Table 19 (Sponsor's Table 4, Vol. 20, pg. 8-4-256): Patient Disposition

Patient Disposition	Active One Week		Active Two Week		Active Four Week		Vehicle		All Patients	
	N	(%)	N	(%)	n	(%)	n	(%)	n	(%)
Total Randomized	38	(100)	41	(100)	40	(100)	58	(100)	177	(100)
Completed Study	37	(97.4)	40	(97.6)	36	(90.0)	57	(98.3)	170	(96.0)
Discontinued Study	1	(2.6)	1	(2.4)	4	(10.0)	1	(1.7)	7	(4.0)
Adverse Event	0		1	(2.4)	2	(5.0)	0		3	(1.7)
With End of Study Efficacy	0		1	(2.4)	2	(5.0)	0		3	(1.7)
Voluntarily left study	1	(2.6)	0		1	(2.5)	1	(1.7)	3	(1.7)
With End of Study Efficacy	0		0		0		0		0	
Protocol deviations	0		0		1	(2.5)	0		1	(0.6)
With End of Study Efficacy	0		0		0		0		0	

Abstracted from Appendix II.F.1.1.2

Table 20 (Sponsor's Table 5, Vol. 20, pg. 8-4-257): Protocol Deviations

Deviation	Number of Patients	Patient Numbers
Use of systemic or topical steroids	1	187
Treatment for actinic keratosis within one month previous to the start of study	21	94, 148, 79, 175, 119, 95, 184, 202, 193, 5, 77, 231, 172, 188, 78, 66, 122, 151, 9, 80, 82
Fewer than five actinic keratosis lesions at baseline	1	62
Use of proscribed medication during the study	7	131, 28, 186, 188, 187, 1, 151
Discontinuation of the study medication except due to facial irritation adverse events	1	137 (used medication for only one day)
Use of the study medication for three or more days beyond the assigned interval of the random treatment assignment	2	104, 134
Less than 25 days of follow-up	6	63, 130, 58, 169, 201, 88
Greater than 35 days of post-treatment follow-up	4	199, 126, 150, 158
Missing or incomplete final post-treatment efficacy evaluations	5	63, 131(missing only overall AK severity), 58, 88, 169.

Abstracted from Appendix IV.C.

Reviewer's comments: *As in Study 9721, cryosurgery was not specifically listed as an exclusion criterion. Patient 94 listed liquid nitrogen applied to arms and hands only. With the exception of Patient 94, it is unclear why these patients were permitted to enter the study unless adjunctive therapy is to be considered. These protocol violators were included in the ITT population as failures.*

Table 21 (Sponsor's Table 11, Vol. 20, pg. 8-4-262): Summary of Baseline Actinic Lesion Counts (Study 9722)

	Active One Week N=38	Active Two Week N=41	Active Four Week N=40	Vehicle N=58	All Patients N=177
Total Count					
Mean[a] (± Std)	12.8 (±6.7)	15.3 (±11.8)	14.1 (±8.2)	16.4 (±11.1)	14.8(±9.9)
Median	12	12	12	13	12
IQR[b]					
Range					

Refer to Section 12, [a] p=0.271 for treatment group contrast. [b]IQR = inter-quartile range

Reviewer's comments: *According to the FDA and Sponsor's assessment, mean contrasts showed no statistically significant difference among treatment groups for regional or total counts of actinic keratosis lesions.*

8.2.21.4.2 Efficacy Results

8.2.2.1.4.2.1 Clinical

Pooled Study Sites

Three study sites (Jones, Ling, and Webster) had qualitatively less than the number of patients at each other study site (ranging from 18 to 39 patients). The site classification for each statistical model pooled data from the Jones/Ling/Webster sites.

As in the previous Phase 3 Study, the primary efficacy endpoint is the proportion of patients with 100% clearance of actinic keratosis, 4 weeks after end of treatment for the ITT population. According to the FDA Statistical Review, Holm procedure was applied for adjustment for the multiplicity of comparisons among the active treatment arms vs. vehicle.

Table 22 (Extracted from FDA Statistical Review):
Proportion of Subjects with 100% Clearance (ITT Population)- 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-Value based on analysis of CMH, adjusting for Center

According to the FDA statistical analysis, statistically significant results ($p \leq 0.05$) were observed when active treatment arms were compared to Vehicle arm. All the One-Week, Two-Week, and Four-Week active treatment arms were statistically significantly superior to vehicle. Unlike the previous Phase 3 study, no clear dose-response trend was observed when active treatment arms were compared against each other. When the active treatment arms were compared against each other, the Four-Week treatment regimen was statistically significantly superior only to the Two-Week ($p=0.02$).

Table 23: Sponsor's ITT Population (Extracted from FDA Statistical Review):
Proportion of Subjects with 100% Clearance (ITT Population)- 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%)				

The discrepancy noted in Tables 22 & 23 between the number of patients in the ITT population with total clearance in the Active 2-Week population is due to protocol violations (i.e., use of cryotherapy within one month of study entry). As previously stated, the protocol violations were counted as failures; however, this did not change the efficacy outcome results.

Table 24 (Extracted from FDA Statistical Review):
Proportion of Subjects with 75% -100% Clearance (ITT Population)- 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%)				

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

A per-lesion analysis was conducted to show the percent change of the total number of lesions from baseline. Results follow in the table below.

Table 25 Extracted from the FDA Statistical Review):
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				

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

Treatment efficacy was compared between patients who completed the assigned treatment regimen and those who discontinued treatment prematurely to determine whether early discontinuation (generally due to facial irritation) predicted treatment efficacy. Two patients in the Active Two Week Group and thirteen patients in the Active Four Week Group discontinued treatment applications prematurely and still returned for a final efficacy evaluation. The efficacy comparisons between patients who completed the Active Two Week and Active Four Week assigned treatment regimen and those who discontinued treatment prematurely due to facial irritation are shown in Table 27 that follows. There was little

evidence, in this small sample, of clinically important differences in results between patients who did or who did not complete their assigned duration of treatment.

Table 26 (Sponsor's Table 12, Vol. 1.20, pg. 8-4-280): Actinic Keratosis Reductions and Total Clearance among Patients Who Did or Did Not Discontinue Study Medication Early

Efficacy Measure	Days of Treatment			
	Active Two Week		Active Four Week	
	< 12 days N= 2	≥ 13 days N= 39	< 25 days N= 13	≥ 26 days N=27
Median % AK Reductions	58.4	85.7	100	85.7
N (%) Patients with Total Clearance of AKs	0 (0)	8 (20.5)	8 (61.5)	11 (40.7)

Abstracted from Appendix II.E.2.6 and Appendix II.F.8. Cochran-Mantel-Haenszel p=0.369 for association between treatment discontinuation and total clearance. For analysis of log(AK/baseline) p>0.50 for effect of treatment discontinuation and p=0.097 for discontinuation by treatment interaction.

8.2.2.4.3 Safety

Safety was evaluated in all 177 patients randomized into the study. At least one adverse event was reported by more than 92% of patients in each of the active treatment groups and by 72.4% of patients in the Vehicle group. The most commonly reported adverse event was facial irritation (COSTART term = Application site reaction) which was reported by more than 92% of patients in each of the active treatment groups compared to 66% of patients in the Vehicle group. Twenty patients (11.3%) discontinued study medication due to a facial irritation adverse event.

Table 27 (Sponsor's Table 13, Vol. 1 20): Summary of Adverse Events

Patients	Active One Week N=38	Active Two Week N=41	Active Four Week N=40	Vehicle N=58
	n (%)	n (%)	N (%)	n (%)
At least one AE	36 (94.7)	38 (92.7)	39 (97.5)	42 (72.4)
Treatment-related AE[a]	36 (94.7)	38 (92.7)	39 (97.5)	36 (62.1)
Facial Irritation[b]	36 (94.7)	38 (92.7)	39 (97.5)	38 (65.5)
Discontinued Study Medication for AE	0	4 (9.8)	15 (37.5)	1 (1.7)
Discontinued from Study for AE	0	1 (2.4)	2 (5.0)	0

Abstracted from Appendix II.F.5.1.1 and II.F.5.1.2

[a] AE with possible, probable, or definite relationship to study medication, or facial irritation AE with remote, possible, probable, or definite relationship to study medication. [b] Facial irritation AEs were collected on a separate case report form and were assigned a COSTART code of "application site reaction". All facial irritation AEs are included in general AE summaries.

Discontinued Study Medication

Fifteen of the 20 patients who discontinued study medication due to an adverse event were in the Active Four Week treatment group.

Discontinued From Study

Three patients discontinued from the study due to an adverse event; one (2.4%) in the Active Two Week group and two (5.0%) in the Active Four Week group. All three patients discontinued the study due to a facial irritation adverse event. There were no serious adverse

events or deaths reported during the study. No post-treatment laboratory evaluations were performed in this study.

Table 28 (Sponsor's Table 14, Vol. 1.20, pg. 8-4-290): Summary of Facial Irritation (Application Site Reaction) Adverse Events (Study 9722)

Patients	Active Treatment Groups					Active Treatments vs. Vehicle			
	One Week N=38	Two Week N=41	Four Week N=40	All N=119	Vehicle N=58	One vs. Vehicle p=	Two vs. Vehicle p=	Four vs. Vehicle p=	All vs. Vehicle p=
	n %	n %	n %	n %	n %				
Had Irritation[a]									
At Baseline	31 (81.6)	33 (80.5)	31 (77.5)	85 (71.4)	45 (77.6)				
On Study	36 (94.7)	38 (92.7)	39 (97.5)	113 (95.0)	38 (65.5)	0.001	0.002	<0.001	<0.001
Maximum Severity[b]									
None	2 (5.3)	3 (7.3)	1 (2.5)	6 (5.0)	20 (34.5)	<0.001	<0.001	<0.001	<0.001
Mild	18 (47.4)	5 (12.2)	3 (7.5)	26 (21.9)	33 (56.9)				
Moderate	16 (42.1)	21 (51.2)	17 (42.5)	54 (45.4)	3 (5.2)				
Severe	2 (5.3)	12 (29.3)	19 (47.5)	33 (27.7)	2 (3.5)				
Relation to Study Drug[b]									
Had No AE	2 (5.3)	3 (7.3)	1 (2.5)	6 (5.0)	20 (34.5)	<0.001	<0.001	<0.001	<0.001
None	0	0	0	0	2 (3.4)				
Remote	0	0	0	0	1 (1.7)				
Possible	2 (5.3)	0	0	2 (1.7)	6 (10.3)				
Probable	6 (15.8)	5 (12.2)	5 (12.5)	16 (13.4)	13 (22.4)				
Definite	28 (73.7)	33 (80.5)	34 (85.0)	95 (79.8)	16 (27.6)				
Action Taken[a]									
No Action Taken	38 (100)	36 (87.8)	22 (55.0)	96 (80.7)	57 (98.3)	>0.50	0.079	<0.001	<0.001
Drug Discontinued	0	4 (9.8)	15 (37.5)	19 (16.0)	1 (1.7)	>0.50	0.157	<0.001	0.004
Drug dose changed	0	0	4 (10.0)	4 (3.4)	0	>0.50	0.157	0.025	0.305
Other Action	0	3 (7.3)	3 (7.5)	6 (5.0)	0	>0.50	0.068	0.065	0.179
Irritation Continues[a,c]	2 (5.3)	5 (12.2)	4 (10.0)	11 (9.2)	4 (6.9)	>0.5	>0.5	>0.5	>0.5

Abstracted from Appendix II.E.1.3.1, Appendix II.F.3.1, and Appendix II.F.5.2.
[a] p value - Fisher's Exact Test, 2-Tail; [b] p value - Cochran-Mantel-Haenszel, General Association
[c] If no cease date for the latest reported facial irritation symptoms was given then irritation was considered to be continuing at the end of study.

During the study, the proportion of patients with facial irritation ranged from 92.7 to 97.5% in the active treatment groups. The proportion of patients with facial irritation in the Vehicle group decreased from 77.6% at baseline to 65.5% on-study.

Facial irritation was considered to be definitely related to study drug treatment in 79.8% of patients in the combined active treatment groups compared to 27.6% of patients in the Vehicle group ($p<0.001$). For most patients with facial irritation in the Active One Week and Active Two Week groups no action was taken, while in the Active Four Week group 37.5% of patients discontinued study medication. The difference from Vehicle in proportions of patients with no action taken or test drug discontinued was statistically significant for the Active Four Week group and the combined active treatment groups.

At final post-treatment evaluations, the proportions of patients in the active treatment groups with an unresolved facial irritation adverse event ranged from 5.3% of patients in the Active One Week treatment to 12.2% of patients in the Active Two Week treatment. These rates

were not significantly different from that of the Vehicle group in which 6.9% of patients had unresolved facial irritation adverse events at the final post-treatment evaluation.

A summary of the number and percentage of patients in each treatment group completing a specific number of treatment application days follows.

Table 29 (Sponsor's Table 15, Vol 1.20, pg. 8-4-284): Extent of Exposure

Number of Treatment Days	Active One Week N=38	Active Two Week N=41	Active Four Week N=40	Vehicle N=58	All Patients N=177
	n %	n %	n %	n %	n %
1-6 days	6 (15.8)	0	2 (5.0)	3 (5.2)	11 (6.2)
7 days	20 (52.6)	1 (2.4)	0	12 (20.7)	33 (18.6)
8-13 days	11 (28.9)	3 (7.3)	2 (5.0)	11 (19.0)	27 (15.3)
14 days	1 (2.6)	28 (68.3)	3 (7.5)	7 (12.1)	39 (22.0)
15-20 days	0	9 (22.0)	2 (5.0)	7 (12.1)	18 (10.2)
21 days	0	0	2 (5.0)	0	2 (1.1)
22-27 days	0	0	5 (12.5)	4 (6.9)	9 (5.1)
28 days	0	0	14 (35.0%)	9 (15.5)	23 (13.0)
29-31 days	0	0	10 (25.0)	5 (8.6)	15 (8.5)

Abstracted from Appendix Table II.F.1.3

Reviewer's comments: *As noted in study 9721,some patients applied the study drug longer than specified in the protocol. These protocol violators in the active treatment arms were perhaps continued on therapy due to lack of efficacy noted at the end of treatment. There may have been a sub-set of patients with thicker lesions prompting continued therapy; however, the thickness of lesions was not captured on the CRF. Two patients (Pt. #6 &#8) in the One-Week treatment arm achieved 100 % clearance (both at 9 days).*

[redacted]

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Table 30 (Sponsor's Table 24, Vol. 1.20. pg. 8-4-288): Summary of Study Drug-Related Adverse Events by Body System, COSTART Term, and Treatment Group (Study 9722)

Patients	Active One Week N=38	Active Two Week N=41	Active Four Week N=40	All Active N=119	Vehicle N=58
	n (%)	n (%)	n (%)	n (%)	n (%)
AT LEAST ONE AE	36 (94.7)	38 (92.7)	39 (97.5)	113 (95.0)	42 (72.4)
Study Drug-Related AE	36 (94.7)	38 (92.7)	39 (97.5)	113 (95.0)	36 (62.1)
BODY AS A WHOLE	0	1 (2.4)	3 (7.5)	4 (3.4)	0
Eyes Swollen	0	1 (2.4)	1 (2.5)	2 (1.7)	0
Fever	0	0	1 (2.5)	1 (0.8)	0
Headache	0	0	1 (2.5)	1 (0.8)	0
DIGESTIVE	0	0	1 (2.5)	1 (0.8)	0
Diarrhea	0	0	1 (2.5)	1 (0.8)	0
SKIN & APPENDAGES	36 (94.7)	38 (92.7)	39 (97.5)	113 (95.0)	36 (62.1)
Application Site Reaction	36 (94.7)	38 (92.7)	39 (97.5)	113 (95.0)	36 (62.1)
Blisters	0	1 (2.4)	0	1 (0.8)	0
Burning Skin	0	0	1 (2.5)	1 (0.8)	0
Herpes Simplex	0	0	1 (2.5)	1 (0.8)	1 (1.7)
Irritation Skin	0	0	1 (2.5)	1 (0.8)	0
Rash Impetiginous	0	0	1 (2.5)	1 (0.8)	0
SPECIAL SENSES	0	1 (2.4)	1 (2.5)	2 (1.7)	1 (1.7)
Eye Irritation	0	0	1 (2.5)	1 (0.8)	1 (1.7)
Taste Perversion of	0	1 (2.4)	0	1 (0.8)	0

Abstracted from Appendix II.F.5.1.1 and II.F.5.1.3.

Reviewer's comments: *The incidence of eye irritation is less in this study than in Study 9721. The reason for the difference is unknown.*

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Table 31 (Sponsor's Table 22, Vol.1.20, pg. 8-4-285): Summary of Adverse Events by Body System, COSTART Term, and Treatment Group

Body System AE COSTART Term	Active One Week N=38	Active Two Week N=41	Active Four Week N=40	All Active N=119	Vehicle N=58
	n (%)	n (%)	n (%)	n (%)	n (%)
At Least One AE[a]	36 (94.7)	38 (92.7)	39 (97.5)	113 (95.0)	42 (72.4)
BODY AS A WHOLE	2 (5.3)	1 (2.4)	4 (10.0)	7 (5.9)	4 (6.9)
Eyes Swollen	0	1 (2.4)	1 (2.5)	2 (1.7)	0
Fever	0	0	1 (2.5)	1 (0.8)	1 (1.7)
Headache	1 (2.6)	0	1 (2.5)	2 (1.7)	0
Injury	1 (2.6)	0	0	1 (0.8)	1 (1.7)
Flu	0	0	1 (2.5)	1 (0.8)	0
Allergy	0	0	0	0	1 (1.7)
Infection Upper Respiratory	0	0	0	0	1 (1.7)
CARDIOVASCULAR	0	0	0	0	1 (1.7)
Hypertension	0	0	0	0	1 (1.7)
DIGESTIVE	0	0	3 (7.5)	3 (2.5)	1 (1.7)
Diarrhea	0	0	1 (2.5)	1 (0.8)	0
Nausea	0	0	1 (2.5)	1 (0.8)	0
Tooth Disorder	0	0	1 (2.5)	1 (0.8)	0
Vomiting	0	0	0	0	1 (1.7)
MUSCULOSKELETAL	0	0	0	0	1 (1.7)
Fracture Bone	0	0	0	0	1 (1.7)
NERVOUS	0	1 (2.4)	1 (2.5)	2 (1.7)	0
Anxiety	0	1 (2.4)	0	1 (0.8)	0
Spasm Muscle	0	0	1 (2.5)	1 (0.8)	0
RESPIRATORY	0	0	0	0	1 (1.7)
Bronchitis	0	0	0	0	1 (1.7)
SKIN & APPENDAGES[c]	36 (94.7)	38 (92.7)	39 (97.5)	113 (95.0)	39 (67.2)
Application Site Reaction	36 (94.7)	38 (92.7)	39 (97.5)	113 (95.0)	38 (65.5)
Herpes Simplex	0	0	1 (2.5)	1 (0.8)	1 (1.7)
Blisters	0	1 (2.4)	0	1 (0.8)	0
Burning Skin	0	0	1 (2.5)	1 (0.8)	0
Dermatitis Contact	0	1 (2.4)	0	1 (0.8)	0
Irritation Skin	0	0	1 (2.5)	1 (0.8)	0
Rash Impetiginous	0	0	1 (2.5)	1 (0.8)	0
Carcinoma Basosquamous	0	0	0	0	1 (1.7)
SPECIAL SENSES	1 (2.6)	1 (2.4)	1 (2.5)	3 (2.5)	2 (3.4)
Eye Irritation	0	0	1 (2.5)	1 (0.8)	2 (3.4)
Cataract	1 (2.6)	0	0	1 (0.8)	0
Taste Perversion Of	0	1 (2.4)	0	1 (0.8)	0
UROGENITAL	0	0	0	0	1 (1.7)
Bladder Infection	0	0	0	0	1 (1.7)

Abstracted from Appendix II.F.5.1.2.

[a] a patient with more than one AE is counted only once here and only once for each body system and COSTART term.

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8.2.2.5 Conclusions Regarding Efficacy Data and Safety

Results of statistical analysis of efficacy for Study DL6025-9722 demonstrates that [redacted] Cream 0.5% is statistically superior to Vehicle ($p \leq 0.04$) in treatment of actinic keratoses located on the face and anterior bald scalp for all three treatment arms (One-week, Two-week, and Four-Week). No statistically significant differences in superiority were found when active treatment arms are compared against each other ($p \geq 0.02$).

Erythema, dryness, and burning were the most common clinical signs and symptoms of facial irritation in each treatment group, including Vehicle. At least 50% of patients in the Active Four Week group also experienced edema, erosion, and pain at some time during the study. The incidence of erythema, dryness, burning, and pain in each of the active treatment groups was significantly greater than that in the Vehicle group. The incidence of dryness, erythema, edema, erosion, pain and burning increased with increasing duration of assigned treatment. The incidence of each type of clinical sign and symptom was significantly higher in Active Four Week treatment group compared to the Vehicle group and in the combined active treatment groups than in the Vehicle group.

No serious adverse event was considered related to study medication. Facial irritation was considered to be definitely related to study drug treatment in 79.8% of patients in the combined active treatment groups compared to 27.6% of patients in the Vehicle group ($p<0.001$). For most patients with facial irritation in the Active One Week and Active Two Week groups no action was taken, while in the Active Four Week group 37.5% of patients discontinued study medication. The difference from Vehicle in proportions of patients with no action taken or test drug discontinued was statistically significant for the Active Four Week group and the combined active treatment groups.

According to the Sponsor, facial irritation occurred within 4-5 days after initiating therapy in most patients and persisted with continuing treatment for all the active treatment regimens. Facial irritation typically resolved in 15-17 days after treatment cessation, irrespective of the duration of treatment. Patients in the Active Two and Four Week treatment groups experienced greater mean overall irritation than patients in the Active One Week group. Patients in the Active Four Week treatment group showed a plateau of facial irritation severity at approximately two weeks of treatment. For all treatment groups, irritation resolved to levels below baseline severity, within two weeks of treatment discontinuation.

Three patients discontinued from the study due to an adverse event; one (2.4%) in the Active Two Week group and two (5.0%) in the Active Four Week group. All three patients discontinued the study due to a facial irritation adverse event.

There were no serious adverse events as defined per protocol; however, adverse events listed for Patient # 186 is clinically significant. According to the Adverse Events Narratives (Vol. 1.20, pg. 8-4-326), Patient #186 (Dr. Menter's site), a 58 year old female in the Active Four Week treatment group, discontinued study treatment after 11 days of treatment due to severe facial irritation, consisting of edema, erythema, dryness, erosion, pain, burning, itching, crusting, and stinging. She also experienced mild diarrhea, low grade fever, and impetigo. She was treated by her physician for the facial irritation and infection. The last post-treatment follow-up evaluation was on Study day 43 at which time the patient still had mild

erythema. All adverse events had resolved when she was seen by her physician 6 months after her final study visit.

As in Study DL6025-97221, these efficacy and safety data do not include treatment of the ears and other sun exposed areas of the body. No deaths occurred during the study. No post-treatment laboratory evaluations were performed in this study.

8.2.3 Reviewer's Trial # 3 Sponsor's Protocol DL-6025-9518

(Study Dates: March 26, 1996 to August 5, 1996)

Reviewer's comments: *Protocol DL-6025-9518 is being reviewed primarily for safety. Post-study clinical laboratory assessments were conducted. Exposure to 5-FU .5% cream was greater (i.e., study drugs were applied twice daily).*

Title: "A Controlled, Randomized, Double-Blinded Study Comparing the Safety and Efficacy of 5-Fluorouracil ——— , and 0.5% Creams, Efudex® Cream 5%, and 5-Fluorouracil Vehicle Cream in the Treatment of Actinic Keratosis"

8.2.3.1 Objective Rationale

To investigate the clinical safety and efficacy of three experimental formulations of 5-FU (——— and 0.5%) in a dose response study, compared to a vehicle control and marketed 5-FU product (Efudex® Cream 5%), for the treatment of actinic keratosis.

8.2.3.2 Design

This is a controlled, double-blind, parallel-group, multi-center, dose response study designed to compare the efficacy and safety of three concentrations of 5-FU ——— and 0.5%) to a vehicle control and marketed 5-FU product (Efudex® Cream 5%), in the treatment of actinic keratosis.

The study consisted of two phases: 1) a treatment phase of four weeks with twice daily application of study drug, and 2) a four week follow-up phase. Treatment areas were the entire face and frontal bald scalp with actinic damage. At the initial visit medical history, physical examination performed, baseline routine laboratory blood and urine samples were obtained. Monitoring for any adverse effects of treatment was done throughout the study.

Primary safety parameters for the evaluation of facial irritation / treatment tolerance were the index (summed) scores of the physician irritation index and patient treatment tolerance ratings. Secondary safety evaluations were components of the irritation index and patient treatment tolerance items. Scores for the physician irritation index and patient treatment tolerance were available only for patients with clinical follow-up evaluations. Evaluations which followed the start of any treatment with corticosteroid, either systemic or to the face, were excluded from treatment group summaries of facial irritation / treatment tolerance.

The physician recorded erythema, dryness, edema, and erosion/ulceration on a scale of 0 to 3, with increments of 0.5. The physician irritation index was the sum of scores for erythema, dryness, edema, and erosion/ulceration.

Blood and urine samples for routine hematology, serum chemistry and urinalysis were obtained at the initial visit (Visit 1) and upon completion of the treatment phase (Visit 5, Day 29) or at early termination for those patients who discontinued from the study or had their treatment stopped.

The urine pregnancy test on females of childbearing potential was conducted at the study center at each visit and the results were interpreted before each visit was completed.

Disposition of Patients

There were 104 patients enrolled at three centers. Table 32 is a summary of the end of study status of all patients enrolled in the study. All of the patients who discontinued for adverse experience, except for Patient #11 of the Efudex treatment, returned for post-treatment follow-up evaluations.

Table 32 (Sponsor's Table 1.1, Vol. 23): Patient Disposition

	Treatment Group Summaries									
	5FU 0.5%		5FU —		5FU —		Efudex		vehicle	
End of Study Status	n	%	n	%	n	%	n	%	n	%
Patients Randomized	25		21		24		22		12	
Patient Completed	16	64.0	10	47.6	2	8.3	14	63.6	11	91.7
DISCONTINUED (reason)										
for Adverse Event	7	28.0	11	52.4	22	91.7	8	36.4		
for Lack of Efficacy									1	8.3
Lost to Follow-Up	1	4.0								
Did not wish to Continue	1	4.0								

Abstracted from Appendix II.F.1. Study completion listed in Appendix IV.A.1.1

Discontinuations

Discontinuations were as follows: 8 patients (32%) in the 0.5% 5-FU treatment, 11 patients (52%) in the — 5-FU treatment, 23 patients (96%) in the — 5-FU treatment, 8 patients (36%) in the Efudex treatment and no patient in the vehicle treatment group. These treatment discontinuation frequencies were significantly greater in each of the experimental 5-FU treatment groups compared to vehicle. The treatment discontinuation frequency of the — 5-FU treatment was significantly greater than that of the Efudex, 0.5% 5-FU, or — 5-FU treatment groups.

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Table 33 (Sponsor's Table 8.1.1) Adverse Experience Incidence Summary by Body System

Body System	COSTART Term	TREATMENT GROUP FREQUENCIES (%)									
		5FU 0.5%		5FU —		5FU —		Efudex		Vehicle	
Summary	All Patients	25	(100.0%)	21	(100.0%)	24	(100.0%)	22	(100.0%)	12	(100.0%)
	Incidence of AE	16	(64.0%)	17	(81.0%)	24	(100.0%)	20	(90.9%)	7	(58.3%)
	Occurrence of AE	35		42		63		37		12	
Body as a Whole		3	(12.0%)	2	(9.5%)	5	(20.8%)	2	(9.1%)	1	(8.3%)
	HEADACHE	2				4		1			
	INJURY ACCID			1						1	
	FLU SYND			1							
	INFECT					1					
	MALAISE			1							
	PAIN			1							
	PAIN BACK	1									
	PAIN CHEST							1			
Cardiovascular		1	(4.0%)					1	(4.5%)		
	CEREBROVASC ACCI							1			
	HYPERTENS	1									
Digestive		1	(4.0%)	1	(4.8%)	1	(4.2%)	1	(4.5%)		
	NAUSEA					1		1			
	RECTAL DIS			1							
	ULCER STOMACH	1									
Endocrine				2	(9.5%)						
	DIABETES MELL			2							
Hemic/Lymphatic				1	(4.8%)						
	THROMBOCYTOPENIA			1							
Metabol/Nutri DO		1	(4.0%)	1	(4.8%)						
	EDEMA PERIPH			1							
	HYPOKALEM	1									
Musculoskeletal				1	(4.8%)			1	(4.5%)	1	(8.3%)
	ARTHRALGIA			1							
	ARTHRITIS							1			
	MYALGIA									1	
Nervous						3	(12.5%)			1	(8.3%)
	INSOMNIA					3					
	DIZZINESS									1	
Respiratory		3	(12.0%)			5	(20.8%)	3	(13.6%)	4	(33.3%)
	RHINITIS	2				3				3	
	PHARYNGITIS					3		1		1	
	SINUSITIS							1		1	
	BRONCHITIS	1									
	COUGH INC	1									
	LARYNGITIS							1			
	LUNG DIS	1									
Skin & Appendages		16	(64.0%)	16	(76.2%)	23	(95.8%)	17	(77.3%)	2	(16.7%)
	APPLICAT SITE RE	8		12		17		14		1	
	SKIN DRY	7		9		9		7		1	
	RASH	6		2		7		2			
	PRURITUS			4		5		3		2	
	URTICARIA	1		1							
	CARCINOMA SKIN					1					
	HERPES SIMPLEX			1							
Special Senses		1	(4.0%)	3	(14.3%)	8	(33.3%)	2	(9.1%)		
	CONJUNCTIVITIS	1		3		8		2			
	DRY EYE					1		1			
	MYDRIASIS	1									

Listings in Appendices IV.A.5.1.1 and IV.A.5.1.2 (COSTART preferred terms)
Each patient counted only once in each row (except 'Occurrence of AE')

The summary by severity that follows, Table 34 (Sponsor's Table 8.3.1), includes a patient with thrombocytopenia (Patient #31 in the — 5-FU treatment group) diagnosed during the screening clinical laboratory evaluation. Severe adverse events reported by at least two patients in any treatment group were application site reactions in the — 5-FU, — , 5-FU, and Efudex treatment groups, dry skin in the — 5-FU, and Efudex treatment groups, and pruritus in the — 5-FU treatment group.

Table 34 (Sponsor's Table 8.3.1): Summary of Adverse Experience Incidence by Severity

Row Summary	TREATMENT GROUP FREQUENCIES (%)									
	5FU 0.5%		5FU		5FU		Efudex		Vehicle	
All Patients	25		21		24		22		12	
Incidence (Pt's Most Severe)										
Severe	2	(8.0%)	4	(19.0%)	10	(41.7%)	8	(36.4%)		
Moderate	13	(52.0%)	11	(52.4%)	12	(50.0%)	10	(45.5%)	3	(25.0%)
Mild	1	(4.0%)	2	(9.5%)	2	(8.3%)	2	(9.1%)	4	(33.3%)
Occurrence (All AE)										
Severe	2		8		28		13			
Moderate	25		33		48		31		6	
Mild	15		22		21		12		7	
Severe Adverse Events										
APPLICATION SITE REACTION			4	(19.0%)	10	(41.7%)	7	(31.8%)		
DRY SKIN					3	(12.5%)	1	(4.5%)		
PRURITUS					2	(8.3%)				
ARTERITIS							1	(4.5%)		
CEREBROVASCULAR ACCIDENT							1	(4.5%)		
CONJUNCTIVITIS					1	(4.2%)				
INSOMNIA					1	(4.2%)				
RASH	1	(4.0%)								
RHINITIS					1	(4.2%)				
URTICARIA	1	(4.0%)								
Moderate Severity										
DRY SKIN	6	(24.0%)	8	(38.1%)	6	(25.0%)	6	(27.3%)	1	(8.3%)
APPLICATION SITE REACTION	6	(24.0%)	7	(33.3%)	6	(25.0%)	5	(22.7%)	1	(8.3%)
RASH	3	(12.0%)	2	(9.5%)	5	(20.8%)	2	(9.1%)		
PRURITUS			3	(14.3%)	3	(12.5%)	3	(13.6%)	2	(16.7%)
CONJUNCTIVITIS			1	(4.8%)	4	(16.7%)	2	(9.1%)		
PHARYNGITIS					1	(4.2%)			1	(8.3%)
RHINITIS					2	(8.3%)				
SINUSITIS							1	(4.5%)	1	(8.3%)
BACK PAIN	1	(4.0%)								
BRONCHITIS	1	(4.0%)								
CHEST PAIN							1	(4.5%)		
COUGH INCREASED	1	(4.0%)								
DIABETES MELLITUS			1	(4.8%)						
DRY EYES							1	(4.5%)		
HEADACHE					1	(4.2%)				
INFECTION					1	(4.2%)				
LUNG DISORDER	1	(4.0%)								
MYDRIASIS	1	(4.0%)								
NAUSEA					1	(4.2%)				
PERIPHERAL EDEMA			1	(4.8%)						
SKIN CARCINOMA					1	(4.2%)				
STOMACH ULCER	1	(4.0%)								
THROMBOCYTOPENIA			1	(4.8%)						
Mild, to more than one Patient										
APPLICATION SITE REACTION	2	(8.0%)	1	(4.8%)	1	(4.2%)	2	(9.1%)		
CONJUNCTIVITIS	1	(4.0%)	2	(9.5%)	3	(12.5%)				
HEADACHE	2	(8.0%)			3	(12.5%)	1	(4.5%)		
RHINITIS	2	(8.0%)							3	(25.0%)
RASH	2	(8.0%)			2	(8.3%)				
PHARYNGITIS					2	(8.3%)	1	(4.5%)		
ACCIDENTAL INJURY			1	(4.8%)					1	(8.3%)
DRY SKIN	1	(4.0%)	1	(4.8%)						
INSOMNIA					2	(8.3%)				

Listings in Appendices IV.A.5.1.1 and IV.A.5.1.2 (COSTART preferred terms)
Each patient counted only once in each row, except for 'Occurrence (ALL AE)' rows

The most frequently reported adverse events considered definitely related to treatment and reported by at least two patients in any treatment group were application site reaction (skin irritation), dry skin, pruritus, conjunctivitis (eye irritation), rash (erythema) and dry eyes. From the list of adverse events affecting the skin, eyes, or respiratory system in Table 10.14,

the verbatim descriptions of two cases of rhinitis reported as definitely related to treatment were 'bilateral nasal labial irritation' by Patient #127 and 'nose discomfort' by Patient #140.

Each of the experimental 5-FU treatment groups had significantly greater incidences of treatment-related adverse events than did the vehicle treatment group. The — 5-FU treatment group had a significantly greater incidence of adverse events related to treatment than did the Efudex treatment or the 0.5% 5-FU treatment or the — 5-FU treatment. Treatment related adverse event incidences were not significantly different in comparisons between Efudex and the 0.5% 5-FU or — 5-FU treatments.

Other Serious Adverse Events
Patients with serious adverse events (Table 8.6) were Patient #153 in the — 5-FU treatment group, diagnosed on Study Day 11 with a squamous cell carcinoma on the forehead, and Patient #11 in the Efudex treatment group, hospitalized with a stroke on study Day 6.

Laboratory Data
All clinically significant laboratory safety results were reported as adverse events. These adverse events were:

- low potassium, at Day 18, to Patient #14 of the 0.5% 5-FU treatment group (the patient was lost to follow-up);
- diabetes mellitus (as reported in the NDA) at the screening (Day 0) evaluation and improved with medication (Glucophage) by Day 35, to patient #3 of the — 5-FU treatment group;
- thrombocytopenia (as reported in the NDA) at the screening (Day 0) evaluation and resolved by Day 28, to patient #137 of the — 5-FU treatment group; and
- CK elevation observed at the screening (Day -6) and final (Day 56) evaluations, to Patient #31 of the — 5-FU treatment group.

According to the submission, all other clinical laboratory results that were flagged out of range or unexpected change from baseline were either unconfirmed on retest or were determined to be not clinically significant or patient abnormal values. No patients discontinued from the study because of facial irritation.

Safety Conclusion
As reported in the Phase 3 studies, most frequently reported adverse events considered definitely related to treatment and reported by at least two patients in any treatment group were application site reaction (skin irritation), dry skin, pruritus, rash (erythema). Eye irritation was also reported. Nasal irritation was not reported as an AE in the Phase 3 studies; however, patients were instructed to apply with care near the eyes, nose, and mouth.

Post-study blood and urine samples for routine hematology, serum chemistry and urinalysis did not reveal any study drug related abnormal results. There were no deaths reported.

8.2.4 Reviewer's Trial # 4 Sponsor's Protocol DL-6025-9625
(Study Dates: November 18, 1997 to March 26, 1997)
Reviewer's comment: *Protocol DL-6025-9625 is being reviewed for safety.*

Title: "A Controlled, Randomized, Investigator-Blinded Study Comparing The Safety And Efficacy Of 5-Fluorouracil 0.5% Cream and Efudex® Cream 5% In The Treatment Of Actinic Keratosis"

8.2.4.1 Objective/Rationale

To investigate the clinical safety and efficacy of an experimental formulation of 5-FU 0.5% in a treatment-time response study, compared to a marketed 5-FU product (Efudex Cream 5%), for the treatment of actinic keratosis.

8.2.4.2 Design

Patients in this placebo-controlled, evaluator-blinded, parallel group study were randomly assigned to treatment groups Efudex, two weeks, b.i.d., 5-fluorouracil two weeks b.i.d., one week b.i.d., or one week q.d., or vehicle cream, two weeks b.i.d.

Reviewer's comments: *This study is being reviewed for safety.*

Results

This placebo controlled, investigator-blinded, parallel group, multi-center treatment regimen response study enrolled 79 patients at three centers. After completing the treatment phase, the planned follow-up phase for all patients was an additional four weeks after the final treatment application.

Table 35 (Partial Extraction of Sponsor's Table 7 (Vol. 1.26, pg. 8-10-32): Demographics and Patient Characteristics

Characteristic	Treatment Groups: Efx_2x2 n=18	5FU_2x2 n=17	5FU_1x2 n=18	5FU_1x1 n=17	Veh_2x2 n= 9	All: Patients n=79	p-value of Global Contrasts*
Age (yr)							
Mean (±Std)	63.6(± 7.5)	64.6(±11.1)	60.7(±16.7)	64.2(±11.1)	65.4(± 9.1)	63.5(±11.6)	Trt: >0.50
n (range)	18 (45-80)	17 (41-86)	18 (30-86)	17 (42-76)	9 (53-77)	79 (30-86)	Site: 0.106
Sex							
Female	3 (16.7%)	4 (23.5%)	2 (11.1%)	3 (17.6%)	2 (22.2%)	14 (17.7%)	Trt: >0.50
Male	15 (83.3%)	13 (76.5%)	16 (88.9%)	14 (82.4%)	7 (77.8%)	65 (82.3%)	Site: >0.50
Race							
Caucasian	18	14 (82.4%)	18	17	9	76 (96.2%)	Trt: 0.238
Hispanic		2 (11.8%)				2 (2.5%)	Site: >0.50
Other		1 (5.9%)				1 (1.3%)	
Complexion							
Fair	8 (44.4%)	7 (41.2%)	11 (61.1%)	9 (52.9%)	5 (55.6%)	40 (50.6%)	Trt: >0.50
Medium	10 (55.6%)	10 (58.8%)	7 (38.9%)	8 (47.1%)	4 (44.4%)	39 (49.4%)	Site: 0.118
Skin Type							
I.		1 (5.9%)		1 (5.9%)	2 (22.2%)	4 (5.1%)	Trt: 0.125
II.	11 (61.1%)	14 (82.4%)	13 (72.2%)	14 (82.4%)	7 (77.8%)	59 (74.7%)	Site: 0.007
III.	7 (38.9%)	1 (5.9%)	5 (27.8%)	2 (11.8%)		15 (19.0%)	
IV.		1 (5.9%)				1 (1.3%)	

Abstracted from Appendix Tables II.F.1.1 (Means), II.F.1.2 (Frequencies) II.E.2.1 (Means contrasts), and II.E.2.2 (Frequency Contrasts).

* Means contrasts from analysis of variance for Treatment and Site and Frequency contrasts from CMH test (general association) for Site effects or Treatment stratified by Site.

Skin Types(reported as 1, 2, 3, or 4 on CRF)were: I. Burns easily, no IPD, never tans; II. Burns easily, trace IPD, minimal tanning; III. Burns minimally, IPD+, tans light; and IV. Burns minimally, IPD++, tans moderate.

8.2.4.4.1 Disposition of Patients

The centers enrolled 26, 43, and 10 patients and the numbers of patients randomized to each treatment group were displayed in Table 29 below, a summary of the end of study status of all patients enrolled in the study. The patient indicated discontinued for adverse event had a fatal cardiac event. All other patients completed the study although some may have discontinued from the treatment phase early as a result of facial irritation.

Table 36 (Sponsor's Table 3): Patient Disposition

Treatment Group Summaries

End of Study Status	Efx_2x2 n	Efx_2x2 %	5FU_2x2 n	5FU_2x2 %	5FU_1x2 n	5FU_1x2 %	5FU_1x1 n	5FU_1x1 %	veh_2x2 n	veh_2x2 %
Number Randomized	18		17		18		17		9	
Patient Completed	18	100.0	17	100.0	18	100.0	16	94.1	9	100.0
Discontinued (reason)										
for Adverse Event							1	5.9		

Study completion listed in Appendix IV.A.1.1

All patients enrolled had follow-up evaluations of physician rated irritation and patient treatment tolerance. There were also 18 visits of the post-treatment phase missing or non-evaluable for physician irritation index and patient treatment tolerance.

8.2.4.4.3 Safety

Adverse events were monitored throughout the study and were recorded on the CRF. At visit days the investigator graded erythema, dryness, edema, and erosion/ulceration. Patient Treatment Tolerance evaluation was made using a visual analog scale. Blood and urine samples for routine hematology, serum chemistry, and urinalysis were obtained prior to the treatment phase only. Urine pregnancy test on females of childbearing potential was conducted at the study entry at the screening visit before stating treatment.

Adverse Events

Treatment safety was evaluated in all 79 patients enrolled in the study. One patient (#44) in the 5-FU 0.5% 1x1 treatment group had a fatal heart attack on Study Day 18. There were no other serious adverse events during the study and no patient discontinued due to adverse events. The overall incidences of adverse events were comparable among treatment groups.

None of the active treatment groups had significantly higher incidences of total adverse events or other specific adverse events compared to vehicle.

Facial Irritation

Each of the experimental 5-Fluorouracil treatments had more severe treatment phase dryness compared to the two-week b.i.d. Efudex treatment. The two-week b.i.d. 5FU treatment also had a more severe irritation index score compared to two-week b.i.d. Efudex. The following contrasts indicated significantly more severe facial irritation in the two-week b.i.d. Efudex treatment compared to experimental 5-Fluorouracil: treatment phase erythema Efx_2x2 > 5FU_1x2; treatment phase erosion Efx_2x2 > 5FU_1x1; post-treatment irritation index

Efx_2x2 > 5FU_1x2, post-treatment erythema Efx_2x2 > (5FU_1x2 and 5FU_1x1); post-treatment edema Efx_2x2 > 5FU_1x2.

The Patient Diary AM average treatment tolerance index of the two-week b.i.d. 5FU treatment were significantly more severe that that of the two-week b.i.d. Efudex treatment and the post-treatment itching of the one-week q.d. 5FU treatment was significantly less severe than that that of the two-week b.i.d. Efudex treatment.

Adverse Events

Table 30 (Sponsor's Table 18) that follows is a summary of all reported adverse experiences in the study. There were 7 patients (39%) in the Efx_2x2 treatment, 9 patients (53%) in the 5FU_2x2 treatment, 6 patients (33%) in the 5FU_1x2 treatment, 6 patients (35%) in the 5FU_1x1 treatment and 4 patients (44%) in the Veh_2x2 treatment with at least one adverse experience.

Table 37 (Sponsor's Table 18) Adverse Experience Incidence Summary by Body System

Body System Summary	COSTART Pref. Term	TREATMENT GROUP FREQUENCIES (%)				
		Efx_2x2	5FU_2x2	5FU_1x2	5FU_1x1	Veh_2x2
Summary	All Patients	18 (100.0%)	17 (100.0%)	18 (100.0%)	17 (100.0%)	9 (100.0%)
	Incidence of AE	7 (38.9%)	9 (52.9%)	6 (33.3%)	6 (35.3%)	4 (44.4%)
	Occurrence of AE	11	13	6	13	6
Body as a Whole		3 (16.7%)	2 (11.8%)	2 (11.1%)	2 (11.8%)	1 (11.1%)
	HEADACHE	1	2		1	1
	INJURY ACCID	2			1	
	FLU SYND		1			
	PAIN BACK			1		
	PHOTOSENSITIVITY			1		
Cardiovascular					1 (5.9%)	
	INFARCT MYOCARD				1	
Musculoskeletal						1 (11.1%)
	MYALGIA					1
Nervous			2 (11.8%)			
	DEPRESSION		1			
	DIZZINESS		1			
Respiratory		4 (22.2%)	4 (23.5%)	3 (16.7%)	5 (29.4%)	3 (33.3%)
	RHINITIS	4	4	3	4	2
	COUGH INC	2	1			
	BRONCHITIS					1
	PHARYNGITIS				1	
	PNEUMONIA		1			
	SINUSITIS				1	
Skin & Appendages		2 (11.1%)	2 (11.8%)		2 (11.8%)	1 (11.1%)
	RASH	2	1		1	
	APPLICAT SITE RE					1
	ECZEMA				1	
	ULCER SKIN		1			
Special Senses				1 (5.6%)	2 (11.8%)	
	CONJUNCTIVITIS			1		
	OTITIS EXT				1	
	PAIN EAR				1	

Listings in Appendices IV.A.5.1.1 and IV.A.5.1.2 (COSTART preferred terms)
Each patient counted only once in each row (except count of occurrences)

Adverse events at least possibly related to the treatment were application site reaction, rash, headache and conjunctivitis (verbatim: irritated eyes).

Deaths, Discontinuations Due To Adverse Events, And Other Serious Adverse Events
Deaths
One patient died during the study. Patient #44 of the 5FU_1x1 treatment experienced a fatal heart attack on Study Day 18. The death was not thought to be related to the study drug.

Of note, according to the submission, the 0.5% cream demonstrated relatively greater dryness as a component of facial irritation when compared to Efudex. Since this was seen across all treatment regimens including vehicle, it is likely a characteristic of the particular cream formulation. Notably, the drying effect resolved quickly after cessation of treatment and effects were not different from Efudex in the post-treatment phase of the study.

8.2. 4.5 Safety Conclusion
Application site reaction, rash, headache and conjunctivitis (reported verbatim as irritated eyes) were most common AEs. Dryness was reported across all treatment regimens of the Sponsor's formulation including vehicle.

One patient died during the study and was not thought related to the study drug. No post-treatment laboratory tests were performed.

9 Overview of Efficacy
The Sponsor's claim of efficacy of 5-fluorouracil 0.5% cream over vehicle in treatment of actinic keratosis of the face and anterior bald scalp was supported by Studies DL6025-9721 and DL6025-9722. Efficacy results were evaluated for the proportion of subjects with 100% clearance of their actinic keratoses 4 weeks after termination of treatment in the ITT population. Total clearance of lesions (Sponsor's Grade 5) was defined as treated areas completely clear of actinic keratosis lesions and the lesions were no longer perceptible to touch, but a slight pink redness could linger at the site. Studies DL6025-9721 and DL6025-9722 also had a dose ranging component in addition to superiority over vehicle claim (i.e., to determine the "optimal" duration of therapy of one, two, or four weeks). Subjects were randomized to one week, two weeks, or four weeks of therapy with 5-fluorouracil 0.5% cream or vehicle with post-treatment follow of 4 weeks. Efficacy results from these studies do not support the duration of therapy as proposed in the Dosage and Administration Section (Vol.1, pg. 2-1-25).

As noted in Table 38, all treatment durations in both studies were superior to vehicle. In Study DL6025-9721 there was a clear trend of greater efficacy resulting from longer duration of therapy; however, no efficacy trend was noted in DL6025-9722.

Table 38 Proportion of Patients with 100% Clearance (ITT Population)

	Study 9721		Study 9722	
One Week	7 (15%)	N =47	10 (26%)	N = 38
Two Week	16 (35%)	N = 46	6 (15%)	N = 41
Four Week	26 (58%)	N = 45	15 (38%)	N = 40
Vehicle (3 arms combined)	0 (0%)	N = 69	2 (3%)	N = 58

Results of Study DL6025-9721 demonstrate that ——— Cream 0.5% is statistically superior to vehicle in treatment of actinic keratoses located on the face and anterior bald scalp. Four weeks of treatment is the most efficacious of the time intervals studied. Treatment duration of 4 weeks is statistically superior to both One –Week ($p=0.001$) and Two – Week ($p=0.02$). Two -Week treatment is statistically superior to One- Week ($p=0.03$). Statistically significant results were observed in Study DL6025-9722 when active treatment arms were compared to Vehicle arm ($p=0.001$). No statistically significant result was achieved when active treatment arms are compared to each other ($p\geq 0.2$). There was no apparent trend noted.

Statistical superiority of active over vehicle for all treatment arms has been demonstrated in two independent studies; however, results of the dose-ranging aspects of the Phase 3 studies are problematic. Efficacy for the optimal duration of therapy is suggestive but not clear cut. Pooling of the efficacy data from the two studies provides an efficacy trend in favor of the Four-Week treatment arm. As noted in Table 39, the number of patients with 100% clearance of AKs at 4 weeks is double that over one week. This trend is also consistent with the results observed in Study 9721.

Table 39 Proportion of Patients with 100% Clearance (ITT Population)

	Combined Efficacy (Studies 9721 and 9722)	
One Week	17 (20%)	N = 85
Two Week	22 (25%)	N = 87
Four Week	41 (48%)	N = 85
Vehicle	2 (2%)	N = 127

Clinically, there would be difficulties associated with making an efficacy assessment immediately after 1, 2, or even 4 weeks of treatment due to the presence of irritation associated with the use of 5-FU 0.5. As discussed under Safety (Section 10), 94.6% of patients in the combined studies developed application site reactions. It would be extremely difficult or impossible for a patient to determine whether clearance of the AKs had been achieved after one or two weeks of therapy due to irritancy. It would be difficult for health care professionals to determine optimal efficacy at one or two weeks of therapy depending upon the degree of irritation present. Additionally, it would require additional office visits by the patient for a treatment duration determination by a health care professional.

The Four-Week treatment duration is being recommended for labeling of this drug product for the following reasons:

1) efficacy trend towards 4 weeks noted in Study 9721 and the pooled study results(Table 39),
2) inconsistent efficacy trend noted between One-Week and Two-Week treatment arms in the Phase 3 studies, and
3) difficulty with making a clinical efficacy judgement to discontinue treatment at either time point (1 or 2 weeks) due to the expected presence of irritation.

Efficacy can not be extrapolated to treatment of actinic keratosis lesions arising on the ears and other sun-exposed areas (e.g., dorsum of hands, and forearms) because these lesions tend to be thicker. Lesion thickness was not evaluated under this NDA. A Phase 4 safety and

efficacy study for treatment of actinic keratosis lesions arising on other sun-exposed areas, especially the ears should be requested as a condition of approval. Long term safety follow-up (e.g., 6 to 12 months) should be required with this study.

10 Overview of Safety

The Sponsor presented safety data from each of nine clinical trials. A total of 567 patients with actinic keratosis were enrolled in the Phase 2 and 3 clinical trials; however, duration of therapy and concentration of the test drug varied. There were 379 patients exposed to three concentrations of the study drug with 151 patients were exposed to study drug for > 2 weeks in the Phase 3 studies plus 11 patients in PK Study DL 6025-9720 in support of this NDA. Table 40 below summaries the extent of Phase 2/3 exposure.

Table 40 (Sponsor's Table 16, Vol. 1.28, pg. 8-12-105): Extent of Exposure to Dermik 5-FU in Phase II and Pooled Phase III Studies

# Treatment Weeks Study	5-FU Treatment Group 5-FU 0.5% N =334*	5-FU [redacted] N = 21	5-FU [redacted] N = 24	All 5-FU Groups N =379
	q.d. n (%)	b.i.d. n (%)	b.i.d. n (%)	b.i.d. n (%)	n (%)
≤1 Week - All Studies	**81 (24.3%)**	**17 (5.1%)**	**1 (4.8%)**	**3 (12.5%)**	**102 (26.9%)**
Adequate and Well-Controlled Studies					
9721/9722 Combined	64 (19.2%)	0	0	0	64 (16.9%)
Supportive Controlled Studies					
9518	0	0	1 (4.8%)	3 (12.5%)	4 (1.1%)
9625	17 (5.1%)	17 (5.1%)	0	0	34 (9.0%)
>1 to ≤ 2 Weeks - All Studies	**90 (26.9%)**	**22 (6.6%)**	**4 (19.0%)**	**10 (41.7%)**	**126 (33.2%)**
Adequate and Well-Controlled Studies					
9721/9722 Combined	90 (26.9%)	0	0	0	90 (23.7%)
Supportive Controlled Studies					
9518	0	4 (1.2%)	4 (19.0%)	10 (41.7%)	18 (4.7%)
9625	0	18 (5.4%)	0	0	18 (4.7%)
>2 to ≤ 4 Weeks - All Studies	**83 (24.9%)**	**20 (6.0%)**	**14 (66.7%)**	**11 (45.8%)**	**128 (33.8%)**
Adequate and Well-Controlled Studies					
9721/9722 Combined	83 (24.9%)	0	0	0	83 (21.9%)
Supportive Controlled Studies					
9518	0	20 (6.0%)	14 (66.7%)	11 (45.8%)	45 (11.9%)
9625	0	0	0	0	0
>4 Weeks - All Studies	**20 (6.0%)**	**1 (0.3%)**	**2 (9.5%)**	**0**	**23 (6.1%)**
Adequate and Well-Controlled Studies					
9721/9722 Combined	20 (6.0%)	0	0	0	20 (5.3%)
Supportive Controlled Studies					
9518	0	1 (0.3%)	2 (9.5%)	0	3 (0.8%)
9625	0	0	0	0	0
Total - All Studies	**274 (82.0%)**	**60 (18.0%)**	**21 (100%)**	**24 (100%)**	**379 (100%)**

*Includes Patient No. 146 in Study 9721, for whom day of last treatment application was unknown and is represented in this table by day of last visit (Day 7).
Source: Appendix A.1A

Table 41 (Extracted from ISS-Table 24): Summary of All Adverse Events Reported in ≥ 1% of Patients in the Combined Active Treatment and Vehicle Groups – Pooled Phase III Studies

9721 and 9722 Combined										
Body System AE COSTART Term*	Active One Week N= 85		Active Two Week N= 87		Active Four Week N= 85		ALL Active Treatments N=257		Vehicle Treatments N=127	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
BODY AS A WHOLE	7	(8.2)	6	(6.9)	12	(14.1)	25	(9.7)	15	(11.8)
Headache	3	(3.5)	2	(2.3)	3	(3.5)	8	(3.1)	3	(2.4)
Common Cold_	4	(4.7)	0		2	(2.4)	6	(2.3)	3	(2.4)
Allergy	0		2	(2.3)	1	(1.2)	3	(1.2)	2	(1.6)
Infection Upper Respiratory	0		0		0		0		2	(1.6)
MUSCULOSKELETAL	1	(1.2)	1	(1.1)	1	(1.2)	3	(1.2)	5	(3.9)
Muscle Soreness	0		0		0		0		2	(1.6)
RESPIRATORY	5	(5.9)	0		1	(1.2)	6	(2.3)	6	(4.7)
Sinusitis	4	(4.7)	0		0		4	(1.6)	2	(1.6)
SKIN & APPENDAGES	78	(91.8)	83	(95.4)	82	(96.5)	243	(94.6)	85	(66.9)
Application Site Reaction	78	(91.8)	83	(95.4)	82	(96.5)	243	(94.6)	83	(65.4)
Irritation Skin	1	(1.2)	0		2	(2.4)	3	(1.2)	0	
SPECIAL SENSES	6	(7.1)	4	(4.6)	6	(7.1)	16	(6.2)	6	(4.7)
Eye Irritation	5	(5.9)	3	(3.4)	6	(7.1)	14	(5.4)	3	(2.4)

Source: extracted from ISS- Table 24: Summary of All Adverse Events - Pooled Phase III Studies (NDA Vol. 1.28, page 8-12-120) and Appendix A.5 (NDA Vol. 1.28, page 8-12-156)

Patients were instructed to use the study drug with care to avoid application of the study drug near the eyes; therefore, the percent of patients reporting eye irritation is unexpected an a safety concern. Eye irritation, described as mild to moderate in intensity, was listed on the CRF as burning from fumes, eyes burning, eyes irritated, eyes running continuously, sensitivity, itching, etc. and occurred across all treatment arms; however, differed across studies. A rationale for differences across studies would not be ascertained. Only one patient in the vehicle group (Study 9722, Pt. # 00105) used a concomitant medication for eye irritation.

Reviewer's comments: *Additional data are needed for labeling instructions regarding avoidance of eye irritation. A rationale for differences across studies between the incidence of eye irritation is unknown (lower incidence in Study 9722 than 9721). The difference could possibly be secondary to the timing of application or perhaps concomitant use with other topicals (moisturizers, etc.). For example, perspiration could transport the medication to the eye (AM application) or medication on bed pillows would be rubbed into the eye (for PM application). Data were not available regarding the timing of application of study drug as morning or evening.*

Safety was evaluated by continuous monitoring of adverse events and for facial irritation. Post-treatment laboratory tests other than pregnancy test were performed in one Phase 2 Study (DL6025-9518) and PK Study DL6025-9720. Five Phase 1 studies were performed with the 0.5% cream concentration. Phase 1 PK Study DL6025-9720 was performed in patients with actinic keratosis and the dermal safety studies enrolled normal healthy volunteers. Additional safety data were presented from Adverse Drug Reactions associated with marketed 5-flurouracil products, and a literature search. The Phase 2 and 3 clinical trials provided for a 4- week post- treatment follow-up. No long-term post-treatment efficacy or

safety follow-up (e.g., 6 or 12 month) data were submitted to determine recurrence rates of actinic keratosis.

10.1 Significant/Potentially Significant Events

10.1.1 Deaths

There were four deaths reported during conduct of the clinical trials. None of the deaths were thought related to the study drug.

- Patient No. 163 in the Active One Week group, Study DL6025-9721, a 75 year old man died of cardiac failure 25 days after last application of study medication
- Patient No. 109 in the Active Two Week group, Study DL6025-9721, a 71 year old man died post-study completion as a result of the stomach cancer.
- Patient No. 146 in the Active Two Week group in Study DL6025-9721, an 81 year old woman died 16 days after starting the study. The last day of study treatment is unknown. Patient was admitted to the Intensive Care Unit (ICU) after a series of serious adverse events (nausea, dehydration, and confusion, transient ischemic episode and recent inferior posterior wall myocardial infarction, primary AV block, decreased blood pressure, and bradycardia, significant holosystolic murmur, dementia, and acute renal failure).
- Patient No. 44 in the Active One Week once daily treatment group, Study DL-6025-9625, experienced a fatal heart attack on Study Day 18.

10.1.2 Other Significant/Potentially Significant Events (e.g., Serious adverse events, dropouts/withdrawals)

A total of five patients, three in the active treatment groups and two in the vehicle group, in Study DL6025-9721 experienced at least one serious adverse event. No patient in Study DL6025-9722 reported a serious adverse event. No serious adverse event was considered related to study drug. Three of these patients died and were discussed above.

Study DL6025-9721

- Patient No. 230 in the Vehicle group in was a 63 year old man with a past medical history of myocardial infarction in 1970 and 1976, coronary artery bypass graft surgery in 1976, and pacemaker/defibrillator implant in 1996 developed 100% reblockage of one coronary artery.
- Patient No. 205, a 72 year old woman with a past medical history of diabetes, peripheral vascular disease, smoking, and previous carotid endarterectomy and femoral/popliteal bypass with unstable angina required emergency cardiac catheterization due to stent occlusion.

Discontinuations

A total of seven patients, two in the Active One Week group, two in the Active Two Week group, and three in the Active Four Week group, discontinued study participation due to adverse events. Two patients, Patients No. 163 and 146 in Study DL6025-9721, who discontinued study participation, died, and were described in the previous section. Patient 109 died post-study completion. The remaining five patients who discontinued study participation are described below.

Active One Week group in Study DL6025-9721

- Patient No. 70, a 48 year old man, reported an adverse event of moderately severe facial irritation (erythema, dryness, pain, burning, and itching) which was considered definitely related to study medication. Discontinued due to a broken kneecap (patella).

Four patients discontinued due to a study drug-related adverse event as follows:

Active Two Week group in Study DL6025-9721

- Patient No. 192, a 66 year old man who experienced a single episode of difficulty breathing and facial swelling which lasted 30 minutes and was of moderate severity on day 3 of the study. The event was considered probably related to study drug and therefore treatment was discontinued. The patient had no history of 5-Fluorouracil treatment.

Active Two Week group in Study DL6025-9722

- Patient No. 183, a 74 year old male who discontinued study medication after 7 days of treatment due to severe facial irritation beginning on Study Day 3 and lasting for 16 days. Symptoms included edema, erythema, dryness, erosion, pain, and burning. All symptoms resolved by 49 days after the final study visit.

Active Four Week group in Study DL6025-9722

- Patient No. 186, a 58 year old female who discontinued study treatment after 11 days of treatment due to severe facial irritation, consisting of edema, erythema, dryness, erosion, pain, burning, itching, crusting, and stinging. She also experienced mild diarrhea, low grade fever, and impetigo.
- Patient No. 201, a 70 year old male who discontinued treatment after 4 days due to severe facial irritation consisting of edema, erythema, dryness, erosion, burning, and itching. This patient had one post-treatment follow-up evaluation on Study day 16, 12 days after discontinuing study treatment. Facial irritation was continuing at that time and he had no further study evaluation.

Discontinued Study Treatment

An additional 25 patients in the two Phase III studies discontinued study treatment early but continued in the study for follow-up evaluations.

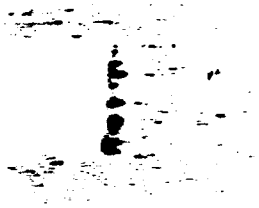

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Table 42 (Sponsor's Table 17) that follows lists discontinuation of therapy due to their degree of facial irritation. Except for three patients, discontinuation of treatment occurred on or after day 11 of treatment.

Table 42 (Sponsor's Table 17, Vol. 1.28, pg. 8-12-132): Listing of Patients Discontinuing Study Medication and Completing Follow-Up Evaluations in Studies DL6025-9721 and 9722

Treatment Group/ Study-Patient #	Adverse Event	Maximum Severity of Facial Irritation	Day of Last Treatment Application	Duration (Days)	Status at Final Visit [a]
Active Two Week					
9721-11[b]	facial irritation	Moderate	7	12	No Irritation
9721-32	facial irritation	Severe	12	28	No Irritation
9721-67[b]	facial irritation	Severe	11	38	No Irritation
9722-131[b]	facial irritation	Severe	11	34	No Irritation
9722-133	facial irritation	Severe	15	33	No Irritation
9722-184	facial irritation	Severe	14	Continuing	Continuing Day 44
Active Four Week					
9721-56[b]	facial irritation	Moderate	16	38	No Irritation
9721-58[b]	facial irritation/eye irritation	Moderate	7	14	No Irritation
9721-71[b]	facial irritation	Moderate	12	29	No Irritation
9721-79	facial irritation	Severe	21	36	No Irritation
9721-226[b]	facial irritation	Severe	25	54	No Irritation
9722-2	facial irritation	Moderate	15	22	No Irritation
9722-10	facial irritation	Severe	15	31	No Irritation
9722-91	facial irritation	Severe	14	22	No Irritation
9722-99	facial irritation	Severe	14	20	No Irritation
9722-103	facial irritation	Severe	21	37	No Irritation
9722-106	facial irritation	Severe	14	36	No Irritation
9722-132	facial irritation	Severe	29	33	No Irritation
9722-145	facial irritation	Severe	23	39	No Irritation
9722-169	facial irritation	Moderate	10	10	No Irritation
9722-172	facial irritation	Moderate	26	36	No Irritation
9722-188[b]	facial irritation	Severe	5	29	No Irritation
9722-227[b]	facial irritation	Severe	22	45	No Irritation
9722-233[b]	facial irritation	Severe	21	42	No Irritation
Vehicle					
9722-134	facial irritation	Mild	31	35	No Irritation

[a] Outcome of facial irritation adverse event or status at final post-treatment follow-up evaluation
[b] Used steroid cream for facial irritation

10.1.3 Over-dosage Exposure

The 5-FU 0.5% cream is intended for once daily cutaneous use only in the expected amounts of approximately one gram per application. Accidental overdose would appear to be unlikely.

According to the submission, results of acute oral toxicity in rats suggests that the median lethal dose (LD 50) is in excess of 250 mg/kg of 5-FU since that dose resulted in no adverse

toxicologic effects. A 30 gram tube (30,000mg) tube of the 0.5% 5-FU formulation contains approximately 150 mg of 5-FU. Accidental ingestion of an entire tube would result in maximal acute exposure of 3 mg/kg (150 mg 5-FU/50 kg person)

10.2 Other Safety Findings

Adverse Drug Reactions Reported to FDA for Topical 5-Fluorouracil Products

The following ADRs were reported to the Epidemiology Branch of the FDA over a time period from 1-January-1968 to 10-June-1997 with two reports dated prior to 1968; one in August of 1959 and one in June of 1966. ADRs comprising at least 0.5% of the total number of reports are shown. The most common types of ADRs were those involving skin irritation, particularly rash and application site reaction, which were each cited in approximately 10% of the reports. Lack of drug effect was cited in approximately 9% of reports.

Table 43 (Sponsor's Table 19, Vol.1.28, 8-12-138): Frequency Distribution of Adverse Drug Reactions Reported to FDA for Topical 5-Fluorouracil Products

Adverse Drug Reaction*	Number of Reports	Percent of Total Reports
TOTAL**	1390	100
Rash	145	10.43
Application Site Reaction	134	9.64
No Drug Effect	129	9.28
Pain	80	5.76
Contact Dermatitis	62	4.46
Allergic Reaction	61	4.39
Pruritus	37	2.66
Edema Face	32	2.30
Rash, Vesicular Bullous	28	2.01
Ulcer Skin	25	1.80
Skin Discoloration	24	1.73
Exfoliative Dermatitis	22	1.58
Paresthesia	22	1.58
Headache	20	1.44
Taste Perversion	19	1.37
Edema	18	1.29
Alopecia	15	1.08
Skin Disorder	15	1.08
Infection	13	0.94
Conjunctivitis	12	0.86
Nausea	12	0.86
Photosensitivity	12	0.86
Aggravated Reaction	12	0.86
Urticaria	12	0.86
Insomnia	11	0.79
Skin hypertrophy	7	0.50
Lymphadenopathy	7	0.50
Nervousness	7	0.50
Pustular Rash	7	0.50

*Topical Adrucil, Efudex, and Fluoroplex ADRs are included. Some reports may be from outside the United States.
** The total number of reports received. Only ADRs which comprised at least 0.5% of the total number of ADRs reported are listed in this table. The total number of patients receiving these products is not available, therefore incidence of ADRs cannot be calculated.

According the Sponsor, there are no published studies of Dermik 5-FU. A literature search of topical 5-fluorouracil was performed using Derwent Drug File, Embase and Medline databases. The review of the literature from 1962 until April of 1999 for other topical 5-fluorouracil products produced 20 reports which included original information on adverse

events in patients treated for actinic keratosis and 4 reports which described adverse events in patients treated with topical 5-fluorouracil for other indications.

The Sponsor indicated that after completion of the formal literature review, a recently published case study (August 1999) of the first 5-FU toxicity from topical administration of the 5% 5-FU was discovered and was included in the literature review. Safety data from the 24 studies including the recently discovered case study were summarized.

According to the review, most adverse events in the literature consisted of local skin reactions associated with application of the treatment. Almost all published reports were for the use of a 5% or higher concentration of topical 5-fluorouracil. Of note was one case of bullous pemphigoid was reported with a self-made preparation of 5-fluorouracil (Bercovitch 1987).

Of importance, the first case of toxicity from topical administration of 5% 5-FU was recently reported in a dihydropyrimidine dehydrogenase (DPD) deficient patient by Johnson et al in August of 1999. In general, a large percentage of 5-FU is catabolized by the enzyme DPD. Inherited deficiencies of DPD can result in shunting of 5-FU to the anabolic pathway, leading to cytotoxic activity and potential toxicities. Sumi at al. (1998) analyzed urine samples from 21,200 healthy Japanese infants to evaluate the prevalence of dihydropyrimidinuria (DHPuria) and 2 asymptomatic cases of DHPuria were found. Based on this result, they estimated the prevalence of DPD deficiency to be approximately 1 in 10,000 births in Japan.

The (DPD) deficient patient, reported by Johnson, was being treated for basal cell carcinoma of the scalp with twice daily applications of 5% 5-FU and developed severe gastrointestinal and hematologic toxicity after one week of treatment. Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever and chills. Further examination revealed severe stomatitis, erythematous skin rash, neutropenia, thrombocytopenia, and inflammation of the esophagus, stomach and small bowel. Testing revealed that the patient demonstrated no DPD enzyme activity and had elevated uracil levels in the plasma and urine. The patient was removed from therapy and recovered. Previous reports of severe 5-FU toxicity in DPD deficient patients have been associated with parenteral administration of 5-FU. As reported by Johnson et al. in Clinical Cancer Research (August 1999), after parenteral administration of 5-FU these patients developed profound toxicity including mucositis, granulocytopenia, neuropathy and even death.

ADR Incidence Tables

Table 44 (Sponsor's Table 19, Vol. 1.28): Summary of All Adverse Events - Pooled Phase III Studies

9721 and 9722 Combined

Body System AE COSTART Term*	Active One Week N= 85		Active Two Week N= 87		Active Four Week N= 85		ALL Active Treatments N=257		Vehicle N=127	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
At least one AE	78	(91.8)	84	(96.6)	83	(97.6)	245	(95.3)	95	(74.8)
BODY AS A WHOLE	7	(8.2)	6	(6.9)	12	(14.1)	25	(9.7)	15	(11.8)
Headache	3	(3.5)	2	(2.3)	3	(3.5)	8	(3.1)	3	(2.4)
Common Cold	4	(4.7)	0		2	(2.4)	6	(2.3%)	3	(2.4)
Allergy	0		2	(2.3)	1	(1.2)	3	(1.2)	2	(1.6)
Injury	1	(1.2)	0		1	(1.2)	2	(0.8)	1	(0.8)
Eyes Swollen	0		1	(1.1)	1	(1.2)	2	(0.8)	0	
Fever	0		0		1	(1.2)	1	(0.4)	1	(0.8)
Knee Pain	1	(1.2)	0		1	(1.2)	2	(0.8)	0	
Abscess	0		0		1	(1.2)	1	(0.4)	0	
Cancer	0		1	(1.1)	0		1	(0.4)	0	
Facial Swelling	0		0		1	(1.2)	1	(0.4)	0	
Flu	0		0		1	(1.2)	1	(0.4)	0	
CARDIOVASCULAR	1	(1.2)	2	(2.3)	2	(2.4)	5	(1.9)	4	(3.1)
Hypertension	0		0		1	(1.2)	1	(0.4)	1	(0.8)
Cardiac Failure	1	(1.2)	0		0		1	(0.4)	0	
Heart Murmur	0		1	(1.1)	0		1	(0.4)	0	
Hypertension Aggravated	0		1	(1.1)	0		1	(0.4)	0	
Myocardial Infarction	0		1	(1.1)	0		1	(0.4)	0	
Transient Ischemic Attacks	0		0		1	(1.2)	1	(0.4)	0	
DIGESTIVE	0		1	(1.1)	5	(5.9)	6	(2.3)	3	(2.4)
Fever Sore	0		1	(1.1)	0		1	(0.4)	1	(0.8)
Diarrhea	0		0		1	(1.2)	1	(0.4)	0	
Indigestion	0		0		1	(1.2)	1	(0.4)	0	
Nausea	0		0		1	(1.2)	1	(0.4)	0	
Stomach Upset	0		0		1	(1.2)	1	(0.4)	0	
Tooth Disorder	0		0		1	(1.2)	1	(0.4)	0	
MUSCULOSKELETAL	1	(1.2)	1	(1.1)	1	(1.2)	3	(1.2)	5	(3.9)
Fracture Bone	1	(1.2)	0		0		1	(0.4)	1	(0.8)
Arthritis	0		1	(1.1)	0		1	(0.4)	0	
Pain Joint	0		0		1	(1.2)	1	(0.4)	0	
NERVOUS	0		2	(2.3)	1	(1.2)	3	(1.2)	1	(0.8)
Anxiety	0		1	(1.1)	0		1	(0.4)	0	
Dementia	0		1	(1.1)	0		1	(0.4)	0	
Spasm Muscle	0		0		1	(1.2)	1	(0.4)	0	
RESPIRATORY	5	(5.9)	0		1	(1.2)	6	(2.3)	6	(4.7)
Sinusitis	4	(4.7)	0		0		4	(1.6)	2	(1.6)
Coughing	1	(1.2)	0		0		1	(0.4)	1	(0.8)
Breathing Difficult	0		0		1	(1.2)	1	(0.4)	0	
SKIN & APPENDAGES	78	(91.8)	83	(95.4)	82	(96.5)	243	(94.6)	85	(66.9)
Application Site Reaction	78	(91.8)	83	(95.4)	82	(96.5)	243	(94.6)	83	(65.4)
Dermatitis Contact	0		2	(2.3)	0		2	(0.8)	1	(0.8)
Irritation Skin	1	(1.2)	0		2	(2.4)	3	(1.2)	0	
Herpes Simplex	0		0		1	(1.2)	1	(0.4)	1	(0.8)
Rash	2	(2.4)	0		0		2	(0.8)	0	
Blisters	0		1	(1.1)	0		1	(0.4)	0	
Burning Skin	0		0		1	(1.2)	1	(0.4)	0	
Erythema	1	(1.2)	0		0		1	(0.4)	0	
Melanoma Malignant	0		1	(1.1)	0		1	(0.4)	0	
Papular Rash	0		1	(1.1)	0		1	(0.4)	0	
Rash Impetiginous	0		0		1	(1.2)	1	(0.4)	0	
Ulcer Skin	0		0		1	(1.2)	1	(0.4)	0	
SPECIAL SENSES	6	(7.1)	4	(4.6)	6	(7.1)	16	(6.2)	6	(4.7)
Eye Irritation	5	(5.9)	3	(3.4)	6	(7.1)	14	(5.4)	3	(2.4)
Cataract	1	(1.2)	0		0		1	(0.4)	0	
Taste Perversion Of	0		1	(1.1)	0		1	(0.4)	0	
UROGENITAL	1	(1.2)	1	(1.1)	0		2	(0.8)	3	(2.4)
Kidney Failure	1	(1.2)	0		0		1	(0.4)	0	
Renal Failure Acute	0		1	(1.1)	0		1	(0.4)	0	

* All events reported by at least one patient treated with 5-FU in a Phase III study. Source: Appendix A.5

Table 45 (Sponsor's Table 20, Vol. 1.28): Summary of Study Drug-Related Adverse Events - Pooled Phase III Studies

9721 and 9722 Combined					
Body System AE COSTART Term	Active One Week N=85	Active Two Week N=87	Active Four Week N=85	ALL Active Treatments N=257	Vehicle Treatments N=127
	n (%)	n (%)	n (%)	n (%)	n (%)
At Least One AE	78 (91.8)	84 (96.6)	83 (97.6)	245 (95.3)	95 (74.8)
At least one study-drug related AE*	78 (91.8)	83 (95.4)	83 (97.6)	244 (94.9)	82 (64.6)
BODY AS A WHOLE	0	2 (2.3)	4 (4.7)	6 (2.3)	1 (0.8)
Eyes Swollen	0	1 (1.1)	1 1.2)	2 (0.8)	0
Headache	0	1 1.1)	1 (1.2)	2 (0.8)	0
Facial Swelling	0	0	1 (1.2)	1 (0.4%)	0
Fatigue	0	0	0	0	1 (0.8)
Fever	0	0	1 (1.2)	1 (0.4)	0
DIGESTIVE	0	0	1 (1.2)	1 (0.4)	0
Diarrhea	0	0	1 (1.2)	1 (0.4)	0
RESPIRATORY	0	0	1 (1.2)	1 (0.4)	1 (0.8)
Breathing Difficult	0	0	1 (1.2)	1 (0.4)	0
Rhinitis	0	0	0	0	1 (0.8)
SKIN & APPENDAGES	78 (91.8)	83 (95.4)	82 (96.5)	243 (94.6)	82 (64.6)
Application Site Reaction	78 (91.8)	83 (95.4)	82 (96.5)	243 94.6)	81 (63.8)
Irritation Skin	1 (1.2)	0	2 (2.4)	3 (1.2)	0
Herpes Simplex	0	0	1 (1.2)	1 (0.4)	1 (0.8)
Rash	2 (2.4)	0	0	2 (0.8)	0
Blisters	0	1 (1.1)	0	1 (0.4)	0
Burning Skin	0	0	1 (1.2)	1 (0.4)	0
Erythema	1 (1.2)	0	0	1 (0.4)	0
Papular Rash	0	1 (1.1)	0	1 (0.4)	0
Rash Impetiginous	0	0	1 (1.2)	1 (0.4)	0
Tenderness Skin	0	0	0	0	1 (0.8)
Ulcer Skin	0	0	1 (1.2)	1 (0.4)	0
SPECIAL SENSES	5 (5.9)	4 (4.6)	6 (7.1)	15 (5.8)	3 (2.4)
Eye Irritation	5 (5.9)	3 (3.4)	6 (7.1)	14 (5.4)	2 (1.6)
Eyes Tearing	0	0	0	0	1 (0.8)
Taste Perversion	0	1 (1.1)	0	1 (0.4)	0

* Related = Remote (facial irritation adverse events only), possible, probable, or definite.
Source: Appendix A.5

10.2.2 Laboratory Findings, Vital Signs, ECGs

Post-treatment laboratory tests other than pregnancy tests were performed only in Phase II study DL6025-9518. Blood and urine tests were obtained at the initial visit and upon completion of the treatment phase (Day 29) or at early termination. Tests performed were a complete blood count (CBC), serum chemistry panel (bilirubin, alkaline phosphatase, ALT, AST, BUN, creatinine, glucose, uric acid, calcium, phosphorus, total protein, albumin, cholesterol, triglycerides, CK, sodium, potassium, chloride, bicarbonate), and a urinalysis

Clinical laboratory results overall were unremarkable. Four test results were reported as adverse events. These adverse events were reported in the NDA as follows: low potassium at Day 18, diabetes mellitus at the screening (Day 0) evaluation that improved with medication (Glucophage) by Day 35, thrombocytopenia at study entry that resolved by Day 28, and CK elevation at screening (Day -6) and again at the final Day 56 evaluation. None were considered related to study drug.

Since systemic 5-FU affects the hematologic system, mean baseline and final results for key hematology parameters for the Dermik 5-FU and vehicle groups are provided in Table 46 (Sponsor's Table 21). No clinically significant changes were observed for any treatment group.

Table 46 (Sponsor's Table 21, Vol. 1.28, pg. 8-12-133): Baseline and Final Mean Hematology Values in Study DL6025-9518

Hematology Test*	5-FU 0.5% N=25		5-FU N=21		5-FU N=24		Vehicle N=12	
	Baseline	Final	Baseline	Final	Baseline	Final	Baseline	Final
Hemoglobin	14.9	14.7	15.0	14.8	14.7	14.9	15.0	15.0
Hematocrit	43.6	43.7	44.4	44.2	43.3	44.0	43.8	44.8
RBC	4.82	4.74	4.95	4.87	4.73	4.78	4.90	4.92
WBC	6.55	6.49	6.77	7.02	6.32	6.65	6.19	6.17
Platelets	240	239	226	223	232	238	236	223

*All values are mean $x10^3$ per µl, unless otherwise noted.
Source: Study Report DL6025-9518 Table 9.2

According to the submission, one (9%) patient in the Dermik 5-FU 0.5% group in Study DL 6025-9518 and three (30%) in the Efudex group had slightly elevated percentages of eosinophils post-treatment.

10.2.3 Special Studies

Summary of Clinical Dermal Safety Studies

A total of six clinical dermal safety studies were conducted with 5-fluorouracil in Microsponge® cream formulations. Initially, a [redacted] cream formulation was used in two studies: a primary irritation study (DL6025-9508) and a repeat insult patch test study (DL6025-9509). Subsequently, 5-fluorouracil 0.5% cream was used in four studies: 1) a 21-day cumulative irritation study (DL6025-9815), 2) a repeat insult patch test study (DL6025-9715), 3) a photoxicity bioassay (DL6025-9713), and 4) an assay for photocontact allergenicity (DL6025-9714). These studies are summarized below.

Study DL6025-9508: Evaluation of Primary Irritation Potential in Humans

(Study Dates: June 6, 1995 – June 9, 1995)

The purpose of this study was to evaluate the irritation potential of three 24-hour successive applications of Dermik [redacted] 5-FU cream (Lot#DLC-029). Efudex® was included as a comparator, and a placebo cream allowed evaluation of the vehicle formulation. Twenty-six healthy volunteers were each administered three patches containing 0.2 ml each of: [redacted] Dermik 5-FU, vehicle cream and 5% Efudex®.

Reviewer's comments: *This study was not performed with the concentration that is the subject of this NDA.*

Study DL6025-9509: Repeated Insult Patch Test (Jordan-King modification of the Draize procedure)

(Study Dates: June 12, 1995 - July 27, 1995)

This study evaluated the contact sensitization potential of Dermik — 5-FU cream (Lot#DLC-029), 5-FU vehicle cream and Efudex® 5% Topical Cream. The study employed a repeat insult patch test method (Jordan-King modification of the Draize procedure). All test materials were applied simultaneously to each of the 28 enrolled subjects. Patches were applied to the inner upper arm three times per week for three weeks (total of nine applications) during the induction phase. Following a 10-17 day rest period, challenge patch applications (of all three test materials) were applied to a naive site for 48 hours. Test sites were scored for any signs of irritation (on a 0-7 scale) after removal of patches and for 72 hours following the challenge application.

Twenty-two subjects completed all phases of the study. The challenge did not show any evidence of delayed contact allergy for any of the three test materials. During the induction phase, Efudex® did show evidence of strong irritation during the third week of applications.

Reviewer's comments: *This study was not performed with the concentration that is the subject of this NDA.*

Study DL6025-9815: A 21-Day Cumulative Irritation Study in Humans
(Study Dates: December 2, 1998 – December 23, 1998)
This study was a 21-day cumulative irritation study. Thirty subjects (25 females and 5 males) completed the study in which 21 consecutive applications of Dermik 5-FU 0.5% cream (Lot#98F003), vehicle-only cream (Lot#98G003), and saline solution were in contact with the skin under occlusion for approximately 23 (± 1) hours. Physiological saline was to serve as a negative control. Each subject received all three test products simultaneously.

Scoring for cumulative irritation was done every 24 hours immediately prior to reapplication or until excessive irritation was noted. Irritation was scored using the 0-7 scoring scale of Berger and Bowman (J. Toxicol. Cut. and Ocular Toxicol. 1,109-115). Effects on the superficial layers of the skin (e.g., slight glazed appearance- small petechial erosions and/or scabs) were recorded as letter grades A-H with @ denoting additional comments. According to the submission, in order to perform statistical analyses, scores containing letter grades were converted to numerical equivalents: A=0, B=1, C=2, and F, G, and H=3.

Results
The Friedman Rank Sum analysis indicated significant differences among test articles on all study days except Day 8 and Day 15. On all study days the highest mean irritation scores occurred with normal saline. Results in the Fisher's LSD test demonstrated that Article B (active 5-Fluorouracil lot #98G003) was shown to be significantly less irritating than the negative saline solution control on days through five, day seven, and days nine through twelve. Article B (vehicle 5-Fluorouracil lot #98G002) on days one through seven, nine, sixteen through twenty-one and overall in the study.

Article B (vehicle 5-Fluorouracil lot #98G002) was found to be less irritating than Article A on days thirteen, fourteen, sixteen through twenty-one, and overall. The saline control demonstrated higher than usual irritancy levels than is normally experienced. This anomalous manifestation of higher irritancy with normal saline could not be explained.

One subject experienced two adverse events during this study, back pain and shaking of both hands. The subject elected not to continue the study. The investigator did not consider these events to be related to any test article in the study.

Conclusion
Under the conditions of Study DL6025-9815, Dermik's 5-FU 0.5% was not considered to be a primary irritant compared to the negative saline control. It is unclear why the saline control demonstrated higher than usual irritancy levels in this study.

Reviewer's comments: *This drug product is a known irritant based on the Phase 2 and 3 studies conducted under this NDA. This irritancy study was the only study performed with [redacted] removed from the [redacted] and is to be the "final-to-be-marketed" formulation.*

Study DL6025-9715: Repeated Insult Patch Test (Jordan-King modification of the Draize procedure)
(Study Dates: October 6,1997 – December 5, 1997)
This study evaluated Dermik 5-FU 0.5% cream (Lot# 970080) and placebo (vehicle cream) for the induction of contact sensitization by repetitive applications to the skin of 253 human volunteers. The design was the Jordan-King modification of the Draize procedure. During the induction period, repetitive 48 hour patch applications of Dermik 5-FU and vehicle cream were made to the same site on the skin for approximately three weeks. Following a rest period of two weeks, subjects received a 48 hour patch application to a naïve site to test for reactions indicative of contact sensitization. Sites were scored 48 and 96 hours after patch application.

Two hundred sixteen subjects completed the induction phase, and two hundred fifteen completed all phases of the study. During the induction period, test scores for both products were generally low, indicating little to mild reactions. During the challenge phase, there were mild erythema responses with both products, but these were not deemed serious by the investigator. No re-challenge was performed.

A total of 65 (26%) subjects experienced at least one adverse event during the study. Five (2%) subjects in Protocol 9715 had an adverse event considered at least possibly related to treatment (metallic/medicine taste in two subjects and application site reaction). Three subjects discontinued the study as a result of adverse events of lower back pain, allergies, or chest pain (stress), none of which were related to study medication.

Conclusion
Based on the results of Study DL6025-9715 the Repeated Insult Patch Test (Jordan-King modification of the Draize procedure) Dermik's 5-FU 0.5% cream does not appear to be a sensitizer.

Study DL6025-9713: An Investigator-blinded Assay of the Phototoxic Potential of Topical 5-fluorouracil (FU) Using the Assay of Phototoxicity Bioassay in Humans
(Study Dates: December 1, 1997 – December 12, 1997)

This study enrolled 20 healthy adult Caucasian volunteers of both sexes who received 24 hour patch applications of Dermik 5-FU 0.5% cream (Code 970080) and vehicle cream to the lower back followed by UV radiation. No reactions were observed with either product immediately, 24 hours, or 48 hours after radiation. No adverse events were reported in this study.

Conclusion
Based on the results of Study DL6025-9713, neither 5-FU 0.5% cream or its vehicle had detectable phototoxicity potential.

Study DL6025-9714: An Investigator-blinded Assay of the Photocontact Allergenic Potential of Topical 5-fluorouracil (FU) Using the Assay for Photocontact Allergenicity in Humans (Study Dates: November 3, 1997 – December 5, 1997)
This study enrolled 28 healthy adult volunteers of both sexes to assess the photoallergenic potential of Dermik 5-FU 0.5% cream. Of these, 25 subjects completed the study. Two subjects voluntarily withdrew and one subject failed to return for follow-up. Dermik's 5-FU 0.5% cream and vehicle cream were applied as patches to the mid-back, followed by exposure to standardized doses of solar simulating radiation to the same test sites repeatedly for a period of three weeks, followed by a single challenge after a rest phase. No reactions were seen in any of the 25 completed subjects at 48 or 72 hours after challenge (no results were recorded for dropped subjects). No adverse experiences or unanticipated reactions were observed or reported during the study.

10.2.4 Drug-Demographic Interactions
Drug demographic interactions were reviewed by clinical analysis of pooled Phase III safety data for female and male patients, and for patients age < 65 years or ≥ 65 years. Interactions were not summarized by race since 378 of the 384 patients in the combined Phase III studies were Caucasian. The non- Caucasian patients were Hispanic. Most of the skin types were types 1, 2, or 3.

According to the Sponsor, there were no notable differences in safety between patients grouped by age or sex. There were no statistically significant differences in efficacy demonstrated between patients age 60 and older. The degree of Dermik 5-FU 0.5% cream induced facial dryness as measured by the difference in the facial dryness reported by patients using the study drug compared to those using vehicle was greater for those younger than 65 than those older than 65.

10.2.5 Drug-Disease Interactions
No drug-disease studies were performed. Since Dermik 5-FU is a topical cream with little systemic absorption, no meaningful interaction with systemic medications or diseases is anticipated. A case of systemic toxicity has been reported with the topical use of 5-fluorouracil (5%) in a patient with dihydropyrimidine dehydrogenase (DPD) deficiency.

10.2.6 Drug-Drug Interactions
No drug-drug studies were performed.

10.2.7 Withdrawal Phenomena/Abuse Potential
No withdrawal effects were observed with Dermik 5-FU 0.5% cream in clinical trials where patients were observed for up to 4 weeks after treatment discontinuation.

10.2.8 Human Reproduction Data

There are no reported studies of pregnant women with either parenteral or topical administration of 5-FU. Two birth defects (cleft lip/palate and ventricular septal defect) have been reported with use of Efudex®, and multiple birth defects have been reported in a fetus of a patient treated with intravenous fluorouracil. However, according to the Sponsor, it appears that the time course of 5-FU administration relative to fetal development suggests a non-causative relationship.

No studies have been performed in animals to evaluate the reproductive effects of 5-FU incorporated into the Microsponge® system. Literature studies have shown that systemic administration of fluorouracil impaired fertility in rats and was teratogenic in rodents. Embryo lethal effects were also demonstrated in monkeys with parenteral administration. However, the amount of 5-FU absorbed following topical administration in human patients is much lower than the doses used parenterally in these animal studies. Nevertheless, the product should not be used in pregnant women or women with childbearing capacity who are not using adequate means of contraception.

10.3 Safety Conclusions

Safety data from the clinical studies presented suggest that Dermik's 5-FU 0.5% cream causes local cutaneous adverse events in a majority of patients treated. No systemic effects with a causal relationship to the study drug were noted during conduct of the clinical trials.

Facial irritation (consisting of dryness, erythema, pain, erosion, burning, etc.) was most common, being experienced by 79.8% to 94.7% of patients on active treatment in the pivotal studies. Erythema and dryness were the most common clinical signs of facial irritation. Intolerable inflammatory responses in 8.7% to 11% of patients requiring discontinuing study medication occurred. Erythema, dryness, and burning were the most common clinical signs and symptoms of facial irritation in each treatment group. The incidence of dryness, erythema, edema, erosion, pain and burning increased with increasing duration of assigned treatment. Patients in the Active Four Week treatment group showed a plateau of facial irritation severity at approximately two weeks of treatment.

According to the Sponsor, facial irritation occurred within 4 days after initiating therapy in most patients and persisted with continuing therapy and typically resolved in 18 –21 days after cessation of therapy irrespective of the duration of therapy. For all treatment groups, irritation resolved to levels below baseline severity, within two weeks of treatment discontinuation; however, some patients required treatment with topical steroids. Patients were not scheduled to be followed after the 4 week post-treatment assessment visit; therefore, there are no data regarding recurrence rates of treated lesions. Recurrence rate data would also assist the risk/benefit decisions since some degree of facial irritation can be expected for most patients and reach intolerance for some.

According to the submission (Vol. 1.28, pg. 8-12-103), one (9%) patient in the Dermik 5-FU 0.5% group in Study DL 6025-9520 and three (30%) in the Efudex group had slightly elevated percentages of eosinophils post-treatment; however, this was not noted in study DL6025-9518. Post-treatment clinical laboratory assessments were not performed in any other

clinical trial. No serious adverse event was considered related to study medication. There were no treatment-emergent adverse events noted due to Dermik's 5-FU 0.5% cream.

Four Phase I dermal safety studies performed in healthy subjects, Dermik 5-FU 0.5% cream, as well as its vehicle cream, showed little irritation potential, and no contact sensitization, phototoxic, or photoallergenic potential. Only one study, Study DL6025-9815 - A 21-Day Cumulative Irritation Study in Humans was performed with the "final to-be-marketed formulation"; however, according to a verbal communication from the FDA Chemist the removal of the ——— would be considered a minor change. From a clinical standpoint, there would be a greater concern with the addition of a ——— as opposed to removal provided that CMC microbiology is not affected.

Although 334 have been exposed to the 5-FU 0.5% formulation in Phase 2 and 3 studies, only 103 patients have been exposed > 2 to ≤ 4 weeks and 21 patients > 4 weeks. A minimum of 200 patients on active drug would have been preferable to demonstrate an adverse event occurrence rate of at least 1 %. Although not logically expected to be problematic from a clinical standpoint, the "to-be marketed" formulation was not tested in the Phase 2 and 3 clinical trials nor dermal safety studies (except primary irritancy).

A Phase 4 study is recommended as a condition of approval to assess post-treatment safety and efficacy. The Phase 4 study should include: 1) safety and efficacy data for treatment of actinic keratosis lesions located on the face, ears, and scalp (other sun-exposed areas might be included),
2) up to one year safety and efficacy post-treatment follow-up for incidence of recurrence,
3) safety of re-treatment of AKs with 5-FU 0.5%, ———————— ,and
4) assessment of eye irritation.

11 **Resistance** (not applicable for this submission)
12 **Labeling Recommendations** (See Labeling Review)
13 **Recommendations**
It is recommended that NDA 20-985 be approved for use of 5-flurouracil cream, 0.5% in treatment of actinic keratosis located on the face (excluding the ears) and anterior bald scalp, provided that Phase 4 studies be conducted as described under Safety Conclusion (Section 10.3). Treatment should be approved for once daily applications up to 4 weeks as tolerated.

[/S/] M.D. 8/8/00

/Brenda E. Vaughan, M.D.
Medical Reviewer
cc:
Archival NDA
HFD-540
HFD-540/Division Director/Wilkin [/S/] 9/12/00
HFD-540/Dermatology Team Leader/Okun
HFD-540/Medical Reviewer/Vaughan
HFD-725/Biostatistics Team Leader/Alosh
HFD-725/Biostatistician/Farr [/S/] 9/28/00
No DFS on 10/15/00

HFD-540/Pharm/Hill
HFD-540/Chemistry/Hathaway
HFD-540/Project Manager/Lutwak

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ON ORIGINAL