CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-108

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 21-108 BM

Addendum to NDA Review – Amendment to Pending NDA
Financial Disclosure and Labeling

AUG 27 2000

NDA 21-108
Serial Number BM
DDDDP # 006210

Correspondence Date: July 17, 2000
CDER Stamp Date: July 19, 2000
Review Date: July 26, 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 July 14, 2000 request for information from the clinical reviewer.

Amendment to NDA

The Applicant was requested to provide a certification for the investigators of clinical study J89-045 to supplement the statement found in Volume 1.1, page 019 00001. The Applicant has provided and adequate statement regarding financial disclosure for the three large multicenter studies that are the basis for the approvable nature of this NDA.

The Applicant was also asked to describe "pea-sized" amount and its relationship to the ——————————that was used in Phase 3 studies. The ——— system delivered 0.25 g of cream, but was not included in the final proposed drug product.

To further clarify the issue, a telecon with the Applicant revealed that the diameter of the dollop squeezed from a syringe, weighing 0.25 grams, was about 5 millimeters.

The average size of a green pea, which has been the pea-size standard for other drug products in this division is 7.8 to 8.5 mm in diameter according to the USA Council for Peas and Lentils (http://www.pea-lentil.com/products.htm) . Thus 5 mm would be below average for a green pea. The 5mm size could be acceptable for a small or baby green pea. Labeling should accurately reflect the size of pea that the Applicant is proposing.

Regulatory Recommendation

The "pea-sized" amount should be referred to as a "small green pea-sized amount" in labeling for the Patient Instructions section, the Patient Package Insert, and the Dosage and Administration section. In the Dosage and Administration section, it should be clear that the diameter of pea is 5 millimeters. This would provide a means to approximate the amount of product used in the Phase 3 clinical studies.

[/S/] 7/26/2000

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
HFD-540/DIVDIR/Wilkin
NDA 21-108

[/S/] 7/26/00

No NFS on 8/27/00

[/S/] 8/27/00

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ON ORIGINAL

AUG 27 2000

Medical Officer's Review of Original NDA 21-108

Labeling Review

NDA 21-108
HFD-540 # 994014

Correspondance Date: August 31, 1999
CDER Stamp Date: September 3, 1999
Review Date: August 9, 2000

Drug: RENOVA (tretinoin emollient cream) 0.02%
Applicant: Johnson & Johnson Consumer Companies, Inc.
199 Grandview Road
Skillman, NJ 08558-9418

Pharmacologic Category: Topical Retinoid

Labeling Review:

Changes made to the recently approved labeling supplement for Renova 0.05% (NDA 19-963 SLR 005 and SLR 007) on August 1, 2000 that were also relevant to this NDA were incorporated into labeling. Where appropriate, information is designated specifically for the Renova 0.02% product, as different studies were used to form the basis for approval.

The Clinical Trials section has additional tables derived from data submitted to NDA 21-108. The efficacy data from the study in Fitzpatrick Skin Types IV and higher are broken out and placed in a separate table. A chart describing the Patient Self-Assessment data is presented. Also, data from the 12 week extension of use (open-label) study is used to describe the effect of discontinuation of use of this medication. Thus, the Clinical Trials section reads as follows:

Clinical Trials

Four adequate and well-controlled multi-center 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 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, [redacted], and laxity. Patients were evaluated at baseline on a 10 unit 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, [redacted] and laxity of the facial skin were thought to be caused by multiple factors which included intrinsic aging or environmental factors, such as chronic sunlight exposure.

Two of the five trials provided adequate demonstration of efficacy for mitigation of fine facial wrinkling. No two of the five trials adequately demonstrated efficacy for mitigation of coarse wrinkling, mottled hyperpigmentation, tactile skin roughness, [redacted], and laxity. [redacted]

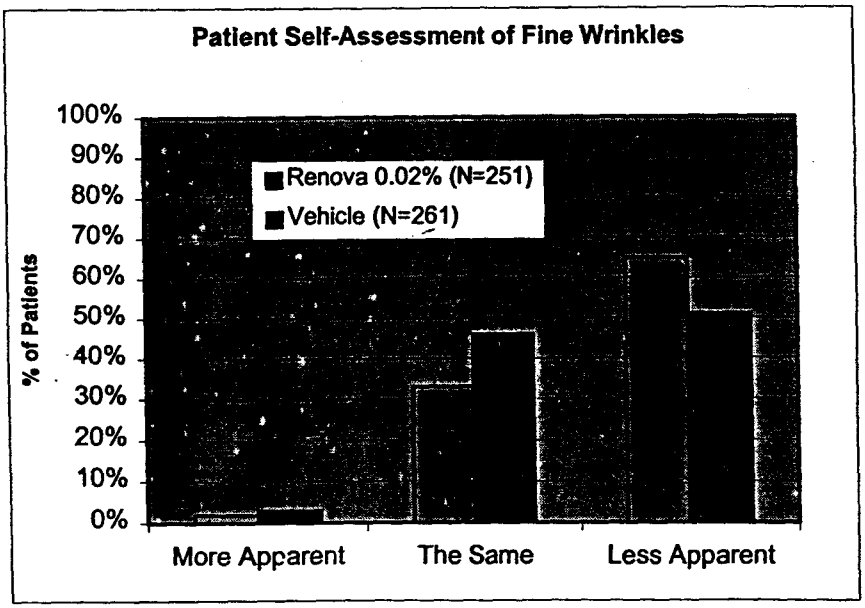
Data for fine wrinkling (the indication for which RENOVA 0.02% demonstrated efficacy) from all five trials (four studies in lightly pigmented subjects and one study in darkly pigmented subjects) is provided below:

FINE WRINKLING IN LIGHTLY PIGMENTED SUBJECTS		
	Subjects using RENOVA 0.02% + CSP* (N = 279)	Vehicle + CSP* (N = 280)
Worsened	1%	3%
No Change	40%	58%
Minimal Improvement	35%	27%
Mild Improvement	15%	9%
Moderate Improvement	10%	3%

[redacted]

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

Self-assessment of fine wrinkles after 24 weeks of treatment with either RENOVA 0.02% or Vehicle from the four studies in lightly pigmented patients showed the following:



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

_____patients may lose some of the mitigating effects of RENOVA 0.02% after 12 weeks of discontinuation of RENOVA 0.02% from their comprehensive skin care and sun avoidance program.

Recommendations: It is recommended that the labeling as attached to this review be used for the Renova 0.02% product. This labeling recommendation supercedes any previous labeling recommendation included in previous reviews or correspondence from this reviewer. The label is derived from information contained in the review of original NDA 21-108 and its amendments. Additional relevant information from the recently approved labeling (SLR005 for NDA 19-963) for Renova 0.05% is incorporated. In addition the PPI has been revised to reflect DDMAC concerns and is consistent with the approved PPI for NDA 19-963.

[/S/]

Markham C. Luke, M.D., Ph.D. 8/9/2000
Medical Officer, Dermatology

cc: HFD-540
HFD-540/CSO/Cintron
HFD-540/Chemist/Timmer
HFD-540/Pharm/ Nostrandt
HFD-540/BioPharm/Bashaw
HFD-540/MO/Luke
HFD-540/Clinical TL/Walker
HFD-540/Clinical TL/Okun
HFD-540/DIVDIR/Wilkin

[/S/] 8/27/00

no DFS on 8/27/00

TL Addendum:
The sole clinical study in which post-treatment follow-up was performed demonstrated that in the per-protocol population, the majority (60%) of patients who had been using Renova .02% during the study experienced no deterioration in their fine wrinkling scores at 12 week post-treatment. Thirty-two percent of patients experienced deterioration in their fine wrinkling scores, while eight percent experienced improvement. Thus the last sentence in the Clinical Studies Section should read:

"Patients may lose some of the mitigating effe of RENOVA .02% after 12 weeks of discontinuation of RENOVA .02% from their comprehensive skin care and sunlight avoidance progr

[/S/]

Agree with MOR and with TL Addendum changes.

[/S/] 8/27/00

Medical Officer's Review of NDA 21-108

AUG 16 2000

1 General Information

1.1 NDA Submission Number 000

1.2 Applicant Identification

1.2.1 *Name:*
Johnson and Johnson Consumer Companies, Inc.

1.2.2 *Address:*
199 Grandview Road
Skillman, New Jersey 08558-9418

1.2.3 *Company official or contact person:*
Paul F. Manley, Worldwide Director, Regulatory Affairs
199 Grandview Road
Skillman, New Jersey 08558-9418
(908) 874-1700

1.3 Submission/Review Dates

1.3.1 Date of submission (date of applicant's letter)
August 31, 1999

1.3.2 CDER stamp date
September 1, 1999

1.3.3 Date submission received by reviewer
September 14, 1999

1.3.4 Date review begun
September 14, 1999

1.3.5 Date 1st draft completed
May 24, 2000

1.3.6 Date 2nd draft completed
June 9, 2000

1.3.7 Date review completed
June 19, 2000 & minor corrections August 16, 2000

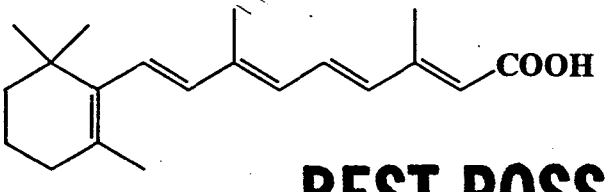
1.4 Drug Identification

1.4.1 Generic name
tretinoin emollient cream 0.02%

1.4.2 Proposed trade name
RENOVA® (tretinoin emollient cream) 0.02%

1.4.3 Chemical name
(all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclonexen-1-yl)-2,4,6,8-nonatetraenoic acid

1.4.4 Chemical structure:



1.4.5 Molecular formula
$C_{20}H_{28}O_2$
1.4.6 Molecular weight
300.44

1.5 Pharmacological Category
Retinoid

1.6 Dosage Form
Emollient Cream

1.7 Route of Administration
Topical

1.8 Proposed Indication & Usage section:
"INDICATIONS AND USAGE: (To understand fully the indication for this product, please read the entire INDICATIONS AND USAGE section of the labeling.)

[ ]

1.9 Proposed Dosage & Administration section:
"DOSAGE AND ADMINISTRATION:
RENOVA should be applied to the face once a day ——— using only enough to cover the entire affected area lightly. Patients should gently wash their face with a mild soap, pat the skin dry, and wait 20 to 30 minutes before applying RENOVA. The patient should apply a ——— amount of cream to cover the entire —— lightly. ——— caution should be taken when applying the cream ———

[ ]

1.10 Related Drugs

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%

1.11 Material Reviewed

1.11.1 NDA Volumes Reviewed

NDA Volumes Reviewed and their Contents

Volume	Contents
1.1-1.2	Application Summary
1.18-1.87	Clinical Data Section
2.1	Amendment to NDA
3.1	Amendment to NDA
5.1	Amendment to NDA
6.1	Amendment to NDA – Safety Update
7.1	Amendment to NDA

1.11.2 Regulatory Documents Reviewed

Labeling and Medical Officer Review of NDA 19-963 Renova 0.05%.

1.11.3 Non-Regulatory Documents Reviewed

Literature and Textbook search on Yellowing/Sallowness Indication.

1.12 Regulatory Background

The regulatory histories of this NDA and NDA 19-963 (RENOVA 0.05%) are complicated. NDA 19-963 was originally submitted for review in 1990, with a proposed indication for the treatment of [redacted] The requirements for the evaluation of this new indication had been discussed at a succession of Dermatologic Drugs Advisory Committee meetings in the late 1980s. It was determined that a panel of subjective assessments by the investigator and the subject, as well as a series of objective histological evaluations, should be utilized to assess [redacted] The applicant, therefore, submitted a series of studies utilizing clinical assessments and histological evaluations of skin sites, pre-treatment, during treatment and post-therapy, in support of the approval of RENOVA for the treatment of [redacted] skin.

During the initial review of NDA 19-963, it was noted that the formulation originally utilized (TEC I) presented stability problems. The applicant withdrew the application and resubmitted the NDA with a revised formula (TEC 1A). FDA Biopharmaceutics experts decided that the changes to the formulation were minor and would not significantly affect the clinical activity of the product. The clinical

data generated with the original formulation were, therefore, utilized to support the new formulation.

The Medical Review for NDA 19-963 concluded that RENOVA 0.05% did not demonstrate adequate safety and efficacy in the treatment of

However, as stated in the secondary review for NDA 19-963, RENOVA was better than vehicle for "several important parameters" such as fine wrinkling, mottled hyperpigmentation and tactile roughness (See Supervisor Medical Officer's Memorandum dated 5/20/1993).

In the secondary review, it was noted "There were statistically significant benefits following treatment with RENOVA compared to vehicle in a variety of individual signs/symptoms of facial skin damage as presented in the table below. These improvements were in global evaluation, overall severity, roughness, mottled hyperpigmentation and fine wrinkling."

EFFICACY ASSESSMENTS FOR RENOVA 0.05% (TEC-I) VERSUS VEHICLE		
Parameter	**G86-074**	**G86-082**
Global evaluation	+	+
Overall severity	+	+
Patient self-assessment	NS	+
Roughness	+	+
Laxity	NS	+
Mottled hyperpigmentation	+	+
Fine wrinkling	+	+
Coarse wrinkling	NS	NS
Telangiectasis	NS	NS
Yellowing	+	NS
Lentigines	NS	NS

+ = statistical significant difference between RENOVA 0.05% and vehicle
NS = lack of statistical significance between RENOVA 0.05% and vehicle

The secondary review concluded that studies of daily use of RENOVA 0.05% for 24 weeks had demonstrated that it has a mitigating effect on several clinical findings that are characteristic of photodamaged facial skin, namely fine wrinkling, mottled hyperpigmentation, and roughness. It was noted, however, that these constitute only a few of the constellation of signs and symptoms commonly understood as "photodamage", so [redacted] indication was not given. Instead, the Applicant for NDA 19-963 was given approval for use of RENOVA 0.05% in "mitigating the conditions of fine wrinkling, mottled hyperpigmentation, and roughness of facial skin..."

NDA 19-963 was approved on December 29, 1995 with five Phase 4 commitments as follows:

1) A commitment to conduct a dermal Segment I reproduction study in rats.
2) A commitment to conduct and submit data from a long-term study using varying dosage regimens (a) and histologic samples (b) to

determine whether the current dosage regimen is the optimal regimen, and to evaluate further the drug's long-term safety.

3) A commitment to conduct and submit data from epidemiologic and animal studies designed to investigate the potential connection between holoprosencephaly and topical tretinoin.
4) Data on the effects of this drug product on darkly pigmented skin.
5) A commitment to provide information pertaining to the follow-up attempts made by the study site to contact subject 3320 in Protocol 91-088 who apparently became pregnant during the trial.

As of May, 2000, the applicant had satisfied Phase 4 commitment numbers 1, 3, and 5. Commitment # 2a was to conduct a dose ranging study and has been waived because (1) the sponsor was preparing an NDA for the 0.02% Renova cream and (2) "the approved labeling makes adequate provision for dose adjustment on a patient by patient basis" (Teleconference Memo dated September 22, 1997). Commitment # 2b was to further evaluate the long-term safety of RENOVA 0.05% clinically and histologically, and is currently under investigation. Studies designed to satisfy Commitment #4 are currently under way as well.

Studies for 21-108 were conducted from 1989 to 1993. Thus, all of the studies were conducted prior to approval of the RENOVA 0.05% product. With the approval of the RENOVA 0.05% product, regulatory precedent for separate evaluation of the various components: fine ——— wrinkles, mottled hyperpigmentation, ——— tactile roughness, and laxity (some of which may be caused by various intrinsic or environmental factors other than chronic sun exposure) was established.

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2 Table of Contents

3 Chemistry/Manufacturing Controls

See Dr. William Timmer's Review of Chemistry/Manufacturing Controls for further information.

Formulation of RENOVA 0.02% proposed for marketing (FD-8203-000-CA-63):

Ingredient	%w/w
Tretinoin, USP	[redacted]
Butylated Hydroxytoluene (BHT), NF	
Edetate Disodium, [redacted], USP	
Propylparaben, NF	
Methylparaben, NF	
[redacted]	
Xanthan Gum [redacted] NF	
Steareth-2 [redacted]	
Benzyl Alcohol, NF	
Stearyl Alcohol, NF	
Cetyl Alcohol, NF	
Stearic Acid [redacted] NF	
Steareth-20 [redacted]	
Caprylic/Capric Triglyceride	
Water, Purified, USP	

The concentration of the active ingredient is [redacted], allowing for a 10% overage according to USP guidelines (see Chemistry Review).

In this review, the formulation proposed as the to-be-marketed formulation is referred to as Renova 0.02% (TEC-II fragranced), the formulations studied in the pivotal trials is referred to as Renova 0.02% TEC-II or TEC-II unfragranced. The only difference between the fragranced and unfragranced formulations is the substitution of [redacted] w/w of [redacted] fragrance for water. The previously marketed formulation of Renova was designated TEC-IA by the Applicant (NDA 19-963). The formulation used to conduct Phase 3 studies for NDA 19-963 is TEC-I (See above comments in Section 1.12 regarding the stability of the TEC-I formulation).

4 Animal Pharmacology/Toxicology

See Dr. Amy Nostrandt's Review of Pharmacology and Toxicology Data for more detail (unavailable when Medical Officer Review was completed).

5 Human Pharmacokinetics/Pharmacodynamics

See Dr. Tapash Ghosh's Review of Pharmacokinetics/Pharmacodynamics for more detail.

5.1 Percutaneous Absorption of Tretinoin

Clinical pharmacokinetic studies were conducted to investigate the absorption, distribution, metabolism and elimination of topically applied tretinoin after a single application, after repeat applications, and after long-term treatment (I88-082 and J89-027). In Study I88-082, 50 μg (100 μCi) of radiolabeled TEC-II 0.05% was applied to subjects as a single dose, or following 28 days of daily pretreatment with a clinical dose of non-radiolabeled TEC-II 0.05%. On average, only 2.02±0.40% of the applied tRA dose was absorbed in those subjects who had received a single application. In the pretreated group 1.38±0.37% of the applied tRA was absorbed. In the single dose group, 1.36±0.28% of the dose was excreted in the urine; 0.66±17% was excreted in the feces. Similar results were obtained in the pretreated subjects.

5.2 Conclusions

Percutaneous absorption of tretinoin from the 0.05% TEC-II formulation does occur, although to a minimal extent. Tretinoin absorption does not appear to increase with repeat administration. Presumably, the percentage absorbed would be an upper limit of what would be absorbed in human use of the to-be-marketed 0.02% TEC-II formulation, which is 2.5x lower in concentration.

6 Human Clinical Experience

6.1 Foreign Experience

As of the date of the application (August 31, 1999), RENOVA Tretinoin Emollient Cream 0.02% (TEC-II) is not marketed anywhere in the world. However, Tretinoin Emollient Cream 0.05% (TEC-IA/RENOVA) is approved or under review in several countries worldwide. Tretinoin emollient cream is marketed under the tradename RENOVA or RETINOVA. No application for tretinoin emollient cream has been rejected by any health authority worldwide for safety reasons, according to the Applicant. RENOVA (tretinoin emollient cream) 0.05% was approved in the United States on December 29, 1995.

Topical tretinoin formulations indicated for acne have been commercially available since 1968 in several dosage forms and strengths worldwide. Topical tretinoin has been on the U.S. market since 1971, when RETIN-A (tretinoin) Solution was approved for the topical treatment of acne vulgaris. The first availability of topical tretinoin outside the U.S. was in Indonesia in 1968. No tretinoin-containing product has been withdrawn from the market or denied approval because of safety concerns, according to the Applicant.

6.2 Post-marketing Experience

RENOVA (tretinoin emollient cream) 0.05% was approved in the United States on December 29, 1995. A total of 6,747 reports of adverse events corresponding to 14,480 adverse reactions (some reports describe more than one reaction) have been received on RENOVA between December 29, 1995 and March 31, 1998. During the 3-month reporting period September 29, 1998 – December 28, 1998 there were 1398 spontaneous non-serious reports submitted through MedWatch and during the one-year reporting period of December 29, 1998 to December 28, 1999 there were 3,239 reports.

In contrast, between October 20, 1971 and March 31, 1998, 4,180 MedWatch reports corresponding to 7,618 adverse reactions had been received on all RETIN-A products (a different drug product containing tretinoin as the active drug substance).

The applicant attributes part of the reason for the comparatively large numbers of adverse event reports for the currently marketed RENOVA compared to the other tretinoin-containing products due to the availability of a toll-free consumer telephone number. Despite this fact, the comparatively large number of adverse events reported with use of the current formulation of RENOVA is remarkable in this reviewer's opinion. Some of the difference may be attributed to the general use of Retin-A for treatment of acne rather than cosmetic indications. The large number of adverse events may reflect the relative nature of severity of adverse event to perceived benefit.

During the most recent one-year reporting period for RENOVA 0.05% there were a total of three thousand two hundred and thirty-nine (3,239) reports that met the criteria for periodic reporting. Four (4) 15-day reports were included in that total. Three thousand two hundred and nine (3,209) spontaneous non-serious reports were submitted.

The four serious adverse event reports included the following:

1) A report of three first trimester miscarriages in a 43 year old woman using Renova for fine lines.
2) A report of a 45 year old woman with tingling on her tongue and chest and loss of voice after using Renova for brown spots.
3) A 46 year old male with palpitations after using Renova for 4 months. The patient had concomitant therapy including multiple unspecified nutrients and herbs.
4) A 34 year old woman with deterioration of vision in her right eye after using the product for 8 months. The patient was diagnosed with a anterior subcapsular cataract.

A clear correlation between use of the drug product and the above events is lacking. These serious adverse events are unlikely to be treatment related.

Of more concern is the large number of non-serious adverse event reports. Of the reports of adverse events presented in the latest Periodic Adverse Event Reporting (one-year period from December 29, 1998 to December 28, 1999) for RENOVA 0.05%, the following appeared to be noteworthy:

ADVERSE EXPERIENCE	NUMBER
Paraesthesia and Hyperaesthesia	516
Periorbital or Facial Edema	152
Photosensitivity Reaction	57
Erythematous Rash	1258
Skin Discoloration/Depigmentation	71
Skin Disorder/Rash Non-specific	634
Skin Dry/Skin Exfoliation	2389

Some of the reports contained more than one adverse experience.

7 Clinical Studies

7.1 Introduction

7.1.1 Summary of Efficacy Studies - Five clinical efficacy studies were included in the submission for NDA 21-108. The Applicant designated two U.S. conducted studies, J89-024 and J89-025, as pivotal. Additionally, Study J89-045, conducted in three European centers (Germany and Sweden) was considered to be pivotal. Study K90-011 was a

single-center double-blind study and was used as supportive evidence. The other supportive clinical efficacy study, L91-026, was conducted in non-Caucasian (mostly African-American) subjects only, as the other studies excluded non-Caucasian subjects from participating. See Table 7A for a summary of all studies pertinent to efficacy. See Table 9A for a summary of all clinical studies that were pertinent to Safety.

Table 7A: All Investigations Pertinent to Efficacy

Protocol #	Country	Study Design	Treatment (Formulation studied)	No. Enrolled	N Age Range (Mean)[a]	% M/F B/C/O[b]	Indications Supported[c]
J89-024	U.S.	24 week, Photodamaged Skin, Phase 3, multicenter, randomized, double-blind, parallel vehicle-controlled	TEC-II 0.02%, 0.25g (unfragranced) Vehicle, 0.25g	90 90	179 45-69 (58.4)	12/88 0/100/0	Fine wrinkling
J89-025	U.S.	24 week, Photodamaged Skin, Phase 3, multicenter, randomized, double-blind, parallel vehicle-controlled	TEC-II 0.02%, 0.25g (unfragranced) Vehicle, 0.25g	90 90	179 43-70 (58.6)	11/89 0/100/0	Mottled hyper-pigmentation
J89-045	Sweden Germany	24-week, Photodamaged Skin, Phase 3, multicenter, randomized, double-blind, parallel vehicle-controlled, 12-week post-therapy	TEC-II 0.02%, 0.25g (unfragranced) Vehicle, 0.25g	60 60	119 44-74 (56.6)	13/87 0/100/0	Fine wrinkling & Yellowing
L91-026	U.S.	24 week, Photodamaged Skin, Phase 2, multicenter, randomized, double-blind, parallel vehicle-controlled and 28 week open-label follow-up phase.	TEC-II 0.02%, 0.25g (fragranced, to-be-marketed) Vehicle, 0.25g	60 60	117 40-74 (55.7)	20/80 91/0/9	None
K90-011	U.S.	24 week, Photodamaged Skin, Phase 3, single center, randomized, double-blind, parallel vehicle-controlled, 12-week post-therapy	TEC-II 0.02%, 0.25g (unfragranced) Vehicle, 0.25g	40 40	80 46-71 (60.1)	11/89 0/100/0	None
K90-054	Sweden Germany	52 week, Photodamaged Skin, Phase 3, multicenter, open-label, long-term	TEC-II 0.02%, 0.25g (unfragranced)	120[f]	120 44-70 (57.0)	11/89 0/100/0	N/A

[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] The following indications were studied: Fine wrinkling, coarse wrinkling, tactile roughness, laxity, mottled hyperpigmentation. L91-026 also studied Lentigines/Dermatosis Papulosa Nigra, but did not study yellowing.

7.1.2 Definitions of Clinical Parameters Studied (as described in the protocols) –

Fine wrinkling – This parameter represents a visual assessment of the number and depth of superficial wrinkles (i.e., shallow indentations or lines). Fine wrinkles, which disappear upon stretching, typically appear in periorbital and perioral regions. Fine wrinkles are usually found further from the eyes and mouth than are coarse wrinkles.

Coarse wrinkling – This parameter represents a visual assessment of the number and depth of coarse wrinkles (i.e., deep lines, furrows, or creases). Coarse wrinkles, which can appear on the forehead, glabella, chin, and nasolabial and periorbital areas, do not disappear with stretching (i.e., a fine line remains) and tend to be located closer to the eyes and mouth than fine wrinkles.

Tactile roughness – This parameter represents a qualitative tactile assessment of skin texture or topography from very smooth (grade=0) to very rough (grade=9). Textural features likely to contribute to this grade include dryness, scaliness, wrinkles, and other surface irregularities. Discrete lesions, such as actinic keratoses, seborrheic keratoses, nevi, and comedones are not included in this grade.

Laxity – This parameter represents an indirect tactile assessment of skin turgor or elasticity from very tight (grade=0 to very loose (grade=9). The grade for this parameter was determined by vertically running one or two fingers over the area from the temple to the zygomatic arch and assessing how much movement of the skin is felt. The greater the degree of movement, the greater the grade for looseness. Visual sagging is not included in this grade.

Yellowing – This parameter represents a visual assessment of color tone from very pink or rosy (grade=0) to very sallow or pale (grade=9). Pinkness is distinguished from more pronounced

degrees of erythema associated with peeling and other elements of skin irritation. (See below under Section 8 for discussion of an indication for yellowing).

Mottled Hyperpigmentation – This parameter represents a visual assessment of light, patchy, mottled hyperpigmentation and solar freckling (including melasma) based on quantitative and qualitative criteria such as the area/density of pigment, color intensity (dark vs. light), and uniformity of distribution (i.e., the more uneven or blotchy, the greater the score).

7.1.4 Regarding the Use of a 10-Point Scale for Assessment of These Indications

The Sponsor provided a photographic guide that was used to instruct the site investigators as to the 10 point scoring system. In this reviewer's opinion, this guide may not have been precise enough to allow 10 point scoring for every indication studied. Photographs were not provided for each point along the 10-point scale and it appears that some photographs were used for evaluation of multiple endpoints. It was not clear how tactile scoring (roughness and laxity) was instructed. Inter- and intra- observer differences were not evaluated.

The scales used in the assessment of these skin parameters ranged from 0 to 9 (a 10-point scale). However, description of each point as represented by each specific parameter was not provided. The 10-point scale was not validated by such means as studies to assess inter- and intra- observer variability. Additionally, the Applicant specifically describes what is intrinsically only a four-point scale (no sign, mild, moderate, and severe). The individual points are further subdivided as follows: no sign (0), mild (1-3), moderate (4-6), and severe (7-9).

Each of the parameters described, fine and coarse wrinkling, tactile roughness, laxity, yellowing, and mottled hyperpigmentation would need to be validated on the 10-point scale if such a scale is to be used. The ability to discern a 1 in 10 difference for one parameter may be different for another.

The 10-point scales used for the studies submitted to NDA 21-108 were identical to those that were submitted to NDA 19-963 (for RENOVA 0.05% TEC-I). It is difficult to effect post-hoc changes to these scales (which were integral to the studies and described in the protocols submitted to IND). However, in the future, studies for these skin parameters should use validated scales or utilize a scale that is consistent with other dermatologic diseases that can be visually assessed (e.g., a 5 point scale - no sign, minimal, mild, moderate, and severe - may be acceptable).

7.2 Pivotal Trial #1 – J89-024

7.2.1 Title - A Double-Blind, Multi-Center, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Tretinoin Emollient Cream (TEC-II) 0.02% in the Treatment of Photodamaged Skin

7.2.2 Dates - Initiated on November 2, 1989 and Ended on August 8, 1990

7.2.3 Sites - The principal investigators for Study J89-024 were as follows:
Charles Ellis, M.D. – University of Michigan Medical Center, Ann Arbor, MI
Norman Levine, M.D. – University of Arizona Health Sciences Center, Tucson AZ
Joel Shavin, M.D. – Gwinnett Clinical Research Center, Snellville, GA

The Snellville, GA site was reviewed by FDA's Bioresearch Monitoring Program, on February 4, 2000 by Investigator Stephanie E. Hubbard of the Good Clinical Practice Branch II, HFD-47, DSI. The report stated the following: "This investigator enrolled 60 subjects in the study. Fifty-five subjects completed the study. D.O. investigator examined 10 subject records. Data audit did not reveal any significant discrepancies and/or deficiencies in the conduct of the study. The data collected from this site appears acceptable."

7.2.4 Objective - The objective of this study was to evaluate the safety and efficacy of tretinoin emollient cream (TEC-II unfragranced) 0.02% in the treatment of moderate to severe photodamaged skin.

7.2.5 Study Design and Protocol Synopsis - This was a randomized, multicenter, double-blind study consisting of two parallel treatment groups (TEC-II 0.02% and a vehicle control). Treatment was once nightly for 24 weeks using a general dosing guideline of 0.25 g per application (this was varied at the discretion of the investigator). A metered dosing system was used (see Overview of Safety section of this review). Subjects in both treatment groups applied a moisturizing sunscreen daily (———— or a similar SPF 15 or higher suncreen was used). Subjects were instructed to wash with ———— soap or similar mild soap prior to applying the study drug. Additionally, ———— or other emollients were used when needed for excessive skin irritation or dryness. Thus, no specific soap, moisturizer or sunscreen appeared to specified for this pivotal trial. Short-term therapy (up to 5 days) with a topical corticosteroid was permissible should excess skin irritation occur. Return visits were scheduled after two and four weeks of treatment for safety monitoring, and at four-week intervals thereafter for the rest of the study for safety and efficacy evaluations. This study was designed identically to J89-025 (see below under Section 7.3).

7.2.6 Inclusion Criteria –

1) Subjects are to be male or female, Caucasian, 45-70 years of age, in good general health.
2) Subjects are to exhibit moderate or severe photodamaged facial skin (overall severity grade of 6-9 out of a scale of 0-9 at baseline) based on clinical evaluation of tactile roughness, fine and coarse wrinkling, mottled hyperpigmentation, yellowing (sallowness) and laxity (looseness).
3) Subjects must discontinue topical and systemic retinoids (other than normal recommended daily allowance of vitamin A) at least 6 months prior to initiation of study therapy. All other topical medications to the face must be discontinued at least 24 hours prior to initiation of study therapy.
1) Subjects should not have applied any emollients to the face for at least 24 hours prior to pre-study evaluations, or cosmetics on the day(s) of pre-study evaluations.
2) If female, the subject must:
    a) be post-menopausal for at least one year, or
    b) have had a hysterectomy, or
    c) have had a tubal ligation, or
    d) agree to use an effective method of contraception (e.g., oral contraception, condoms and spermacide)
3) If female and pre-menopausal with an intact uterus, the subject must have :
    a) had a normal menstrual flow within 30 days prior to initiation of study therapy, and
    b) a negative urine pregnancy test immediately prior to initiation of study therapy.
4) Subjects (or their authorized representative) must read and sign the informed consent form after the nature of the study has been fully explained and the Confidential Follow-Up Form has been completed.

7.2.7 Exclusion Criteria -

1) Subjects are not to be pregnant or nursing.
2) Subjects are not to have a history of basal cell or squamous cell carcinoma on the face within the past five years or any history of malignant melanoma at any site.
3) Subjects are not to have received any prior therapy (e.g. Zyderm®, silicone, blepharoplasty, facelift, dermabrasion) that may confound the evaluation of drug safety or efficacy.

4) Subjects are not to exhibit any skin condition (e.g., multiple clinically visible facial actinic keratoses, rosacea, psoriasis) that may require concurrent therapy or may confound the evaluation of drug safety or efficacy.
5) Subjects are not to have a history of psychotic or affective disorders, including bipolar disorder, major depression, and schizophrenia. NOTE: Antidepressants or antipsychotic drugs are not to be used prior to or during the study.
6) Subjects are not to have a history of hypersensitivity to any of the formulation components.
7) Subjects are not to have received any experimental drug or used any experimental device 30 days prior to initiation of study therapy.
8) Subjects are not to have excessive facial hair (e.g., beards, sideburns, moustache).

7.2.8 - Study Population - The study population, summarized below, consisted of healthy Caucasian subjects 45-69 years of age (mean age 58). Eighty-eight percent of subjects were female and 70% exhibited severe photodamage at baseline. The baseline score for the treatment and vehicle groups were similar. All but one subject were valid for safety. That one subject (#343) did not have data beyond baseline and apparently did not start medication (no MEDSTART date).

Summary of Information about Subjects Enrolled

	TEC-II 0.02%	Vehicle	Total
No. Enrolled	90	90	180
No. Completed	77	83	160
No. Discontinued:	13	7	20
Adverse Event	4	0	4
Personal	7	3	10
Lost to Follow-Up	2	4	6
No. Valid for Safety	90	89	179
Mean Age (Range)[a]	58.5	58.4	58.4
% Female/%Male[a]	87/13	90/10	88/12
% Moderate/% Severe[a]	27/73	34/66	30/70

[a] Based on subjects valid for safety

7.2.9 Applicant's Interpretation of Efficacy Results -

Study J89-024 was conducted prior to approval of RENOVA 0.05% (TEC-IA formulation) in December of 1995. No regulatory agreements had been made regarding endpoints and the outcomes that would be needed for approval prior to start of Phase 3 studies for NDA 21-108.

This section summarizes the Applicant's conclusions. However, the Agency does not rely on these conclusions for regulatory decisions. The data supplied by the Applicant is analyzed according to FDA standards. The determination of the clinical relevance and statistical validity of conclusions are made independent of the Applicant's interpretations.

According to the Applicant, TEC-II 0.02% consistently outperformed vehicle based on the various investigator evaluations, subject self-assessments, and computer-generated skin replica measures. Based on clinical observations by both subjects and investigators, more subjects exhibited overall improvement in photodamage as well as improvement in specific clinical signs, especially fine wrinkling, after TEC-II 0.02%

therapy than after vehicle therapy. In addition, the degree of improvement was determined by both subjects and investigators to be greater in TEC-II 0.02%-treated subjects than in vehicle-treated subjects. The differences between TEC-II 0.02% and vehicle were consistent from center to center, and became evident within 4 to 12 weeks of therapy depending on the parameter.

Each of the three primary efficacy measures at week 24 (investigator's global evaluation, investigator's evaluation of overall severity of photodamage, and the overall subject self-assessment) showed a highly statistically significant ($p<0.001$) difference between TEC-II 0.02% and vehicle. Improvement rates of 79%, 68%, and 83% were found in the TEC-II 0.02% group, compared with 60%, 41%, and 64%, respectively, in the vehicle group. This dynamic assessment of improvement is inherently less reliable and was not used to make any final determinations of efficacy by Agency. In addition to differences in improvement rates, the magnitude of the improvement was greater for TEC-II 0.02%-treated subjects than for vehicle-treated subjects. Such global evaluations were considered to be less reliable by Agency with regard to the assessment of cosmetic products and therefore, the primary efficacy data per protocol for this study were not used towards determination of approval of this drug product.

Of the six clinical signs evaluated by the investigators, fine wrinkling showed the greatest response to TEC-II 0.02% therapy relative to vehicle. TEC-II 0.02%-treated subjects also showed significantly greater reductions from baseline to week 24 in coarse wrinkling, mottled hyperpigmentation, and yellowing (sallowness). Roughness and laxity were not significantly improved relative to vehicle. TEC-II 0.02%-treated subjects also reported significantly greater improvement than vehicle-treated subjects in all six individual self-assessment features at week 24 (small wrinkles, pink/rosy tone, color ("brown spots"/blotchiness), texture, tightness, and pores). According to the Applicant, the skin replica measurements independently corroborated the clinical findings (See below regarding regulatory significance of the skin replica surrogate endpoint). The differences between TEC-II 0.02% and vehicle, which were greater on the cheek than on the crow's feet, were statistically significant for all six cheek parameters and three of the six crow's feet parameters. The following tables summarize the results of clinical signs, individual subject self-assessments, and skin replicas:

INDIVIDUAL CLINICAL SIGNS AND SUBJECT SELF-ASSESSMENTS AT WEEK 24

	CLINICAL SIGNS					
	FW	MH	Roughness	CW	Yellowing	Laxity
TEC-II 0.02% (N=77)						
% Subjects Improved[a]	66	73	55	43	51	35
Mean Change	-0.9*	-1.2*	-0.9	-0.5*	-1.0*	-0.5
Vehicle (N=83)						
% Subjects Improved[a]	37	61	52	25	48	36
Mean Change	-0.5	-1.0	-0.9	-0.3	-0.7	-0.4

SUBJECT SELF-ASSESSMENTS						
	SW	Tone	Color	Texture	Tightness	Pores
TEC-II 0.02% (N=77)						
% Subjects Improved	73	58	64	90	75	52
Mean Score[b]	2.8*	2.5*	2.8*	3.2*	2.9*	2.6*
Vehicle (N=83)[c]						
% Subjects Improved	49	39	36	72	51	38
Mean Score[b]	2.5	2.3	2.3	2.9	2.5	2.4

[a] Improvement = reduction from baseline to week 24 of one or more units on 0-9 scale

[b] 1=Worse, 2=The Same, 3=Somewhat Improved, 4=Much Improved

[c] N=82 for pores

* Denotes statistically significant difference from vehicle (one-sided $p \leq 0.05$) based on an analysis of variance model applied to the mean changes from baseline to week 24 for clinical signs and on a categorical linear model analysis applied to the mean week 24 scores for subject self-assessments.

NOTE: FW = Fine Wrinkling, MH = Mottled Hyperpigmentation, CW = Coarse Wrinkling, SW = Small Wrinkles

SKIN REPLICA RESULTS

Crow's Feet Replicas						
	Ra-NS	Ra-EW	Rz-NS	Rz-EW	Shadows-NS	Shadows-EW
TEC-II 0.02%	-4.4	-10.7*	-5.6*	-12.6*	-11.1	-18.6
Vehicle	1.5	-4.4	-0.8	-4.2	-1.1	-11.8
Cheek Replicas						
	Ra-NS	Ra-EW	Rz-NS	Rz-EW	Shadows-NS	Shadows-EW
TEC-II 0.02%	-17.5*	-14.3*	-17.9*	-13.2*	-42.4*	-36.7*
Vehicle	-7.3	-3.1	-7.2	-0.8	-17.3	-16.2

NOTE: NS= North-South; EW=East-West

Values represent percent change from baseline mean to week 24 mean. N=76 of the 77 subjects valid for efficacy in the TEC group for both the crow's feet and cheek analyses; N=82 of the 83 valid subjects in the vehicle group for the crow's feet analysis and 83 for the cheek analysis.

* Denotes statistically significant difference from vehicle (one-sided $p \leq 0.05$) based on an analysis of variance model applied to the mean change from baseline to week 24.

Statistical analysis of this pivotal trial results (as provided by the Applicant) using a Modified Intent to Treat Population (excluding from consideration those patients whose scores in that individual endpoint was 0 or 1 at baseline) results in the following:

Applicant's Holm's Adjusted p-values and Mean Changes from Baseline at 24 Weeks

Indication	Unadjusted p-value	Holm's adjusted p-value	Difference in treatment group mean change*	95% Confidence Interval*
Fine Wrinkling	0.001	0.006	0.4	0.6 to 0.2
Coarse Wrinkling	0.036	0.144	0.2	0.4 to 0.0
Tactile Roughness	0.722	0.722	0.0	0.4 to –0.5
Laxity	0.109	0.327	0.1	0.4 to –0.1
Yellowing	0.023	0.115	0.4	0.8 to 0.0
Mottled Hyperpigmentation	0.110	0.327	0.3	0.6 to –0.1

*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.

Discussion by the Agency and the Applicant regarding the data resulted in utilization of a Modified Intent to Treat Population which excluded a Baseline value of 0 or 1. It was thought that with a Baseline of 0 or 1 there was little room for improvement and would tend to mask overall improvement. A Holm's adjusted p-value was used due to the presence of multiple endpoint comparisons in this trial. It was agreed by the Agency that we would use these statistical methods to determine efficacy for this trial and the other submitted clinical trials.

7.2.10 Reviewer's Assessment of Clinical Efficacy –

No single center in this trial appeared to drive the efficacy results (see review by FDA Biostatistician). The FDA Biostatistics review agreed with the conclusions provided by the Applicant.

Study J89-024 Holm's Adjusted p-values	
Fine Wrinkling	.0099 *
Coarse Wrinkling	.2734
Yellow-brown discoloration	.2734
Mott Hyperpig.	.5223
Laxity	.5223
Tactile Roughness	.5223

Based on the data above, using the Holm's adjusted p-value to accommodate multiple endpoints, the Applicant demonstrates efficacy for fine wrinkling from Study J89-024. As the difference in treatment group mean change may not have as great a clinical relevance as the relative number of patients improved, a table is included demonstrating an increased percentage of improved vs. baseline for the MITT population, Week 24, LOCF between treatment and vehicle:

Study J89-024: Difference from Baseline in Fine Wrinkling Score (as per Biostatistics review)

Difference in Score from Baseline	MITT Week 24 LOCF Renova 0.02% Number of Subjects (% of Subjects)	MITT Week 24 LOCF Vehicle Number of Subjects (% of Subjects)
≤ -3 (at least moderate improvement)	0 (0 %)	2 (2 %)
-2 (mild improvement)	20 (22 %)	5 (6 %)
-1 (minimal improvement)	33 (37 %)	26 (29 %)
0 (no change)	36 (40 %)	57 (63 %)
≥ +1 (worsened)	0 (0%)	0 (0 %)

The numbers in each category ≤ –3, -2, -1, 0 and 1, were also calculated and the sums of the numbers for each category are included in the Summary of Clinical Efficacy section of this review.

Skin replicas were not considered as a valuable surrogate marker for wrinkles. This method has not been validated towards an endpoint of wrinkling. While such data may provide some degree of quantitation, the clinical significance of changes in skin replica scoring is unclear. This method is not used in the routine clinical setting (i.e. healthcare provider's office) to determine efficacy of treatment. The most suitable

endpoint for determination of effect of a treatment on the appearance of wrinkles is the actual appearance of the wrinkles themselves (i.e., a visual assessment). Fine wrinkling was defined as wrinkles that disappear after stretching of the skin and coarse wrinkling remains, so a tactile element may also be involved in the assessment of wrinkling. Such a tactile element is not accounted for with skin replica analysis. Thus, the skin replica results provided for this study were not statistically assessed for this study and other studies submitted to this NDA.

7.2.11 Safety – Skin irritation, although it occurred in most TEC-II 0.02% treated subjects and was more prevalent in the TEC-II 0.02% group than in the vehicle group, was usually mild and well-tolerated. The various signs and symptoms of skin irritation, such as erythema, peeling, and burning/stinging, peaked during the first two weeks of therapy and gradually declined to negligible levels by week 24. There was good compliance with the once-daily treatment regimen, as 90% of subjects valid for safety completed at least 90% of TEC-II 0.02% applications and 88% of subjects reported no missed applications of TEC-II 0.02% due to skin irritation. Four subjects (4%) in the TEC-II 0.02% group discontinued the study due to an adverse event, including three for whom the adverse event was at least possibly related to TEC-II 0.02% therapy. Similarly, topical steroid therapy for TEC-II 0.02%-related skin irritation was reported by only four (4%) subjects. No other serious adverse events related to TEC-II 0.02% therapy were reported, and adverse events not associated with the treatment site were evenly distributed between the TEC-II 0.02% and vehicle groups. See Overview of Safety for a detailed analysis of adverse events related to this study and other studies submitted.

7.3 Pivotal Trial #2 – J89-025

7.3.1 Title - A Double-Blind, Multi-Center, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Tretinoin Emollient Cream (TEC-II) 0.02% in the Treatment of Photodamaged Skin

7.3.2 Dates – The study was initiated on November 7, 1989 and ended on September 5, 1990.

7.3.3 Sites - The principal investigators for Study J89-025 were as follows:
Wilma F. Bergfield, M.D. – The Cleveland Clinic Foundation, Cleveland, OH
Ronald C. Savin, M.D. – Adult & Adolescent Dermatology, P.C., New Haven, CT
Jonathan S. Weiss, M.D. – The Emory Clinic, Section of Dermatology, Atlanta, GA

The Cleveland, Ohio site was reviewed by FDA's Bioresearch Monitoring Program between December 13 and 28, 1999 by Investigator Frederick M. Lochner of the Good Clinical Practice Branch II, HFD-47, DSI. The report stated the following: "This investigator enrolled 60 subjects in the study. Fifty-four subjects completed the study. The D.O. investigator examined 12 subject records. This audit did not reveal any significant discrepancies and/or deficiencies. The data collected from this site appears acceptable."

The Atlanta, GA site was reviewed by FDA's Bioresearch Monitoring Program between December 7 and 13, 1999 by Investigator Stephanie E. Hubbard of the Good

Clinical Practice Branch II, HFD-47, DSI. The report stated the following: "This investigator enrolled 60 subjects in the study. Fifty-six subjects completed the study. Four subjects were lost to follow-up. The D.O. investigator examined 8 subject records. Data audit did not reveal any significant discrepancies and/or deficiencies in the conduct of the study. The data collected from this site appears acceptable."

7.3.4 Objective - The objective of this study was to evaluate the safety and efficacy of tretinoin emollient cream (TEC-II unfragranced) 0.02% in the treatment of moderate to severe photodamaged skin.

7.3.5 Study Design and Protocol Synopsis - This was a randomized, multicenter, double-blind study consisting of two parallel treatment groups (TEC-II 0.02% and a vehicle control). Treatment was once nightly for 24 weeks using a general dosing guideline of 0.25 g per application (this was varied at the discretion of the investigator). The extent of variation was not described, nor was a rationale for varying the amount of RENOVA 0.02% to be applied. A metered dosing system was used (see Overview of Safety for a discussion). Subjects in both treatment groups applied a moisturizing sunscreen daily ([redacted] or a similar SPF 15 or higher suncreen was used). Subjects were instructed to wash with [redacted] soap or similar mild soap prior to applying the study drug. Additionally, [redacted] or other emollients were used when needed for excessive skin irritation or dryness. Short-term therapy (up to 5 days) with a topical corticosteroid was permissable should excess skin irritation occur. Return visits were scheduled after two and four weeks of treatment, and at four-week intervals thereafter for the rest of the study. This study was designed identically to study J89-024.

7.3.6 Inclusion Criteria -

1) Subjects are to be male or female, Caucasian, 45-70 years of age, in good general health.
2) Subjects are to exhibit moderate or severe photodamaged facial skin (overall severity grade of 6-9 at baseline – see section 7.1.4 of this review for description of grading) based on clinical evaluation of tactile roughness, fine and coarse wrinkling, mottled hyperpigmentation, yellowing (sallowness) and laxity (looseness).
3) Subjects must discontinue topical and systemic retinoids (other than normal recommended daily allowance of vitamin A) at least 6 months prior to initiation of study therapy. All other topical medications to the face must be discontinued at least 24 hours prior to initiation of study therapy.
4) Subjects should not have applied any emollients to the face for at least 24 hours prior to pre-study evaluations, or cosmetics on the day(s) of pre-study evaluations.
5) If female, the subject must:
    a) be post-menopausal for at least one year, or
    b) have had a hysterectomy, or
    c) have had a tubal ligation, or
    d) agree to use an effective method of contraception (e.g., oral contraception, condoms and spermacide)
6) If female and pre-menopausal with an intact uterus, the subject must have :
    a) had a normal menstrual flow within 30 days prior to initiation of study therapy, and
    b) a negative urine pregnancy test immediately prior to initiation of study therapy.
7) Subjects (or their authorized representative) must read and sign the informed consent form after the nature of the study has been fully explained and the Confidential Follow-Up Form has been completed.

7.3.7 Exclusion Criteria -

1) Subjects are not to be pregnant or nursing.
2) Subjects are not to have a history of basal cell or squamous cell carcinoma on the face within the past five years or any history of malignant melanoma at any site.
3) Subjects are not to have received any prior therapy (e.g. Zyderm®, silicone, blepharoplasty, facelift, dermabrasion) that may confound the evaluation of drug safety or efficacy.
4) Subjects are not to exhibit any skin condition (e.g., multiple clinically visible facial actinic keratoses, rosacea, psoriasis) that may require concurrent therapy or may confound the evaluation of drug safety or efficacy.
5) Subjects are not to have a history of psychotic or affective disorders, including bipolar disorder, major depression, and schizophrenia. NOTE: Antidepressants or antipsychotic drugs are not to be used prior to or during the study.
6) Subjects are not to have a history of hypersensitivity to any of the formulation components.
7) Subjects are not to have received any experimental drug or used any experimental device 30 days prior to initiation of study therapy.
8) Subjects are not to have excessive facial hair (e.g., beards, sideburns, moustache).

7.3.8 Study Population - The study population, summarized below, consisted of subjects 43-70 years of age (mean age 58.6). Eighty-nine percent of subjects were female and 70% exhibited severe photodamage at baseline. All but one subject were valid for safety. That subject (#329) did not have data past baseline and apparently did not start on medication.

Summary of Subject Population Data

	TEC-II 0.02%	Vehicle	Total
No. Enrolled	90	90	180
No. Completed	82	86	168
No. Discontinued:	8	4	12
Adverse Event	2	1	3
Personal	1	1	2
Lost to Follow-Up	5	2	7
No. Valid for Safety	89	90	179
Mean Age (Range)[a]	58.7	58.5	58.6
% Female/%Male[a]	89/11	89/11	89/11
% Moderate/% Severe[a]	29/71	30/70	30/70

[a] Based on subjects valid for safety

7.3.9 Applicant's Interpretation of Efficacy Results -

This section summarizes the Applicant's conclusions. However, the Agency does not rely on these conclusions for regulatory decisions. The data supplied by the Applicant is analyzed according to FDA standards. The determination of the clinical relevance and statistical validity of conclusions are made independent of the Applicant's interpretations, although the Applicant's arguments are considered.

According to the Applicant, TEC-II 0.02% consistently outperformed vehicle based on the various investigator evaluations, subject self-assessments, and computer-generated skin replica measures. Of the 27 efficacy parameters evaluated at week 24, 22 showed statistically significant differences in favor of TEC-II 0.02%. This includes two of the three primary efficacy measures, all six investigator-graded clinical signs, five of the six individual subject self-assessment features, and nine of the 12 skin replica

parameters. The differences between TEC-II 0.02% and vehicle became evident within 4 to 12 weeks of therapy depending on the parameter.

Two of the three primary efficacy measures at week 24 (investigator's global evaluation and investigator's evaluation of overall severity of photodamage) showed a highly statistically significant ($p<0.001$) difference between TEC-II 0.02% and vehicle, with improvement rates of 87% and 71% in the TEC-II 0.02% group, compared with 44% and 36%, respectively, in the vehicle group. The difference between TEC-II 0.02% and vehicle was not significant for the third primary measure, overall subject self-assessment, in which the majority of subjects in both treatment groups graded their skin as improved, with TEC-II 0.02%-treated subjects giving slightly more favorable responses to therapy than vehicle-treated subjects (83% vs. 72%).

PRIMARY EFFICACY MEASURES

	TEC-II 0.02% (N=82)	Vehicle (N=86)[a]	p-value[b] (TEC vs. Vehicle)
Global Evaluation at Week 24			
% Subjects Improved	87	44	
Mean Score[c]	3.3	2.6	<0.001
Overall Severity at Week 24			
% Subjects Improved From Baseline	71	36	
Mean Change From Baseline (0-9 scale)	-0.9	-0.4	<0.001
Overall Subject Self-Assessment at Week 24			
% Subjects Improved	83	72	
Mean Score[d]	3.1	3.0	0.069

[a] N=85 for overall subject self-assessment

[b] Statistical results are based on categorical linear model analyses for the global evaluation and the overall subject self-assessment and on an analysis of variance model for overall severity.

[c] 1=Worse, 2=No Change, 3=Slightly Improved, 4=Improved, 5=Much Improved

[d] 1=Worse, 2=The Same, 3=Somewhat Improved, 4=Much Improved

All six clinical signs evaluated by the investigator (fine wrinkling, mottled hyperpigmentation, roughness, coarse wrinkling, yellowing [sallowness], and laxity [looseness]) showed significantly greater reductions from baseline to week 24 for TEC-II 0.02%-treated subjects than vehicle-treated subjects, with mottled hyperpigmentation showing the greatest response to TEC-II 0.02% therapy relative to vehicle. The difference between TEC-II 0.02% and vehicle in fine wrinkling was due largely to the results at one of the three study centers, while results at one center showed greater reductions in the vehicle group than in the TEC-II 0.02% group, resulting in a significant treatment by investigator interaction. TEC-II 0.02%-treated subjects also reported significantly greater improvement than vehicle-treated subjects in five of the six individual self-assessment features at week 24 (pink/rosy tone, color ["brown spots/blotchiness], texture, tightness, and pores). Small wrinkles were also improved to a greater extent in the TEC-II 0.02% group than the vehicle group, but the difference between the treatments was not statistically significant. The skin replica measurements independently corroborated the clinical findings, revealing consistently greater reductions

in wrinkle measurements from baseline to week 24 in TEC-II 0.02%-treated subjects than in vehicle-treated subjects. The differences between TEC-II 0.02% and vehicle, which were greater on the cheek than on the crow's feet, were statistically significant for all six cheek parameters and three of the six crow's feet parameters (the significant differences for two of the crow's feet parameters were in the presence of a significant treatment by investigator interaction). The skin replica surrogate endpoints were not critically assessed due to lack of validation and proven clinical correlation (See reviewer conclusions for Study J89-024). The following tables summarize the results of clinical signs, individual subject self-assessments, and skin replicas.

INDIVIDUAL CLINICAL SIGNS AND SUBJECT SELF-ASSESSMENTS AT WEEK 24

	CLINICAL SIGNS					
	FW	MH	Roughness	CW	Yellowing	Laxity
TEC-II 0.02% (N=82)						
% Subjects Improved[a]	57	72	85	38	59	38
Mean Change	-0.9*,#	-1.1*	-1.7*	-0.5*	-0.9*	-0.5*
Vehicle (N=86)						
% Subjects Improved[a]	40	30	71	22	35	22
Mean Change	-0.6	-0.4	-1.3	-0.3	-0.5	-0.3
SUBJECT SELF-ASSESSMENTS						
	SW	Tone	Color	Texture	Tightness	Pores
TEC-II 0.02% (N=82)						
% Subjects Improved	70	67	56	87	71	62
Mean Score[b]	2.8	2.8*	2.6*	3.1*	2.9*	2.8*
Vehicle (N=85)[c]						
% Subjects Improved	54	41	38	69	59	46
Mean Score[b]	2.7	2.5	2.4	3.0	2.7	2.5

[a] Improvement = reduction from baseline to week 24 of one or more units on 0-9 scale
[b] 1=Worse, 2=The Same, 3=Somewhat Improved, 4=Much Improved
[c] Of the 86 subjects valid for efficacy, 85 completed the week 24 subject self-assessment questionnaire.
* Denotes statistically significant difference from vehicle (one-sided $p \leq 0.05$) based on an analysis of variance model applied to the mean changes from baseline to week 24 for clinical signs and on a categorical linear model analysis applied to the mean week 24 scores for subject self-assessments.
# Denotes significant treatment by investigator interaction.
NOTE: FW = Fine Wrinkling, MH = Mottled Hyperpigmentation, CW = Coarse Wrinkling, SW = Small Wrinkles

SKIN REPLICA RESULTS

	CROW'S FEET REPLICAS					
	Ra-NS	Ra-EW	Rz-NS	Rz-EW	Shadows-NS	Shadows-EW
TEC-II 0.02%	-2.2	-14.0*,#	-4.1	-16.7*	-4.0	-25.2*,#
Vehicle	1.4	0.0	-2.0	0.4	2.9	0.6
CHEEK REPLICAS						
	Ra-NS	Ra-EW	Rz-NS	Rz-EW	Shadows-NS	Shadows-EW
TEC-II 0.02%	-15.2*	-16.1*,#	-15.2*,#	-15.1*	-36.3*	-37.2*
Vehicle	-5.8	-6.2	-5.2	-3.8	-12.5	-15.9

NOTE: NS= North-South; EW=East-West

Values represent percent change from baseline mean to week 24 mean. N=79 of the 82 subjects valid for efficacy in the TEC group for the crow's feet analyses and 81 for the cheek analyses; N=81 of the 86 valid subjects in the vehicle group for the crow's feet analysis and 83 for the cheek analysis.
* Denotes statistically significant difference from vehicle (one-sided $p \leq 0.05$)
based on an analysis of variance model applied to the mean change from baseline to week 24.
# Denotes significant treatment by investigator interaction.

The Applicant provided statistical analysis of this pivotal trial results using a Modified Intent to Treat Population (excluding from consideration those patients whose scores in that individual endpoint was 0 or 1 at baseline):

Applicant's Holm's Adjusted p-values and Mean Changes from Baseline at 24 Weeks

Indication	Unadjusted p-value	Holm's adjusted p-value	Difference in treatment group mean change*	95% Confidence Interval*
Fine Wrinkling	0.039	0.117	0.3	0.6 to 0.0
Coarse Wrinkling	0.014	0.056	0.2	0.4 to 0.0
Tactile Roughness	0.094	0.120	0.3	0.7 to –0.1
Laxity	0.060	0.120	0.2	0.4 to 0.0
Yellowing	0.007	0.035	0.3	0.6 to 0.1
Mottled Hyperpigmentation	0.001	0.006	0.7	0.9 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.

Based on the data above, using the Holm's adjusted p-value to accommodate multiple endpoints, the Applicant claims efficacy in yellowing and mottled hyperpigmentation from Study J89-025.

7.3.10 Reviewer's Determination of Clinical Efficacy –

The FDA Biostatistician's review included the following calculations for Holm's Adjusted p-values:

Study J89-025 - Holm's Adjusted p-values (From FDA Biostatistician)	
Mott Hyperpigmentation	.0001 *
Yellow-brown discoloration	.0634
Coarse Wrinkling.	.0805
Fine Wrinkling.	.1712
Laxity	.1712
Tactile Roughness	.1789

The FDA Biostatistician notes that for Study J89-025, the comparison for yellow-brown discoloration or "yellowing" as described by the Sponsor is "almost, but not quite, statistically significant." If an ITT population were used then the p-value for this comparison would e significant with an adjusted p of 0.0366. However, using the FDA Biostatistician's Holm's adjusted p-values to adjust for multiple comparisons for the MITT population which excludes subjects who start with a baseline score of 0 or 1, efficacy is only demonstrated for the indication of mottled hyperpigmentation. The p-value for mottled hyperpigmentation is quite significant with an adjusted p-value of 0.0001.

The table below shows the number of subjects who improved using RENOVA 0.02% or Vehicle for each category of either improvement or worsening (MITT population, Week 24, LOCF):

Study J89-025: Difference from Baseline in Mottled Hyperpigmentation Score

Difference in Score from Baseline	MITT Week 24 LOCF Renova 0.02% Number of Subjects (% of Subjects)	MITT Week 24 LOCF Vehicle Number of Subjects (% of Subjects)
≤ -3 (at least moderate improvement)	5 (6 %)	0 (0 %)
-2 (mild improvement)	20 (23 %)	10 (11 %)
-1 (minimal improvement)	34 (39 %)	16 (18 %)
0 (no change)	28 (32 %)	61 (69 %)
≥ +1 (worsened)	0 (0%)	1 (1 %)

7.3.11 Safety – Safety results were similar to the other pivotal trial J89-024. Skin irritation, although it occurred in most TEC-II 0.02% treated subjects and was more prevalent in the TEC-II 0.02% group than in the vehicle group, was usually mild and well-tolerated. The various signs and symptoms of skin irritation, such as erythema, peeling, and burning/stinging, peaked during the first two weeks of therapy and gradually declined to negligible levels by week 24. There was good compliance with the once-daily treatment regimen, as 87% of subjects valid for safety completed at least 90% of TEC-II 0.02% applications and 93% of subjects reported 10 or fewer applications of TEC-II 0.02% due to skin irritation. Two subjects (2%) in the TEC-II 0.02% group discontinued the study due to an adverse event, including one for whom the adverse event was at least possibly related to TEC-II 0.02% therapy. Similarly, topical steroid therapy for TEC-II 0.02%-related skin irritation was reported by six (7%) subjects. No other serious adverse events related to TEC-II 0.02% therapy were reported, and adverse events not associated with the treatment site were evenly distributed between the TEC-II 0.02% and vehicle groups. See Overview of Safety for a detailed analysis of adverse events related to this study and other studies submitted.

7.4 Pivotal Study #3 – J89-045

7.4.1 Title - A Double-Blind, Multi-Center, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Tretinoin Emollient Cream (TEC-II) 0.02% in the Treatment of Photodamaged Skin

7.4.2 Dates - The study was initiated on April 23, 1990 and ended on February 25, 1991 with Follow-up on May 21, 1991.

7.4.3 Sites/Investigators –

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7.4.4 Objective - The objective of this study was to evaluate the safety and efficacy of tretinoin emollient cream (TEC-II unfragranced) 0.02% in the treatment of moderate to severe photodamaged skin.

7.4.5 Study Design and Protocol Synopsis - This was a randomized, multicenter, double-blind study consisting of two parallel treatment groups (TEC-II 0.02% and a vehicle control). Treatment was once nightly for 24 weeks using a general dosing guideline of 0.25 g per application (this was varied at the discretion of the investigator). Subjects in both treatment groups applied a moisturizing sunscreen daily ([redacted] or a similar SPF 15 or higher suncreen was used). Subjects were instructed to wash with [redacted] soap or similar mild soap prior to applying the study drug. Additionally, [redacted] or other emollients were used when needed for excessive skin irritation or dryness. Short-term therapy (up to 5 days) with a topical corticosteroid was permissible should excess skin irritation occur. Subjects returned for scheduled visits after two and four weeks of treatment, and at four-week intervals thereafter during the 24-week on-therapy and 12-week off-therapy phases of the study.

7.4.6 Key Inclusion/Exclusion Criteria -

1) Subjects must be healthy, Caucasian males or females, 45-70 years of age, exhibiting moderate or severe photodamaged facial skin.
2) Topical and systemic retinoids are to be discontinued at least six months prior to initiation of study.
3) All other topical medications to face are to be discontinued at least 24 hours prior to initiation of study.
4) All experimental drugs or devices are to be discontinued at least 30 days prior to initiation of study.
5) All experimental drugs or devices are to be discontinued at least 30 days prior to initiation of study.
6) Pregnant or nursing women will be excluded.
7) Subjects with a known hypersensitivity to any of the formulation components will also be excluded.
8) Subjects with a history of basal cell or squamous cell carcinoma on the face within the past five years or any history of malignant melanoma at any site are to be excluded.
9) Subjects are also not to exhibit any skin condition or have received any prior therapy that may confound the evaluation of drug safety or efficacy.
10) Subjects with a history of psychotic or affective disorders are to be excluded.
11) Subjects with excessive facial hair (e.g. beards) will also be excluded.
12) A negative urine pregnancy test, a normal menstrual flow within 30 days, and an effective method of contraception are required for entry of premenopausal females with an intact uterus.

7.4.7 Study Population - The study population, summarized below, consisted of healthy Caucasian subjects 44-74 years of age (mean age 57). Eighty-seven percent of subjects were female and 67% exhibited severe photodamage at baseline. Of the 120 subjects enrolled, 114 completed the study and 113 were valid for efficacy. All but one subject were valid for safety.

Summary of Study Population Data

	TEC-II 0.02%	Vehicle	Total
No. Enrolled	60	60	120
No. Completed	56	58	114
No. Discontinued:	4	2	6
Adverse Event	3	0	3
Personal Reasons	1	2	3
No. Valid for Safety	60	59	119
Mean Age (Range)[a]	56.7 (45-68)	56.6 (44-74)	56.6 (44-74)
% Female/%Male[a]	90/10	83/17	87/13
% Moderate/% Severe[a]	30/70	36/64	33/67

[a] Based on subjects valid for safety

7.4.8 Applicant's Assessment of Efficacy - TEC-II 0.02% consistently outperformed vehicle based on the various investigator evaluations. More subjects exhibited overall improvement in photodamage as well as improvement in specific clinical signs, most notably fine wrinkling, after TEC-II 0.02% therapy than after vehicle therapy. The relative differences between TEC-II 0.02% and vehicle were usually consistent from center to center, and became evident within 8 to 12 weeks of therapy depending on the parameter. In contrast to the investigator evaluations, improvement based on subject self-assessments was approximately the same in both groups. Except for one parameter, there were no statistically significant differences between the groups in skin topography based on the skin replica assessments.

The per protocol primary efficacy measures for this study were not utilized in the final assessment of NDA 19-963. Therefore, data from this study from the per protocol primary efficacy measures (global in nature) have no regulatory significance. Instead the efficacy determinations will focus on the component efficacy assessments. Of particular note regarding this study, there was little difference between TEC-II 0.02% and vehicle in the overall subject self-assessment, in which the majority of the subjects graded their skin as improved.

Of the six clinical signs evaluated by the investigators, fine wrinkling showed the most favorable response to TEC-II 0.02% therapy relative to vehicle. TEC-II 0.02%-treated subjects also showed significantly greater reductions from baseline to week 24 in yellowing (sallowness), laxity, and coarse wrinkling. The % of subjects improved for these four signs ranged from 62-85% in the TEC-II 0.02% group, compared with 47-55% in the vehicle group. The incremental benefit provided by TEC-II 0.02% was also reflected in the greater proportions of subjects in the TEC-II 0.02% group showing higher levels of improvement for fine wrinkling, coarse wrinkling, and yellowing. For example, 55% of subjects treated with TEC-II 0.02% showed a reduction in yellowing of ≥2 units compared with 26% of those who received vehicle. In addition, for fine wrinkling and coarse wrinkling, approximately 20-30% of TEC-II 0.02%-treated subjects compared with approximately 5% of vehicle-treated subjects, had a decrease in severity of ≥3 units. There was little difference between TEC-II 0.02% and vehicle in roughness and mottled hyperpigmentation, with high improvement rates in both treatment groups. The dynamic scoring used by the Applicant as described was not used in the Agency determination of efficacy due to inherent unreliability of such a method. Instead static scoring was used

with comparisons of Baseline to 24-weeks (LOCF) using a modified intent to treat population (excluding Baseline scores of 0 or 1).

Little or no difference was observed between the two groups in self-assessment features at week 24 (small wrinkles, pink/rosy tone, color ["brown spots"/blotchiness], texture, tightness, and pores). Likewise, there was little difference between TEC-II 0.02% and vehicle in the skin replica parameters.

The following tables summarize the results of clinical signs, individual subject self-assessments, and skin replicas:

INDIVIDUAL CLINICAL SIGNS AND SUBJECT SELF-ASSESSMENTS AT WEEK 24

	CLINICAL SIGNS					
	FW	MH	Roughness	CW	Yellowing	Laxity
TEC-II 0.02% (N=55)						
% Subjects Improved[a]	85	80	67	62	82	80
Mean Change	-1.7*	-1.9	-1.1	-1.2*	-1.7*	-1.7*
Vehicle (N=58)						
% Subjects Improved[a]	47	72	69	47	52	55
Mean Change	-0.6	-1.6	-1.1	-0.7	-0.8	-1.0

	SUBJECT SELF-ASSESSMENTS					
	SW	Tone	Color	Texture	Tightness	Pores
TEC-II 0.02% (N=55)						
% Subjects Improved	45	38	38	56	42	44
Mean Score[b]	2.5	2.4	2.4	2.6	2.5	2.5
Vehicle (N=58)						
% Subjects Improved	40	26	31	53	53	33
Mean Score[b]	2.4	2.3	2.4	2.6	2.6	2.4

[a] Improvement = reduction from baseline to week 24 of one or more units on 0-9 scale

[b] 1=Worse, 2=The Same, 3=Somewhat Improved, 4=Much Improved

NOTE: FW = Fine Wrinkling, MH = Mottled Hyperpigmentation, CW = Coarse Wrinkling, SW = Small Wrinkles

*Denotes statistically significant difference from vehicle based on an analysis of variance.

SKIN REPLICA RESULTS

	Crow's Feet Replicas					
	Ra-NS	Ra-EW	Rz-NS	Rz-EW	Shadows-NS	Shadows-EW
TEC-II 0.02%	-12.8	-5.6	-12.0	-6.5	-22.0	-20.3
Vehicle	-16.5	-1.5	-12.3	4.0	-26.0	-14.0

	Cheek Replicas					
	Ra-NS	Ra-EW	Rz-NS	Rz-EW	Shadows-NS	Shadows-EW
TEC-II 0.02%	-1.4	-1.6	-2.5	-1.9	-4.5	-8.7
Vehicle	-6.2	-5.3	-1.6	-2.6	-19.2	-14.7

NOTE: NS= North-South; EW=East-West

Values represent percent change from baseline mean to week 24 mean. Negative numbers indicate improvement. N=48 and 53 of the 55 subjects valid for efficacy in the TEC-II 0.02% group for the crow's feet and cheek analyses, respectively; N=57 and 58 of the 58 valid subjects in the vehicle group for the crow's feet and cheek analysis, respectively.

*Denotes statistically significant difference from vehicle based on an analysis of variance model applied to the mean change from baseline to week 24.

The skin replica results (an unvalidated surrogate marker) were not analyzed critically and did not have a regulatory contribution towards an efficacy determination for this NDA. See Reviewer's Assessment of J89-024 for further discussion.

The Applicant concluded in its protocol summary, "Investigators, but not subjects, were able to discern a difference between TEC-II 0.02% and vehicle in this study." This comment demonstrates a need for future consideration of the use of subject evaluation for cosmetic endpoints. While investigators may be able to discern a difference, the most important determination of efficacy may be that of the patients themselves. Drugs for cosmetic indications are more often than not given due to a patient complaint rather than a healthcare provider initiated diagnosis. Such a use pattern would support patient self-evaluation as an important primary endpoint for cosmetic indication trials. Use of such endpoints should be explored further.

The Applicant submitted a modified Statistical analysis of this pivotal trial's results using a Modified Intent to Treat Population [Excluding Baseline = 0 or 1] after discussion with the Agency (see Biostatistics review for description). These statistical analyses are presented in the following table:

Study J89-045 – Summary of statistical data submitted

Indication	Unadjusted p-value	Holm's adjusted p-value	Difference in treatment group mean change*	95% Confidence Interval*
Fine Wrinkling	0.001	0.006	1.0	1.3 to 0.6
Coarse Wrinkling	0.039	0.117	0.4	0.8 to 0
Tactile Roughness	0.733	0.733	-0.1	0.4 to –0.6
Laxity	0.010	0.040	0.7	1.3 to –0.2
Yellowing	0.001	0.006	0.8	1.3 to 0.3
Mottled Hyperpigmentation	0.220	0.440	0.3	0.9 to –0.2

*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.

Based on the data above, using the Holm's adjusted p-value to accommodate multiple endpoints, the Applicant demonstrates efficacy in fine wrinkling, laxity, and yellowing from Study J89-045.

7.4.9 Reviewer's Assessment of Clinical Efficacy –

In this trial, no one center appeared to drive the study. The Agency's calculated Holm's Adjusted p-values are listed in the following table:

Study J89-045 – Holm's Adjusted p-values (Agency calculated)	
Fine Wrinkling	.0001 *
Yellow-brown discoloration	.0029 *
Laxity	.0235 *
Coarse Wrinkling	.0821
Mott Hyperpig.	.2987
Tactile Roughness	.7153

The difference in treatment group mean change (as was provided by the Applicant – see above) may not provide enough information to make a clinical determination.

Tables, below, are included demonstrating an increased percentage of improved vs. baseline for the MITT population, Week 24, LOCF between treatment and vehicle:

Study J89-045: Difference from Baseline in Fine Wrinkling Score

Difference in Score from Baseline	MITT Week 24 LOCF Renova 0.02% Number of Subjects (% of Subjects)	MITT Week 24 LOCF Vehicle Number of Subjects (% of Subjects)
≤ -3 (at least moderate improvement)	16 (27 %)	2 (3 %)
-2 (mild improvement)	10 (17 %)	10 (17 %)
-1 (minimal improvement)	24 (40 %)	15 (25 %)
0 (no change)	10 (17 %)	28 (47 %)
≥ +1 (worsened)	0 (0%)	5 (8 %)

Study J89-045: Difference from Baseline in Yellowing Score

Difference in Score from Baseline	MITT Week 24 LOCF Renova 0.02% Number of Subjects (% of Subjects)	MITT Week 24 LOCF Vehicle Number of Subjects (% of Subjects)
≤ -3 (at least moderate improvement)	17 (28 %)	7 (12 %)
-2 (mild improvement)	14 (23 %)	8 (13 %)
-1 (minimal improvement)	17 (28 %)	15 (25 %)
0 (no change)	10 (17 %)	25 (42 %)
≥ +1 (worsened)	2 (3%)	5 (8 %)

Study J89-045: Difference from Baseline in Laxity Score

Difference in Score from Baseline	MITT Week 24 LOCF Renova 0.02% Number of Subjects (% of Subjects)	MITT Week 24 LOCF Vehicle Number of Subjects (% of Subjects)
≤ -3 (at least moderate improvement)	14 (23 %)	9 (15 %)
-2 (mild improvement)	15 (25 %)	12 (20 %)
-1 (minimal improvement)	19 (32 %)	11 (18 %)
0 (no change)	11 (18 %)	25 (42 %)
≥ +1 (worsened)	1 (2%)	3 (5 %)

7.4.10 Safety - Based on cutaneous irritation ratings and adverse event reports, TEC-II 0.02% demonstrated a favorable 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 weeks of therapy and declined sharply to approximately baseline levels by week 8. While most TEC-II 0.02%-treated subjects experienced at least mild skin irritation based on these elicited signs and symptoms, only 38% of TEC-II 0.02%-treated subjects reported an adverse event at 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 17% of vehicle-treated subjects (p=0.013). These adverse events were of mostly mild or moderate severity. There was good compliance with the once-daily treatment regimen, as 87% of subjects completed at least 90% of TEC-II 0.02% applications and 73% 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 4 (7%) subjects. See Overview of

Safety for a detailed analysis of adverse events related to this study and other studies submitted.

Three subjects, all in the TEC-II 0.02% group, discontinued the study due to an adverse experience. Two of these subjects discontinued due to an adverse skin reaction, stopping therapy after approximately 3-4 months due to moderate skin reactions considered by the investigators to be probably related to the study drug. The third subject discontinued the study after being diagnosed with bronchial carcinoma considered by the investigator to be unrelated to the study drug. No serious adverse events associated with the use of the study drug were reported.

Adverse events not associated with the treatment site were evenly distributed between the TEC-II 0.02% and vehicle groups. The most frequently reported adverse event not associated with the treatment site was upper respiratory infection, with a subject incidence of 10% and 7% in the TEC-II 0.02% and vehicle groups, respectively, and viral infection, reported by 8% and 14% of subjects in the TEC-II 0.02% and vehicle groups, respectively.

7.4.11 Post-Therapy Phase – Upon completion of the Therapy portion of this study, the subjects were continued on a post-therapy evaluation phase. The subjects were re-examined at week 12. Ten percent of the subjects on RENOVA 0.02% were lost to follow-up in the post-therapy phase of this study (55 completed the first part of the study and only 50 were included for assessment in the post-therapy phase).

Investigator Evaluations of Clinical Signs of Photodamaged Skin at Week 12 Post-therapy
(Subjects valid for Efficacy in Protocol J89-045 Post-therapy)

	Vehicle (N=57)	TEC-II 0.02% (N=50)
Roughness		
% Subjects Improved	9	16
% Subjects No Change	60	52
% Subjects Worse	32	32
Fine Wrinkling		
% Subjects Improved	18	8
% Subjects No Change	67	60
% Subjects Worse	16	32
Coarse Wrinkling		
% Subjects Improved	7	8
% Subjects No Change	75	64
% Subjects Worse	18	28
Mottled Hyperpigmentation		
% Subjects Improved	9	16
% Subjects No Change	67	48
% Subjects Worse	25	36
Yellowing		
% Subjects Improved	9	6*
% Subjects No Change	68	63*
% Subjects Worse	23	31*
Laxity		
% Subjects Improved	11	8
% Subjects No Change	70	62
% Subjects Worse	19	30

*N=49

The data from this table indicates that there is a trend towards worsening after discontinuation of therapy (at week 24). A greater percentage of subjects discontinued on TEC-II 0.02% show signs of worsening fine and coarse wrinkling, yellowing, and laxity than do subjects on vehicle when compared to week 24. In conclusion, discontinuation of treatment may result in worsening of the condition treated. It is stressed that the word "may" should be incorporated in any such statement as dynamic scoring, as was used in this study, is not as relevant for a regulatory analysis of data submitted for the indications treated.

7.5 Supportive Study – K90-011

7.5.1 Title - A Double-Blind, Single-Center, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Tretinoin Emollient Cream (TEC-II) 0.02% in the Treatment of Photodamaged Skin

7.5.2 Dates - The study was Initiated on July 6, 1990 and Ended on May 30, 1991 with Follow-Up on July 22, 1991.

7.5.3 Investigator - Gerald Weinstein, M.D.
University of California - Irvine
California College of Medicine, Irvine, CA

7.5.4 Objective - The primary objective of this study was to characterize the histopathology of moderate to severe photodamaged skin and determine the histologic effects of TEC-II 0.02% in this group of subjects.

7.5.5 Study Design and Protocol Synopsis - This was a randomized, single-center, double-blind study consisting of two parallel treatment groups (TEC-II 0.02% and a vehicle control). Treatment was once nightly for 24 weeks using a general dosing guideline of 0.25 g per application (using a metered dosing system – see Overview of Safety for discussion). Subjects in both treatment groups applied 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 during the 24 week on-therapy and 12-week off-therapy phases of the study. Facial punch biopsies (size not specified) were obtained at baseline and after 24 weeks of therapy (placed in [redacted]) and were processed and evaluated by a central dermatopathology laboratory ([redacted]) An additional biopsy was taken at the week 12 post-therapy visit. This report will only present data from the 24-week on-therapy phase of the study.

7.5.6 Inclusion Criteria -

1) Subjects are to be male or female, Caucasian, 45-70 years of age, in good general health.
2) Subjects are to exhibit moderate or severe photodamaged facial skin (overall severity grade of 6-9 at baseline) based on clinical evaluation of tactile roughness, fine and coarse wrinkling, mottled hyperpigmentation, yellowing (sallowness) and laxity (looseness).
3) Subjects must discontinue topical and systemic retinoids (other than normal recommended daily allowance of vitamin A) at least 6 months prior to initiation of study therapy. All other topical medications to the face must be discontinued at least 24 hours prior to initiation of study therapy.

4) Subjects should not have applied any emollients to the face for at least 24 hours prior to pre-study evaluations, or cosmetics on the day(s) of pre-study evaluations.
5) If female, the subject must:
    a) be post-menopausal for at least one year, or
    b) have had a hysterectomy, or
    c) have had a tubal ligation, or
    d) agree to use an effective method of contraception (e.g., oral contraception, condoms and spermacide)
6) If female and pre-menopausal with an intact uterus, the subject must have :
    a) had a normal menstrual flow within 30 days prior to initiation of study therapy, and
    b) a negative urine pregnancy test immediately prior to initiation of study therapy.
7) Subjects (or their authorized representative) must read and sign the informed consent form after the nature of the study has been fully explained and the Confidential Follow-Up Form has been completed.

7.5.7 Exclusion Criteria -

1) Subjects are not to be pregnant or nursing.
2) Subjects are not to have a history of basal cell or squamous cell carcinoma on the face within the past five years or any history of malignant melanoma at any site.
3) Subjects are not to have received any prior therapy (e.g. Zyderm®, silicone, blepharoplasty, facelift, dermabrasion) that may confound the evaluation of drug safety or efficacy.
4) Subjects are not to exhibit any skin condition (e.g., multiple clinically visible facial actinic keratoses, rosacea, psoriasis) that may require concurrent therapy or may confound the evaluation of drug safety or efficacy.
5) Subjects are not to have a history of psychotic or affective disorders, including bipolar disorder, major depression, and schizophrenia. NOTE: Antidepressants or antipsychotic drugs are not to be used prior to or during the study.
6) Subjects are not to have a history of hypersensitivity to any of the formulation components.
7) Subjects are not to have received any experimental drug or used any experimental device 30 days prior to initiation of study therapy.
8) Subjects are not to have excessive facial hair (e.g., beards, sideburns, moustache).

7.5.8 Study Population - The study population, summarized in Table 1, consisted of healthy Caucasian subjects 46-71 years of age (mean age 60). Eighty-nine percent of subjects were female and 64% exhibited severe photodamage at baseline. Of the 80 subjects enrolled, 71 completed the study and 70 were valid for efficacy. All of the subjects were valid for safety.

	TEC-II 0.02%	Vehicle	Total
No. Enrolled	40	40	80
No. Completed	36	35	71
No. Discontinued:	4	5	9
Adverse Event	1	1	2
Personal	1	2	3
Lost to Follow-Up	1	2	3
Protocol Violation	1	0	1
No. Valid for Safety	40	40	80
Mean Age (Range)	60.0 (46-71)	60.1 (49-70)	60.1 (46-71)
% Female/% Male	85/15	93/8	89/11
% Moderate/% Severe	28/73	45/55	36/64

7.5.9 Histology - Subjects treated for 24 weeks with TEC-II 0.02% showed a significantly greater increase in granular cell layer thickness and stratum corneum compaction compared with vehicle-treated subjects. Subjects in the TEC-II 0.02% group also showed a significantly greater increase in mucin following 24 weeks of therapy due primarily to changes in four TEC-II 0.02%-treated subjects. Such increases in mucin content, granular cell thickness, and stratum corneum compaction may be seen with chronic irritation. No significant differences between TEC-II 0.02% and vehicle were found for any of the other histologic parameters.

PERCENT CHANGE FROM BASELINE TO WEEK 24	TEC-II 0.02% (N=35)[a]	Vehicle (N=33)[b]	P-value[c]
Area of Epidermis [Epidermal Thickness]	39%	33%	0.345
Granular Layer Thickness	49%	11%	<0.001
Melanin Content	-26%	-16%	0.348
Area of Papillary Dermis	19%	22%	0.423
Elastic Tissue Content	7%	5%	0.820

PERCENT OF SUBJECTS CATEGORIZED BY CHANGE FROM BASELINE TO WEEK 24	TEC-II 0.02% (N=35)	Vehicle (N=33)[b]	P-value[c]
Perivascular Inflammation			
Increased	14%	21%	0.108
No Change	69%	76%	
Decreased	17%	3%	
Keratinocytic Atypia			
Increased	3%	9%	0.970
No Change	97%	85%	
Decreased	0%	6%	
Melanocytic Atypia			
Increased	3%	0%	0.727
No Change	86%	94%	
Decreased	11%	6%	
Mucin			
Absent-->Present	11%	0%	0.036
No Change	86%	91%	
Present-->Absent	3%	9%	
Stratum Corneum Morphology			
Increase in Compaction	40	24	0.032
Woven-->Compact	14	0	
Both-->Compact	6	9	
Woven-->Both	20	15	
No Change	40	36	
Decrease in Compaction	20	39	
Compact-->Both	11	12	
Both-->Woven	6	15	
Compact-->Woven	3	12	

[a] N=34 for Melanin Content and Area of Papillary Dermis

[b] N=32 for Area of Papillary Dermis and Mucin and N=31 for Melanin Content

[c] Statistical test results are based on a two-sided Wilcoxon Rank Sum Test with normal approximation of week 24 value minus baseline value.