CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-955

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 20-985
Original

SEP 28 2000

1.1 NDA Submission number/type NDA 20-985

1.2 Applicant identification Dermik Laboratories, Inc.
500 Arcola Road
Collegeville, PA 19426

01.3 Submission/Review Dates

1.3.1	Date of submission (date of applicant's letter)	10-28-99
1.3.2	CDER stamp date	10-28-99
1.3.3	Date submission received by reviewer	01-04-00
1.3.4	Date review initiated	08-07-00
1.3.5	Date review completed	

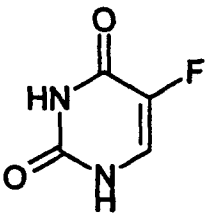
11.4 Drug Identification

1.4.1 Generic name 5-flurouracil

1.4.2 Proposed trade name

1.4.3 Chemical name 5-Fluro-2,4(1H,3H)-Pyrimidinedione

1.4.4 Chemical structure



1.4.5 Molecular formula: $C_4H_3FN_2O_2$

1.4.6 Molecular weight: 130.08

1.5 Pharmacological Category: Antineoplastic, Antimetabolite

1.6 Dosage form: Cream

1.7 Route of Administration: Topical

1.8 Proposed Indication & Usage section

[redacted] is indicated for the topical treatment of multiple actinic or solar keratoses of the face and scalp.

1.9 Proposed Dosage & Administration section

[redacted] Local irritation is not markedly increased by extending treatment from 2 to 4 weeks, and is generally resolved within 2 weeks of cessation of treatment.

Reviewer's comment: *As noted above, the proposed area of application for the 5-FU is limited to the face. Although the face tends to have greater sun exposure, actinic keratoses occur on sun exposed areas other than the face. Lesions located on the ears were not counted during the Phase 3 clinical studies.*

1.10 Related Drugs

Formulations of 5-flurouracil for topical treatment of actinic or solar keratoses reviewed by the FDA under INDs sponsored by Dermik Laboratories, Inc. were studied under IND ———

Related Reviews: Biopharm Review dated: 05-01-00
Chemistry Review dated: (pending)
Pharm/Tox Review dated: (pending)
Statistical Review dated: 06- -00

1.11.1 NDA Volumes Reviewed

This review is based on the following volumes: 1.1, 1.14, and 1.17 – 1.33.

Document Identification	Date Received
NDA 20-985 BL	01-20-00
NDA 20-985 NC	06-22-00
NDA 20-985 BM	06-26-00

1.11.1 Other Documents Reviewed

1.11.2 Amendments with Dates

1.12 Regulatory Background

On October 28, 1999, Dermik Laboratories, Inc. submitted New Drug Application 20-985. The application proposes the use of ———fluorouracil cream) Cream 0.5% in treatment of patients with multiple actinic or solar keratosis of the face and scalp. An End-of Phase 2 Meeting was held on January 29, 1997 and a Pre-NDA Meeting was held on July 26, 1999 between the Sponsor and the Division. According to the Sponsor there were no protocol amendments submitted to the Phase 3 protocols.

According to End of Phase 2 Meeting Minutes (Meeting ID# 582, held 01/29/97), the Sponsor indicated that evaluation of "endpoint ——— ' was for assessment of ——— effects. The Division conveyed to the Sponsor that ——— effect is more specific and the sponsor would need to discuss how they would assess ——— before the Agency could agree. There were no additional discussions or commitments between the Sponsor and the Agency regarding the ——— effect claims.

The Sponsor was advised at the Pre-NDA Meeting that the Sponsor needed to adjust for multiple comparisons among arms using a Bonferroni or any other appropriate adjustment procedure if the Sponsor desired to demonstrate superiority of any or all three duration of treatment vs. vehicle. The Sponsor indicated that no labeling or marketing claims with regards to the 5-flurouracil Microsponge® formulation are planned.

The Pre-NDA meeting minutes reflects that there was a primary CMC issue regarding the ——— According to the minutes, the Sponsor had 18 months of stability data with — and 6 months without — The Agency wanted to make sure that the pivotal clinical trials were performed with drug product that was within specification for 5-FU.

Table of Content

3 **Chemistry/Manufacturing Controls (See Chemistry Review)**

Dermik's 5-flurouracil 0.5% cream (DL 6025) is a topical preparation containing flurouracil the fluorinated pyrimidine 5-fluoruracil, an anti-neoplastic anti-metabolite. The topical cream contains 0.5% 5-fluoruracil on a w/w% basis. The 5-fluorouracil is added to the preparation in two forms. The first form is 5-flurouracil, USP, ——— The second form is as 5-fluorouracil —— in a methyl methacrylate/ ——glycol dimethacrylate — (Microsponge®) and ——— dimethicone, ——— manufactured by ——— The chemical components are as follows:

Ingredient	Quantity w/w %
5-Fluorouracil	
Carbomer 940, NF	
Glycerine, USP	
Polyethylene Glycol 400, NF	
Polysorbate 80, NF	
Sorbitan monooleate, NF	
Octyl hydroxy sterate, NF	
Methyl Gluceth-20,	
Stearic Acid, NF	
5-FU in acrylates ———	
— Dimethicone in acrylates ———	
Trolamine, — NF	
Propylene Glycol, USP	
Methyl Paraben, NF	
Propyl Paraben, NF	
Purified water, USP	

According to the Sponsor, ——— that is one component of the ——— was removed due to a chemical incompatibility detected between — and the active pharmaceutical ingredient, 5-FU following Phase 3. The dosage forms used in the Phase 3 clinical studies were from Lot 970080. Dermal safety studies except DL-6025-9815, the 21-Day cumulative irritation test, were also performed without — PK study DL-6025-9726 was performed with three 0.5% formulations with and without —

According to the Sponsor (Vol. 1.33, pg. 3-1-49), stability data included in this application for Lot 970080 that was used in the Phase 3 clinical trials demonstrate that the test article was within the proposed specification for 5-fluorouracil assay during the treatment period of the clinical trials. This issue is currently being addressed by Chemistry.

4 **Animal Pharmacology/Toxicology** (See Pharm/Tox Review)
The mechanism of action of 5-FU has been extensively studied; therefore, the Sponsor conducted a literature review in support of this NDA.

A single dose oral toxicity study comparing — 5-FU in Microsponge® to the marketed formulation of 5.0% Efudex was conducted. Seven repeat dermal dose toxicity studies were conducted. According to the submission, except for an increase in circulating neutrophils at the highest dose (6 mg/kg/day of the active ingredient, 5-FU) in the 90-day rat study, there has been no evidence of significant systemic toxicity in any of the non-clinical studies conducted with 5-FU in the Microsponge® formulation. However, there was one high dose male rabbit treated with 400 mg/kg/day of — 5-FU cream (20 mg/kg/day of the active ingredient, 5-FU) in a 5-day dermal range study conducted at the ——— that died at study day 3. According to the submission, no gross changes were observed other than skin irritation at the site of administration. Additionally, an outbreak of mucoid enteritis in a 30-day rabbit study conducted at the same laboratory caused death and subsequent early termination of the study. The Sponsor is inferring a similar type cause of death at study day 3 in the one high dose male rabbit rather than a treatment related death.

Effects at the dermal administration site have been observed in a number of studies with either the 0.5% or — Microsponge® formulation. These changes have included dermal irritation, inflammation and ulceration in rats, rabbits and/or Yucatan micropigs following repeated topical administration of 5-FU formulations.

Absorption, distribution, metabolism, excretion (ADME) studies with 5-FU formulations with the Microsponge® were as follows: a 14-day study in Yucatan micropigs, an 8-week study in Yucatan micropigs, and two studies utilizing permeation models. No carcinogenicity potential studies, reproductive toxicity, or mutagenicity studies of 5-FU incorporated into the Microsponge® have been performed in animals in support of this NDA.

Safety evaluation of the Microsponge® (acrylates ———) alone was conducted. According to the Sponsor, the Microsponge® system material, i.e., acrylate — as been used at least ten years in cosmetics and is listed in the Cosmetics, Toiletries and Fragrance Association, 7th Edition, pages 26 and 2126, 1997. According to the submission, results of three *In Vivo toxicology* studies demonstrated that the polymers did not cause acute oral toxicity and were not irritating to skin or eyes. Mutagenicity studies with other Microsponge® ——— were negative at all doses.

4 **Microbiology**
The Sponsor is not seeking an ——— indication for the 5-Flourouracil 0.5% cream (DL6025).

6 **Human Pharmacokinetics/Pharmacodynamics** (See Clinical Pharmacology/Biopharmaceutics Review dated 04/20/00 for details.)

Florouracil is an antineoplastic agent containing a fluorinated pyrimidine. As a pyrimidine analog, florouracil acts as an anti-metabolite to uracil. Florouracil interferes with DNA synthesis by competitive inhibition of thymidylate synthestase. Death of proliferating cells by 5-FU is primarily through the inhibition of DNA synthesis. To inhibit DNA synthesis, 5-FU first goes through biochemical activation (i.e., metabolism) to form 5-fluoro-deoxyuridine monophosphate (FdUMP). The metabolite FdUMP subsequently leads to inhibition of thymidylate synthetase, an enzyme essential for DNA synthesis.

To a lesser extent, florouracil inhibits the formation of RNA. 5-FU can be metabolized to 5-fluorouridine-triphosphate (FUTP). The metabolite FUTP can subsequently be incorporated into all species of RNA and affect many processes important to RNA function. These effects on RNA can lead to errors in protein synthesis that contribute to cell death.

Flourouracil is approved as an intravenous injection. Florouracil is also approved as a topical 5-flurouracil (5-FU) solution and cream in the following formulations: Efudex® (5% cream and 2% or 5% solution) and Fluoroplex® as a 1% cream or solution for treatment of actinic keratosis. The Sponsor's formulation, 0.5% 5-FU cream is not marketed in any country. The 5-FU is —— in a methacrylate/ —— glycol dimethacrylate ——— (Microsponge®) ——— dimethicone as a ———

The Sponsor conducted the following studies in support of the NDA: one multiple dose pharmacokinetic study (DL-6025-9720) in patients with actinic keratosis and two in vitro percutaneous absorption studies (DL-6025-9522 and DL-625-9726). A review of the literature was also performed.

Study DL-6025-9720 is titled "A Multiple Dose Pharmacokinetic Study of 5-Fluorouracil in Patients with Actinic Keratosis Treated with Either — 5-FU (0.5%) Topical Cream or Efudex® (5.0%) Topical Cream". Twenty-one male and female Caucasian patients with a mean age of 64 years with small (3), medium (11), and large (7) frames entered the study. Each treatment group on average had 8-9 actinic keratosis lesions at baseline (range of 3 – 34 lesions). Eleven were randomized for treatment with 0.5% 5-FU and 10 with Efudex and 20 patients completed the study. One patient in the 0.5% 5-FU group was dropped from the study by the investigator for noncompliance.

— 5-FU (0.5%) Topical Cream (1 gram) was applied once daily in the morning to the face and anterior bald scalp for 28 doses and Efudex® (5.0%) Topical Cream (1 gram) was applied twice daily for maximum of 55 doses. Plasma and urine samples were analyzed for the presence of 5-FU by specific ——— assays with lower limits of quantitation of —— ng/ml and — ng/ml, respectively.

It was difficult to draw a conclusion regarding systemic exposure to — 5-FU and Efudex® Cream based on plasma concentrations of flurouracil. Three patients in the Dermik 0.5% 5 –FU cream had detectable plasma concentrations of 5-FU. Only one patient had sufficient data points to calculate pharmacokinectic parameters. The highest individual concentration values observed ranged from ——— ng/ml.

For urine concentrations, the mean Cum Ae over 24 hours was 2.737µg with a maximum excretion rate — µg /hr for Dermik 0.5% cream. The mean Cum Ae over 24 hours was 119.833 µg /hr for Efudex® Cream, with a maximum excretion rate of —— µg /hr. The maximum excretion rate occurred during the 0-2 hour interval post final dose.

In terms of the applied dose of 5-FU, according to the Biopharmaceutics review of Study DL-6025-9720, the data suggests that 0.055% of the applied final 1 g dose of 0.5% Dermik cream and 0.24% of the 1 g dose of 5% Efudex® cream was excreted in the urine. Investigators have suggested that less than 10% of the systemically available 5-FU is excreted in the urine. Based on this urinary excretion data, there is a 0.55% (0.055% x 10) systemic absorption of 5FU from Dermik's cream and 2.4% (0.24% x 10) systemic absorption from 1 g dose of the Efudex® cream; however, based on the Efudex® package insert, systemic absorption is 5.96%. A difference in analytical methodology might explain the discrepancy in that the original Efudex® study was a ^{14}C radiolabeled study that did not distinguish between parent and metabolites.

According to the Biopharm review, the Sponsor demonstrated lower but not proportionate systemic exposure of flurouracil as 0.5% cream compared to currently marketed 5% Efudex® Cream.

At least one adverse event (AE) was reported during the trial in 14 (67%) of the patients. AEs were reported in 4 of 11 patients in the — 5-FU treatment group and 10 (100%) of patients in the Efudex® Cream treatment group. Most of the AEs were application site reaction, exfoliative dermatitis, and headache in the — 5-FU treatment group. Maculopapular rash, application site reaction, and erythema were the most common AEs reported in the Efudex® Cream treatment group.

Reviewer's comments: *Exfoliative dermatitis is a potentially serious AE. This AE was reported with use of Efudex in this clinical study and has been reported previously with use of 5-FU.*

No clinically significant trends in vital signs, physical examinations, or routine clinical laboratory tests were observed. According to the submission, one (9%) patient in the Dermik 5-FU group and three (30%) in the Efudex group had slightly elevated percentages of eosinophils post-treatment. There were no deaths reported or dropouts due to AEs during the study. Three Efudex® Cream

treatment group patients discontinued application after 18 days because of facial irritation.

Among the overall conclusions in the Biopharm Review, *in vitro* percutaneous absorption studies (DL-6025-9522 and DL-625-9726) demonstrated that absorption of 5-FU was site dependent (legs showing greater absorption than the trunk).

Reviewer's comments: *The inclusion criterion (Vol. 1.14, pg. 6-1-70) permitted entry with 3 or more actinic keratosis lesions present at baseline with application of study drug limited to the face. The Phase 3 clinical trials required a minimum of 5 lesions for entry. The range of lesion counts at baseline was 3-43 for the PK study; for the Phase 3 studies, the range was 4-94. For the PK study, patients with extensive disease should have been studied.*

7 Human Clinical Experience

7.1 Foreign Experience

The Sponsor's formulation, 0.5% 5FU cream is not marketed in any country nor are applications pending in any country.

7.2 Post-Marketing Experience

There is no post-marketing experience with the Sponsor's formulation to report; however, florouracil is approved in the United States as a topical 5-flurouracil (5-FU) solution and cream in the following formulations: Efudex® (5% cream and 2% or 5% solution) and Fluoroplex® as a 1% cream or solution.

8 Clinical Studies

8.1 Introduction

The sponsor lists the NDA for 5-fluorouracil 0.5% cream as a 505(b)(1) application. This dosage form has been studied under IND ———

Actinic keratosis lesions are the result of cumulative ultraviolet radiation and may be precursors of squamous cell carcinoma of the skin (Preston DS, Stern, N Engl J Med, 327: 1649 –1662, 1992). Actinic keratoses (AKs), also referred to as solar keratoses, are cutaneous dysplasias of the epidermis that occur on sun-exposed body areas of middle-aged or elderly, fair-skinned individuals and are the most common pre-cancerous lesion among these individuals living in sunny locations. Lesions appear as skin colored to reddish brown or yellowish black ill-defined macules or papules varying from pinhead size to several centimeters in diameter.

Dermik's 5-FU 0.5% cream is a topical preparation containing the fluorinated pyrimidine 5-fluorouracil, an anti-neoplastic anti-metabolite. The anti-metabolite fluorouracil was first synthesized in 1957. Improvement of actinic keratoses was observed during the use of systemic 5-fluorouracil for treatment of cancer. The systemic absorption of topically administered 5-fluorouracil is thought to be limited, thereby, its cellular effects can be targeted to skin lesions in the area of

application. Topical 5-fluorouracil solution and cream are approved for treatment of actinic keratosis and are available in concentrations of 1% (Fluoroplex®) as well as 2% (Efudex® -solution only) and 5% (Efudex®).

Eleven clinical trials were conducted by the Sponsor to support this NDA for use of 5-FU 0.5% cream for treatment of AKs. These studies are listed as Table 1 (Sponsor's Table 11, Vol. 1.33, pg. 3-1-83). Two identical clinical trials (Study DL-6025-9721 and Study DL-6025-9722) for treatment of actinic or solar keratoses with topical 5-FU 0.5% cream formulation were identified as Phase 3 studies. Studies DL-6025-9518 and DL-6025-9618 are listed as Phase 2 supportive controlled clinical trials.

Special studies submitted include Pharmacokinetic Study DL-6025-9720, and dermal safety studies (DL-6025-9508, DL-6025-9509, DL-6025-9713, DL-6025-9714, DL-6025-9715, and DL-6025-9815).

[redacted]

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[redacted]

Table 1 (Sponsor's Table 11): Table of Clinical Studies for DL-6025

Study #/ Investigator/ #Centers	Type of Study	Start Date - Stop Date	Treatments/ Dose Concentration	Duration of Treatment	# Subjects/ Patients on each Treatment	Age Range (Yrs) Sex (M:F) Race	Safety Assessments
Preliminary Phase I Dermal Safety Studies with 5-FU 5.0% Cream Formulation							
Study DL-6025-9508 Hilltop Research/ Richard S.Berger, MD One site	Evaluation of Primary Irritation Potential in Humans	6/6/1995 - 6/9/1995	Experimental 5-FU Cream Experimental 5-FU Vehicle Cream Efudex® Cream	24 hour occluded application	26 healthy subjects received 24 hour applications of each of the three materials.	"Adult" "Male and Female"	Scoring of Skin Irritation at application site
Study DL-6025-9509 Hilltop Research/ Richard S.Berger, MD One site	Repeated Insult Patch Test (Jordan-King Modification of the Draize Procedure)	6/12/1995 - 7/27/1995	Experimental 5-FU Topical Cream — Experimental 5-FU Vehicle Cream Efudex® 5% Topical Cream	Each test material applied for three weeks, followed by 2 wks rest, then challenge application	28 healthy subjects each received all three test materials simultaneously.	"Adult" "Male and Female"	Evaluation for delayed contact allergy; Adverse events

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Table 1 (Sponsor's Table 11): Table of Clinical Studies for DL-6025 (cont'd.)

Study #/ Investigator/ #Centers	Type of Study	Start Date - Stop Date	Treatments/ Dose Concentration	Duration of Treatment	#Subjects/ Patients on each Treatment	Age Range (Yrs) Sex (M:F) Race	Safety Assessments
Phase I Dermal Safety Studies with 5-FU 0.5% Cream in Normal Subjects							
Study DL-6025-9713 Ivy Labs/ Kays Kaiby, MD One Site	Phototoxicity	12/1/1997 - 12/12/1997	5-FU Cream 0.5%, Placebo for 5-FU Cream	24 hr. patch application to duplicate sites on lower midback; one set of sites irradiated; reactions graded immediately, 24 and 48 hrs. post irradiation (approx. four days total)	20 subjects treated with both active and placebo	18-59 9:11 20 Cauc.	Skin responses to each patch application; Adverse events
Study DL-6025-9714 Ivy Labs/ Kays Kaiby, MD One Site	Photoallergy	11/3/1997 - 12/5/97	5-FU 0.5% Cream Placebo for 5FU Cream	24 hr. patch application followed by 3 MED doses; MED recorded 24 hrs. later. Test repeated 6 times at same test site 10-14 day rest period followed by duplicate site 24 challenge/ irradiation. Evaluated 48 and 72 hrs. post irradiation (total duration 6 weeks)	28 subjects treated with both active and placebo	18-58 12:16 28 Cauc.	Skin responses to each patch application; Adverse events

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Table 1 (Sponsor's Table11): Table of Clinical Studies for DL-6025 (cont'd)

Study #/ Investigator/ #Centers	Type of Study	Start Date - Stop Date	Treatments/ Dose Concentration	Duration of Treatment	# Subjects/ Patients on each Treatment	Age Range (Yrs) Sex (M:F) Race	Safety Assessments
	Phase I Dermal Safety Studies with 5-FU 0.5% Cream in Normal Subjects (Continued)						
Study DL-6025-9715 Hill Top Research/ Richard S. Berger, MD One Site	Repeated Insult Patch Test (Jordan-King Modification of Draize Procedure)	10/6/1997 – 12/5/1997	5-FU 0.5% Cream Placebo for 5-FU Cream	48 hr patch applications repeated for 3 weeks, followed by 2 week rest, then 48 hr challenge application	253 enrolled; 215 completed. Subjects rec'd both test articles at the same time.	18-81 39:214 235 Cauc. 6 Black 9 Hisp. 3 Asian	Skin responses to each patch application; Adverse events
Study DL-6025-9815 Hill Top Research/ Anthony J. Parisse, Ph.D. One Site	Cumulative Irritation	12/2/1998 – 12/23/1998	5-FU Cream 0.5%, * Placebo for 5-FU Cream* Saline	24 hr. applications repeated for 21 days with scoring for cumulative irritation every 24 hrs.	31 subjects treated with active, placebo and saline	18-66 26:5 27 Cauc. 3 Black 1 Hisp.	Skin responses to each patch application; Adverse events

*to-be-marketed formulation

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Table 1 (Sponsor's Table 11): Table of Clinical Studies for DL-6025 (cont'd)

Study #/ Investigator/ #Centers	Type of Study	Start Date - Stop Date	Treatments/ Dose Concentration	Duration of Treatment	# Subjects/ Patients on each Treatment	Age Range (Yrs) Sex (M:F) Race	Safety Assessments
Phase I Pharmacokinetic Study with 5-FU 0.5% Cream in Patients							
Study DL-6025-9720 MDS Harris Labs/ Irving E. Westin, M.D. One Site	A Multiple Dose Pharmacokinetic Study of 5-Fluorouracil in Patients with Actinic Keratosis Treated with Either 5-FU (0.5%) Topical Cream or Efudex® (5.0%) Topical Cream	4/5/98- 6/1/98	5-FU 0.5% Cream – QD Efudex® 5% Cream – BID	28 days of treatment followed by 24 hr. post final treatment blood collection (11 samples)	21 total patients 11 (5-FU 0.5%) 10 (Efudex® 5%)	50-85 15:6 Caucasian	Sitting vital signs, physical exams, laboratory samples, adverse events, and evaluations of facial irritation

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Table 1 (Sponsor's Table 11): Table of Clinical Studies for DL-6025 (cont'd.)

Study #/ Investigator/ #Centers	Type of Study	Start Date - Stop Date	Treatments/ Dose Concentration	Regimen/ Duration of Treatment	Indication # Subjects/ Patients on each Treatment	Age Range (Yrs) Sex (M:F) Race	Safety Assessments
Supportive Controlled Clinical Trials (Phase II)							
Study DL-6025-9518 Multicenter (U.S.) Three sites	Phase II, Controlled, Randomized, Double-blinded Study	3/26/1996 - 8/5/1996	5-FU 0.5% Cream 5-FU — Cream 5-FU — Cream Efudex® 5% Cream Vehicle (Microsponge® Polymer Cream)	5 treatment groups: Each of the treatment groups applied cream twice daily for 4 weeks	Actinic Keratosis 104 total patients: 25 (5-FU 0.5%) 21 (5-FU —) 24 (5-FU —) 22 (Efudex 5%) 12 (Vehicle)	43 - 82 83:21 104 Cauc.	Adverse events Facial Irritation Laboratory Evaluation
Study DL-6025-9625 Multicenter (U.S.) Three sites	Phase II, Controlled, Randomized, Investigator-Blinded Study	11/18/1996 - 3/26/1997	5-FU 0.5% Cream Efudex® 5% Cream Vehicle (Microsponge® Polymer Cream)	5 treatment groups: 5-FU BID x 2 wks or 5-FU BID x 1 wk or 5-FU QD x 1 wk or Efudex® BID X 2 wks or Vehicle BID x 2 wks	Actinic Keratosis 79 total patients: 17 (5-FU 2x2) 18 (5-FU 1x2) 17 (5-FU 1x1) 18 (Efudex 2x2) 9 (Vehicle)	30 - 86 65:14 Caucasian (96%) Hispanic (3%) Other (1%)	Adverse events Facial Irritation

Table 1 (Sponsor's Table 11): Table of Clinical Studies for DL-6025 (cont'd.)

Study #/ Investigator/ #Centers	Type of Study	Start Date - Stop Date	Treatments/ Dose Concentration	Regimen/ Duration of Treatment	Indication # Subjects/ Patients on each Treatment	Age Range (Yrs) Sex (M:F) Race	Safety Assessments
Adequate and Well Controlled Clinical Trials (Phase III)							
Study DL-6025-9721 Multicenter (U.S.) 9 Sites	Phase III, Vehicle controlled, Randomized, Double-blinded Study	1/12/1998 7/14/1998	5-FU 0.5% Cream Vehicle (Microsponge® Polymer Cream)	Six treatment groups: 5-FU QD x 1 wk 5-FU QD x 2 wks 5-FU QD x 4 wks Vehicle QD x 1 wk Vehicle QD x 2 wks Vehicle QD x 4 wks	Actinic Keratosis 207 Patients: 47 (Active 1 wk) 46 (Active 2 wk) 45 (Active 4 wk) 69 (Vehicle)	39-86 166:41 201 Cauc.; 6 Hispanic	Adverse Events Facial Irritation
Study DL-6025-9722 Multicenter (U.S.) 9 Sites	Phase III, Vehicle-controlled, Randomized, Double-blinded Study	1/16/1998 7/16/1998	5-FU 0.5% Cream Vehicle (Microsponge® Polymer Cream)	Six treatment groups: 5-FU QD x 1 wk 5-FU QD x 2 wks 5-FU QD x 4 wks Vehicle QD x 1 wk Vehicle QD x 2 wks Vehicle QD x 4 wks	Actinic Keratosis 177 Patients: 38 (Active 1 wk) 41 (Active 2 wk) 40 (Active 4 wk) 58 (Vehicle)	35-89 152:25 177 Cauc.	Adverse Events Facial Irritation

8.2 Indication #1 Treatment of Actinic Keratosis

This study was designed to compare the efficacy and safety of three different treatment durations of an experimental topical 5-FU 0.5% cream formulation to that of vehicle control treatment.

8.2.1 Reviewer's Trial #1 Sponsor's Protocol DL-6025-9721

(Study Dates: January 12, 1998 to July 14, 1998)

Title: "A Vehicle-Controlled, Randomized, Double-Blinded Study Comparing the Safety and Efficacy of DL-6025 0.5% Cream versus Vehicle in the Treatment of Actinic Keratosis"

8.2.1.1 Objective Rationale

The objective of this study was to investigate the clinical safety and efficacy of an experimental formulation of 5-fluorouracil 0.5% cream in a treatment regimen response study, compared to vehicle control, for the treatment of actinic keratosis.

8.2.1.2 Design

This was a randomized, controlled, double-blinded, parallel-group, multi-center, six-arm treatment response study conducted in the United States designed to compare the efficacy and safety of an experimental 5-FU 0.5% cream applied once daily for one, two or four weeks to a vehicle control in the treatment of actinic keratosis.

8.2.1.3 Protocol Overview

8.2.1.3.1 Population Procedures

Diagnosis & Significant Inclusion/Exclusion Criteria

Adult male or female patients with 5 or more actinic keratoses that were either palpable or visible to the unaided eye on the face and/or anterior bald scalp were enrolled. At least 5 of the lesions had to measure ≥ 4 mm in longest diameter. Prior treatment with systemic 5-fluorouracil or systemic cancer therapy within six months of study start, with systemic steroids within 2 months of study start, or with retinoids or topical corticosteroids within 1 month of study start was not permitted.

Female patients were either post-menopausal for at least one year, or had a hysterectomy, or had a tubal ligation. If of childbearing potential, agreed to abstain from sexual intercourse, or use oral/systemic contraceptives, an intrauterine device (IUD) or Norplant starting at least 28 days prior to study entry and throughout the study. Female patients of childbearing potential had to have a negative urine pregnancy test prior to the first application of test medication. Female patients of childbearing potential had to have a normal menstrual flow within approximately one month prior to study entry. Pregnant or lactating females were excluded.

Patients treated with other topical agents for the treatment of actinic keratosis within 1 month prior to the start of the study were prohibited, including, but not limited to, Actinex, glycolic acid products, alpha-hydroxy acid products, and chemical peeling agents. These topical agents for treatment of actinic keratosis were prohibited during conduct of the study.

Concomitant Medication

Systemic or topical use of corticosteroids to the treatment area during any part of the study was prohibited. If the patient's degree of irritation required topical or systemic steroid therapy, the patient was discontinued from treatment phase of study but assessed for efficacy at the study end evaluation. Hytone ® 2.5 % Cream was provided by the sponsor for patients who required topical steroids. The use of steroids was recorded on Case Report Form.

Reviewer's comments: *Although Hytone ® 2.5 % Cream was permitted per protocol for use for facial irritation, more potent topical steroids were used in Study DL-6025-9722 in two patients (e.g. Temovate E Cream, Lidex Cream, and Westcort).*

No other topical medications, cosmetics (except for eye makeup and lipstick), or sunscreens are to be applied to the face during the study. If needed, a sunscreen/moisturizer, provided by the sponsor, may be used. Patients were instructed to avoid excessive exposure to sunlight was during the study.

Screening Visit–
In addition to other screening procedures, the potential for severe irritation reaction was fully explained and documented. Since patients receiving 5-FU treatment often experience severe irritation, it was imperative that they be forewarned of the nature of the treatment. During the visit it was recommended that prospective patients be shown photographs of typical reactions that occur with 5-FU treatment.

Study Plan and Randomization
After qualifying for the study, subjects were randomized 2:1 (active vs. vehicle) and assigned to one of six experimental treatment groups. The study procedures consisted of a screening visit within two weeks prior to first drug application, a baseline clinical evaluation including randomization and first treatment (Visit 1, Day 1), a treatment phase, and a 4 week post-treatment follow-up phase scheduled at weekly intervals to complete a total of four weeks. 5-FU 0.5% cream in a Microsponge® formulation or vehicle were applied topically once daily to the affected areas of the face and/or anterior bald scalp for either 1, 2, or 4 weeks. Planned duration of treatment was 1, 2, or 4 weeks, followed by 4 weeks of follow-up (Total of up to 5 to 8 weeks).

Study Drug
All active product was from Lot #970080. All vehicle products were from Lot #970051.

Application of Medication
The first application was made at the study center under the supervision of a designated staff member. The Patient Instruction Sheet (received 06-26-00) indicated that patients were to apply the study medication 10 minutes after thoroughly washing, rinsing, and drying the face. The study medication was applied as a thin film entirely across the face (using care to avoid near the eyes, nose, and mouth) stopping at the hairline, ears, and jaw line. Medication was to be applied as a thin film, massaging it into the skin each morning or evening at 24-hour intervals in accordance with assigned treatment schedule.

Reviewer's comments: *The protocol and Patient Instruction Sheet did not address who decided timing of application of medication (e.g., morning or evening). These data were not captured on the CRF are not in the database. Additionally, removal of medication or sharing of towels used in removal was not addressed.*

Should a facial moisturizer/sunscreen be desired, the patient was to apply the product provided for this purpose and this should be recorded on the Case Report Form. The

moisturizer/sunscreen could be applied two hours after the study material had been applied. Each patient received a detailed patient instruction sheet at the initial visit.

The patient was instructed to use an adequate amount of the study material to cover the entire forehead, cheeks, nose, chin and frontal scalp (if included as a treatment area) regions. If more than two study drug applications were missed within a treatment week the patient was to be dropped from the study as a protocol deviation.

Reviewer's comments: *Patients were not provided with or instructed to apply medication with* ———

During the treatment phase, patients were seen on Days 1 and 8 (1 week treatment groups), or Days 1, 8, and 15 (2 week treatment groups), or Days 1, 8, 15, and 29 (4 week treatment groups). Patients were seen weekly during the follow-up phase. Visits were to be completed within 1(±) calendar day of the actual treatment calendar day in both the treatment and follow-up phases. The point of cure was the last post-treatment follow-up evaluation.

Efficacy Assessments:
The Sponsor's primary assessments were: 1) the Regional Count of Visible and/or Palpable Actinic Lesions performed at baseline and the post-treatment follow-up evaluation and 2) the Physician Global Assessment of Improvement rating to determine actinic keratosis total clearance (Physician Global Evaluation Score of the Case Report Form) performed at the last post-treatment follow-up visit. The Physician Global Assessment of Improvement rating is the evaluation of percent improvement over baseline.

The Sponsor's secondary assessments were 1) the Physician Global Assessment of Improvement (all ratings) evaluated at the final post-treatment visit, 2) ——— Assessment and 3) Overall Severity Rating of Actinic Keratoses.

Reviewer's comments: ——— *assessments were not reviewed in this NDA. According to the pre-NDA Meeting Minutes, the Sponsor indicated they are looking for* ——— *effect as plans for "endpoint overall severity of* ———. *The minutes indicated that* ——— *is more specific and the Sponsor would need to discuss how they would assess* ——— *before the Agency could agree. There are no known discussions between the Sponsor and the Division regarding how* ——— *were assessed during the study.* ——— *assessments are not secondary efficacy endpoints. The Sponsor is encouraged to submit studies for a separate claim.*

Regional Count of Visible and Palpable Actinic Lesions Only lesions that were either visible to the unaided eye or palpable on the face (defined as the hairline superiorly, the mandibular angle inferiorly, and the tragus (laterally) and/or frontal scalp (defined by an imaginary longitudinal line drawn directly across the scalp from the right tragus to the left tragus), if this was included as a treatment area, were counted. Lesions were carefully counted in four separate quadrants. The location of each actinic keratosis lesion was recorded. This diagram was used at the post-treatment evaluation as a reference.

Safety Assessments
Safety was evaluated by continuous monitoring of adverse events. A specific adverse event Case Report Form (CRF) was used to collect information regarding adverse events affecting facial skin and scalp. Blood and urine samples for routine hematology, serum chemistry and urinalysis evaluations were obtained only prior to the treatment phase.

Women of childbearing potential were required to have a negative urine pregnancy test prior to treatment. A urine pregnancy test was to be repeated at the completion of the treatment phase, however, the case report form was designed to collect pregnancy test results at each visit which prompted site personnel to do so for the 7 women of child bearing potential. Urine pregnancy tests were conducted at the study site.

Reviewer's comments: *A rationale for not repeating clinical laboratory test at the end of treatment phase was not provided. No data were provided regarding subjects excluded prior to randomization based on abnormal laboratory abnormalities.*

Patient Discontinuation (Removal of Patients from Therapy or Assessments)
Patients were discontinued from therapy if they experienced an adverse event of sufficient degree to warrant a change or discontinuation of therapy. Those patients whose treatments were discontinued early due to intolerable inflammatory response were considered to have successfully completed the treatment phase and were entered into the post-treatment follow-up phase. Patients requiring topical or systemic steroid therapy for skin irritation were discontinued from the treatment phase of the study. A treatment failure was not considered an adverse event.

Photography
Baseline and weekly on treatment and follow-up visit photographs of actinic keratosis lesions were performed at two centers (Dr. Stewart and Dr. Bucko).

Data Analysis (*See Statistical Review for details)*
According to the Sponsor, no interim analyses were planned or performed. There were no protocol amendments. Treatment efficacy and safety summaries were based on the intent-to-treat (ITT) population (all patients randomized to treatment).

Efficacy Parameters
The Sponsor's primary efficacy variables were actinic keratosis lesion reduction from baseline and actinic keratosis total clearance. The Sponsor's secondary efficacy variables were the Physician Global Assessment of Improvement (PGAI) score, the Overall Severity Rating of Actinic Keratosis, and the [redacted] Assessment, each evaluated at the last post-treatment follow-up evaluation.

The proportion of patients with treated lesions totally cured vs. the similar proportion in the placebo group is the primary efficacy assessment evaluated by the FDA. Other efficacy comparisons are considered secondary endpoints. As previously stated, [redacted] Assessment will not be reviewed.

The statistical significance of the following pair-wise treatment differences was to be evaluated within the context of the statistical model for each efficacy or skin irritation evaluation:

1) 5-FU (0.5%) x 4 weeks vs. 5-FU (0.5%) x 2 weeks
2) 5-FU (0.5%) x 4 weeks vs. 5-FU (0.5%) x 1 week
3) 5-FU (0.5%) x 2 weeks vs. 5-FU (0.5%) x 1 week
4) 5-FU (0.5%) x 4 weeks vs. combined vehicle treatment groups
5) 5-FU (0.5%) x 2 weeks vs. combined vehicle treatment groups
6) 5-FU (0.5%) x 1 week vs. combined vehicle treatment groups

A Dunnett adjustment was to be applied if the contrasts 4, 5, and 6 have comparison-wise significance levels greater than p=0.03. The interpretation of contrasts 1, 2, and 3 were to be conditional upon finding each of the active treatments significantly more effective than the vehicle. Confidence intervals (90%) about treatment differences 1, 2, and 3 will also be reported.

Statistical Methodology (Safety)
In this study all randomized patients applied at least one dose of study medication or vehicle. Incidence of Adverse Events (All adverse events or subsets): Incidence frequencies in each treatment group were summarized for all AEs, by severity and relationship to treatment were assessed. Details of Facial Irritation as Maximum Severity of Facial Irritation Adverse Events, Facial Irritation Symptom Incidence Onset and duration of Facial Irritation Adverse Events, Severity of Facial Irritation by Visit, and Facial Irritation Symptoms by Visit were analyzed.

Financial Disclosure
The Sponsor has submitted certification for financial interests and arrangements of clinical investigators participating in Study DL6025-9721. According to the Sponsor, no investigator participating in the study received compensation that was dependent on favorable study outcome, has ownership in of stock in the company that cannot be readily determined through reference to public prices, nor has a proprietary interest in the drug product.

8.2.1.4 Study Results
A total of 207 patients were randomized, 138 were randomized into one of the three active treatment groups and 69 were randomized into one of three Vehicle treatment groups. A total of 203 (98.1%) patients completed the study. Tables 2-6 list principal investigators, randomization by investigator, patient disposition, and demographics/ baseline characteristic data.

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Table 2: (Sponsor's Table 1): Principal Investigators (Vol. 1.18, pg. 8-2-36)

Investigator Name, Affiliation, and Address	Dermik Investigator No.	# of Patients Enrolled
Alicia Bucko, D.O. Academic Dermatology Associates 1203 Coal SE Albuquerque, NM 87106	US03068	23
Steven Davis, M.D. Diseases & Surgery of the Skin 8038 Wurzbach Road, #450 San Antonio, TX 78229	US03036	36
Paul Espy, M.D. Espy Research Group 900 Campbell Hill St. Marietta, GA 30060	US02986	18
Peter Hino, M.D. Dermatology Center of Dallas 8230 Walnut Hill Lane, #500 Dallas, TX 75231	US02121	18
Joseph Jorizzo, M.D. Bowman Gray Dermatology Dept. Clinical Sciences Bldg., 9th Fl, Medical Ctr. Blvd. Winston-Salem, NC 27157-1071	US01971	25
Stephen J. Kraus, M.D. Georgia Clinical Research Center, Inc. 5671 Peachtree Dunwoody Rd. Suite 520 Atlanta, GA 30342	US00657	0
David Rodriguez, M.D. International Dermatology Research 8370 West Flagler St., #200 Miami, FL 33144	US03006	15
Ronald Savin, M.D. Savin Dermatology Center, P.C. 134 Park St. New Haven, CT 06511	US00530	22
Daniel Stewart, D.O. Midwest Cutaneous Research 43900 Garfield, #106 Clinton Twp., MI 48038	US02120	34
Dow Stough, M.D. The Stough Clinic One Mercy Lane, #304 Hot Springs, Arkansas 71913	US01964	16

8.2.1.4.1 Demographics and Baseline Characteristics

Four (2%) patients, all in the active treatment groups, discontinued the study early due to an adverse event. Of the four patients, three (Pt. #'s 70, 163 and 146) did not have a post-treatment follow-up efficacy evaluation.

Table 3 (Sponsor's Table 2, Vol. 18, pg. 8-2-67): Demographics and Baseline Characteristics (Study 9721)

Characteristic	Active One Week N=47	Active Two Week N=46	Active Four Week N=45	Vehicle N=69	All Patients N=207	Trt Group Contrasts p=
Age (yr)						
Mean (±Std)	64.4(±10.7)	64.9(±10.7)	66.7(±9.9)	64.4(±9.5)	65.0(±10.1)	>0.50
Median	66.0	66.0	67.0	65.0	66.0	
(Range)	(39-83)	(40-82)	(46-85)	(42-86)	(39-86)	
Sex n(%)						
Female	9 (19.1)	8 (17.4)	7 (15.6)	17 (24.6)	41 (19.8)	>0.50
Male	38 (80.9)	38 (82.6)	38 (84.4)	52 (75.4)	166 (80.2)	
Child-bearing Potential:						
n,% of females	0	2 (25.0)	1 (14.3)	3 (17.6)	6 (14.6)	
Race: n(%)						
Caucasian	46 (97.9)	43 (93.5)	43 (95.6)	69 (100)	201 (97.1)	0.092
Hispanic	1 (2.1)	3 (6.5)	2 (4.4)	0	6 (2.9)	
Skin Type: [b] n(%)						
I	21 (44.7)	15 (32.6)	15 (33.3)	29 (42.0)	80 (38.6)	0.258
II	23 (48.9)	27 (58.7)	22 (48.9)	27 (39.1)	99 (47.8)	
III	3 (6.4)	4 (8.7)	8 (17.8)	12 (17.4)	27 (13.0)	
IV	0	0	0	1 (1.4)	1 (0.5)	
Prior AK Therapy: n(%)	26 (55.3)	24 (52.2)	25 (55.6)	43 (62.3)	118 (57.0)	>0.50
Prior AK Therapy Type[c]: n %)						
Efudex® Cream 5%	4 (8.5)	1 (2.2)	4 (8.9)	6 (8.7)	15 (7.2)	0.484
Efudex® Sol 5%	1 (2.1)	1 (2.2)	0	1 (1.4)	3 (1.4)	>0.50
Actinex®	0	2 (4.3)	1 (2.2)	5 (7.2)	8 (3.9)	0.216
Alpha-hydroxy Acid	0	0	0	1 (1.4)	1 (0.5)	0.463
Glycolic Acid	0	1 (2.2)	0	0	1 (0.5)	0.212
Chemical Peel	0	0	0	1 (1.4)	1 (0.5)	>0.50
Cryosurgery	19 (40.4)	20 (43.5)	21 (46.7)	33 (47.8)	93 (44.9)	>0.50

Abstracted from Appendix II.F.2.1 (means and medians), II.F.2.2 (frequencies), II.E.2.1.1 (means contrasts), and II.E.2.1.2 (frequency contrasts)

[a] Means contrasts from analysis of variance (treatment, site). Frequency contrasts from CMH test (general association) for site effects or treatment stratified by site. [b] Skin Types: 1=Always burn, never tan; 2=Always burn, but sometimes tan; 3=Sometimes burn, but always tan; 4=Never burn, always tan. [c] A patient was counted more than once if they received more than one prior therapy.

There was no statistically significant ($p<0.05$) difference among treatment groups for any of the baseline characteristics. No baseline laboratory abnormality was considered by the investigator to preclude study participation.

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Table 4 (Sponsor's Table 3): Patient Disposition (Vol. 18, pg. 8-2-65)

Patient Disposition	Active One Week		Active Two Week		Active Four Week		Vehicle		All Patients	
	n	(%)	n	%	n	%	n	%	N	%
Total Randomized	47	(100)	46	(100)	45	(100)	69	(100)	207	(100)
Completed Study	45	(95.7)	45	(97.8)	44	(97.8)	69	(100)	203	(98.1)
Discontinued due to adverse event	2	(4.3)	1	(2.2)	1	(2.2)	0		4	(1.9)
With End* Efficacy	0		0		1	(2.2)	0		1	(0.5)

Abstracted from Appendix II.F.1.1.2
*from last post-treatment follow-up efficacy evaluation

Table 5 (Sponsor's Table 4): Protocol Deviations

Deviation	Number of Patients	Patient Numbers
Treatment for actinic keratosis unknown date or within one month previous to the start of study (all cryosurgery)	14	8, 16, 23, 24, 25, 27, 35, 38, 55, 63, 133, 205, 217, 239
Use of proscribed medication during the study	6	67, 77, 121, 156, 173, 240
Use of the study medication for three or more days beyond the assigned interval of the random treatment assignment	4	5, 84, 85, 145
Less than 25 days of follow-up[a]	4	70, 146, 163, 192
Missing or incomplete post-treatment follow-up efficacy evaluations[a]	3	70, 163, 146
Completed study but missed two or more follow-up visits	6	36, 63, 71, 203, 218, 226

[a]Patient No. 70 in the Active One Week group discontinued the study due to an unrelated adverse event and was unable to return to the study center due to knee rehabilitation. Patient No. 163 in the Active One Week group and Patient No. 146 in the Active Two Week group both discontinued the study early due to serious adverse events and death.; Abstracted from Appendix IV.C.

Reviewer's comments: *According to the exclusion criteria, patients treated with other topical agents for the treatment of actinic keratosis within 1 month prior to the start of the study were prohibited. Cryosurgery was not specifically listed as an exclusion criterion; however, it is certainly a common topical treatment modality for actinic keratosis. It is unclear why these patients were permitted to enter the study unless adjunctive therapy was to be considered. These protocol violators were included in the ITT population as failures.*

Table 6 (Sponsor's Table 5): Summary of Baseline Actinic Lesion Counts (Study 9721)

	Active One Week N=47	Active Two Week N=46	Active Four Week N=45	Vehicle N=69	All Patients N=207
Total Count					
Mean[a] (± Std)	14.6 (±8.1)	15.8 (±10.2)	15.4 (±8.0)	15.6 (±12.0)	15.4 (±9.9)
Median	12	12	14	12	13
IQR[b]	[redacted]				
Range	[redacted]				

Refer to Appendix II.F.3.2
[a] p>0.50 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.*

8.2.1.4.2 Efficacy

8.2.1.4.2.1 Clinical

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

The following table shows the Sponsor's analysis of the proportion of patients with total clearance in each arm.

Table 8 (Sponsor's Table 14, Vol. 1.18, pg. 8-2-79):
Summary of Patients with Total Clearance of Actinic Keratosis

Total Clearance of Actinic Keratosis Lesions	Active One Week N= 47	Active Two Week N= 46	Active Four Week N= 45	Vehicle N= 69
Yes: n (%)	7 (14.9)	17 (37.0)	26 (57.8)	0
Pair-wise contrasts (p=)[a]				
Contrasts to Vehicle	<0.001	<0.001	<0.001	-
Contrasts to Active One Week	-	0.014	<0.001	-
Contrasts to Active Two Week	-	-	0.029	-

Abstracted from Appendix II.E.1.2 and Appendix II.F.4.2.
[a] from Generalized Linear Model: d.f. Error=24 Pearson Chi-SQ=26.27. Global Sites Contrast p=0.255 (DF=8) Global Treatment Contrast p=<0.001 (DF=3).

The discrepancy noted in Tables 7 & 8 above between 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.

As observed in Tables 7 and 8 above, statistical significance is demonstrated for active over vehicle at for one, two, and four weeks treatment arms (p=0.001).

Secondary Endpoint Parameter

Secondary Endpoint Parameter assessed by the Division is the rate of patients with 75% - 100% clearance of their actinic keratosis. The P-Value is based on analysis of CMH, adjusting for center in Table 9 that follows.

Table 9 (Extracted from FDA Statistical Review):
Proportion of Subjects with At Least 75% Clearance (ITT Population)- 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%)				

According to the FDA statistical review, highly statistical significant results were observed when One-Week treatment was compared to Two -Week and Four-Week treatment arms ($p=0.001$). However, there was no statistical significance demonstrated between Two – Week and Four- Week treatment arms ($p<0.5$).

Patients Who Prematurely Discontinued Treatment (Post-Hoc Analysis)

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. Table 10 (Sponsor's Table 6) below presents the Incidence of actinic keratosis total clearance for two patients of the Active Two Week treatment and six patients of the Active Four Week treatment who discontinued treatment applications and returned for a final efficacy evaluation. There was little evidence, in this small sample, of clinically important differences in results between patients who did or did not complete their assigned duration of treatment.

Table 10 (Sponsor's Table 6, Vol. 1.18, pg. 8-2-89): Total Clearance of Actinic Keratosis among Patients Who Did or Did Not Discontinue Study Medication Prematurely

	Days of Treatment			
	Active Two Week		Active Four Week	
Efficacy Measure	< 12 days N=2	≥ 13 days N=43	< 25 days N=6	≥ 26 days N=39
Median % AK Reduction	88.2	87.0	83.3	100
N (%) Patients with Total Clearance of AKs	0 (0)	17 (39.5)	3 (50.0)	23 (59.0)

Abstracted from Appendix II.E.2.6 and Appendix II.F.8. Cochran-Mantel-Haenszel $p=0.356$ for association between treatment discontinuation and total clearance. For analysis of log(AK/baseline) $p=0.428$ for effect of treatment discontinuation and $p=0.390$ for discontinuation by treatment interaction.

8.2.1.4.3 Safety

Safety was evaluated in all 207 patients randomized into the study. At least one adverse event was reported in 89.4% to 100% of patients in each of the active treatment groups and in 76.8% of patients in the Vehicle group. The most commonly reported adverse event was facial irritation (COSTART term: application site reaction), reported in 89.4% to 97.8% of patients in the active treatment groups compared to 65.2% of patients in the Vehicle group.

Table 11 Sponsor's Table 20 (Vol. 1.18, pg. 8-2-91): Summary of Adverse Events (Study 9721)

Patients	Active One Week N=47	Active Two Week N=46	Active Four Week N=45	All Active N=138	Vehicle N=69
	n %	n %	n %	n %	n %
At least one AE	42 (89.4)	46 (100)	44 (97.8)	132 (95.7)	53 (76.8)
Treatment-related AE[a]	42 (89.4)	45 (97.8)	44 (97.8)	131 (94.9)	46 (66.7)
Facial Irritation[b]	42 (89.4)	45 (97.8)	43 (95.6)	130 (94.2)	45 (65.2)
Discontinued study medication for AE	1 (2.1)	4 (8.7)	7 (15.6)	12 (8.7)	0
Discontinued study due to AE	2 (4.3)	1 (2.2)	1 (2.2)	4 (2.9)	0
Serious AE	1 (2.1)	2 (4.3)	0	3 (2.2)	2 (2.9)
Death	1 (2.1)	2 (4.3)	0	3 (2.2)	0

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

[a] AE with possible, probable, or definite relationship, or facial irritation AE with remote, possible, probable, or definite relationship to study treatment. [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.

Clinical and Laboratory Evaluations

According to the submission, no comments were made during the study concerning any non-actinic keratosis abnormal physical examination findings or vital sign abnormalities. No routine follow-up physical examinations or tests were planned in the protocol, other than the planned efficacy and facial irritation evaluations. No post-treatment laboratory studies were performed as per protocol, except Treatment Phase pregnancy tests for women of child-bearing potential.

Adverse events occurring in at least 1% of patients (2 patients) in the combined active treatment groups (All Active) are summarized by body system, and COSTART preferred term. Application site reaction was the COSTART term used to code facial irritation adverse events within the Skin and Appendages system and was by far the most commonly reported adverse experience.

Table 13 (Sponsor's Table 25, Vol. 1.18, pg. 8-2-98): Summary of Facial Irritation (Application Site Reaction) Adverse Events

Patients	Active Treatment Regimens				Vehicle	Active Treatments vs. Vehicle			
	One Week N=47	Two Week N=46	Four Week N=45	All N=138	N=69	One vs. Vehicle p=	Two vs. Vehicle p=	Four vs. Vehicle p=	All vs. Vehicle p=
	n %	n %	n %	N %	n %				
Had Irritation [a]									
Baseline	22 (45.8)	27 (58.7)	23 (51.1)	72 (52.2)	36 (52.2)				
On-Study	42 (89.4)	45 (97.8)	43 (95.6)	130 (94.2)	45 (65.2)	0.004	<0.001	<0.001	<0.001
Maximum Severity [b]						<0.001	<0.001	<0.001	<0.001
None	5 (10.6)	1 (2.2)	2 (4.4)	8 (5.8)	24 (34.8)				
Mild	23 (48.9)	8 (17.4)	7 (15.6)	38 (27.5)	39 (56.5)				
Moderate	18 (38.3)	21 (45.7)	19 (42.2)	58 (42.0)	6 (8.7)				
Severe	1 (2.1)	16 (34.8)	17 (37.8)	34 (24.6)	0				
Relation to Study Drug [b]						<0.001	<0.001	<0.001	<0.001
Had No AE	5 (10.6)	1 (2.2)	2 (4.4)	8 (5.8)	24 (34.8)				
Remote	1 (2.1)	0	0	1 (0.7)	4 (5.8)				
Possible	1 (2.1)	0	1 (2.2)	2 (1.4)	9 (13.0)				
Probable	12 (25.5)	4 (8.7)	5 (11.1)	21 (15.2)	12 (17.4)				
Definite	28 (59.6)	41 (89.1)	37 (82.2)	106 (76.8)	20 (29.0)				
Action Taken [a]									
No Action Taken	47 (100)	40 (87.0)	36 (80.0)	123 (89.1)	69 (100)		0.003	<0.001	0.003
Drug Discontinued	0	3 (6.5)	5 (11.1)	8 (5.8)	0		0.061	0.008	0.054
Drug dose changed	0	0	1 (2.2)	1 (0.7)	0			0.395	>0.50
Other Action	0	3 (6.5)	3 (6.7)	6 (4.3)	0		0.061	0.059	0.182
Irritation Continues [a,c]	3 (6.4)	4 (8.7)	5 (11.1)	12 (8.7)	3 (4.3%)	>0.50	>0.50	0.479	>0.50

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 recorded on the CRF, then irritation was considered to be continuing at the end of study.

Reviewer's comments: *Overall Severity rating of facial irritation is listed as mild, moderate, and severe on the CRF (Facial Irritation Clinical Adverse Events Since Last Visit). The categories were not defined on the CRF or in the protocol; therefore, this assessment perhaps varied widely among investigators.*

Facial irritation categories should have been defined and assessed based on the status at that visit vs. since the last visit. For greater consistency, clinical signs and symptoms should have been assessed using a scoring scale with clearly defined morphological descriptors or visual analog scale (for patients) similar to those employed by the Sponsor in the Phase 2 studies.

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Table 13 (Sponsor's Table 7, Vol. 1.18, pg. 8-2-107): Summary of Facial Irritation Signs and Symptoms

Clinical Signs [a]	Active Treatment Groups				Vehicle	Contrasts Active Treatments vs. Vehicle			
	One Week N=47	Two Week N=46	Four Week N=45	All N=138	N=69	One vs Vehicle	Two vs. Vehicle	Four vs. Vehicle	All vs. Vehicle
	N %	n %	n %	n %	n %				
Dryness	26 (55.3)	39 (84.8)	40 (88.9)	105 (76.1)	27 (39.1)	0.092	<0.001	<0.001	<0.001
Erythema	42 (89.4)	44 (95.7)	43 (95.6)	129 (93.5)	42 (60.9)	<0.001	<0.001	<0.001	<0.001
Edema	7 (14.9)	17 (37.0)	25 (55.6)	49 (35.5)	2 (2.9)	0.030	<0.001	<0.001	<0.001
Erosion	17 (36.2)	27 (58.7)	34 (75.6)	78 (56.5)	13 (18.8)	0.051	<0.001	<0.001	<0.001
Pain	15 (31.9)	16 (34.8)	27 (60.0)	58 (42.0)	1 (1.4)	<0.001	<0.001	<0.001	<0.001
Burning	27 (57.4)	39 (84.8)	38 (84.4)	104 (75.4)	12 (17.4)	<0.001	<0.001	<0.001	<0.001
Other: Stinging	1 (2.1)	6 (13.0)	8 (17.8)	15 (10.9)	5 (7.2)				
Other: Tender/Sore	1 (2.1)	3 (6.5)	4 (8.9)	8 (5.8)	0				
Other: Itching/Pruritus	10 (21.3)	17 (37.0)	19 (42.2)	46 (33.3)	9 (13.0)				
Other: Scaling	2 (4.3)	4 (8.7)	2 (4.4)	8 (5.8)	3 (4.3)				
Other: Crusting	2 (4.3)	3 (6.5)	3 (6.7)	8 5.8)	0				

Abstracted from Appendix II.E.1.3.2 (fisher's exact 2-tailed test) and II.F.5.2.

[a] The six clinical signs -- Erythema, Dryness, Pain, Erosion, Burning, and Stinging -- were standardly collected on the Case Report Form. Other terms -- Stinging, Itching/Pruritus, Scaling, Crusting -- were extracted from reported other signs.

Twenty-four patients discontinued study medication due to intolerable inflammatory responses. Twelve of the 24 patients who discontinued study medication due to an AE were in the Active Four Week treatment group.

The average scores for Overall Severity of facial irritation (1=Mild, 2=Moderate, 3=Severe) reported for each treatment group at the last treatment visit and at each of the post-treatment follow-up visits (Follow-up Phase Weeks 1, 2, 3, and 4) were assessed. According to the Sponsor, mean severity scores declined for each active treatment group over the first two weeks of post-treatment follow-up to an average severity near the baseline severity.

According to the Sponsor, facial irritation occurred within 4 days after initiating therapy in most patients treated with active drug for all concentrations. Erythema, dryness, burning, and erosion were the most common clinical signs (Vol. 1.18, pg. 8-2-106). Additionally, the incidences of edema, erosion, and pain were more common in the Active 4-Week than in the Active 2-Week group at the end of treatment and had decreased to zero or near zero by the final evaluation.

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Table 14 (Sponsor's Table 8, Vol. 1.18, pg. 8-2-92): Extent of Exposure

Number of Treatment Days	Active One Week N=47		Active Two Week N=46		Active Four Week N=45		All Active N=138		Vehicle N=69	
	n	%	n	%	n	%	n	%	n	%
Unknown	0		1	(2.2)	0		1	(0.7)	0	
1-6 days	1	(2.1)	0		1	(2.2)	2	(1.4)	0	
7 days	30	(63.8)	1	(2.2)	1	(2.2)	32	(23.2)	13	(18.8)
8-13 days	16	(34.0)	9	(19.6)	1	(2.2)	26	(18.8)	13	(18.8)
14 days	0		16	(34.8)	0		16	(11.6)	13	(18.8)
15-20 days	0		18	(39.1)	1	(2.2)	19	(13.8)	8	(11.6)
21 days	0		1	(2.2)	1	(2.2)	2	(1.4)	0	
22-27 days	0		0		4	(8.9)	4	(2.9)	3	(4.3)
28 days	0		0		26	(57.8)	26	(18.8)	10	(14.5)
29-31 days	0		0		10	(22.2)	10	(7.2)	9	(13.0)

Abstracted from Appendix Table II.F.1.3

Table 14 (**Sponsor's Table 8**) above is a summary of the number and percentage of patients in each treatment group completing a specific number of treatment application days. Patients were to apply the study medication once a day for 7 days (Active One Week), 14 days (Active Two Week), or 28 days (Active Four Week).

Reviewer's comments: *As noted in Table 14 above, 16 (34%) patients assigned to 7 days of therapy continued use of the study drug for 8 –13 days; however, only one patient (Pt. 85) in this group achieved 100 % clearance. Lack of efficacy at end of one, two, and four weeks of treatment perhaps prompted the investigators to continue therapy; however, continued treatment beyond a specified time period should have been pre-specified as prtocol violations. One would have to question the clarity of instructions provided by the Sponsor to the investigators.*

Table 15 (Sponsor's Table 9): Summary of Adverse Events Occurring in ≥ 1% of Patients in The Combined Active Treatments, by Body System, and COSTART Term

Body System AE COSTART Term [b]	Active One Week N=47	Active Two Week N=46	Active Four Week N=45	All Active N=138	Vehicle N=69
	n (%)	n (%)	n (%)	n (%)	n (%)
At least one AE	42 (89.4%)	46 (100%)	44 (97.8%)	132 (95.7%)	53 (76.8%)
BODY AS A WHOLE	5 (10.6%)	5 (10.9%)	8 (17.8%)	18 (13.0%)	11 (15.9%)
Common Cold	4 (8.5%)	0	2 (4.4%)	6 (4.3%)	3 (4.3%)
Headache	2 (4.3%)	2 (4.3%)	2 (4.4%)	6 (4.3%)	3 (4.3%)
Allergy	0	2 (4.3%)	1 (2.2%)	3 (2.2%)	1 (1.4%)
Knee Pain	1 (2.1%)	0	1 (2.2%)	2 (1.4%)	0
RESPIRATORY	5 (10.6%)	0	1 (2.2%)	6 (4.3%)	5 (7.2%)
Sinusitis	4 (8.5%)	0	0	4 (2.9%)	2 (2.9%)
SKIN & APPENDAGES	42 (89.4%)	45 (97.8%)	43 (95.6%)	130 (94.2%)	46 (66.7%)
Application Site Reaction [c]	42 (89.4%)	45 (97.8%)	43 (95.6%)	130 (94.2%)	45 (65.2%)
Irritation Skin	1 (2.1%)	0	1 (2.2%)	2 (1.4%)	0
Rash	2 (4.3%)	0	0	2 (1.4%)	0
SPECIAL SENSES	5 (10.6%)	3 (6.5%)	5 (11.1%)	13 (9.4%)	4 (5.8%)
Eye Irritation	5 (10.6%)	3 (6.5%)	5 (11.1%)	13 (9.4%)	1 (1.4%)

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

Reviewer's comments: *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 and a safety concern. A rationale for this adverse event could not be ascertained.*

Table 16 (Sponsor's Table 10, Vol.1.18, pg. 8-2-131): Summary of Adverse Events by Body System and COSTART Term

Body System AE COSTART Term	Active One Week N=47	Active Two Week N=46	Active Four Week N=45	All Active N=138	Vehicle N=69
	n (%)	n (%)	n (%)	n (%)	n (%)
At least one AE*	42 (89.4%)	46 (100%)	44 (97.8%)	132 (95.7%)	53 (76.8%)
BODY AS A WHOLE	5 (10.6%)	5 (10.9%)	8 (17.8%)	18 (13.0%)	11 (15.9%)
Common Cold	4 (8.5%)	0	2 (4.4%)	6 (4.3%)	3 (4.3%)
Headache	2 (4.3%)	2 (4.3%)	2 (4.4%)	6 (4.3%)	3 (4.3%)
Allergy	0	2 (4.3%)	1 (2.2%)	3 (2.2%)	1 (1.4%)
Knee Pain	1 (2.1%)	0	1 (2.2%)	2 (1.4%)	0
Abscess	0	0	1 (2.2%)	1 (0.7%)	0
Accident	0	0	0	0	1 (1.4%)
Back Ache	0	0	0	0	1 (1.4%)
Cancer	0	1 (2.2%)	0	1 (0.7%)	0
Facial Swelling	0	0	1 (2.2%)	1 (0.7%)	0
Fatigue	0	0	0	0	1 (1.4%)
Infection Upper Respiratory	0	0	0	0	1 (1.4%)
Injury	0	0	1 (2.2%)	1 (0.7%)	0
Toothache	0	0	0	0	1 (1.4%)
CARDIOVASCULAR	1 (2.1%)	2 (4.3%)	2 (4.4%)	5 (3.6%)	3 (4.3%)
Angina Pectoris	0	0	0	0	1 (1.4%)
Cardiac Failure	1 (2.1%)	0	0	1 (0.7%)	0
Fibrillation Atrial	0	0	0	0	1 (1.4%)
Heart Murmur	0	1 (2.2%)	0	1 (0.7%)	0
Hypertension	0	0	1 (2.2%)	1 (0.7%)	0
Hypertension Aggravated	0	1 (2.2%)	0	1 (0.7%)	0
Hypertension Malignant	0	0	0	0	1 (1.4%)
Myocardial Infarction	0	1 (2.2%)	0	1 (0.7%)	0
Transient Ischemic Attack	0	0	1 (2.2%)	1 (0.7%)	0
DIGESTIVE	0	1 (2.2%)	2 (4.4%)	3 (2.2%)	2 (2.9%)
Fever Sore	0	1 (2.2%)	0	1 (0.7%)	1 (1.4%)
Diverticulitis	0	0	0	0	1 (1.4%)
Indigestion	0	0	1 (2.2%)	1 (0.7%)	0
Stomach Upset	0	0	1 (2.2%)	1 (0.7%)	0
METABOL/NUTRITION	0	0	0	0	1 (1.4%)
Xanthomatosis	0	0	0	0	1 (1.4%)
MUSCULOSKELETAL	1 (2.1%)	1 (2.2%)	1 (2.2%)	3 (2.2%)	4 (5.8%)
Muscle Soreness	0	0	0	0	2 (2.9%)
Arthritis	0	1 (2.2%)	0	1 (0.7%)	0
Bursitis	0	0	0	0	1 (1.4%)
Fracture Bone	1 (2.1%)	0	0	1 (0.7%)	0
Muscle Ache	0	0	0	0	1 (1.4%)
Pain Joint	0	0	1 (2.2%)	1 (0.7%)	0
NERVOUS	0	1 (2.2%)	0	1 (0.7%)	1 (1.4%)
Dementia	0	1 (2.2%)	0	1 (0.7%)	0
Sleep Disorder	0	0	0	0	1 (1.4%)

RESPIRATORY	5 (10.6%)	0	1 (2.2%)	6 (4.3%)	5 (7.2%)
Sinusitis	4 (8.5%)	0	0	4 (2.9%)	2 (2.9%)
Coughing	1 (2.1%)	0	0	1 (0.7%)	1 (1.4%)
Breathing Difficult	0	0	1 (2.2%)	1 (0.7%)	0
Rhinitis	0	0	0	0	1 (1.4%)
Sinus Congestion	0	0	0	0	1 (1.4%)
Sore Throat	0	0	0	0	1 (1.4%)
SKIN & APPENDAGES	42 (89.4%)	45 (97.8%)	43 (95.6%)	130 (94.2%)	46 (66.7%)
Application Site Reaction	42 (89.4%)	45 (97.8%)	43 (95.6%)	130 (94.2%)	45 (65.2%)
Dermatitis Contact	0	1 (2.2%)	0	1 (0.7%)	1 (1.4%)
Irritation Skin	1 (2.1%)	0	1 (2.2%)	2 (1.4%)	0
Rash	2 (4.3%)	0	0	2 (1.4%)	0
Erythema	1 (2.1%)	0	0	1 (0.7%)	0
Melanoma Malignant	0	1 (2.2%)	0	1 (0.7%)	0
Papular Rash	0	1 (2.2%)	0	1 (0.7%)	0
Peeling	0	0	0	0	1 (1.4%)
Tenderness Skin	0	0	0	0	1 (1.4%)
Ulcer Skin	0	0	1 (2.2%)	1 (0.7%)	0
SPECIAL SENSES	5 (10.6%)	3 (6.5%)	5 (11.1%)	13 (9.4%)	4 (5.8%)
Eye Irritation	5 (10.6%)	3 (6.5%)	5 (11.1%)	13 (9.4%)	1 (1.4%)
Disorder Ear	0	0	0	0	1 (1.4%)
Ear Disorder	0	0	0	0	1 (1.4%)
Eyes Tearing	0	0	0	0	1 (1.4%)
UROGENITAL	1 (2.1%)	1 (2.2%)	0	2 (1.4%)	2 (2.9%)
Endometrial Disorder	0	0	0	0	1 (1.4%)
Kidney Failure	1 (2.1%)	0	0	1 (0.7%)	0
Renal Failure Acute	0	1 (2.2%)	0	1 (0.7%)	0
Urinary Tract Infection	0	0	0	0	1 (1.4%)

Abstracted from Appendix II.F.5.1.2

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

Four patients discontinued the study participation, all due to an adverse event. Serious adverse events were reported in a total of five patients, three in the active treatment groups and two in the Vehicle group. The three patients with serious adverse events in the active treatment groups died as a result of their illness. These deaths are discussed under Safety (Section 10.1.1). No serious adverse event or death was considered related to study medication.

8.2.1.5 Conclusions Regarding Efficacy Data and Safety

Efficacy Conclusion:

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 with four weeks of treatment being the most efficacious of the time intervals studied. The Four-Week treatment arm was statistically superior to both One –Week (p=0.001) and Two – Week (p=0.02). Two -Week treatment arm was statistically superior to One- Week (p=0.03).

In this study, 94.7% of 136 patients on active treatment experienced facial irritation considered mild, moderate, or severe during the study versus 55.1% of the 69 patients on vehicle. Twenty-four patients discontinued study medication due to intolerable inflammatory responses. Erythema and dryness were the most common clinical signs of facial irritation. 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.

The following serious adverse event was considered probably related to study medication. Patient No.192 (Bucko's Site) had difficult breathing and facial swelling. On Day 3 of study drug treatment, this 66 year old man experienced a single episode of difficulty breathing and facial swelling which lasted 30 minutes and was of moderate severity. The event was considered probably related to study drug and therefore treatment was discontinued. The patient had no prior history of 5-Fluorouracil treatment.

According to the submission, no comments were made during the study concerning any non-actinic keratosis abnormal physical examination findings or vital sign abnormalities. End of study laboratory evaluations was not performed. No post-treatment laboratory studies were performed as per protocol, except Treatment Phase pregnancy tests for women of childbearing potential. None had a positive pregnancy test during the study.

Three deaths were reported during conduct of the clinical trial. No deaths were considered related to study medication.

Indication #1 Treatment of Actinic Keratosis

This study was designed to compare the efficacy and safety of three different treatment durations of an experimental topical 5-FU 0.5% cream formulation to that of vehicle control treatment.

8.2.2 Reviewer's Trial #2 Sponsor's Protocol DL-6025-9722

(Study Dates: January 16, 1998 to July 16, 1998)

Title: "A Vehicle-Controlled, Randomized, Double-Blinded Study Comparing the Safety and Efficacy of DL-6025 0.5% Cream versus Vehicle in the Treatment of Actinic Keratosis"

8.2.2.1 Objective Rationale

The objective of this study was to investigate the clinical safety and efficacy of an experimental formulation of 5-fluorouracil 0.5% cream in a treatment regimen response study, compared to vehicle control, for the treatment of actinic keratosis.

8.2.2.2 Design

This was a randomized, controlled, double-blinded, parallel-group, multi-center treatment response study conducted in the United States designed to compare the efficacy and safety of an experimental 5-FU 0.5% cream applied once daily for one, two or four weeks to a vehicle control in the treatment of actinic keratosis.

Reviewer's comments: *Protocol DL-6025-9721 is identical to Protocol DL-6025-9722.*

Financial Disclosure

The Sponsor has submitted certification for financial interests and arrangements of clinical investigators participating in Study DL6025-9722. According to the Sponsor, no investigator participating in the study received compensation that was dependent on favorable study outcome, has ownership in of stock in the company that cannot be readily determined through reference to public prices, nor has a proprietary interest in the drug product.

8.2.2.4 Study Results

Nine sites enrolled a total of 177 patients in the study (Active: Vehicle ratio of 2:1). A total of 170 (96.0%) patients (range: 90.0% in the Active Four-Week group to 98.3% in the Vehicle group) completed the study. Table 17 (Sponsor's Table 1) that follows lists the nine

principal investigators, their Dermik Laboratories investigator numbers, and the number of patients enrolled at each site.

Table 17 (Sponsor's Table 1,Vol. 2?, pg. 8-4-226): Principal Investigators –Study 9722

Investigator Name, Affiliation, and Address	Dermik Investigator No.	# of Patients Enrolled
Oscar Hevia, M.D. Dermatology Assoc. of Tallahassee 1707 Riggins Rd./ P.O. Box 13834 Tallahassee, FL 32308	US01974	39
Terry Jones, M.D. J&S Studies, Inc. 4309 Wellborn Rd. Bryan, TX 77801	US02619	3
Mark Ling, M.D.* (Calvin McCall, M.D.) Emory U. Sch. of Med./ Dermatology 1365 Clifton Rd., 1st Floor Atlanta, GA 30322	US02985	9
Alan Menter, M.D. Texas Dermatology Associates Tollhill Office Park West, 5310 Harvest Hill Rd., #260 Dallas, TX 75230	US04145	31
Toivo Rist, M.D. Dermatology Associates of Knoxville St. Mary's Prof. Bldg., #511, 930 Emerald Ave. Knoxville, TN 37917	US03034	25
Janet Roberts, M.D. NW Cutaneous Research Specialists 2222 Northwest Lovejoy, #419 Portland, Oregon 97210	US03004	18
Jerald Sklar, M.D. Dallas Associated Dermatologists, P.A. 3600 Gaston Ave., #1051 LB76 Dallas, TX 75246	US02987	18
Guy Webster, M.D. Jefferson Dermatology Associates Walnut Towers, 5th Floor, 211 South 9th St. Philadelphia, PA 19107	US04146	7
Jonathan Weiss, M.D. Gwinnett Clinical Research Ctr. 2366 Lenora Church Rd. Snellville, GA 30278	US01962	27

*Dr. Ling was replaced with Dr. Calvin McCall as the primary investigator after all patients had completed the study. All patient listings report data under investigator name Ling.

8.2.2.4.1 Demographics, Evaluability

Table 18 (Sponsor's Table 6, Vol. 1.20, pg. 8-4-259): Demographics and Patient Characteristics

Characteristic	Active One Week N=38	Active Two Week N=41	Active Four Week N=40	Vehicle N=58	All Patients N=177	Contrasts (p=)[a] Sites	Trt
Age (yr)							
Mean (±Std)	62.9(±11.4)	63.2(±11.2)	62.7(±11.1)	63.6(±11.0)	63.2(±11.1)	0.221	>0.50
Median	65.0	63.0	60.0	64.5	64.0		
(Range)	(35-86)	(42-89)	(40-81)	(39-86)	(35-89)		
Sex, n (%)							
Male	32 (84.2)	35 (85.4)	30 (75.0)	55 (94.8)	152 (85.9)	0.071	0.046
Female	6 (15.8)	6 (14.6)	10 (25.0)	3 (5.2)	25 (14.1)		
Child-bearing Potential, n (%) of females	2 (33.3)	1 (16.7)	1 (10.0)	1 (33.3)	5 (20.0)		
Race, n (%)							
Caucasian	38 (100.0)	41 (100)	40 (100.0)	58 (100.0)	177 (100.0)		
Skin Type[b], n (%)							
Type 1	13 (34.2)	14 (34.1)	18 (45.0)	24 (41.4)	69 (39.0)	<0.001	0.279
Type 2	16 (42.1)	19 (46.3)	17 (42.5)	29 (50.0)	81 (45.8)		
Type 3	9 (23.7)	8 (19.5)	5 (12.5)	5 (8.6)	27 (15.3)		
Prior AK Therapy, n (%)	26 (68.4)	33 (80.5)	29 (72.5)	45 (77.6)	133 (75.1)		
Prior AK Therapy Type, n (%)							
Efudex® Cream 5%	10 (26.3)	9 (22.0)	12 (30.0)	7 (12.1)	38 (21.5)	0.002	0.133
Efudex® Sol 5%	1 (2.6)	1 (2.4)	1 (2.5)	2 (3.4)	5 (2.8)	0.068	>0.50
Efudex® Sol 2%	1 (2.6)	0	1 (2.5)	1 (1.7)	3 (1.7)	0.059	>0.50
Actinex®	0	2 (4.9)	0	0	2 (1.1)	>0.50	0.061
Alpha-hydroxy Acid	1 (2.6)	0	0	2 (3.4)	3 (1.7)	0.479	0.444
Glycolic Acid	0	0	1 (2.5)	0	1 (0.6)	0.183	0.321
Chemical Peel	0	0	0	1 (1.7)	1 (0.6)	>0.50	0.485
Cryosurgery	17 (44.7)	26 (63.4)	16 (40.0)	32 (55.2)	91 (51.4)	<0.001	0.108

Abstracted from Appendix II.F.2.1, Appendix II.F.2.2, Appendix II.E.2.1.1, and Appendix II.E.2.1.2.

[a] Means contrasts from analysis of variance (treatment, site). Frequency contrasts from CMH test (general association) for site effects or treatment stratified by site. [b] Skin Types: 1= Always burn, never tan; 2= Always burn, but sometimes tan; 3= Sometimes burn, but always tan; 4= Never burn, always tan.

With a single exception (gender), there was no statistically significant ($p<0.05$) differences among treatment groups for any of these demographic or baseline characteristics. According to the Sponsor, the observed significant ($p=0.046$) difference in proportions of female patients compared among treatment groups reported appears to have been an artifact of the small number of female patients in the study and the large number of treatment groups.

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