These results show some difference in histology that appear to correlate with application of an irritant chronically to the skin. Whether any of the histologic changes correlate with the observed clinical effects cannot be determined. The data do not support any claims regarding increased collagen or elastin. The histologic data do support changes consistent with chronic mild irritation of skin.

7.5.10 Clinical Results -

As with the other studies, even though more subjects may have exhibited overall improvement in photodamage after TEC-II 0.02% therapy than after vehicle therapy, the use of global evaluations were discounted in the final evaluation of this drug product. Also, there were no statistically significant differences between the treatment groups in the reduction of individual clinical signs (i.e., fine wrinkling, mottled hyperpigmentation, roughness, yellowing, laxity). In the individual subject self-assessment features, there were no significant differences between the two treatment groups.

Applicant provided statistical analysis of this pivotal trial results using a Modified Intent to Treat Population (Excluding Baseline = 0 or 1) results in the following:

K90-011 - Applicant's Statistical Analysis: p-values, mean change from baseline.

Indication	Unadjusted p-value	Holm's adjusted p-value	Difference in treatment group mean change*	95% Confidence Interval*
Fine Wrinkling	0.268	1.000	0.2	0.5 to –0.2
Coarse Wrinkling	0.006	0.036	0.4	0.6 to 0.1
Tactile Roughness	0.812	1.000	0.1	0.5 to –0.4
Laxity	0.156	0.780	0.3	0.6 to –0.1
Yellowing	0.546	1.000	0.1	0.5 to –0.3
Mottled Hyperpigmentation	0.702	1.000	0.1	0.5 to –0.4

*Positive numbers indicate net improvement on a 10 point scale of RENOVA 0.02% vs. vehicle. Negative numbers indicate worsening. A zero would signify no difference.

The FDA Biostatistician derived p-values from the study data from which similar conclusions as from the Applicant provided p-values:

Study K90-011 – Holm's Adjusted P-values	
Coarse Wrinkling	.0295 *
Laxity	.7330
Fine Wrinkling	1.0
Yellow-brown discoloration	1.0
Mott Hyperpig.	1.0
Tactile Roughness	1.0

Based on the data above, using the Holm's adjusted p-value to accommodate multiple endpoints, the Applicant demonstrated a statistically significant difference in the coarse wrinkling endpoint with this study.

7.5.11 Skin Replica Results -

Skin replica trials have not been considered as a valuable surrogate endpoint for wrinkles. While such data may provide some degree of quantitation, these trials are not used in the clinical setting (i.e. healthcare provider's office) on a routine basis to determine effectiveness of treatment. Additionally, there is no better endpoint for determination of effect of treatment on the appearance of wrinkles than the appearance of the wrinkles themselves (i.e., a visual assessment). Thus, the skin replica results provided for this study are not statistically assessed. The data is noted below. The Applicant states that no statistically significant differences were found between the two treatments except for one crow's feet (Ra-EW) and one cheek parameter (Ra-NS).

Data from Silicon Replica Analysis

	Crow's Feet Replicas - % Change from Baseline Mean to Week 24 Mean					
	Ra-NS	Ra-EW	Rz-NS	Rz-EW	Shadows-NS	Shadows-EW
TEC-II 0.02% (N=32)	-6.0	-0.5*	-6.9	-1.3	-9.0	-3.2
Vehicle (N=33)	-3.6	10.4	-3.7	8.0	-2.8	27.3
	Cheek Replicas - % Change from Baseline Mean to Week 24 Mean					
	Ra-NS	Ra-EW	Rz-NS	Rz-EW	Shadows-NS	Shadows-EW
TEC-II 0.02% (N=32)	-10.8*	-20.8	-3.9	-17.5	-29.6	-39.1
Vehicle (N=33)	-3.0	-9.5	0.0	-7.6	-11.4	-15.8

NOTE: NS= North-South; EW=East-West
*Denotes statistically significant difference from vehicle (one-sided p<0.05)

7.5.12 Safety Results -

Based on cutaneous irritation ratings and adverse event reports, TEC-II 0.02% demonstrated an acceptable safety profile over the 24-week treatment period. Skin irritation, while more prevalent in TEC-II 0.02%-treated subjects than in vehicle-treated subjects, was usually mild and well-tolerated. The various signs and symptoms of skin irritation graded at each visit, such as erythema, peeling, and burning/stinging, peaked during the first two to four weeks of therapy, declined sharply by week 8, and remained relatively constant thereafter except for slight fluctuations over the last 8 weeks. While most TEC-II 0.02%-treated subjects experienced at least mild skin irritation based on these elicited signs and symptoms, 33% of TEC-II 0.02%-treated subjects reported an adverse event associated with the treatment site (skin irritation was considered an adverse event only if it resulted in a missed application, required topical steroid treatment, or was otherwise significant), compared with 18% of vehicle-treated subjects (p=0.196). There was good compliance with the once-daily treatment regimen, as 92% of subjects valid for safety completed at least 90% of TEC-II 0.02% applications and 90% of subjects reported no missed applications of TEC-II 0.02% due to skin irritation. Topical steroid therapy for TEC-II 0.02%- related skin irritation was reported by 2 (5%) subjects.

Two subjects, one in each treatment group, discontinued due to an adverse skin reaction. One subject (141) discontinued vehicle therapy due to a severe facial irritant dermatitis, considered probably related to study drug. The second subject (175) discontinued TEC-II 0.02% after one application due to a facial allergic contact dermatitis

considered possibly related to study drug. No other serious adverse events associated with the study drug were reported.

Adverse events not associated with the treatment site occurred more often in the vehicle group (overall incidence of 83%) than in the TEC-II 0.02% group (overall incidence of 60%). The most frequently reported adverse events were upper respiratory infection and headache, with a subject incidence of 18% and 5% in the TEC-II 0.02% group and 30% and 18% in the vehicle groups, respectively.

No physical examinations or laboratory tests were performed.

7.6 Supportive Study – L91-026

7.6.1 Title - A Double-Blind, Multicenter, Vehicle-controlled Study to Evaluate the Safety and Efficacy of Tretinoin Emollient Cream (TEC-II) 0.02% in the Treatment of Non-Caucasian Photodamaged Skin

7.6.2 Dates - The study was Initiated on February 27, 1992 and Ended on December 8, 1993.

7.6.3 Investigators -

David Friedman M.D. - Roger Williams Medical Center, Brown University, Providence, RI; USA

A. Paul Kelly, M.D. - Martin Luther King/Charles R. Drew Medical Center, Los Angeles, CA; USA

Scott B. Phillips, M.D. - Massachusetts General Hospital, Boston, MA; USA

7.6.4 Objectives - The objective of this study was to evaluate the safety and efficacy of tretinoin emollient cream (TEC-II) 0.02% compared with TEC-II vehicle cream in the treatment of non-Caucasian photodamaged skin and to obtain long-term safety and efficacy data on TEC-II 0.02%.

7.6.5 Study Design and Protocol Synopsis - This was a double-blind, multicenter, vehicle-controlled, Phase 2 study in non-Caucasian men and women with mild to moderate photodamaged skin. Subjects were randomized to apply TEC-II 0.02% or vehicle once nightly for 24 weeks after which all subjects were to apply TEC-II 0.02% once nightly for 28 weeks (open-label phase). Thus, there were two treatment groups, the TEC-II 0.02%/TEC-II 0.02% and a vehicle/TEC-II group. A general dosing guideline of 0.25 g per application was used and subjects were to apply a moisturizing sunscreen daily with additional emollients and sunscreens to be used as needed. Return visits were scheduled after two and four weeks of treatment and at four-week intervals thereafter for the remainder of the study.

7.6.6 Number of Subjects -

Planned: 120 to provide 60 subjects per double-blind treatment group;

Analyzed: 120 (60 and 60 randomized to treatment with TEC-II 0.02% or vehicle, respectively) analyzed as the intent to-treat group; 117 (60 and 57 randomized to TEC-II 0.02% or vehicle, respectively) analyzed for safety evaluations; and 107 (55 and 52 randomized to TEC-II 0.02% or vehicle, respectively) analyzed for efficacy evaluations.

In the TEC-II 0.02%/TEC-II 0.02% treatment group, 47 subjects were analyzed for efficacy and of the 52 subjects in the vehicle/TEC-II treatment group, 52 were analyzed for safety evaluations and 37 were analyzed for efficacy evaluations.

7.6.7 Inclusion Criteria -
To be eligible for entry in the study, subjects were to be healthy male or female non-Caucasians (skin color may vary from fair skinned, discernible brown to moderate or darker brown), 40 to 75 years of age in good general health, with mild to moderate facial photodamage (grades 1 to 6 on a 0 to 9 scale, defined as 0 = none, 1 to 3 = mild, 4 to 6 = moderate, and 7 to 9 = severe) based on the investigator's baseline clinical global evaluation.

7.6.8 Exclusion Criteria -

Eligible subjects were not to have been of Asian descent, have a history of keloid formation, or have any skin condition (e.g., rosacea; multiple clinically visible facial actinic keratoses; psoriasis) that might require concomitant therapy or confound the safety and efficacy evaluations. Subjects were also excluded for any of the following reasons: basal cell or squamous cell carcinoma on the face within the past five years or any prior history of malignant melanoma; history of psychotic or affective disorders (e.g., bipolar disorder, major depression, schizophrenia), including past or present use of antidepressant or antipsychotic drugs for disorders of this nature; prior therapy (e.g., collagen or silicone injections, surgical procedures) that might have confounded the study evaluations; hypersensitivity to any of the study drug components; experimental drug or device within 30 days prior to starting study therapy; and excessive facial hair (e.g., beards).

Study drug therapy was not initiated unless all topical and systemic retinoid therapy had been discontinued at least six months prior to the study, and all topical preparations other than makeup were stopped for at least 24 hours prior to the pre-study evaluations. No facial skin cosmetics were worn on the day(s) of pre-study evaluations.

Pregnant or nursing women were excluded. Females who were not postmenopausal for at least one year or who had not had a hysterectomy or tubal ligation were to use an effective method of contraception throughout the study. Premenopausal females with an intact uterus were also to have had a normal menstrual flow within 30 days prior to initiating study therapy and a negative urine pregnancy test immediately prior to initiating study therapy.

7.6.9 Applicant's Assessment of Efficacy Results -

Based on clinical observations by both subjects and investigators, non-Caucasian subjects who received 24 weeks of double-blind TEC-II 0.02% exhibited improvement in photodamage that was comparable to or slightly less than that exhibited by subjects who received 24 weeks of double-blind vehicle. This includes the investigator's global evaluation, the investigator's evaluation of overall severity, the overall subject assessment, six of seven individual clinical signs, and three of five individual subject self-assessments; vehicle-treated subjects showed significantly greater reductions than TEC-II 0.02%-treated subjects in the clinical sign, fine wrinkling and two individual self-assessments, wrinkles and tightness. Comparable results were exhibited by subjects in both treatment groups for the remaining six clinical signs (localized and generalized

mottled hyperpigmentation, lentigines/DPN, tactile roughness, coarse wrinkling, and laxity (looseness) and three individual self-assessment features, color, texture, and pores. Whereas the subjects graded tightness more favorably than investigators graded the corresponding parameter of laxity, there was good agreement between subjects and investigators for the remaining assessments.

Each of the three global efficacy measures (investigator's global evaluation at Week 24, the change from baseline to Week 24 in the investigator's evaluation of overall severity of photodamage, and the overall subject self-assessment at Week 24) showed comparable results for double-blind TEC-II 0.02% and vehicle therapy, with improvement rates ranging from 15% to 80% in the TEC-II 0.02% group, compared with 29% to 83% in the vehicle group. Based on these composite assessments, the investigator and subject assessments showed consistent results.

For subjects in both the vehicle/TEC-II 0.02% treatment group who received 28 weeks of open-label TEC-II 0.02% therapy and subjects in the TEC-II 0.02%/TEC-II 0.02% treatment group who received 52 weeks of TEC-II 0.02% therapy, improvement in photodamage was comparable to or slightly higher than that of subjects in the double-blind TEC-II 0.02% treatment group after 24 weeks of TEC-II 0.02% therapy. This includes all efficacy parameters including the seven individual clinical signs and five individual subject self-assessments.

In conclusion, TEC-II 0.02% lacks efficacy for the proposed indications when applied once daily for up to 52 weeks in non-Caucasian (mostly African-American) skin.

7.6.10 Safety Results -

Based on cutaneous irritation ratings and adverse event reports, TEC-II 0.02% demonstrated a favorable safety profile. Skin irritation, the most frequently reported adverse event associated with the treatment site, was somewhat more prevalent in both the double-blind and open-label TEC-II 0.02% treatment groups compared to the vehicle group but was usually mild and well-tolerated. Topical steroid therapy for TEC-II 0.02%-related skin irritation was reported by six (10.0%) subjects. Adverse events not associated with the treatment site were evenly distributed between the double-blind TEC-II 0.02%- and vehicle-treated groups. The various signs and symptoms of skin irritation, such as erythema, peeling, and burning/stinging, peaked during the first two to four weeks of vehicle and TEC-II 0.02% therapy and generally declined gradually throughout the remainder of therapy. There was good compliance with the 52-week, once-daily treatment regimen, as 95% of TEC-II 0.02%-treated subjects valid for safety completed at least 90% of TEC-II 0.02% applications and 83% of subjects reported no missed applications of TEC-II 0.02% due to skin irritation.

Serious adverse events were reported by two vehicle-treated subjects during the double-blind phase and one subject in the TEC-II 0.02%/TEC-II 0.02% treatment group during the open-label phase of the study. All three subjects were diagnosed with cancer (brain, breast and prostate) and were discontinued from the study.

Five subjects (two in the TEC-II 0.02% treatment group and three in the vehicle treatment group) discontinued from the double-blind phase of study because of an adverse event. Three of the five subjects (two TEC-II 0.02%-treated subjects and one vehicle-treated subject) discontinued due to a skin reaction classified by the investigator as probably related to therapy. An additional four subjects (one TEC-II 0.02%/TEC-II

0.02%-treated subject and three vehicle/TEC-II 0.02%-treated subjects) discontinued from the open-label phase of the study because of an adverse event.

7.7 ADME Study – I88-082

7.7.1 Title – An Open-Label Study to Determine the Percutaneous Absorption of ^{3}H-Tretinoin From Each of Three 0.05% Cream Formulations in Normal Male Volunteers

7.7.2 Dates – This study was initiated on April 20, 1989 and completed on May 25, 1989.

7.7.3 Principal Investigator - James C. Kisicki, M.D.
Harris Laboratories, Inc.
624 Peach Street
Lincoln, NE 68501

7.7.4 Study Objective – The objective of this study was to determine the percutaneous absorption of ^{3}H-tretinoin from each of three 0.05% cream formulations following single and repeated application. The three formulations tested were RETIN-A, RENOVA 0.05% TEC-1, RENOVA 0.05% TEC-2.

7.7.5 Study Design – The study was an open-label, parallel, single-center, Phase 1 study in 42 normal male volunteers. The subjects were equally randomized into one of six treatment groups, single application or pretreatment with the same formulation (non-radioactive) for a maximum of 28 days followed by a single radioactive application. Each subject received a single application of radiolabeled drug containing 100 microcuries of tritium in 100 mg of formulation. The drug was applied to 50 cm2 of facial skin (forehead and cheek), with a skin wash after 10 hours. Urine and feces were collected for a seven-day period, with venous samples collected for 72 hours. Weekly cutaneous exams were made to evaluate cutaneous irritation.

7.7.6 Study Population – 42 male, Caucasian subjects, ages 19-57 (mean age of 29), in good general health were enrolled.

7.7.7 Results – See Biopharm review for more detail. An small increase in the average endogenous levels of tretinoin will occur with the approximate 2% systemic absorption of topically applied tretinoin 0.05%. The percutaneous absorption of 3H-tretinoin is minimal following topical administration and was unaffected by either the cream formulation or dosage (single or pretreatment) regimen.

7.8 Tolerance Study – J89-011

7.8.1 Title – Evaluation of the Cumulative Irritation Potential of Tretinoin Emollient Cream (TEC-II) 0.05%

7.8.2 Principal Investigators - Lewis P. Stolman, M.D.
Lynne B. Harrison, Ph.D.
Harrison Research Laboratories, Inc.
1624 Springfield Avenue
Maplewood, NJ 07040

7.8.3 Objective – The objective of this study was to evaluate the cumulative irritation potential of tretinoin emollient cream (TEC-II) 0.05% and TEC-II 0.02% compared with TEC-II vehicle, TEC-1 0.05%, TEC-I vehicle, RETIN-A Cream 0.05%, RETIN-A Cream 0.025%, and RETIN-A Cream vehicle.

7.8.4 Study Design – This was a single-center, double-blind, controlled, randomized Phase 1 study using 25 healthy subjects. Eight study drugs were randomly applied to semi-occlusive patches on each subject's back five times weekly for three weeks. Each site was evaluated 24 hours (or 72 hours on weekends) after each application.

7.8.5 Study Population – Twenty-five Caucasian subjects, ages 19 to 60 (mean of 44), in good general health were enrolled into the study. Of the 25 subjects, 20 were female. Twenty-three subjects completed the study. Two subjects were lost to follow-up after one study drug application.

7.8.6 Study Results –

Cumulative irritation scores % of Maximum Score

Study Drug	2-week score/max (%)	3-week score/max (%)
Retin-A Cream 0.05%	78.5/920 (8.5%)	267.5/1380 (19.4%)
TEC-I 0.05%	65.0/920 (7.1%)	263/1380 (19.1%)
TEC-II 0.05%	54.5/920 (5.9%)	200/1380 (14.5%)
Retin-A Cream 0.025%	59.5/920 (6.5%)	181/1380 (13.1%)
TEC-II 0.02%	24.5/920 (2.7%)	92.5/1380 (6.7%)
TEC-II Vehicle	0/920 (0%)	10/1380 (0.7%)
Retin-A Cream Vehicle	5.0/920 (0.5%)	9.5/1380 (0.7%)
TEC-I Vehicle	1/920 (0.1%)	7.5/1380 (0.5%)

These scores are achieved upon once daily application to the back. The face is expected to be a more sensitive substrate for irritation. Comparative studies were not done using the face. The formulation of TEC-II 0.02% used in this study did not contain fragrance. The TEC-I 0.05% formulation is not the marketed formulation of RENOVA 0.05% which is TEC-1A.

7.8.7 Safety – Five (22%) of the 23 evaluable subjects reported an adverse event during the study, none of which were classified by the investigator as related to the study drugs. We can conclude from this study that there is at least a mild irritation associated with use of the TEC-II 0.02% unfragranced RENOVA. Irritation with the fragranced, to-be-marketed formulation was not studied in this tolerance study. The irritation score for the TEC-II formulation may not be significantly less irritating than that of the TEC-I formulation. No claims for less irritation for the new formulation should be allowed.

7.9 Tolerance Study – K90-016

7.9.1 Title – The Cumulative Irritation Potential of Tretinoin Emollient Cream (TEC-II) 0.05% and 0.02% with Fragrance

7.9.2 Dates – The study began on September 16, 1991 and ended on October 15, 1991.

7.9.3 Principal Investigator - Lynne B. Harrison, Ph.D.
Harrison Research Laboratories, Inc.
Maplewood, NJ

7.9.4 Study Objectives – To evaluate the cumulative irritation potential of TEC-II 0.05% and 0.02% with fragrance compared with TEC-II 0.05% without fragrance, TEC-II vehicle with fragrance, and TEC-II vehicle without fragrance.

7.9.5 Study Design – Single-center, double-blind, vehicle-controlled, randomized Phase 1 study in healthy Caucasian subjects. Five study drugs were applied randomly to semi-occlusive patches on each subjects back five times weekly for three weeks. Each site was evaluated 24 hours (72 hours on weekends) after each application.

7.9.6 Subjects – 25 male or female Caucasian subjects 18 to 60 years of age, and in good general health were enrolled and analyzed.

7.9.7 Study Results – Total cumulative irritation was measured at 2-weeks and at 3-weeks based on 25 completed subjects.

Cumulative irritation scores % of Maximum Score

Study Drug	2-week score/max (%)	3-week score/max (%)
TEC-II Vehicle With Fragrance	6.5/1000 (0.7%)	23/1500 (1.5%)
TEC-II Vehicle Without Fragrance	5.0/1000 (0.5%)	17/1500 (1.1%)
TEC-II 0.05% With Fragrance	58.5/1000 (5.9%)	284.5/1500 (19.0%)
TEC-II 0.05% Without Fragrance	55.5/1000 (5.6%)	257.5/1500 (17.2%)
TEC-II 0.02% With Fragrance	31.5/1000 (3.2%)	122.5/1500 (8.2%)

These scores are achieved upon once daily application to the back. The face is expected to be a more sensitive substrate for irritation. Comparative studies were not done using the face.

In conclusion, the data appear to point to a greater degree of irritation with the formulations containing fragrance than those without for the TEC-II 0.05% and the TEC-II vehicle (No estimate of variation was provided therefore the significance of any of these numbers cannot be assumed). This conclusion is contrary to that made at the pre-NDA meeting for NDA 21-108 regarding the comparability of the fragranced and unfragranced products. The TEC-II 0.02% with fragrance was not compared in this study with TEC-II 0.02% without fragrance.

7.10 Tolerance Study – J89-012

7.10.1 Title – Evaluation of the Contact Sensitizing Potential of Tretinoin Emollient Cream (TEC-II) 0.05%

7.10.2 Principal Investigators - Lewis P. Stolman, M.D.
Lynne B. Harrison, Ph.D.
Harrison Research Laboratories, Inc.
1624 Springfield Avenue

Maplewood, NJ 07040

7.10.3 Objective – To evaluate the contact sensitizing potential of tretinoin emollient cream (TEC-II) 0.05% compared with its vehicle cream.

7.10.4 Study Design – Single-center, double-blind, controlled, randomized, Phase 1 study using 220 healthy volunteers. The study drugs were randomly applied to semi-occlusive patches on each subject's back three times weekly for three weeks during the induction phase, followed by a two-week rest period and a challenge application of each study drug to previously untreated sites. Each site was evaluated three times weekly during the induction period and 24, 48, and 96 hours after the challenge application.

7.10.5 Study Population – Two hundred twenty Caucasian subjects, ages 18 to 60 (mean of 41), in good general health were enrolled into the study. Of the 220, 168 (76%) were female. Two hundred seven subjects completed the study.

7.10.6 Study Results –

Of the 207 subjects who completed the study, 61 subjects showed mild, transient reactions at (+/- or 1+) at the TEC-II 0.05% site during the induction phase. At the vehicle site, eight subjects exhibited reactions of +/-. One subject developed a reaction of 2+ at both the TEC-II and vehicle sites after the second induction application. The reactions at the TEC-II 0.05% site were more frequent and persistent than those at the vehicle site.

No reactions greater than faint erythema were observed during the challenge phase at either the TEC-II 0.05% or vehicle test sites. Fourteen (7%) subjects exhibited a faint, transient erythema at the TEC-II 0.05% site after the challenge application and six subjects (3%) exhibited faint erythema at the vehicle-treated site after the challenge application. In all but two cases, the +/- reaction was seen at only one of the three challenge phase evaluations.

Based on these results, it appears that TEC-II 0.05% may be responsible for at least a mild, transient reaction [14 (7%) patients vs. 6 (3%)]. Also, it may be possible that a component of TEC-II vehicle may result in irritation, as 1 subject out of 207 had a 2+ reaction at both the TEC-II 0.05% and vehicle sites. This study utilized a formulation of TEC-II that did not contain fragrance. Study K90-017 studied the contact sensitizing potential of the TEC-II 0.02% formulation with fragrance.

7.10.7 Safety – Of the 13 subjects who discontinued from the study, eight discontinued due to personal reasons, one due to a non-drug-related adverse even (fractured left elbow), and four were lost to follow-up. Seven (3.2%) of the 220 subjects enrolled reported at least one adverse event. None of the reported adverse events were considered related to the study drugs.

7.11 Tolerance Study – K90-017

7.11.1 Title – The Contact Sensitizing Potential of Tretinoin Emollient Cream (TEC-II) 0.02% with Fragrance: Full Integrated Statistical and Clinical Report

7.11.2 Investigators - Lewis P. Stolman, M.D.
Lynne B. Harrison, Ph.D.
Harrison Research Laboratories, Inc.
1624 Springfield Avenue
Maplewood, N.J. 07040

7.11.3 Study Objective – This study evaluated the contact sensitizing potential of tretinoin emollient cream (TEC-II) 0.02% with fragrance. TEC-II 0.02% with fragrance was compared with its vehicle and vehicle without fragrance.

7.11.4 Study Design – This was a double-blind, single-center, controlled, randomized, Phase 1 study using 219 healthy volunteers. The two study drugs (TEC-II 0.02% with fragrance and its vehicle) were randomly applied to semi-occlusive patches on each subject's back three times weekly for three weeks during the induction phase, followed by a rest period of approximately two weeks, and a challenge application of three study drugs (TEC-II 0.02% with fragrance, its vehicle, and TEC-II vehicle without fragrance) to previously untreated sites. Each site was evaluated three times weekly during the induction period and 24, 48, and 96 hours after the challenge application.

7.11.5 Study Population – 219 Caucasian subjects, ages 18 to 60 (mean of 41.1 years), in good general health were enrolled into the study. Of the 219, 154 (70%) were female. 198 of the 219 subjects completed the study.

7.11.6 Results – Mild irritation, primarily at the TEC-II 0.02% with fragrance test site, was observed only in a small number of subjects during the induction phase. Of the 200 subjects who completed the induction phase, 10 exhibited grade +/- or 1+ erythema at the TEC 0.02% with fragrance test site at least once. One additional subject exhibited a grade 2+ reaction at the final induction phase evaluation. No grade 1+ or higher reactions were found at the vehicle site during the induction phase with one subject exhibiting faint erythema (+/-) on two occasions.

During the challenge phase, no grades higher that +/- were observed at any time point. No reactions were observed at the 24- and 96- hour readings. At the 48-hour reading, one subject exhibited faint erythema (grade +/-) at the TEC 0.02% with fragrance test site and at both vehicle sites (with and without fragrance). One other subject exhibited faint erythema (grade +/-) at 48 hours at the vehicle without fragrance test site.

7.11.7 Safety – During the induction phase 35 (16%) of the 219 subjects enrolled reported an adverse event. Headache, reported by 16 (7%) subjects and upper respiratory infection, reported by 11 (5%) subjects, were the most frequently reported adverse events. Toothache was reported by 3 (1%) subjects.

Six (3%) of the 198 subjects who completed the study reported an adverse event during the challenge phase. Of the four subjects with an adverse event appearing for the first time during the challenge phase, one subject reported headache, one reported diarrhea, one reported a tooth abscess, and one reported upper respiratory infection.

From this study, we can conclude that TEC-II 0.02% is mildly irritating at worst, and has limited potential to sensitize.

7.12 Tolerance Study – J89-020

7.12.1 Title – Evaluation of the Phototoxic Potential of Tretinoin Emollient Cream (TEC-II) 0.05%

7.12.2 Investigator – Richard Berger, M.D.
Hill Top Research, Inc.
223 Highway 18, Suite 203
East Brunswick, NJ 08816

7.12.3 Objective – The objective of this study was to evaluate the phototoxic potential of tretinoin emollient cream (TEC-II) 0.05% compared with its placebo vehicle.

7.12.4 Study Design – This was a single-center, double-blind, placebo controlled, randomized, Phase 1 study using 10 healthy volunteers to evaluate the phototoxic potential of TEC-II 0.05%. Each subject received semi-occlusive applications of TEC-II 0.05% to two sites on the mid-back. Each subject also received semi-occlusive applications of vehicle to two different sites on the mid-back. Approximately six hours later, two of the treated sites (one treated with TEC-II and one treated with vehicle) and an untreated control site were irradiated with 16-20 joules/cm^2 of UVA and evaluated approximately 0, 24, and 48 hours after photoexposure.

7.12.5 Study Population – Ten female Caucasian subjects, ages 24 to 46, in good general health were enrolled into the study. All 10 subjects completed the study.

7.12.6 Results – None of the 10 subjects showed any reaction at either the irradiated or unirradiated TEC-II 0.05% or vehicle sites at any of the evaluation times. Neither TEC-II 0.05% nor its placebo vehicle showed any phototoxicity under the conditions stated.

The irradiation was performed with UVA. Significant exposure to UVB or visible light was not provided. No claims for lack of phototoxicity can be made with this product unless the product absorbs only in the UVA spectrum. Additionally, unfragranced product was used for this study. See Summary of Safety for Phase 4 commitments.

7.13 Tolerance Study – J89-021

7.13.1 Title – Evaluation of the Photosensitizing Potential of Tretinoin Emollient Cream (TEC-II) 0.05%

7.13.2 Investigator - Richard Berger, M.D.
Hill Top Research, Inc.
223 Route 18, Suite 203
East Brunswick, NJ 08816

7.13.3 Objective – The objective of this study was to evaluate the photosensitizing potential of TEC-II 0.05% compared with its vehicle.

7.13.4 Study Design – A single-center, double-blind, placebo-controlled, randomized Phase 1 study using 25 healthy volunteers to evaluate the photosensitizing potential of TEC-II 0.05%. Each subject received repetitive semi-occlusive applications of TEC-II 0.05% and placebo vehicle to two different sites of 4 cm2 on the mid-back during the induction phase. Applications were twice weekly (Mondays and Thursdays) for three weeks during this phase. The test sites were irradiated with ultraviolet A (UVA) and ultraviolet B (UVB) approximately 24 hours after each application (Tuesdays and Fridays) during the induction period. All photoexposures consisted of two times the minimal erythema dose (MED) established for each subject prior to the study. Each test site was evaluated 24 hours after the first irradiation of the week (Wednesdays) and 72 hours after the second irradiation of the week (Mondays) throughout the induction phase. Approximately 14 days after induction, each subject received a final challenge application of each study drug to two pairs of previously untreated sites on the mid-back. Two sites (one treated with TEC-II 0.05% and one treated with placebo) were irradiated with UVA (4 joules/cm2) approximately 24 hours later, while the remaining sites served as unirradiated controls. All four sites were evaluated approximately 48 and 72 hours after the challenge phase photoexposure.

7.13.5 Study Population – 25 Caucasian subjects ages 18 to 55 (mean age 39.4), in good general health were enrolled into the study. Of the 25 subjects, 23 were female. All 25 subjects completed the study.

7.13.6 Results – 24 of the 25 subjects showed no response at any of the four test sites at either 48 or 72 hours after the elicitation phase photoexposure. One subject developed a transient grade 1 reaction at the irradiated TEC-II 0.05% site 48 hours after the photoexposure. The Applicant did not consider this to be photosensitization response. This study was performed using the unfragranced RENOVA TEC-II 0.05% product. See Summary of Safety for Phase 4 commitment recommendations.

7.13.7 Safety – Seventeen (68%) of the 25 subjects reported one or more adverse events. Headache, reported by 40% of subjects, was the most common adverse event. None of the adverse events were classified by the investigator as related to the study drug.

7.14 Safety (52 Week) Study – K90-054

7.14.1 Title – A Long-Term, Open-Label, Multi-Center Study of Tretinoin Emollient Cream (TEC-II) 0.02% in the Treatment of Photodamaged Skin

7.14.2 Dates – The study began on February 18, 1991 and was completed on June 9, 1992

7.14.3 Investigators –
Häkan Gisslén, M.D., Peter Nordin, M.D., Västra Frölunda sjukhus, Gothenborg, Sweden
Professor Sture Lidén, M.D., Karolinska sjukhuset, Stockholm, Sweden

Gerd Plewig, M.D., and Percy Lehmann, M.D., Heinrich-Heine Universitäts, Düsseldorf, Germany

7.14.4 Objective – The primary objective of this open-label study was to obtain long-term safety data on tretinoin emollient cream (TEC-II) 0.02% for the treatment of photodamaged skin. Efficacy data for TEC-II 0.02% after chronic therapy were also obtained.

7.14.5 Study Design – This was a multi-center, open-label study. Subjects who completed 24 weeks of double-blind therapy with TEC-II 0.02% or vehicle followed by 12 weeks off-therapy (regression phase) under PRI protocol J89-045 were eligible to participate in this study. A sufficient number of new subjects were enrolled to provide a study population of 120 subjects. In this 52-week study, subjects applied TEC-II 0.02% once nightly, using a general dosing guideline of 0.25 gram per application. Subjects applied a moisturizing sunscreen daily, with additional emollients and sunscreens to be used as needed. Subjects returned for scheduled visits every four weeks during the 52-week study.

7.14.6 Study Population – Healthy Caucasian subjects 44-70 years of age (mean age 57). Eighty-nine percent of subjects were female and 56% exhibited moderate photodamage at baseline. Of the 120 subjects enrolled, 101 subjects completed the previous PRI study J89-045, of whom 47 and 54 received approximately 24 weeks of TEC-II 0.02% and vehicle therapy respectively, followed by approximately 12 weeks off-therapy (regression phase). Nineteen additional new subjects were enrolled. Of the 120 subjects enrolled, 109 completed the study and 108 were valid for efficacy. All subjects were valid for safety.

7.15.7 Efficacy – As this was an open label study, no comparisons were made to a vehicle formulation. Thus, no comparison could be made regarding efficacy results.

7.15.8 Safety – Cutaneous treatment effects, while common, were usually mild and well-tolerated. Overall irritation and the various individual signs and symptoms of skin irritation (e.g., erythema, peeling, and burning/stinging) had mean severity scores of less than 1.0 (0 to 9 scale) throughout the 52-week study. Overall irritation peaked at week 4 of TEC-II 0.02% therapy, then decreased to approximately baseline levels by week 16. A slight increase in the overall irritation rating occurred between weeks 28 and 32 (may be seasonal), prior to returning to the baseline level at week 52.

There was high compliance with the once-daily treatment regimen, as 89% of subjects valid for safety completed at least 90% of TEC-II 0.02% applications and 85% of subjects reported 10 or fewer missed applications due to skin irritation. Five percent of the subjects missed 31 or more days of TEC-II 0.02% applications with 2% of those subjects modifying the frequency of applications to every other day to minimize facial irritation.

Facial skin irritation was reported by 43% of the subjects as an adverse event with the majority being of mild or moderate severity.

Of the seven (6%) subjects who discontinued the study due to an adverse event, five had completed the previous study J89-045 (4 assigned to vehicle and one to TEC-II 0.02%) and two were new enrollees. Five subjects, all of whom had not had previous exposure to TEC-II 0.02%, dropped out due to drug-related skin reactions. The remaining two subjects discontinued the study due to cutaneous adverse events unrelated to TEC-II 0.02%. Topical steroid therapy for TEC-II 0.02% related adverse events was reported by 11 (9%) subjects with the majority of the subjects requiring therapy for five days or less. No serious adverse events related to TEC-II 0.02% therapy were reported.

The most frequently reported adverse event not associated with the treatment site was upper respiratory infection with a subject incidence of 32%.

In conclusion, it appears that 52 week use of TEC-II 0.02% appears to result in no serious adverse events. The adverse events seen during 52 weeks of use were no different than that seen in studies of shorter duration.

7.15 Additional Supportive Studies

The Sponsor also submitted study synopses for five clinical trials: J89-022, J89-023, J89-033, K90-010 and J89-035, which were conducted under IND . These studies involved a higher concentration of the active ingredient, tretinoin and were included for safety assessment.

Three Protocols (J89-022, J89-023, and J89-033) shared a common design: each was a double-blind, randomized, single-center, vehicle-controlled, parallel study of either TEC-II 0.05% in 40 patients or vehicle in 40 patients applied to the face once at bedtime for a treatment period of 24 weeks. Patients from these studies were eligible for Protocol K-90-010, which was an additional 12 weeks of observation without any treatment. These studies were previously submitted to NDA 19-963 as part of a safety update for the TEC I/IA formulation of RENOVA 0.05%. Please refer to NDA 19-963 regarding the safety of the TEC I/IA formulation of RENOVA 0.05%.

Protocol J89-035 used a double-blind, randomized, single-center, vehicle-controlled, design with four treatment groups of TEC-II 0.05% applied to one or two of three of the following treatment areas: the face, the right forearm/hand, and the left forearm/hand. Originally intended to recruit 10 non-Caucasian patients for each treatment group, the study was discontinued after enrolling 17 patients because enrollment had been slow and because the program for this formulation was discontinued. Biopsies were obtained from patients in this study and sent to and embedded in paraffin blocks. However, no sections were prepared, stained, or read. These specimens are lost for the purpose of analysis as they were unavailable from the pathologist at

These studies using RENOVA TEC-II 0.05% alone do not provide an adequate basis for comparison of the currently marketed RENOVA TEC IA 0.05% formulation with the proposed RENOVA TEC II 0.02% formulation. For a comparison to be made, a head-to-head comparison of the safety and efficacy of RENOVA TEC-IA 0.05% and RENOVA TEC-II 0.02% would be needed.

8 Overview of Efficacy

'Thou canst not see one wrinkle in my brow; Mine eyes are grey and bright, and quick in turning; My beauty as the spring doth yearly grow... William Shakespeare (from Venus and Adonis)

8.1 Applicant's Proposed Clinical Trials Data Section for Labeling

The results of these assessments are as follows:

FINE WRINKLING			
	NO IMPROVEMENT	MINIMAL IMPROVEMENT	MODERATE IMPROVEMENT
RENOVA 0.02% + CSP*	39%	39%	22%
Vehicle + CSP	62%	27%	11%

COARSE WRINKLING			
	NO IMPROVEMENT	MINIMAL IMPROVEMENT	MODERATE IMPROVEMENT
RENOVA 0.02% + CSP*	60%	30%	10%
Vehicle + CSP	76%	18%	6%

MOTTLED HYPERPIGMENTATION			
	NO IMPROVEMENT	MINIMAL IMPROVEMENT	MODERATE IMPROVEMENT
RENOVA 0.02% + CSP*	29%	36%	35%
Vehicle + CSP	58%	27%	19%

SKIN YELLOWING			
	NO IMPROVEMENT	MINIMAL IMPROVEMENT	MODERATE IMPROVEMENT
RENOVA 0.02% + CSP*	45%	25%	30%
Vehicle + CSP	58%	25%	17%

TACTILE SKIN ROUGHNESS			
	NO IMPROVEMENT	MINIMAL IMPROVEMENT	MODERATE IMPROVEMENT
RENOVA 0.02% + CSP*	33%	27%	40%
Vehicle + CSP	39%	30%	31%

* CSP = Comprehensive skin protection and sun avoidance programs including use of sunscreens, protective clothing, and emollient cream.

In comparative irritation studies RENOVA 0.02% was shown to be significantly less irritating than RENOVA 0.05%.
With discontinuation of RENOVA from their comprehensive skin care and sun avoidance program, a majority of patients will lose some of the mitigating effects of RENOVA."

8.2 Currently Marketed RENOVA 0.05% Clinical Trials Data Section of Label

Two adequate and well-controlled trials were conducted involving a total of 161 evaluable patients (under 50 years of age) treated with RENOVA and 154 evaluable patients treated with the vehicle emollient cream on the face for 24 weeks as an adjunct to a comprehensive skin care and sun avoidance program, to assess the effects on fine wrinkling, mottled hyperpigmentation, and tactile skin roughness. Patients were evaluated at baseline on a 10 point scale and changes from that baseline rating were categorized as follows:

No Improvement:	No change or an increase of 1 unit or more.
Minimal Improvement:	Reduction of 1 unit.
Moderate Improvement:	Reduction of 2 units or more.

In these trials, the fine wrinkles, mottled hyperpigmentation, and tactile roughness of the facial skin were thought to be caused by multiple factors, which included intrinsic aging or environmental factors, such as chronic sun exposure.
The results of these assessments are as follows:

FINE WRINKLING			
	NO IMPROVEMENT	MINIMAL IMPROVEMENT	MODERATE IMPROVEMENT
RENOVA + CSP*	36%	40%	24%
Vehicle + CSP	62%	30%	8%

MOTTLED HYPERPIGMENTATION			
	NO IMPROVEMENT	MINIMAL IMPROVEMENT	MODERATE IMPROVEMENT
RENOVA + CSP	35%	27%	38%
Vehicle + CSP	53%	21%	27%

TACTILE SKIN ROUGHNESS			
	NO IMPROVEMENT	MINIMAL IMPROVEMENT	MODERATE IMPROVEMENT
RENOVA + CSP	49%	35%	16%
Vehicle + CSP	67%	23%	10%

* CSP = Comprehensive skin protection and sun avoidance programs including use of sunscreens, protective clothing, and emollient cream.

Most of the improvement in these signs was noted during the first 24 weeks of therapy. Thereafter, therapy primarily maintained the improvement realized during the first 24 weeks.

A majority of patients will lose most mitigating effects of RENOVA on fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin with discontinuation of a comprehensive skin

care and sun avoidance program including RENOVA; however, the safety and effectiveness of using RENOVA daily for greater than 48 weeks have not been established.

8.3 Statistical Analysis of Endpoints from Efficacy Studies

It did not make clinical sense to include patients with little or no room for improvement in the analysis of subjects being treated for a given skin parameter. Subjects who began with a Baseline score of 0 or 1, were excluded, resulting in an MITT population that was more clinically relevant. Holm's Adjusted P-values for the MITT population with exclusion of subjects Baseline = 0 or 1 were determined for each indication and each study by the FDA Biostatistician (See Table 8A). "Holm's method performs testing in decreasing order of significance, i.e. starting at the smallest p-value. Testing is continued until a null hypothesis is accepted, i.e. an observed p-value is larger than the corresponding Holm's p-value. Thus the 6 endpoints adjust for Type I error."

Table 8A - Adjusted P-values from ANOVA test of treatment differences (RENOVA versus vehicle) MITT using LOCF

Study J89-024		Study J89-025		Study J89-045	
Fine Wrinkling	.0099 *	Mott Hyperpig .	.0001 *	Fine Wrinkling	.0001 *
Coarse Wrinkling	.2734	Yellow-brown discoloration	.0634	Yellow-brown discoloration	.0029 *
Yellow-brown discoloration	.2734	Coarse Wrinkling.	.0805	Laxity	.0235 *
Mott Hyperpig.	.5223	Fine Wrinkling.	.1712	Coarse Wrinkling	.0821
Laxity	.5223	Laxity	.1712	Mott Hyperpig.	.2987
Tactile Roughness	.5223	Tactile Roughness	.1789	Tactile Roughness	.7153

Study K90-011		Study L91-026	
Coarse Wrinkling	.0295 *	Laxity	.4015
Laxity	.7330	Fine Wrinkling	.9341
Fine Wrinkling	1.0	Tactile Roughness	1.0
Yellow-brown discoloration	1.0	G. Mott. Hyperpig.	1.0
Mott Hyperpig.	1.0	L. Mott. Hyperpig.	1.0
Tactile Roughness	1.0	Coarse Wrinkling	1.0

*Significant p-value adjusted using the method of Holms for multiple comparisons

Based on the FDA statistician's derived p-values, the Applicant has demonstrated adequately an effect on fine wrinkling in two multi-center studies.

Thus, for NDA 21-108, RENOVA (tretinoin emollient cream) 0.02% (TEC-II formulation), after a thorough analysis, the applicant appears to have demonstrated efficacy for an indication of fine wrinkling.

Table 8B - Data Regarding Amount of Improvement for Each of the Studies used for Efficacy

	J89-024		J89-025		J89-045		K90-011		L91-026	
Fine Wrinkling	Treatment	Vehicle	Treatment	Vehicle	Treatment	Vehicle	Treatment	Vehicle	Treatment	Vehicle
At least –3	0	2	10	4	16	2	1	0	0	0
At least –2	20	7	17	13	26	12	5	0	3	6
At least –1	53	33	48	35	50	27	14	13	13	22
0 (No Change)	36	57	42	54	10	28	23	24	31	28
1 (or worse)	0	0	0	1	0	5	3	3	1	2

	Sum of Subjects from Studies		**% of Total Studied**			**Individual Improvement Categories**	**% of Total in Each Improvement Category**	
Fine Wrinkling	Treatment	Vehicle	Treatment	Vehicle			Treatment	Vehicle
At least -3	27	8	8%	2%	≤ -3	Moderate Improvement	27 (8%)	8 (2%)
At least -2	71	38	22%	11%	-2	Mild Improvement	44 (14%)	30 (9%)
At least -1	178	130	55%	39%	-1	Minimal Improvement	107 (33%)	92 (28%)
0 (No Change)	142	191	44%	58%	0	No Change	142 (44%)	191(58%)
1 (or worse)	4	11	1%	3%	1	Worsened	4 (1%)	11 (3%)

The above Table shows the comparative percent of subjects in each improvement category for fine wrinkling and the data used to derive the percentages. This data could be used in labeling.

8.4 Regarding use of RENOVA as an Adjunctive Treatment

The Applicant proposes language for labeling for the Indications and Usage section that allows for the use of RENOVA 0.02% as therapy for mitigation (palliation) of certain signs of photodamage contrary to current labeling for RENOVA 0.05%. However, all of the efficacy studies (including the pivotal trials) submitted to this NDA have in the protocols the fact that, "Subjects in both treatment groups applied a moisturizing sunscreen daily, with additional emollients and sunscreens to be used as needed." Therefore, it is appropriate that RENOVA be indicated for use as an adjunctive treatment. The language used in the indications section for the current RENOVA 0.05% should be preserved in the label for the new RENOVA 0.02%.

8.5 Reviewer's Proposed Clinical Trials Section of Labeling

"Clinical Trials

Four adequate and well-controlled trials and one single center randomized, controlled trial were conducted involving a total of 324 evaluable patients treated with RENOVA 0.02% and 332 evaluable patients treated with the vehicle emollient cream on the face for 24 weeks with a comprehensive skin care and sun avoidance program, to assess the effects on fine and coarse wrinkling, mottled hyperpigmentation, tactile skin roughness, yellowish-brown discoloration, and laxity. Patients were evaluated at baseline on a 10 point scale and changes from that baseline rating were categorized as follows:

Worsening	Increase of 1 unit or more.
No improvement:	No change.
Minimal improvement:	Reduction of 1 unit.
Mild improvement:	Reduction of 2 units.
Moderate improvement:	Reduction of 3 units or more.

In these trials, the fine and coarse wrinkling, mottled hyperpigmentation, tactile roughness, yellowish-brown discoloration, and laxity of the facial skin were thought to be caused by multiple factors which included intrinsic aging or environmental factors, such as chronic skin exposure.

Two of the five trials provided adequate demonstration of efficacy for fine wrinkling. The five trials, as a group, failed to provide a statistically significant demonstration of efficacy with coarse wrinkling, mottled hyperpigmentation, tactile skin roughness, yellow-brown (citrine) discoloration, and laxity. Yellowish-brown (citrine) discoloration was only studied in subjects with Fitzpatrick Skin Types I-III. Data from all five trials combined for fine wrinkling, the only indication for which RENOVA 0.02% demonstrated efficacy, is provided below.

FINE WRINKLING		
	Subjects using RENOVA 0.02% + CSP*	Vehicle + CSP*
Worsened	1%	3%
No Change	44%	58%
Minimal Improvement	33%	28%
Mild Improvement	14%	9%
Moderate Improvement	8%	2%

* CSP = Comprehensive skin protection and sun avoidance programs including use of sunscreens, protective clothing, and emollient cream.

No studies have been conducted comparing the irritation of RENOVA 0.02% to RENOVA 0.05% (older marketed formulation).

With discontinuation of RENOVA from their comprehensive skin care and sun avoidance program, a majority of patients will lose some of the mitigating effects of RENOVA."

9 Overview of Safety

9.1 Investigations Pertinent to Safety

For the evaluation of safety of RENOVA 0.02%, it is important to keep in mind that the indications sought for this drug product are relatively minor and cosmetic. Thus, any adverse events, including those that are minor and cosmetic would be important to assess.

It is important to note that a majority of the studies submitted to this NDA used an unfragranced product. The fragrance, ————————, is to be used in the proposed to-be-marketed RENOVA 0.02% TEC-II at a concentration of ———The fraganced formulation of TEC-II 0.02% (Formula FD-08203-000-CA-63) was only used in studies K90-016, K90-017, and L91-026. All of the other studies that were submitted to this NDA, including the Phase 3 pivotal trials, utilized a TEC-II formulation without fragrance (Formula FD-08203-000-BH-63). See Tables 4 and 5 of Volume 3.2 pages 00006-00010 of submission (December 16, 1999).

Table 9A summarizes all investigations pertinent to safety.

Table 9A: All Investigations Pertinent to Safety

Protocol #	Country	Study Design	Treatment	No. Enrolled	N Age Range (Mean)[a]	% M/F B/C/O[b]	Duration of Study
I88-082	U.S.	Percutaneous absorption of ^{3}H-tretinoin, Phase 1, single-center, randomized, parallel, open-label[c]	TEC-II 0.05% TEC-I 0.05% RETIN-A 0.05%	42	42 19-57 (28.6)	100/0 0/100/0	28 days
J89-011	U.S.	Cumulative Irritation Potential, Phase 1, single-center, randomized, double-blind vehicle-controlled	TEC-II 0.05% TEC-II 0.02% w/o fragrance TEC-II Vehicle TEC-I 0.05% TEC-I Vehicle RETIN-A 0.05% RETIN-A 0.025% RETIN-A Vehicle	25	23 23-60 (44.9)	22/78 0/100/0	3 Weeks
J89-012	U.S.	Contact Sensitizing Potential, Phase 1, single-center, randomized, double-blind, vehicle-controlled, washout period with challenge application	TEC-II 0.05% Vehicle	220	220 18-60 (41.1)	24/76 0/100/0	5 Weeks
J89-020	U.S.	Phototoxicity Potential, Phase 1, single-center, randomized, double-blind, vehicle-controlled	TEC-II 0.05% Vehicle No-treatment control	10	10 24-46 (32.6)	0/100 0/100/0	2 Days
J89-021	U.S.	Photosensitizing Potential, Phase 1, single-center, randomized, double-blind, vehicle-controlled	TEC-II 0.05% Vehicle	25	25 18-55 (39.4)	8/92 0/100/0	5 Weeks
K90-016	U.S.	Cumulative Irritation Potential, Phase 1, single-center, randomized, double-blind, vehicle-controlled	TEC-II 0.05% w/ fragrance TEC-II 0.05% w/o fragrance TEC-II 0.02% w/fragrance Vehicle w/ fragrance Vehicle w/o fragrance	25	25 29-60 (45.1)	28/72 0/100/0	3 Weeks
K90-017	U.S.	Contact Sensitizing Potential, Phase 1, single-center, randomized, double-blind, vehicle-controlled, washout period with challenge application	TEC-II 0.02% w/fragrance Vehicle w/fragrance Vehicle w/o fragrance	219	219 18-60 (41.1)	30/70 0/100/0	5 Weeks
J89-024	U.S.	Photodamaged Skin, Phase 3, multicenter, randomized, double-blind, parallel vehicle-controlled	TEC-II 0.02%, 0.25g Vehicle, 0.25g	90 90	179 45-69 (58.4)	12/88 0/100/0	24 Weeks
J89-025	U.S.	Photodamaged Skin, Phase 3, multicenter, randomized, double-blind, parallel vehicle-controlled	TEC-II 0.02%, 0.25g Vehicle, 0.25g	90 90	179 43-70 (58.6)	11/89 0/100/0	24 Weeks
J89-045	Sweden Germany	Photodamaged Skin, Phase 3, multicenter, randomized, double-blind, parallel vehicle-controlled, 12-week post-therapy	TEC-II 0.02%, 0.25g Vehicle, 0.25g	60 60	119 44-74 (56.6)	13/87 0/100/0	24 Weeks
L91-026	U.S.	Photodamaged Skin, Phase 2, multicenter, randomized, double-blind, parallel vehicle-controlled	TEC-II 0.02%, 0.25g Vehicle, 0.25g	60 60	117 40-74 (55.7)	20/80 91/0/9	24 Weeks
L91-026	U.S.	Photodamaged Skin, Phase 2, multicenter, open-label, long-term	TEC-II, 0.25g	60[d]	60 40-74 (55.8)	20/80 87/0/13	28 Weeks
			Vehicle/TEC-II, 0.25g	52[e]	52 40-74 (56.0)	19/81 94/0/6	
K90-011	U.S.	Photodamaged Skin, Phase 3, single center, randomized, double-blind, parallel vehicle-controlled, 12-week post-therapy	TEC-II 0.02%, 0.25g Vehicle, 0.25g	40 40	80 46-71 (60.1)	11/89 0/100/0	24 Weeks
K90-054	Sweden Germany	Photodamaged Skin, Phase 3, multicenter, open-label, long-term	TEC-II 0.02%, 0.25g	120[f]	120 44-70 (57.0)	11/89 0/100/0	52 Weeks

[a] Results are for subjects valid for safety.
[b] Percent of males (M), females (F), blacks (B), Caucasians (C), and other races (O) for subjects valid for safety.
[c] Phase 1 Study I88-082 included single and repeat application treatment groups for each 0.05% formulation.
[d] These subjects received TEC-II 0.02% in the double-blind phase of L91-026 and continued treatment in the open-label phase.
[e] These subjects received vehicle in the double-blind phase of L91-026. This results in 52 new subjects exposed to TEC-II 0.02%.
[f] Includes 47 TEC-II 0.02% and 54 vehicle subjects from J89-045, and 19 newly enrolled subjects. This results in 73 new subjects exposed to TEC-II 0.02%.

9.2 Local adverse events – In all Phase 3 studies, skin adverse events (see Table 9B) occurred in more TEC-II 0.02%-treated subjects (31%) than in vehicle-treated subjects (13%) (p<0.001).

Table 9B: Summary of Adverse Events Associated with the Treatment Site - Subjects Valid for Safety (Pool 1 - 24-Week TEC 0.02% Studies J89-024, J89-025, J89-045, K90-011 and L91-026 Combined)

	Number and Percent of Subjects[a]									
	TEC-II 0.02% (N=339)					Vehicle (N=335)				
Primary Term	Mild	Moderate	Severe	Total	%[b]	Mild	Moderate	Severe	Total	%[b]
Irritation, Skin/Subcutaneous	16	25	7	48	14	5	5	1	11	3
Keratoderma	11	10	2	23	7	1	3	1	5	1
Erythema	9	6	1	16	5	4	2	0	6	2
Dermatitis	6	4	1	11	3	5	0	0	5	1
Pain, Skin	6	3	1	10	3	1	0	0	1	<1
Rash	4	2	0	6	2	2	0	0	2	<1
Photodamaged Skin (actinic keratosis)	3	1	0	4	1	2	0	0	2	<1
Pruritus	0	4	0	4	1	0	1	0	1	<1
Irritation, Eye	0	1	1	2	<1	0	0	0	0	0
Burns, Skin	2	0	0	2	<1	0	1	0	1	<1
Dyschromia, Skin	1	1	0	2	<1	2	1	0	3	<1
Edema, Skin/Subcutaneous	0	2	0	2	<1	0	0	0	0	0
Lesions, Skin	1	1	0	2	<1	0	0	0	0	0
Allergy, Plants	1	0	0	1	<1	1	0	0	1	<1
Edema	1	0	0	1	<1	0	0	0	0	0
Acne	0	1	0	1	<1	3	0	0	3	<1
Headache	0	1	0	1	<1	0	0	0	0	0
Folliculitis	1	0	0	1	<1	0	0	0	0	0
Candidiasis, Skin	1	0	0	1	<1	0	0	0	0	0
Cellulitis	0	0	1	1	<1	0	0	0	0	0
Pyoderma	0	1	0	1	<1	0	0	0	0	0
Skin Infections, Bacterial	0	1	0	1	<1	0	0	0	0	0
Abrasions, Skin	1	0	0	1	<1	2	0	0	2	<1
Papules, Skin	1	0	0	1	<1	4	0	0	4	1
Ulcer, Skin	1	0	0	1	<1	0	0	0	0	0
Urticaria	0	1	0	1	<1	0	1	1	2	<1
Vesicle(s) Skin	1	0	0	1	<1	1	0	0	1	<1
Purpura	0	0	0	0	0	0	0	1	1	<1
Abscess, Skin	0	0	0	0	0	0	1	0	1	<1
Stomatitis	0	0	0	0	0	1	0	0	1	<1
Bites, Skin	0	0	0	0	0	1	0	0	1	<1
Cyst, Skin/Subcutaneous	0	0	0	0	0	1	0	0	1	<1
Erythema Multiforme	0	0	0	0	0	1	0	0	1	<1
Overall*	41	53	10	104	31	28	12	4	44	13

[a] Adverse events are categorized based on the maximum severity reported by a given subject for that adverse event.
[b] Percentages are based on the total number of subjects reporting that adverse event.
* Number of subjects reporting any adverse event at the treatment site of a given intensity. Since some subjects reported more than one adverse event (primary term), the overall count does not represent the sum of individual primary term incidences.

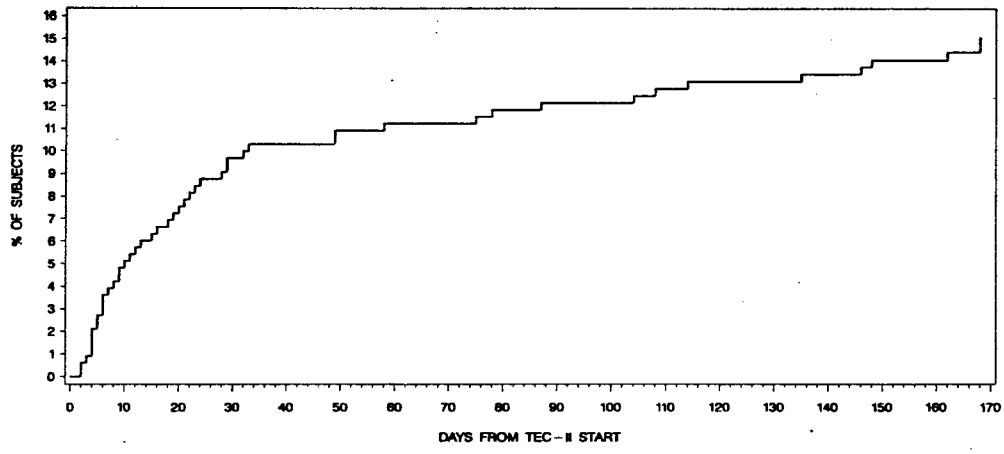
The most common adverse event, skin irritation, was reported by 14% of subjects in the TEC-II 0.02% group and 3% of subjects in the vehicle group (p<0.001). Keratoderma (dry/peeling skin) (p=0.001) was reported by 7% of TEC-II treated subjects vs. 1% of vehicle treated subjects. Erythema (p=0.049) was reported by 5% of TEC-II treated subjects and 2% of vehicle treated subjects. Also statistically significant was skin pain (3% of TEC-II 0.02% treated subjects vs. <1% of vehicle-treated subjects) (p=0.011). 12 out of 340 subjects treated with TEC-II 0.02% (slightly more than 3.5%) discontinued from these studies because of an adverse event (11 of these were due to skin reactions). In comparison, only 5 of the 340 treated with vehicle (about 1.5%) dropped out from these studies due to an adverse event (2 of these were skin reactions).

Table 9C: Local adverse events from trials submitted to NDA 21-108

ADVERSE EVENT	RENOVA TEC-II TREATED SUBJECTS	VEHICLE TREATED SUBJECTS	P VALUE
Skin irritation	14%	3%	<0.001
Keratoderma (dry/peeling skin)	7%	1%	0.001
Erythema	5%	2%	0.049
Skin Pain	3%	<1%	0.011

Skin irritation, reported by 14% of subjects in the TEC-II 0.02% group, largely occurred within the first month of application (See Figure 9-1 below). Severity and duration of skin irritation did not appear to have been assessed.

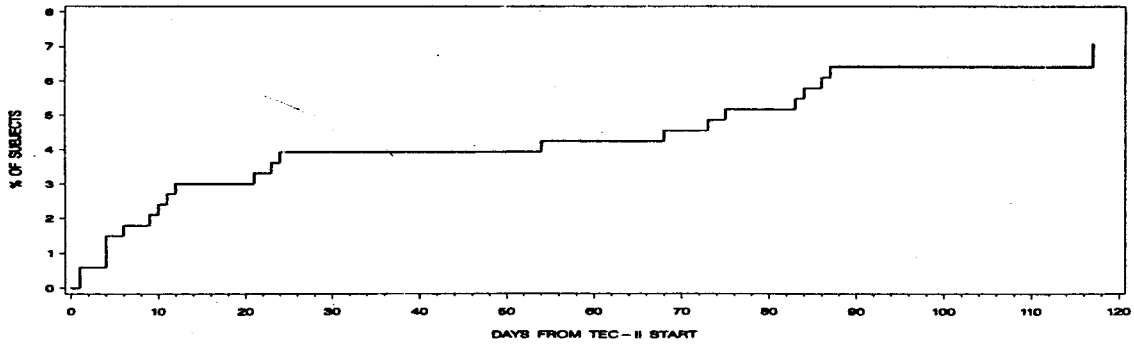
Figure 9-1: Plot of the Incidence of Irritation, Skin/Subcutaneous by the Day of First Occurrence* Associated with the Treatment Site - Subjects Valid for Safety
(Pool 1 - 24-Week TEC-II 0.02% Studies J89-024, J89-025, J89-045, K90-011, and L91-026 Combined)



* BASED ON KAPLAN-MEIER METHOD OF ESTIMATION.

Keratoderma, reported by 7% of subjects in the TEC-II 0.02% group, had onset of occurrence apparently, in two distinct time periods (the first within the first 30 days, and the second between 60 and 90 days).

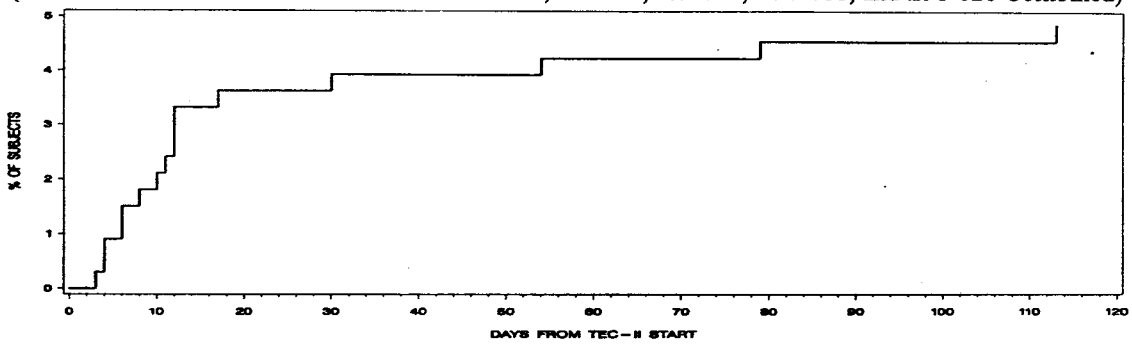
Figure 9-2: Plot of the Incidence of Keratoderma by the Day of First Occurrence* Associated with the Treatment Site - Subjects Valid for Safety
(Pool 1 - 24-Week TEC-II 0.02% Studies J89-024, J89-025, J89-045, K90-011, and L91-026 Combined)



* BASED ON KAPLAN-MEIER METHOD OF ESTIMATION.

Erythema, reported by 5% of the subjects in the TEC-II 0.02% group, had an onset of occurrence within the first two weeks (see Figure 9-3). Severity and duration of erythema was not assessed.

Figure 9-3: Plot of the Incidence of Erythema by the Day of First Occurrence* Associated with the Treatment Site - Subjects Valid for Safety
(Pool 1 - 24-Week TEC-II 0.02% Studies J89-024, J89-025, J89-045, K90-011, and L91-026 Combined)



* BASED ON KAPLAN-MEIER METHOD OF ESTIMATION.

9.3 Deaths – One death was reported in study J89-023. Subject #117 (using Renova TEC-II 0.05%) died from acute myocardial infarction. No deaths were reported in the studies originally submitted to NDA 21-108. J89-023 was submitted as an amendment on October 26, 1999.

The death of Subject #117 was apparently unrelated to use of Renova TEC-II. The Subject was a 63 year old woman with hypothyroidism and diabetes who died of an acute myocardial infarction on 4/10/1990, about 5 months into the study.

9.4 Serious adverse events – An evaluation of all subject pools revealed that 18 subjects in the TEC-II 0.02% treatment group and 12 subjects in the vehicle treatment group reported a serious adverse event during study drug administration (see Table 9D). The serious adverse events reported mainly included gastrointestinal conditions and musculoskeletal disorders.

The serious adverse events were considered by the investigators to be unrelated to the study drug in all but one case; RENOVA TEC-II 0.02%-treated subject #328 who had facial cellulitis. This event was considered to be "possibly related" to the study drug. One month after initiating therapy, the patient developed a facial cellulitis that required admission for intravenous antibiotics. The patient developed post-inflammatory hyperpigmentation. It is not known if the post-inflammatory hyperpigmentation resolved. It is likely that this event was related to the irritation from this drug. The onset of this adverse event suggests a correlation with administration of RENOVA 0.02%.

Table 9D: Subjects with Serious or Potentially Serious Adverse Events (J89-024, J89-025, J89-045, K90-011, K90-054, and L91-026)

Study	Subject	Investigator	Age	Sex	Days on Therapy	Onset Day, Duration[a]	Adverse Event	Relation to Therapy	Outcome
TEC-II 0.02%									
J89-024	328	Levine	60	Male	37	37, 3 weeks	facial cellulitis (probably erysipelas)	possible	discontinued study due to this adverse event
J89-024	346	Levine	53	Female	170	27, 4 days	Hypertension	none	completed study
J89-025	136	Savin	61	Female	164	64, continuing	chronic lymphocytic leukemia	none	completed study
J89-045	103	Gisslen	68	Female	179	09/--/90 continuing	cerebrovascular accident and associated severe right optic nerve damage	none	completed study
J89-045	129	Gisslen	67	Female	77	78, continuing	bronchial carcinoma	none	discontinued study due to this adverse event
J89-045	218	Liden	63	Female	20	07/--/90, continuing	broken bones due to automobile accident	none	discontinued study for personal reasons
J89-045	326	Plewig	58	Male	175	09/--/90, continuing	carcinoma of the lung	none	completed study
						10/10/90, continuing	renal metastasis		
K90-011	127	Weinstein	64	Female	171	135, continuing	pelvic fracture	none	completed study
K90-011	145	Weinstein	63	Female	178	135, 10 days	basal cell carcinoma on left lateral back	none	completed study
K90-011	153	Weinstein	64	Male	127	Unknown, Unknown	colon polyps	none	subject was lost to follow-up
						Unknown, Continuing	depression		
K90-054	136	Gisslen	48	Female	362	155, 6 days	anal fistula	none	completed study
K90-054	231	Liden	52	Female	363	7, 3 days	pulmonary emboli	none	completed study
K90-054	241	Liden	59	Female	364	165, 24 days	erysipelas on right side of face	none	completed study
K90-054	303	Plewig	54	Female	356	196, 1 day	sinus surgery for sinusitis	none	completed study
K90-054	318	Plewig	48	Male	356	69, 4 days	left knee arthrosis	none	completed study
K90-054	331	Plewig	55	Female	378	136, 13 days	torn meniscus	none	completed study
K90-054	335	Plewig	49	Male	363	223, 7 days	bronchial viral infection	none	completed study
L91-026	237*	Friedman	68	Male	283	269, continuing	brain cancer (tumor)	none	discontinued study due to this adverse event
Vehicle									
J89-024	128	Ellis	58	Female	165	68, 10 weeks	fractured left hip	none	completed study
J89-024	302	Levine	67	Female	171	Unknown, Unknown,	intestinal polyp	none	completed study
						153, continuing	Stage C Duke rectal cancer		
J89-024	321	Levine	62	Female	168	11, continuing	erythema multiforme	none	completed study
J89-024	341	Levine	67	Female	173	92, continuing	breast cancer recurrence-neck	none	completed study
J89-025	127	Savin	63	Female	167	57, continuing	Cholelithiasis	none	completed study
J89-025	203	Weiss	68	Female	174	121, continuing	left breast cancer	none	completed study
J89-025	232	Weiss	57	Female	179	150, continuing	basal cell carcinoma, nose	none	completed study
J89-025	234	Weiss	57	Female	174	22, 90 days	ruptured disc	none	completed study
J89-025	249	Weiss	46	Female	167	61, 51 days	kidney stones	none	completed study
J89-045	139	Glissen	51	Female	171	68, 4 days	Subileus	none	completed study
						138, 13 days	Subileus		
L91-026	419	Phillips	54	Female	113	103, unknown	left breast cancer	none	discontinued from study due to this adverse event
L91-026	422	Phillips	60	Male	66	80, continuing	prostate cancer	none	discontinued from study due to this adverse event

[a] Continuing indicates that the adverse event was ongoing at the completion of the study.

9.5 Dropouts/withdrawals – 12 out of 340 subjects treated with TEC-II 0.02% (slightly more than 3.5%) discontinued from these studies because of an adverse event (11 of these were due to skin reactions). In comparison, only 5 of the 340 treated with vehicle (about

1.5%) dropped out from these studies due to an adverse event (2 of these were skin reactions).

Table 9E identifies the reasons for discontinuation of therapy from the TEC-II 0.02% studies.

Table 9E: Reasons for Discontinuation of Therapy – Intent-to-Treat (Pool 1 - 24-Week TEC-II 0.02% Studies J89-024, J89-025, J89-045, K90-011, and L91-026)

	TEC-II (N=340)		Vehicle (N=340)		Total (N=680)	
	N	(%)	N	(%)	N	(%)
All Studies Combined	(N=340)		(N=340)		(N=680)	
Personal reasons	11	3.24	12	3.53	23	3.38
Adverse event	12	3.53	5	1.47	17	2.50
Protocol violation	1	0.29	0	0.00	1	0.15
Lost to follow-up	10	2.94	9	2.65	19	2.79
Total	34	10.00	26	7.65	60	8.82

9.6 Overdosage exposure – No instances of overdosage with RENOVA TEC-II were reported in clinical trials. The package insert should state that: "Application of larger amounts of medication than recommended will not lead to more rapid or better results, and marked redness, peeling, or discomfort may occur. Oral ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A."

9.7 Comparison with RENOVA tretinoin emollient cream 0.05% - The Applicant has placed in the proposed label under the Clinical Trials Data Section the following, "In comparative irritation studies RENOVA 0.02% was shown to be significantly less irritating than RENOVA 0.05%." No comparative studies between TEC-I 0.05% and TEC-II 0.02% (to-be marketed) formulation were conducted. Therefore, a comparison of safety between the two products may not be accurate.

The new formulation proposed with NDA 21-108 has a lower concentration of tretinoin (0.02% compared to 0.05%). A lower concentration of a topical agent may not necessarily result in lower irritancy. Unfortunately, no direct comparisons have been tested between the currently marketed formulation and the new proposed TEC-II formulation. Study J89-011 tested the cumulative irritation potential of TEC-I 0.05% and TEC-II 0.02% (unfragranced) along with other formulations in a single-center, double-blind, controlled, randomized Phase 1 study on healthy volunteers (See Table 9F).

Table 9F – Cumulative Irritation as per Study J89-011.

STUDY DRUG	2-WEEK SCORE[A]	3-WEEK SCORE[B]
Retin-A Cream 0.05%	78.5	267.5
TEC-I 0.05%	65.0	263.0
TEC-II 0.05%	54.5	200.0
Retin-A Cream 0.025%	59.5	181.0
TEC-II 0.02% (without fragrance)	24.5	92.5
TEC-II Vehicle	0.0	10.0
Retin-A Cream Vehicle	5.0	9.5
TEC-I	1.0	7.5

[A]Maximum score of 920 based on 10 applications in 23 completed subjects.
[B]Maximum score of 1380 based on 15 applications in 23 completed subjects.

These cumulative irritation scores may not be of clinical significance due to the fact that the study drug was applied to the back and not to the face. It is known that facial skin is more sensitive to irritation. (Periorbital application of drug product for treatment of periorbital rhytids may be especially relevant to this discussion.) Thus, the relevance and sensitivity for detection of difference with an irritancy study for back skin is questionable.

9.8 ADR Incidence Tables

Table 9G is a summary table of all Treatment Site Adverse Events associated with relatively short-term use (24 weeks) of the TEC-II formulation of RENOVA as garnered from the studies submitted to NDA 21-108.

Table 9G: Summary of Adverse Events Associated with the Treatment Site - Subjects Valid for Safety (Pool 1 – 24-Week TEC 0.02% Studies J89-024, J89-025, J89-045, K90-011 and L91-026 Combined)

	Number and Percent of Subjects[a]										
	TEC-II 0.02% (N=339)					Vehicle (N=335)					Statistical Test Results[c]
Primary Term	Mild	Moderate	Severe	Total	%[b]	Mild	Moderate	Severe	Total	%[b]	p-value
Irritation, Skin/Subcutaneous	16	25	7	48	14	5	5	1	11	3	<0.001
Keratoderma	11	10	2	23	7	1	3	1	5	1	0.001
Erythema	9	6	1	16	5	4	2	0	6	2	0.049
Dermatitis	6	4	1	11	3	5	0	0	5	1	0.205
Pain, Skin	6	3	1	10	3	1	0	0	1	<1	0.011
Rash	4	2	0	6	2	2	0	0	2	<1	0.286
Photodamaged Skin (actinic keratosis)	3	1	0	4	1	2	0	0	2	<1	0.686
Pruritus	0	4	0	4	1	0	1	0	1	<1	0.373
Irritation, Eye	0	1	1	2	<1	0	0	0	0	0	0.499
Burns, Skin	2	0	0	2	<1	0	1	0	1	<1	1.000
Dyschromia, Skin	1	1	0	2	<1	2	1	0	3	<1	0.685
Edema, Skin/Subcutaneous	0	2	0	2	<1	0	0	0	0	0	0.499
Lesions, Skin	1	1	0	2	<1	0	0	0	0	0	0.499
Allergy, Plants	1	0	0	1	<1	1	0	0	1	<1	1.000
Edema	1	0	0	1	<1	0	0	0	0	0	1.000
Acne	0	1	0	1	<1	3	0	0	3	<1	0.371
Headache	0	1	0	1	<1	0	0	0	0	0	1.000
Folliculitis	1	0	0	1	<1	0	0	0	0	0	1.000
Candidiasis, Skin	1	0	0	1	<1	0	0	0	0	0	1.000
Cellulitis	0	0	1	1	<1	0	0	0	0	0	1.000
Pyoderma	0	1	0	1	<1	0	0	0	0	0	1.000
Skin Infections, Bacterial	0	1	0	1	<1	0	0	0	0	0	1.000
Abrasions, Skin	1	0	0	1	<1	2	0	0	2	<1	0.622
Papules, Skin	1	0	0	1	<1	4	0	0	4	1	0.215
Ulcer, Skin	1	0	0	1	<1	0	0	0	0	0	1.000
Urticaria	0	1	0	1	<1	0	1	1	2	<1	0.622
Vesicle(s) Skin	1	0	0	1	<1	1	0	0	1	<1	1.000
Purpura	0	0	0	0	0	0	0	1	1	<1	0.497
Abscess, Skin	0	0	0	0	0	0	1	0	1	<1	0.497
Stomatitis	0	0	0	0	0	1	0	0	1	<1	0.497
Bites, Skin	0	0	0	0	0	1	0	0	1	<1	0.497
Cyst, Skin/Subcutaneous	0	0	0	0	0	1	0	0	1	<1	0.497
Erythema Multiforme	0	0	0	0	0	1	0	0	1	<1	0.497
Overall*	41	53	10	104	31	28	12	4	44	13	<0.001

[a] Adverse events are categorized based on the maximum severity reported by a given subject for that adverse event.
[b] Percentages are based on the total number of subjects reporting that adverse event.
[c] Statistical results are based on Two-Sided Fisher's Exact Tests comparing the total number of subjects in each treatment group with a particular adverse event.
* Number of subjects reporting any adverse event at the treatment site of a given intensity. Since some subjects reported more than one adverse event (primary term), the overall count does not represent the sum of individual primary term incidences.

Table 9H shows all adverse events that are not associated with the treatment site (arranged by region – U.S. vs. outside the U.S.). The incidence of these adverse events

was somewhat lower outside the United States: 46% of subjects in the TEC-II 0.02% vs. 51% in the vehicle groups in the United States, and 30% vs. 25%, respectively, outside the United States. Only one individual adverse event (based on primary terms) was reported in the United States by at least 5% of subjects in either treatment group: upper respiratory infection (11% in the TEC-II 0.02% group and 16% in the vehicle group) (p=0.139).

Table 9H: Summary of Adverse Events Not Associated with the Treatment Site by Region - Subjects Valid for Safety
(Pool 1 - 24-Week TEC-II 0.02% Studies J89-024, J89-025, J89-045, K90-011, and L91-026 Combined)

Adverse Events Categorized by Body System	TEC II 0.02% (N=279)		Vehicle (N=276)		Test Results[a]
Body System					p-value
Region: U.S.	N	(%)	N	(%)	
Respiratory Infections/Inflammations	48	17	64	23	0.091
Skin Conditions	17	6	13	5	0.574
Infections, Body As A Whole	15	5	16	6	0.855
Infections/Inflammations, GI	14	5	20	7	0.293
General Disorders	13	5	13	5	1.000
Disorders, Central Nervous System	10	4	13	5	0.531
Vascular Conditions	9	3	4	1	0.261
GI Conditions	8	3	18	7	0.046
Joint Disorders	6	2	4	1	0.752
Muscle Disorder	6	2	6	2	1.000
Allergy, Non-Drug	5	2	0	0	0.061
Musculoskeletal Disorders	5	2	0	0	0.061
Respiratory Conditions	5	2	7	3	0.575
Infections/Inflammations, Ophth.	4	1	1	<1	0.373
Joint Inflammations	4	1	5	2	0.751
Infection/Inflammation, Urinary Tract	3	1	7	3	0.220
Inflammation/Infection, Ears	3	1	2	<1	1.000
Psychological Disorder(s)	3	1	1	<1	0.624
Bone Disorders	2	<1	4	1	0.448
Eye Conditions	2	<1	5	2	0.284
Genital/Repro. Conditions, Female	2	<1	0	0	0.499
Infections, Skin	2	<1	1	<1	1.000
Tendon Inflammations	2	<1	2	<1	1.000
Abnormal Blood Chemistry Values	1	<1	1	<1	1.000
Blood Cell Disorders	1	<1	0	0	1.000
Bone Inflammations	1	<1	0	0	1.000
Cardiac Disorders	1	<1	2	<1	0.622
Cardiovascular Conditions	1	<1	1	<1	1.000
Cartilage Disorders	1	<1	2	<1	0.622
Devices, Mouth	1	<1	0	0	1.000
Disorders of Thyroid	1	<1	0	0	1.000
Infections, Hair & Hair Follicles	1	<1	0	0	1.000
Nail Conditions	1	<1	1	<1	1.000
Peripheral Nervous System Disorders	1	<1	3	1	0.371
Surgery, Dental/Periodontal	1	<1	0	0	1.000
Urinary Tract Conditions	1	<1	1	<1	1.000
Blood Disorders	0	0	2	<1	0.247
Breast Disorders	0	0	3	1	0.122
Conditions, Sebaceous Glands	0	0	1	<1	0.497
Disorders of Vision	0	0	1	<1	0.497
Genital Reproductive Condition, Male	0	0	1	<1	0.497
Infec./Inflam., Genit./Repro., Female	0	0	2	<1	0.247
Menopausal & Post Menopausal Disorder	0	0	1	<1	0.497
Menstrual Disorders	0	0	6	2	0.015
Metabolic Disorders	0	0	1	<1	0.497
Nail Infections	0	0	1	<1	0.497
Overall	128	46	141	51	0.235

Table 9H: Summary of Adverse Events Not Associated with the Treatment Site by Region - Subjects Valid for Safety (Continued)
(Pool 1 - 24-Week TEC-II 0.02% Studies J89-024, J89-025, J89-045, K90-011, and L91-026 Combined)

Adverse Events Categorized By Body System

Body System	TEC II 0.02% (N=60)		Vehicle (N=59)		Test Results[a] p-value
Region: Outside U.S.	N	(%)	N	(%)	
Respiratory Infections/Inflammations	8	13	5	8	0.558
Infections, Body As A Whole	6	10	8	14	0.582
General Disorders	2	3	1	2	1.000
Infections/Inflammations, GI	2	3	1	2	1.000
Respiratory Conditions	2	3	0	0	0.496
Autoimmune Disease (s)	1	2	0	0	1.000
Eye Conditions	1	2	0	0	1.000
Infections, Skin	1	2	0	0	1.000
Infections/Inflammations, Ophth.	1	2	1	2	1.000
Musculoskeletal Disorders	1	2	0	0	1.000
Peripheral Nervous System Disorders	1	2	0	0	1.000
Urinary Tract Conditions	1	2	0	0	1.000
Vascular Conditions	1	2	0	0	1.000
Disorders, Central Nervous System	0	0	1	2	0.496
GI Conditions	0	0	1	2	0.496
Infection/Inflammation, Urinary Tract	0	0	1	2	0.496
Menopausal & Postmenopausal Disorder	0	0	1	2	0.496
Psychological Disorder(s)	0	0	1	2	0.496
Overall	18	30	15	25	0.683

Summary of Most Common Adverse Events - Primary Terms Reported by ≥5% Subjects

Body System	TEC II 0.02% (N=279)		Vehicle (N=276)		Test Results[a] p-value
Region: U.S.	N	(%)	N	(%)	
Upper Respiratory Infection	32	11	44	16	0.139

[a] Statistical results are based on Two-Sided Fisher's Exact Tests comparing the total number of subjects in each treatment group with a particular adverse event.

9.9 Special Studies Conducted

9.9.1 Contact sensitivity - Contact sensitizing potential was evaluated in two Phase 1 studies (J89-012 and K90-017). Study K90-017 used the closest formulation to the to-be-marketed formulation. In study K90-017, mild irritation, primarily with TEC-II 0.02% with fragrance was observed in 11 of 200 subjects who completed the induction phase (Compared to 1 subject in the vehicle arm). No significant inflammation was seen in the challenge phase.

9.9.2 Phototoxicity/Photosensitizing Potential - Following a single irradiation after a six-hour application period on the back in two double-blind, vehicle-controlled, Phase 1 studies in normal subjects (J89-020 and J89-021), neither TEC-II 0.05% or TEC-II Vehicle showed any evidence of phototoxicity. Repeated applications of TEC-II 0.05%, followed by irradiation 24 or 72 hours after each treatment application in the induction phase and irradiation 24 hours after the challenge application (after a two-week rest period) did not provide any evidence of photosensitizing potential of TEC-II 0.05% or its vehicle (J89-021). These studies were not conducted with the fragranced formulation of TEC-II 0.02% (to-be-marketed formulation). However, information regarding phototoxicity for TEC-II 0.02% unfragranced may be extrapolated from TEC-II 0.05%.

The fragrance [redacted] according to the Sponsor was previously approved in the currently marketed RENOVA 0.05%. The spectrum of photoabsorption for RENOVA 0.02% fragranced was not provided. Phototoxicity and photosensitivity testing should be performed for the RENOVA 0.02% fragranced product if any labeling other than what is current for RENOVA 0.05% is used regarding phototoxicity (see current RENOVA 0.05% label).

9.10 Drug-Demographic Interactions

9.10.1 Age - Adverse events associated with the treatment site were analyzed for the following age categories for the subjects treated with TEC-II 0.02% or vehicle for both the shorter and longer term TEC-II studies: ≤50 years, 51-64 years, and ≥65 years. The overall total percent of subjects reporting treatment-site events was greater for TEC-II 0.02% than for the vehicle; however, there were no notable percentage differences between age categories for either treatment group.

The adverse events ≥5% associated with the treatment site for any age category across the TEC-II 0.02% and vehicle treatment groups were dermatitis (0-5%), erythema (0-6%), skin/subcutaneous irritation (5-16%), and keratoderma (dry/peeling skin) (1-7%). Although the total percent of subjects reporting these treatment-site events was greater for TEC-II 0.02% than for the vehicle, there were no notable percentage differences between age categories for either treatment group.

In longer-term studies, acne and skin pain occurred most frequently (7%) for ages ≤50 years; dermatitis occurred most frequently (6%) for ages 51-64 years; erythema (8%), skin photodamage (13%), and rash (5%) occurred most frequently for ages ≥65 years; and skin/subcutaneous irritation (33% to 36%) and keratoderma (6% to 10%) occurred with similar frequency for all age categories. However, skin/subcutaneous irritation was more severe at 51-64 years (3%) than for the other age groups (0% each). Keratoderma was more severe for subjects ≤50 years (5%) than for the other age groups (0-1%).

There were no apparent with age-related adverse events not associated with the treatment site for either shorter or longer term studies. The pivotal studies included patients from age 45 to 70. Labeling should reflect lack of safety data beyond age 70 and ages less than 45.

9.10.2 Gender - Adverse events associated with the treatment site were analyzed by gender for subjects treated with TEC-II 0.02% or vehicle. Overall 31% of TEC-II 0.02%-treated subjects reported at least one adverse event at the treatment site: 15% for males (N=46) and 33% for females (N=293); and 13% of vehicle-treated subjects: 5% for males (N=43) and 14% for females (N=292). The overall total percent of subjects reporting treatment-site events was greater for TEC-II 0.02% than for the vehicle; more females than males reported treatment site adverse events in both treatment groups. This gender representation of adverse event reporting held true for both the shorter and longer term studies. No apparent significant correlation with gender for adverse events not associated with the treatment site were evident for either shorter or longer term studies.

9.10.3 Race - Clinically meaningful adverse events were not apparent to a significant extent between races in the TEC-II 0.02% studies. Adverse events associated with the

treatment site were analyzed by race (Caucasian, Black, Hispanic, American Indian, and Other) for subjects treated with TEC-II 0.02% or vehicle.

The two pivotal studies enrolled only Caucasian subjects. Most of the non-Caucasian subjects were enrolled into Study L91-026. This study enrolled only non-Caucasian subjects. Exclusion of study subjects by race is unusual for most NDAs submitted to the Agency. Due to this exclusion, it is difficult to draw conclusions regarding the effect of race on the safety profile of RENOVA TEC-II 0.02%.

Subjects with Asian skin were excluded from all studies submitted to this NDA (Study L91-026 also excluded Asian subjects). Asian skin may be more sensitive to post-inflammatory hyperpigmentation with tretinoin. Additionally the presence of post-inflammatory hyperpigmentation in Asians and Hispanics (largely Fitzpatrick Skin Type IV) may be more notable. Knowledge regarding safety and efficacy may be gained from a study that exposes Asian subjects to RENOVA TEC-II 0.02%.

Also, due to the relatively small sample size of races other than Caucasian and Black, it is difficult to draw conclusions regarding either treatment site or systemic side effects of RENOVA TEC-II 0.02%. Studies regarding safety and efficacy in Hispanic skin may similarly provide useful data.

9.11 Drug-Drug Interactions

Due to the limited absorption of tretinoin and the lack of effect on endogenous levels, no formal drug-drug interaction pharmacokinetic or pharmacodynamic studies have been conducted with RENOVA TEC-II 0.02%. A total of 79.9% of subjects treated with TEC-II 0.02% and 76.4% treated with vehicle took at least one concomitant drug during the study. The most frequently used drugs taken by TEC-II 0.02% subjects (N=339) were Premarin® (68 subjects), Provera® (27 subjects), aspirin (22 subjects), Synthroid® (21 subjects), Tylenol® tablets (18 subjects), and bacitracin topical (17 subjects). Consistent with the use and labeling of other topical tretinoin products a statement regarding drug interaction is proposed, "Concomitant topical medications, medicated or abrasive soaps, shampoos, cleansers, cosmetics with a strong drying effect, products with high concentrations of alcohol, astringents, spices or lime, permanent wave solutions, electrolysis, hair depilatories or waxes, and products that may irritate the skin should be used with caution in patients being treated with RENOVA because they may increase irritation with RENOVA." Also due to the fact that tretinoin may cause an increased sensitivity to sunlight, "RENOVA should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity."

9.12 Long-Term Adverse Effects – The results of the long-term studies did not reveal any delayed adverse events while using TEC-II 0.02% therapy for treatment of up to 52 weeks. Study K90-054 evaluated the safety of TEC-II 0.02% therapy in Caucasian subjects with moderate or severely photodamaged skin for up to 52 weeks of once-daily application. Study L91-026 evaluated the safety of the formulation in non-Caucasian subjects with mild or moderate photodamaged skin once daily for up to 52 weeks.

9.13 Withdrawal Phenomena – While no specific drug withdrawal events were noted, there may be a tendency toward partial reversal of some histologic changes and clinical

changes induced by TEC-II 0.02% therapy upon cessation of therapy (Studies J89-045 and K90-011).

9.14 Abuse Potential – Tretinoin has no potential for abuse and is neither pharmacologically or structurally related to any other drug known to have abuse potential.

9.15 Human Reproduction – No pregnancies occurred to any women enrolled in any of the studies included in NDA 21-108. A total of 260 out of 962 (about 27%) subjects enrolled were females at or less than the age of 50 years. As no pregnancies occurred during the trials, there is no subject data to make a human assessment of risk to pregnancy. However, the current formulation of RENOVA (tretinoin emollient cream) carries a Pregnancy Category of C with a warning that the drug should not be used in pregnancy. This reviewer proposes that the TEC-II 0.02% formulation of RENOVA should have the same Pregnancy Category and warning regarding use in pregnancy as the RENOVA 0.05% that is currently being marketed. Below is suggested labeling to be incorporated with pre-clinical information:

Pregnancy:
Teratogenic effects: Pregnancy Category C.
... With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty cases of temporally-associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin (Retin-A). Although no definite pattern of teratogenicity and no causal association has been established from these cases, 5 of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

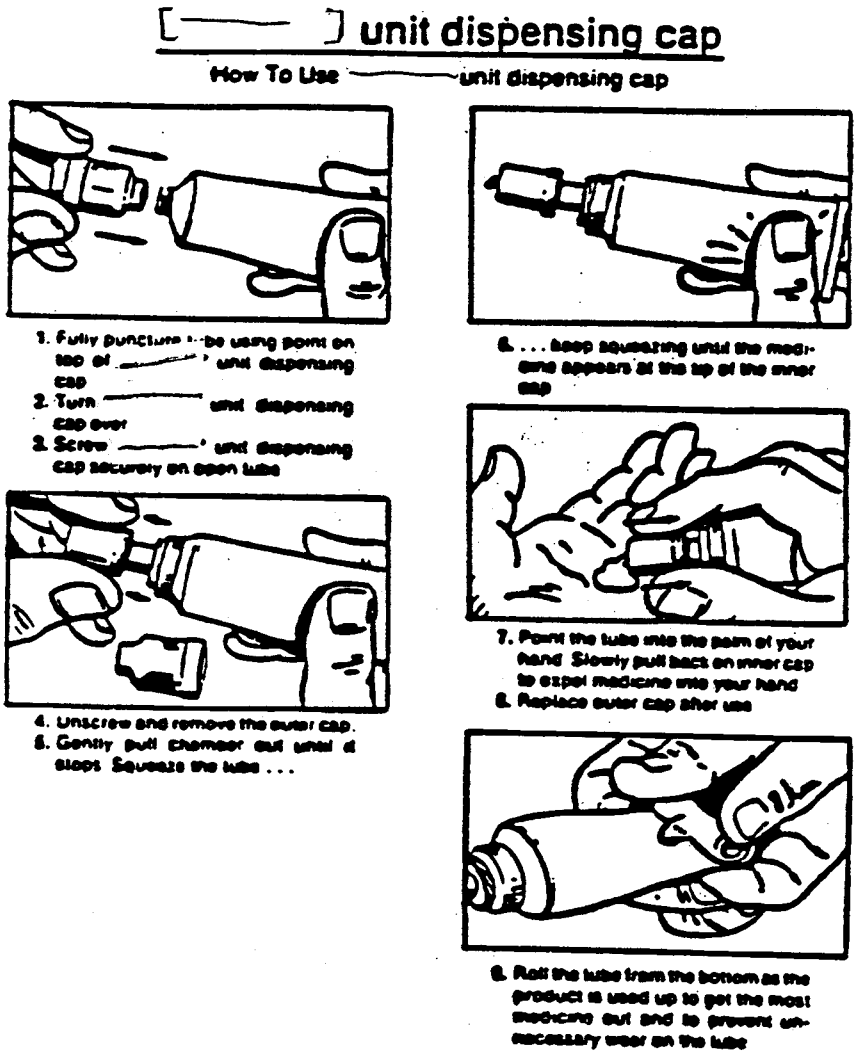
[ ]

9.16 Safety-Related Concerns Regarding Final To-Be-Marketed Formulation

A metered dosing system as was used during the pivotal studies, from which the safety database for this product is derived (see Figure 9-4 for instructions of use for the ——— dispensing system). This dispensing system is not proposed for the final to-be-marketed formulation. The amount used by patients prescribed Renova without such a dispensing system may differ significantly from the amount used in the Phase 3 trials. However, it is apparent that there was some leeway regarding amount used in the pivotal trials. A general dosing guideline of 0.25g was specified, but investigators were allowed some discretion.

It appears from the amended (February, 1990) protocol for J89-024, that the cap may have been responsible for splitting of the drug product tubes during the pivotal trials. Labeling should reflect the fact that the studies were done with metered dosing. An attempt should be made to clearly define the amount of cream to be applied by the potential user of this product. An illustration could be provided in the patient portion of the package insert demonstrating the amount of cream to be used relative to fingertip size or a metered dosing system (to dispense 0.25g) with a strengthened tube (to prevent splitting) could be used.

Figure 9-4: From Protocols J89-024 and J89-025.



The Phase 3 pivotal studies J89-024, J89-025, and J89-045 were conducted using formula FD-08203-000-BH-63, 0.02% TECII (unfragranced). The to-be-marketed formulation utilizes formula FD-08203-CA-63, 0.02% TEC-II (fragranced) which contains the addition of ———— Thus the to-be-marketed formulation is not the same formulation as was used in the Phase 3 pivotal studies. Extrapolation with the small number of studies and relatively small number of subjects exposed to RENOVA 0.02% with fragrance suggest that this formula may also have an acceptable safety profile. A direct relative comparison of the two formulations (fragranced vs. unfragranced RENOVA 0.02% TEC-II) should be made in Phase 4 and the safer formulation should be used.

9.17 Safety Conclusions

Adequate and well-controlled studies have demonstrated that TEC-II formulation of RENOVA 0.02% has an acceptable safety profile when applied once daily to the face. The once-daily dosing regimen was generally well-tolerated in these studies. Skin

irritation and related signs and symptoms were usually mild and well-tolerated. Patients using RENOVA who experience adverse symptoms should be instructed to decrease the frequency of application or temporarily discontinue use as was done in the studies.

Care should be taken to ensure similar dosing for the to-be-marketed product as was done in the pivotal studies. The addition of —————— (fragrance) provides an unknown quantity to the safety of the to-be-marketed product vs. that used in the pivotal studies. Hypersensitivity to fragrance is a relative contra-indication to use of the proposed formulation of RENOVA (tretinoin emollient cream) 0.02%.

From the safety data submitted, comparative conclusions regarding safety and efficacy of the proposed new formulation and the currently marketed 0.05% RENOVA cannot be drawn.

9.18 Safety Recommendations

1) A metered dosing system as was used during the pivotal studies from which the safety database for this product is derived. An attempt should be made to ensure patient use of a similar amount of drug product as was used in the pivotal studies. This could be done via use of a similar metered dosing system or through careful labeling. Use of a "pea-sized" amount has been proposed by the Sponsor and is acceptable. An illustration in the Patient Package Insert should be provided, regarding the amount of drug to be used.
2) The Phase 3 pivotal studies J89-024 and J89-025 were conducted using formula FD-08203-000-BH-63, 0.02% TECII (unfragranced). The to-be-marketed formulation utilizes formula FD-08203-CA-63, 0.02% TEC-II (fragranced) which contains the addition of —————— A Phase 4 study to bridge the relative safety of these formulations should be performed. No such study was provided in any submissions to this NDA. The results of such a study should be submitted within a prescribed time frame.
3) As was done in the studies, patients should decrease the frequency of application or temporarily discontinue drug application in order to ameliorate the results of excessive skin irritation.
4) No comparative studies were conducted between the to-be-marketed formulation of the new fragranced TEC-II with the old currently marketed formulation of RENOVA. If approved, the approval letter should clearly state that the Applicant should make no comparative claims between the old 0.05% RENOVA formulation and the new RENOVA 0.02% formulation. If the same tradename is used (i.e. RENOVA) to market the new drug, the Applicant should, as a Phase 4 commitment, conduct comparative efficacy and safety studies between the two products. The results of such a study should be submitted within a prescribed time frame.
5) The sentence in the proposed label under the Clinical Trials Data Section: —— —————————————— —————— should be deleted. Please see Proposed Clinical Trials Data Section under Section 8.6 of this review.
6) Although Asian subjects were excluded from all of the studies submitted to this NDA, it may be possible to infer general safety (but not local intolerance) in Asians from the other studies submitted. A very limited number of Hispanic patients were included for study with this NDA. A Phase 4 study to examine local intolerance and

incidence of post-inflammatory hyperpigmentation in Asian and Hispanic skin should be required as a Phase 4 commitment.

10 Labeling Recommendations

See Labeling Review, Proposed Clinical Trials Section under Overview of Efficacy (Section 8.6) and under Safety Recommendations of this Review.

10.1 Proposed Indications and Usage Section

Specifically regarding the Indications and Usage Section, the following language may be used:

INDICATIONS AND USAGE: (To understand fully the indication for this product, please read the entire INDICATIONS AND USAGE section of the labeling.)
RENOVA (tretinoin emollient cream) 0.02% is indicated as an adjunctive agent (see second bullet point below) for use in the mitigation (palliation) of fine wrinkles of facial skin in patients **RENOVA DOES NOT ELIMINATE WRINKLES, REPAIR SUN DAMAGED SKIN, REVERSE PHOTOAGING, or RESTORE A MORE YOUTHFUL or YOUNGER**

- RENOVA 0.02% has demonstrated NO MITIGATING EFFECT on significant signs of chronic sun exposure such as coarse or deep wrinkling, tactile roughness, yellowing, mottled hyperpigmentation, lentigines, telangiectasia, skin laxity, keratinocytic atypia, melanocytic atypia, or dermal elastosis.

- RENOVA should be used under medical supervision as an adjunct to a comprehensive skin care and sun avoidance program that includes the use of effective sunscreens (minimum SPF of 15) and protective clothing when desired results on fine wrinkles, mottled hyperpigmentation, and roughness of facial skin have not been achieved with a comprehensive skin care and sun avoidance program alone.

- Patients with visible actinic keratoses and patients with a history of skin cancer were excluded from clinical trials of RENOVA. Thus the effectiveness and safety of RENOVA in these populations are not known at this time.

- Neither the safety nor the effectiveness of RENOVA for the prevention or treatment of actinic keratoses or skin neoplasms has been established.

- Neither the safety nor the efficacy of using RENOVA 0.02% daily for greater than 52 weeks has been established, and daily use beyond 48 weeks has not been systematically and histologically investigated in adequate and well-controlled trials. (See **WARNINGS** section.)

10.2 Comments Regarding Comparison of RENOVA 0.02% and RENOVA 0.05%

No comparisons should be made between RENOVA 0.02% TEC-II and the currently marketed (under NDA 19-963) RENOVA 0.05% TEC-IA, other than the indications for which each are approved. RENOVA 0.02% is only approved for mitigation of fine wrinkling of facial skin, while RENOVA 0.05% is approved for mitigation of fine wrinkling, mottled hyperpigmentation, and tactile roughness.

While the two formulations utilize the same active, tretinoin, the concentration in the formulations are different. At the lower concentration no efficacy was demonstrated for mottled hyperpigmentation and tactile roughness. A 1998 study by Dr. Jag Bhawan (International J. of Dermatology, 1998, 37:266-292), demonstrated, after 6 months of application along with sun avoidance and a comprehensive skin care program including sunscreen use, that there was a significant decrease in melanin content between treatment and vehicle arms for the 0.05% concentration of tretinoin emollient cream, but not the 0.01% concentration. Thus, it would seem that the 0.02% dose, which is between 0.01% and 0.05% may not be high enough to illicit a clinical demonstration of the mitigation of mottled hyperpigmentation.

11 Recommendations

11.1 Approval, Approvable

It is recommended that this application be approved, provided that Phase 4 studies (as outlined below) are undertaken. The indication for which RENOVA (tretinoin emollient cream) 0.02% should be approved is the mitigation of fine wrinkling of facial skin.

11.2 Phase 4 Studies

To permit more complete assessment of the safety profile of RENOVA 0.02% Emollient Cream, the following Phase 4 studies are suggested:

1) If the same tradename is used (i.e. RENOVA) to market RENOVA 0.02%, the Applicant should, as a Phase 4 commitment, conduct comparative efficacy (in fine wrinkling only) and safety studies between RENOVA 0.02% and the currently marketed RENOVA 0.05% (TEC-IA). The results of such a study should be submitted within a prescribed time frame. No comparisons between RENOVA 0.02% and the previously marketed RENOVA 0.05% are to be made with regard to ——— or safety without such a study. The Applicant should clearly state in any material used for marketing the sole indications for each strength/formulation of RENOVA.
2) Although Asian subjects were excluded from all of the studies submitted to this NDA, it may be possible to infer general safety, but not local intolerance in Asians, from the other studies submitted. A very limited number of Hispanic patients were included for study with this NDA. A Phase 4 study to examine local (facial skin) intolerance and incidence of post-inflammatory hyperpigmentation in Asian and Hispanic skin should be conducted and the results submitted within a prescribed time frame.

3) The Applicant should, as a phase 4 commitment, conduct a sufficiently powered comparative irritancy study between the fragranced and unfragranced RENOVA TEC-II 0.02% formulations. The Applicant should also perform a phase 4 study to evaluate the phototoxicity and photosensitizing nature of the fragranced RENOVA TEC-II 0.02%. The results of such studies should be submitted within a prescribed time frame. Any increased irritancy of the fragranced compared to unfragranced product in the comparative irritancy study is expected to result in submission by the Applicant of a manufacturing supplement to market the unfragranced product in place of the fragranced product.

11.3 Labeling changes

See Labeling Review. Some changes to labeling have been suggested in this Review, specifically to the Clinical Studies and Indications and Usage sections. The labeling for Renova 0.02% should have similar warnings and language for other sections as that of Renova 0.05%. Labeling proposed for any such sections for Renova 0.02% should be considered for inclusion/substitution in labeling for the 0.05% currently marketed product.

12 Signature Block and Distribution List

[/S/] 8/16/2000
Markham C. Luké, M.D., Ph.D.
Medical Officer, Dermatology

Cc:
Archival NDA
HFD-540
HFD-540/Division Director/Wilkin [/S/] 8/16/00
HFD-540/Dermatology Team Leader/Okun
HFD-725/Acting Biostatistics Team Leader/Alosh
HFD-725/Biostatistician/Thomson
HFD-880/Biopharm/Bashaw/Ghosh
HFD-540/Pharm/Nostrandt [/S/] 8/16/00
HFD-540/Chemistry/Timmer
HFD-540/Project Manager/Cintron

Medical Officer's Review of NDA 21-108 BZ

Addendum to NDA Review – Pediatric Rule and Financial Disclosure

AUG 15 2000

NDA 21-108
Serial Number BZ

Correspondence Date: October 25, 1999
CDER Stamp Date: October 26, 1999
Review Date: July 14, 2000

Applicant: Johnson & Johnson Consumer Companies, Inc.
199 Grandview Road
Skillman, New Jersey 08558-9418
(908) 874-1700

Contact: Paul F. Manley, Worldwide Director, Regulatory Affairs

Drug Generic Name: tretinoin emollient cream 0.02%
Proposed trade name: **RENOVA® (tretinoin emollient cream) 0.02%**
Pharmacologic category: Retinoid
Dosage form: Emollient cream
Route of Administration: Topical

Background

NDA 21-108 is a New Drug Application for a different formulation (TEC-II) of RENOVA emollient cream. The Sponsor submitted an Amendment on October 25, 1999 regarding Financial Disclosure and the Pediatric Rule.

Amendment to NDA

The Applicant submits that there is an absence of financial interests and arrangements for the investigators of the trial as per 21 CFR 54. All clinical studies submitted to NDA 21-108 were concluded prior to the end of 1994 (prior to the implementation of the financial disclosure rule). No financial disclosure forms were submitted for studies other than the J89-024 and J89-025.

The Applicant signed a financial disclosure form to the following effect: "Johnson & Johnson Consumer Companies, Inc. certifies that no investigator involved in the clinical trials to support the safety and efficacy of Tretinoin Emollient Cream 0.02% was compensated in a manner that the amount of compensation would be affected by the outcome of the study (e.g. compensation would have been greater for a favorable result). No investigator involved in the clinical trials to support the safety and efficacy of Tretinoin Emollient Cream 0.02% holds a proprietary interest in the product (e.g. trademark, patent, copyright, or licensing agreement)." This is signed by Robert Armstrong, M.D. The investigators listed were Wilma F. Bergfield, Charles Ellis, Norman Levine, Ronald C. Savin, Joel Shavin, and Jonathan Weiss. The investigators for J89-045 were not listed in this submission. The Applicant was asked to provide additional financial disclosure statements for J89-045 investigators due to the pivotal nature of this study. In a telecon with the Sponsor on July 14, 2000, the Sponsor

indicated that it will provide a financial disclosure statement for the investigators in J89-045.

Additionally, regarding the Pediatric Rule, the Applicant seeks a full waiver of the requirements under 21 CFR 314.55(a), because the drug product RENOVA 0.02% does not represent a meaningful therapeutic benefit and is not likely to be used in a substantial number of pediatric patients.

Reviewer's Comments - The indication of mitigation of fine wrinkles is unlikely to see wide use in the pediatric population. The active ingredient tretinoin is present in Retin-A, which is an acne agent and is used widely among pediatric patients. At this time it is unclear whether RENOVA 0.02% will see use among pediatric patients for off label indications (e.g. acne). However, as a waiver is granted for the specific indication, the Sponsor should be given a waiver for the indication of fine wrinkling with regard to 21 CFR 314.55(a).

Regulatory Recommendations

1) Financial disclosure is adequate for studies J89-024 and J89-025. The Sponsor has indicated that it shall provide additional financial disclosure for its third pivotal study, J89-045.
2) The Sponsor should be given a waiver for the indication of mitigation of fine facial wrinkling with RENOVA 0.02% with regard to 21 CFR 314.55(a).

[/S/] 7/14/2000
Markham C. Luke, M.D., Ph.D.
Medical Officer, Dermatology

cc: HFD-540
HFD-540/CSO/Cintron
HFD-540/MO/Luke
HFD-540/Clinical TL/Okun [/S/]7/14/00
HFD-540/DIVDIR/Wilkin
NDA 21-108
[/S]8/15/00
No VFS 8/16/00

Medical Officer's Review of NDA 21-108 BM

Addendum to NDA Review – Amendment to Pending NDA

AUG 15 2000

NDA 21-108
Serial Number BM
DDDDP # 006101

Correspondence Date: June 23, 2000
CDER Stamp Date: June 26, 2000
Review Date: July 7, 2000

Applicant: Johnson & Johnson Consumer Companies, Inc.
199-Grandview Road
Skillman, New Jersey 08558-9418
(908) 874-1700

Contact: Paul F. Manley, Worldwide Director, Regulatory Affairs

Drug Generic Name: tretinoin emollient cream 0.02%
Proposed trade name: **RENOVA® (tretinoin emollient cream) 0.02%**
Pharmacologic category: Retinoid
Dosage form: Emollient cream
Route of Administration: Topical

Background

NDA 21-108 is a New Drug Application for a different formulation (TEC-II) of RENOVA emollient cream. The Sponsor provides this submission in response to a June 19, 2000 request for information from the clinical reviewer.

Amendment to NDA

The Applicant was requested to provide any available information regarding topical steroid use on or near the treatment site due to an adverse event for any of the clinical trials used to determine safety and efficacy. The Sponsor provided information compiled from protocols J89-024, J89-025, J89-045, L91-011, and K90-054.

From the data provided in this amendment and from the original NDA, 4 out of 90 patients on RENOVA 0.02% in Study J89-024 required some topical steroid to improve their condition, 6 out of 90 in J89-025, and 4 out of 60 in J89-045, 4 out of 60 in L91-026, 2 out of 40 in K90-011, and 11 out 120 in the 52 week open-label study K90-054. So overall, 6.7 % of the subjects in the efficacy/safety studies for RENOVA 0.02% (a total of 31 out of 460 subjects) had used topical steroids to alleviate some symptoms of irritation that were either definitely or possibly caused by use of the product. Only 3 (0.65 or less than 1 %) of the subjects using vehicle had used topical steroids to alleviate local irritation.

The topical steroid that was most often used was hydrocortisone (as should be for the face). Other steroids including [redacted] were also used.

Regulatory Recommendation

Labeling should reflect the 10-fold higher use of topical steroid to alleviate local irritation at the site of treatment application in subjects using RENOVA compared to vehicle.

[/S/] 7/7/2000
Marknam C. Luke, M.D., Ph.D.
Medical Officer, Dermatology

TL Addendum
The appropriate place for this information in the label would be in the Clinical Studies section.
[/S/] 7/14/00

cc: HFD-540
HFD-540/CSO/Cintron
HFD-540/MO/Luke
HFD-540/Clinical TL/Okun
HFD-540/DIVDIR/Wilkin
NDA 21-108

As above per both MO and TL, A statement could be added to the effect that the safety of corticosteroid preparations used on the face is not established, [/S/] 8/15/00

No DFS 8/16/00

APPEARS THIS WAY
ON ORIGINAL

APR 6 2000

Medical Officer's Review of NDA 21-108 SU

Safety Update

NDA 21-108
Serial Number SU
DDDDP # 004791

Correspondence Date: December 20, 1999
CDER Stamp Date: December 21, 1999
Review Date: March 30, 2000

Applicant: Johnson & Johnson Consumer Companies, Inc.
199 Grandview Road
Skillman, New Jersey 08558-9418
(908) 874-1700

Contact: Paul F. Manley, Worldwide Director, Regulatory Affairs

Drug Generic Name: tretinoin emollient cream 0.02%
Proposed trade name: **RENOVA® (tretinoin emollient cream) 0.02%**
Pharmacologic category: Retinoid
Dosage form: Emollient cream
Route of Administration: Topical

Background

NDA 21-108 is a New Drug Application for a different formulation (TEC-II) of RENOVA emollient cream. The Sponsor provides this submission as a Safety Update during our ongoing review of NDA 21-108.

Safety Update

The Sponsor states that "There are no clinical trials in progress using the TEC II; therefore, there is no update to this information." The Sponsor refers to the annual report for IND ——— for the most recent reporting period. Also the Sponsor refers to periodic reports for its various tretinoin products.

NDA	Product
19-963	RENOVA (tretinoin emollient cream) 0.05%
17-340	RETIN-A (tretinoin) Cream 0.1%
17-522	RETIN-A (tretinoin) Cream 0.05%
17-579	RETIN-A (tretinoin) Gel 0.025%
17-955	RETIN-A (tretinoin) Gel 0.01%
19-049	RETIN-A (tretinoin) Cream 0.025%
20-475	RETIN-A MICRO (tretinoin gel) microsphere, 0.1%

The Sponsor provided additional data regarding studies with TEC II 0.05% (J89-022, J89-023, and J89-033) which had not been submitted with the original NDA submission. Safety data for those studies were requested on February 7, 2000 and were submitted to the NDA on March 1, 2000.

Please refer to Safety Review for NDA 21-108 for review of relevant safety data submitted.

[/S/] 3/30/2000

Markham C. Luke, M.D., Ph.D.
Medical Officer, Dermatology

cc: HFD-540
HFD-540/CSO/Cintron
HFD-540/MO/Luke
HFD-540/Clinical TL/Okun [/S/] 4/3/00
HFD-540/DIVDIR/Wilkin
NDA 21-108
1, DFS

[/S/] 4/6/00
DFS

APPEARS THIS WAY
ON ORIGINAL