatment arms in regards to the demographics and baseline characteristics of the subjects ($p \geq 0.05$). However, gender showed a borderline significance ($p=0.05$) and baseline overall severity showed a statistically significant difference ($p=0.03$), indicating the more severe subjects in the vehicle group. However, it should be noted that we are having multiple testing and for this, one might adjust for multiplicity.

Clinical Efficacy Analysis & Results:

The primary efficacy endpoint is the proportion of subjects with 100% clearance of their AK, 4 weeks after their treatment termination, in the ITT population. According to the reviewing medical officer, all the subjects who had not finished the study or had protocol violations or had a baseline value of total lesions less than 5 (one subject) were set to failure in this review. One subject in the One-Week group, one subject in the Four-Week arm and one patient in the vehicle arm left the study voluntarily. In addition, one subject in the Two-Week arm and two subjects in the Four-Week arm did not complete the study because of adverse events, and one patient in the four-week arm had dropped out of the study for non-compliance. As a result, the number of successes in the FDA table will be different from the sponsor's numbers.

A total of 177 subjects were included in these analyses.

Table VIII: FDA Intent-To-Treat (ITT) Population
Proportion of Subjects With 100% Clearance, Study 9722

	Cure Rate	P-Values*			
		One-Week	Two-Week	Four-Week	Vehicle
One-Week (n=38)	10 (26%)		0.2	0.3	0.001
Two-Week (n=41)	6 (15%)			0.02	0.05
Four-Week (n=40)	15 (38%)				0.001
Vehicle (n=58)	2 (3%)				

*P-values based on the CMH test, adjusting for Center.

As seen in Table VIII, statistically significant results ($p \leq 0.05$) were observed when ——— Cream arms were compared to the vehicle arm relative to cure rate at the end of treatment period. As it was mentioned before in this review, Holm procedure was applied for adjustment for the multiplicity of comparisons among the active treatment arms vs. Vehicle. If the smallest p-value is ≤ 0.017, then the second smallest p-value will be compared to the alpha level of 0.025 (0.05/2), and the third p-value will be compared to 0.05 (0.05/1). As it is seen in the above table, when One and Four-Week arms was compared to the Vehicle arm, both the p-values were smaller than 0.017. In addition, the third p-value is less than 0.05. Therefore, all the different dosage regimens are statistically significantly superior to the Vehicle arm. However, when the active treatment arms were compared against each other, the Four-Week

regimen was only superior to the Two-Week (p=0.02). Therefore, no clear dose-response trend was observed in this study.

Controlling for race, gender, skin type, any previous treatment, baseline overall severity did not change these results.

Table IX presents sponsor's results.

Table IX: Sponsor's (ITT) Population
Proportion of Subjects With 100% Clearance, Study 9722

	Cure Rate	P-Values*			
		One-Week	Two-Week	Four-Week	Vehicle
One-Week (n=38)	10 (26%)		0.418	0.055	0.001
Two-Week (n=41)	8 (19.5%)+			0.005	0.009
Four-Week (n=40)	19 (47.5%)+				0.001
Vehicle (n=58)	2 (3%)				

Source: Study Report DL6025-0722, Table 14
* P-values based on generalized linear model
+The discrepancy between the FDA's data and the Sponsor data is due to the subjects with protocol violations.

The secondary endpoint parameter is the rate of subjects with 75% clearance of their AK.

Table X: FDA's Intent-To-Treat (ITT) Population
Proportion of Subjects With at Least 75% Clearance, Study 9722

	Cure Rate	P-Values*			
		One-Week	Two-Week	Four-Week	Vehicle
One-Week (n=38)	18 (47%)		0.2	0.2	0.001
Two-Week (n=41)	26 (63%)			0.9	0.001
Four-Week (n=40)	25 (63%)				0.001
Vehicle (n=58)	6 (10%)				

* P-values based on the CMH adjusting for center

Highly statistically significant results were observed when the active treatment arms were compared to the Vehicle arm (p=0.001). However, no statistically significant result was achieved when the active treatment arms were compared with each other ($p \geq 0.2$).

In addition to per-person analysis, a per-lesion analysis was conducted to show the percent change of the total number of lesions from baseline. The results of these analyses are shown in Table XI.

Table XI: FDA's Intent-To-Treat (ITT) Population
Percent Change from Baseline, Study 9722

	Mean ± Std %	P-Value*			
		One-Week	Two-Week	Four-Week	Vehicle
One-Week	67 ± 32		0.9	0.5	0.001
Two-Week	68 ± 34			0.4	0.001
Four-Week	71 ± 37				0.001
Vehicle	2 ± 34				

*P-values based on ANOVA test

Highly statistically significant results were observed when the active treatment arms were compared to the Vehicle arm (p=0.001). However, no statistically significant result was achieved when the active treatment arms were compared with each other (p≥0.2).

Appendix "A" is a graphical representation for the efficacy results (Proportion of subjects with 100% Clearance, Proportion of subjects with at least 75% clearance and the Percent reduction in lesion count from baseline) for study 9721 and 9722 side by side.

Safety Analysis:

To evaluate safety, the two pivotal studies were pooled. The safety data is reported on 380 subjects. Table XII summarizes the results of signs and symptoms at the end of the treatment for the whole population. These results should be interpreted with caution, since the clinical trials were not designed for testing safety.

Table XII: Signs & Symptoms
Whole Population, Both Studies Combined

	One-Week (n=83)	Two-Week (n=87)	Four-Week (n=84)	Vehicle (n=126)	P-Values		
					1 vs. 2	1 vs. 4	2 vs. 4
Burning:					0.1	0.5	0.3
Absent	35 (42%)	26 (30%)	31 (37%)	109 (87%)			
Present	48 (58%)	61 (70%)	53 (63%)	17 (13%)			
Dryness:					0.05	0.001	0.02
Absent	72 (87%)	65 (75%)	48 (57%)	123 (98%)			
Present	11 (13%)	22 (25%)	36 (43%)	3 (2%)			
Edema:					0.4	0.04	0.2
Absent	10 (12%)	7 (8%)	3 (4%)	66 (52%)			
Present	73 (88%)	80 (92%)	81 (96%)	60 (48%)			
Erosion:					0.3	0.03	0.2
Absent	60 (72%)	57 (66%)	47 (56%)	124 (98%)			
Present	23 (28%)	30 (34%)	37 (44%)	2 (2%)			
Erythema:					0.004	0.003	0.9
Absent	28 (34%)	13 (15%)	12 (14%)	84 (67%)			
Present	55 (66%)	74 (85%)	72 (86%)	42 (33%)			
Overall Severity:					0.02	0.001	0.002
Absent	18 (22%)	25 (29%)	45 (54%)	2 (2%)			
Mild	48 (59%)	56 (66%)	31 (37%)	47 (37%)			
Moderate	13 (16%)	4 (5%)	5 (6%)	62 (49%)			
Sever	3 (4%)	0 (0%)	2 (2%)	15 (12%)			

As seen in Table XII, at the end of treatment period, statistically significant results were observed in regards to dryness and overall severity, indicating a rise in the severity of these signs and symptoms as the usage was increased. The same pattern was observed in edema, erosion and erythema. However, no statistically significant results ($p \geq 0.1$) were observed when different durations of —— Cream were compared to each other, relative to the burning.

Subset Analysis:

The two data sets were merged and subset analysis was done based on gender, age category (60 and younger and older than 60), skin type, baseline overall severity and any previous treatment. The purpose of these analyses was, solely, to demonstrate the trend among different treatment arms.

A total of 82 subjects had 100 clearance in both studies combined.

Since the majority (83%) of the population was male and more than 90% were white, no subset analysis was performed on these two sub-populations.

Table XIII shows the proportion of subjects who were 100 cleared by age category (60 and younger and older than 60), skin type, baseline overall severity and any previous treatment.

Table XIII: Sub-Group Analyses
Proportion of Subjects With 100% Clearance
Both Studies Combined

(n = number of Cured Subjects)	One-Week (n=17)	Two-Week (n=22)	Four-Week (n=41)	Vehicle (n=2)
Age:				
60 & Younger (n=35)	5 (29%)	12 (55%)	18 (44%)	0 (0%)
Older Than 60 (n=47)	12 (71%)	10 (45%)	23 (56%)	2 (2%)
Skin Type:				
1 (n=26)	5 (29%)	6 (27%)	15 (37%)	0 (0%)
2 (n=46)	11 (65%)	14 (64%)	19 (46%)	2 (100%)
3 (n=10)	1 (6%)	2 (9%)	7 (17%)	0 (0%)
Baseline Overall Severity:				
1 (n=24)	4 (24%)	8 (36%)	12 (29%)	0 (0%)
2 (n=47)	10 (59%)	10 (45%)	25 (61%)	2 (2%)
3 (n=11)	3 (18%)	4 (18%)	4 (10%)	0 (0%)
Previous AK Treatment:				
No (n=33)	8 (47%)	8 (36%)	16 (39%)	1 (50%)
Yes (n=49)	9 (53%)	14 (64%)	25 (61%)	1 (50%)

As it can been seen the subjects who are older than 60 years old had a better efficacy profile that the younger group in the One-Week arm. Also, higher cure rates were observed in the subjects in skin type 2 and baseline overall severity score of 2 in all the different regimen arms. Moreover, subjects with previous AK treatment had better results in all three active regimens.

III. CONCLUSIONS:

The results of the analyses of efficacy of Study DL6025-9721, given in Table III, demonstrate that all three regimens (One-Week, Two-Week and Four-Week) of—— Cream Topical Cream, 0.5% were statistically significantly better than Vehicle in the treatment of Actinic Keratoses of the face and anterior scalp ($p=0.001$). In addition, a clear dose-response trend was observed among the different treatment arms. The Four-Week treatment arm showed a better efficacy to both One-Week ($p=0.001$) and Two-Week ($p=0.02$) treatment, and Two-Week demonstrated better efficacy results to One-Week of treatment ($p=0.03$).

The results of the analyses of efficacy of Study DL6025-9722, given in Table VIII, demonstrate that all three regimens (One-Week, Two-Week and Four-Week) of —— Cream Topical Solution, 0.5% were statistically significantly better than Vehicle in the treatment of Actinic Keratoses of the face and anterior scalp ($p\leq 0.05$). However, the results of this study did not show a linear dose response of the active arms among each other.

For adverse events, no statistically significant results ($p\geq 0.1$) were observed when different durations of —— Cream were compared to each other, relative to the burning. However, in regards to dryness and overall severity, statistically significant results were observed, indicating a rise in the severity of these signs and symptoms as the usage was increased. The same pattern was observed in edema, erosion and erythema. It should be noted, however, that the studies were not designed for safety comparisons, and therefore the comparison results should be interpreted with caution.

The subset analyses relative to gender and age category (60 & younger, older than 60), skin type, baseline overall severity and previous AK therapy indicated that the subjects who were older than 60 years old had a better efficacy profile that the younger group in the One-Week arm. Also, higher cure rates were observed in the subjects in skin type 2 and baseline overall severity score of 2 in all the different regimen arms. Moreover, subjects with previous AK treatment had better results in all three active regimens.

Study DL6025-9721 showed a clear dose-response trend implying the superiority of the Four-Week to One and Two-Week regimens. However, study DL6025-9722 does not provide statistical evidence to support the superiority of Four-Week to either one of the other arms. In addition, no clear dose-response trend was observed in this study. Nevertheless, the studies DL6025-9721 and DL6025-9722 indicate the superiority of One-Week, Two-Week and Four-Week regimens to the Vehicle. Thus, the sponsor's claim of efficacy and safety of —— Cream Topical Cream, 0.5%% vs. vehicle in both of the pivotal studies for the treatment of AK of face and interior scalp is supported.

[/S/] 8/14/00
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HFD-725/Dr. Alosh
HFD-725/Dr. Huque
Chron.
This review contains 14 pages plus 3 pages of Appendices.
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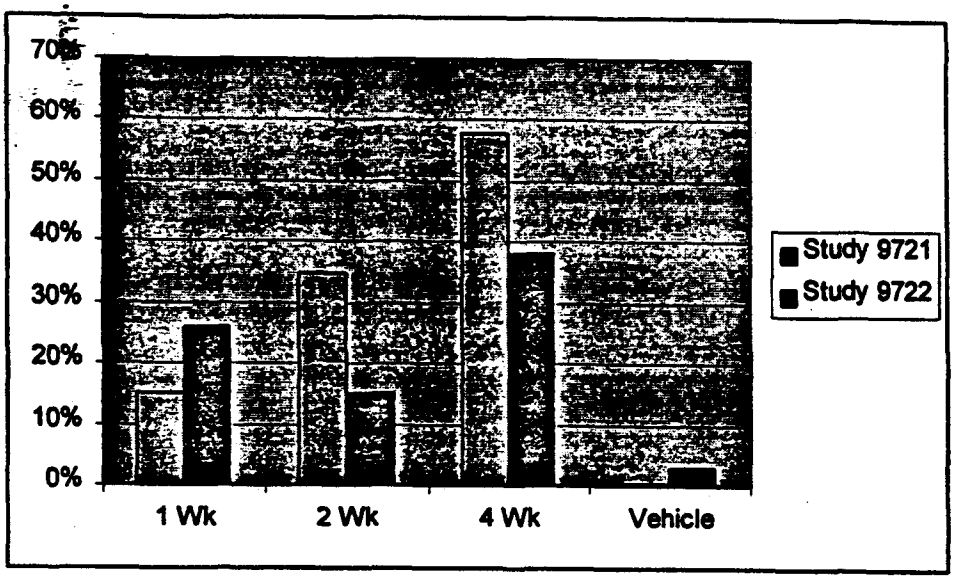
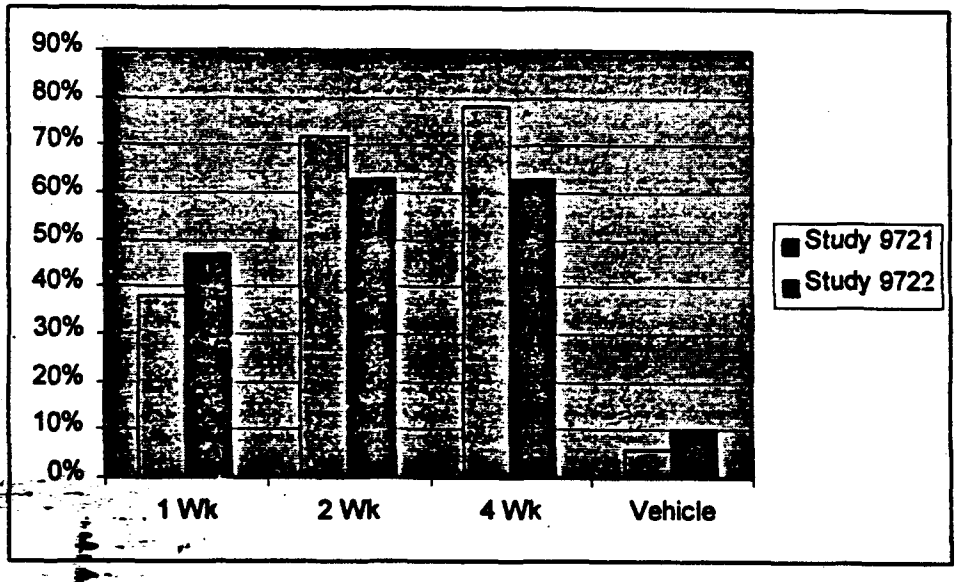
Appendix A:
Graphical Representation of Efficacy for Study 9721 and 9722

A.1. Proportion of Subjects with 100% Clearance



A.2. Proportion of Subject with at Least 75% Clearance



A.3. Percent Reduction in Lesion Count from Baseline