CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-184/002

Medical Review(s)

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MEDICAL OFFICER'S REVIEW OF SUPPLEMENT TO NDA 21-184
S-002

DATE: March 25, 2002

SPONSOR: Allergan Pharmaceuticals
Irvine, CA

DRUG: Tazorac (tazarotene) cream 0.1%

PHARMACOLOGIC CLASS: Retinoid

INDICATION: Photodamaged skin

Proposed labeling indication:

[redacted]

DOSAGE AND ADMINISTRATION: Applications once daily.

RELATED APPLICATIONS: Tazarotene formulations were studied under IND [redacted] Approved applications for Tazorac formulations are as follows.

Application	Formulation	Indication
NDA 21-184	Tazorac cream 0.1% and 0.05%	Psoriasis
NDA 20,600	Tazorac gel 0.1% and 0.05%	Psoriasis
NDA 20,600	Tazorac gel 0.1%	Acne
NDA 21-184	Tazorac cream 0.1%	Acne

Other applications approved for the signs of photodamage of the skin are as follows.

Application	Product	Active ingredient
NDA 19-963	Renova 0.05% (Johnson & Johnson)	tretinoin
NDA 21-108	Renova 0.02% (Johnson & Johnson)	tretinoin

PHARMACOLOGY AND CONTROLS REVIEWS: These are currently pending.

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Medical Officer's review

Study results

Executive summary

1) Recommendations on approvability: The NDA is not felt to be approvable for the proposed indication

2) Summary of clinical findings.

A. Overview of clinical trials.

Tazorac (tazarotene) cream 0.1% is a retinoid formulation which is administered topically, and has previously been approved for the treatment of psoriasis and acne. There are two pivotal clinical studies on the safety and effectiveness of Tazorac for the clinical signs of premature aging of the skin due to overexposure to the sun, namely, Studies 33C and 34C. Both were double blind, multicenter comparisons of Tazorac with its vehicle, with applications once daily for 24 weeks. There were 563 patients enrolled in Study 33C and 568 patients enrolled in Study 34C. The efficacy was assessed at each return visit by a grading of each of the clinical signs on a five point scale. A comparison was made of the proportion of patients who had a baseline score of at least 2 (mild), who had achieved a score of 0 (none) or 1 (minimal) at endpoint.

B. Efficacy.

As was stated by the Division at the End of Phase 2 meeting, the clinical signs of photodamage should be the primary endpoints, and these are acceptable as individual indications if the product is shown to be effective for the particular signs.

Nine clinical signs were evaluated in this study, Of the nine signs, fine wrinkling and mottled hyperpigmentation were considered by the sponsor to be primary efficacy variables; lentigines and elastosis were considered secondary variables, and irregular depigmentation, tactile roughness, coarse wrinkling, telangiectasia, and pore size were 'other' variables.

The protocol for Study 33C was reviewed by the Agency subsequent to the End of Phase 2 meeting. In the comments, which were conveyed to the sponsor, the Agency stated that the primary efficacy parameters (i.e., fine wrinkling and mottled hyperpigmentation) are acceptable, but that the inter- and intra- observer consistency should be addressed. It was also stated that the validation for the measurement of the secondary and 'other' parameters should be presented. Study 37C was submitted to address inter- and intra-rater reliability. This study is supportive of the primary efficacy

variables, but does not provide clinical validation of the scoring scales for the secondary and 'other' endpoints.'

The additional clinical signs, designated as secondary and other variables by the sponsor, have not been accompanied by demonstration of clinical validity or adequate scoring scales for approval as novel claims. In particular, pore size and elastosis are not considered to be accompanied by adequate clinical validation. The sponsor has not demonstrated the method by which pore size was assessed during the clinical trial.

Therefore, the evaluation of the results by this reviewer is restricted to the changes in fine wrinkling and mottled hyperpigmentation found with treatment. It was felt that the most appropriate method of analysis is a comparison of the proportion of subjects with an improvement of at least two grades from baseline.

Both of the pivotal studies demonstrated the effectiveness of Tazorac cream 0.1% for the clinical signs fine wrinkling and mottled hyperpigmentation. The magnitude of effect and the p values are presented in the following tables.

Subjects with clinical improvement of two grades or more Study 33C			
	Tazarotene n=283	Vehicle n=280	p value
Fine wrinkling	5.3%	1.4%	0.011
Mottled hyperpigmentation	17.3%	0.7%	< 0.001

Subjects with clinical improvement of two grades or more Study 34C			
	Tazarotene n=283	Vehicle n=280	p value
Fine wrinkling	13.4%	4.9%	< 0.001
Mottled hyperpigmentation	28.2%	9.5%	< 0.001

C. Safety

The adverse events of the skin and appendages with Tazorac cream were primarily dryness, peeling, burning, and erythema of the treated areas. There were no serious adverse events.

The double blind period of Study 33C was followed by an open label treatment period, with applications of Tazorac cream once daily for

an additional 28 weeks. The adverse events during the open label phase were similar to those in the double blind period, but were somewhat lower in intensity and frequency.

Plasma levels of tazarotenic acid, the major metabolite of tazarotene, were determined throughout the 52 week treatment period in Study 33C. The plasma levels were similar during the entire study, indicating that no drug accumulation occurred.

Financial disclosure

The sponsor states as follows in regard to the financial interests and arrangements of the clinical investigators.

'The following is the list of investigators who require certifying the absence of financial interests or arrangements. .... The sponsor has not entered into any financial arrangement with these investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).Each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose such interests. Doctors ___ were the recipients of significant payments of other sorts as defined in 21 CFR 54.2(f) and described in the attached Certification/Disclosure Forms.'

All of the five investigators designated above conducted studies under the Phase 3 protocols 33C and 34C. Their responses to the financial disclosure questions were as follows.

1) Dr. ___ - has received payments from Allergan of more than ___ ,stated to be for through ___

2) Dr. ___ - has received payments from Allergan of more than described as

3) Dr. ___ - has received payments of ___ for

4) Dr. has received payments of more than ___ from Allergan for

5) Dr. ___ responded to the question as to whether has received payments of more than ___ from Allergan

Financial disclosure forms were not submitted for three investigators who participated in Study 33C; these were The remainder of the

investigators in Studies 33C and 34C did not have significant financial interests.

End of Phase 2 meeting

An end of phase 2 meeting was held on August 20, 1999. The briefing package submitted to IND [redacted] on 7/19/99 described the proposed studies 33C and 34C. Study 33C was to be a double blind, randomized, parallel group comparison of tazarotene cream 0.1% with its vehicle in the treatment of photodamaged facial skin, with applications once daily for 24 weeks. This was to be followed by an open label phase of an additional 24 weeks. The primary efficacy measurement was to be the overall assessment of photodamage, rated on a six point severity scale. Secondary measurements were to be fine wrinkling, mottled hyperpigmentation, lentigines, irregular depigmentation, tactile roughness, coarse wrinkling, telangiectasia, elastosis, and actinic keratoses, graded on a six point severity scale, and pore size, graded on a scale of size. Global response to treatment and a patient assessment were also to be secondary measurements. The primary efficacy variable was to be the percentage of patients with at least a one grade improvement from baseline in the Overall Integrated Assessment of photodamage. The design, measurements, and the primary efficacy variable were the same in Study 34C as in Study 33C, with the exception that it did not include an open label phase.

The minutes of the clinical and biostatistical portion of the meeting (as paraphrased or edited in part) was as follows.

a) Clinical

1. Sponsor's regulatory question: The NDA submission will be based on 24 weeks of treatment from two phase 3 studies; the final results from the one year study for safety will be determined later, upon availability. Is this acceptable to the FDA?

   Agency response: No information on a separate one year study is available. Details of this one year study should be given by the sponsor. The submission may be acceptable if the results are submitted by the 120 day Safety Update, but not later.

2. Sponsor's clinical question 1: Allergan believes that their proposed Phase 3 clinical plan is adequate to support the indication [redacted]' Does the FDA concur?

   Agency response: As stated before, the treatment of photodamage has to be determined on the basis of reversal of the long term process, especially for such components as carcinogenesis. A trial that evaluates the manifestations arising from photodamage is essentially looking at surrogates but may not necessarily lead to a claim of treatment of photodamage. In addition, it may be difficult

to dissect some of the effects of UV radiation from those of chronological aging.

3. The Agency's comments on the protocols submitted are as follows.

Protocol # 190168-033C

a. Comments on overall study design.

- Are the randomization, number of centers, and blinding acceptable. Yes.

- How many arms in the trial, what are the comparisons being made, are they appropriate? Total of 400 patients, with tazarotene 0.1% and vehicle creams for 24 weeks, then tazarotene 0.1% open label for an additional 28 weeks for all. Appropriate.

b. Comments on Inclusion/Exclusion criteria.

- Do these reflect the target population? Yes. The sponsor is encouraged to have proper representation of all demographic groups in their proposed studies. Exclusion of Fitzpatrick Skin Types V and VI will not be an NDA fileability issue.

- Are there unjustified exclusions that may affect labeling? No.

- Are the washout periods appropriate? Yes.

- Are the clinical criteria appropriate for the proposed indication? See the above comment on 'photodamage'. The clinical signs can be acceptable as individual indications if the drug is shown to be effective for those particular signs.

c. Comments on endpoints.

- What is the appropriate primary efficacy variable(s)? Is the 'success' category clearly stated?

  No known appropriate primary efficacy variable for 'photodamage' is available at this point. The primary endpoint being used, 'overall integrated assessment of photodamage', has been used in the Phase 3 trial. Evidence of validation has not been presented. The success category is clearly defined (one grade improvement in the OIA), but validity of this endpoint is not determined, especially with the effects of the covariate of age. Since 'photodamage' will not be an acceptable indication, this parameter should not be the primary endpoint. Clinical signs of photodamage should be the primary endpoints. The sponsor should determine from the Phase 2 trial which signs they intend to select as primary; otherwise severe penalty may be incurred for multiplicity.

- What is the appropriate secondary efficacy variable? See the answer to the last question.

- Are the scoring scales appropriate? Yes, however, it is recommended that the sponsor reconsider having more narrow scales and provide consistency across centers by proper investigator training. Reproducibility of scoring by the same investigator should also be demonstrated.

- Is the point of cure very clearly identified in the protocol? Yes, week 24.

d. Comments on safety.

- What are the criteria being used to evaluate safety? Adverse event reporting, pregnancy tests.

- Are these criteria adequate? Yes, clinical laboratory tests are not needed, as such safety data have been amply collected for the same formulation in psoriasis studies that involve usage over a much larger body surface area.

Protocol 190168-034C

This is almost identical to protocol 190168-033C, but without the open label 28 week extension, biopsy, skin replica and therapeutic drug monitoring. Thus, the comments are the same as for 190168-033C.

3. Sponsor's clinical question 2: Allergan believes that the clinical pharmacokinetics plan is adequate to make a determination of pregnancy Category C, should systemic absorption prove to be low. Does FDA concur?

   Agency response: Tazorac (tazarotene topical gel) 0.05% and 0.1%, currently has a Pregnancy Category X, which states that the drug is contraindicated in pregnancy. This involves a risk-benefit analysis. The sponsor needs to explain why a teratogen can be justified in the treatment of a cosmetic indication in pregnancy in order to not incur Pregnancy Category X.

4. Sponsor's clinical question 3: How would the absence of positive histological changes affect the labeling?

   Agency response: The presence of histological changes per se will not result in a claim unless supported by pertinent clinical data. Absence of benefit shown histologically suggests that the treatment is not acting on the process of photodamage. Histologic findings may be reported in the mechanism of action under the CLINICAL PHARMACOLOGY section of the package insert.

Biostatistics

The Agency's comments were as follows.

1) Specific signs would be more appropriate as separate indications. These could be dichotomized, by taking the proportion of subjects who appear at the end of the study to have minimal involvement in that response, or, by taking the proportion with minimal or mild involvement. Alternatively, the sponsor could consider the proportion who achieve at least a one or two step improvement from baseline. Perhaps even the original 6 step response could be used. In any event, it would seem that some study of both intrarater and interrater reliability would be useful to help justify interpretation of these endpoints.

2) Appropriate attention to any multiple comparisons issues will need to be addressed. Also, the method of analysis should be specified prior to initiation of the study.

3) The sponsor proposes to define the intent-to-treat group of patients as all randomized patients who receive at least one application of study medication, with at least one followup visit. The preferred DDDDP definition is all patients dispensed treatment.

4) The sponsor's proposed methods of analysis seem quite appropriate. This reviewer was able to essentially reproduce the sponsor's power calculations; however, they need to be addressed for each separate indication.

Review of Phase 3 protocols

Subsequent to the End of Phase 2 meeting, the sponsor submitted two Phase 3 protocols for our review, Protocols 190168-033C and 190168-034C. These were submitted on 9/21/99, and although the sponsor had no agreement on the studies at the End of Phase 2 meeting, the studies were initiated shortly thereafter, on 9/30/99 and 9/29/99.

The following comments on these protocols were conveyed by the Agency to the sponsor.

1. It is reiterated to the Sponsor that treatment of photodamage has to be determined on the basis of reversal of the long term process, especially for such components like carcinogenesis. A trial that evaluates the manifestations arising from photodamage is essentially looking at surrogates but may not necessarily lead to a claim of treatment of photodamage. In addition, it may be difficult to dissect some of the effects of UV radiation vs those of chronological aging.

2. As these are multi-center studies, the Sponsor should present the qualifications of all investigators for review.

3. Sample size calculation is based on data from the Phase 2 study that uses 6 point scales for the primary parameters. As the grading in Phase 3 stdies uses 5 point scales, validity of this adjustment should be addressed.

4. The Sponsor has been encouraged at the End of Phase 2 meeting to have proper representation of all demographic groups in their proposed studies. Exclusion of Fitzpatrick Skin Types V and VI will not be a NDA filability issue.

5. The primary parameters are acceptable. These are regarded as individual indications and not as primary endpoints for the indication of 'photodamage'.

6. The intra- and inter-observer consistency in the evaluation of the primary parameters, mottled hyperpigmentation and fine wrinkling, should be addressed. In this submission, the photonumeric guide for the investigators on these parameters or overall integrated assessment of photodamage has not been presented. The validation for the measurement of the secondary and 'other' parameters such as lentigines, elastosis, coarse wrinkling, irregular depigmentation, tactile roughness, telangiectasia, pore size and actinic keratosis should be presented. The patient's overall self-assessment of photodamage is not of regulatory value, as this parameter has no clear definition applicable to all patients.

7. Avoidance of sun exposure (e.g., sunlight, tanning booths) and extremes in weather (e.g., wind or cold), wearing of protective clothing when exposed to sunlight (e.g., hat, sun visor), and use of sunscreen on the face (SPF of >15) at least every morning is part of the treatment regime in this study. The Sponsor is advised that these ancillary measures may ultimately constitute an important part of the treatment package in the labeled use of this medication.

8. The utility of the UV photography and the degree of repeated UV exposure arising from it (spectrum and dosage) should be addressed.

9. The Sponsor is reminded that at the End of Phase 2 meeting, they have been advised that absence of benefit shown histologically would suggest that the treatment is not acting on the process of photodamage. The proposed Phase 3 studies have no histologic component. This may deprive the clinical data of valuable support.

10. The Sponsor proposes to define the intent-to-treat group of patients as all randomized patients who receive at least one application of study medication, with at least one follow-up visit. The preferred DDDDP definition is all patients dispensed treatment.

<u>Pre-NDA meeting</u>

A pre-NDA meeting was held on February 21, 2001. The minutes of the clinical and biostatistical portion of the meeting (as paraphrased or edited in part) was as follows.

Clinical

1. Allergan believes that under the Guidance document "Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees Under the Prescription Drug User Fee Act of 1992' a Clinical Efficacy Supplement may be submitted for the use of tazarotene cream 0.1% for the treatment of

   NDA 21-184. This is further supported by the precedent of the Clinical Efficacy Supplement for the treatment of acne vulgaris submitted to this NDA on December 8, 2000.

   Agency response: Acceptable.

2. It is Allergan's intention that the labeling and tradename of tazarotene cream 0.1% for the treatment of photodamage will be separate and distinct from the labeling and trade name Tazaroc for tazarotene cream 0.1% that will be marketed for psoriasis and acne. The FDA has previously and recently approved such a supplement for NDA 18-936 for fluoxetine hydrochloride (Prozac/Serafem). Does the FDA concur with the concept of having a separate tazarotene cream product, with a name other than Tazorac, which is appropriately labeled only for

   Agency response: The issue of tradenames has to be discussed with OPDRA. The case of fluoxetine is not comparable, as Prozac and Serafem are different products containing different inactive ingredients. Justification for having two labels should be based on safety grounds with compelling public health arguments.

3. Allergan is planning on submitting a fully electronic archival copy of the application in accordance with 21 CFR Part 11, and would like to submit all review copies of the Clinical Efficacy Supplement/NDA electronically as well. Does the FDA concur?

   Agency response: Concur for the clinical portion of the electronic submission. The sponsor states that they will provide the CDs for back up.

Clinical Pharmacokinetics/Clinical safety and efficacy/Clinical Pharmacology

1. This was answered earlier by the Biopharm reviewer.

2. Adequate for filing. The indications will be a review issue. It

should be noted that the primary hypothesis in the trials was with fine wrinkling and mottled hyperpigmentation. Secondary variables were lentigines and elastoses. Irregular depigmentation and pore size were 'other' measures.

3. The sponsor previously received comment on the histological study. In the protocol to that study, the term 'histological safety profile' was not defined, and the sponsor did not give a list of preplanned parameters to be evaluated. As such, this study might not necessarily have regulatory value. The parameters for histologic evaluation should have been delineated a priori, and the hypothesis clearly defined. The sponsor is advised to provide documentation of their preplanned analytical methodology of this study, and reference to the pertinent IND submissions.

4. The information recommended by the ICH EIA guideline should be submitted at the time of filing of the NDA. The material submitted at the time of filing would form the basis of the action on the application. Depending on the time of closure of the reviews, late information may or may not be included in the labeling.

5. Biostatistics question #2: Concerning the analysis plans for the Integrated Summary of Safety (ISS) and the Integrated Summary of Efficacy (ISE), are the age categories for subgroup analyses acceptable to the Agency (i.e., patients > 40 years, patients 40 to 65 years, patients > 65 years)?

   Agency response: The Medical Reviewer has no objections to the subdivisions for age analysis.

Biostatistics

1. Significant interactions were seen for some of the primary and secondary variables in both studies. If at least one center favored the vehicle at study endpoint, then sensitivity analyses were performed, which excluded one center in each direction. If no centers favored the vehicle, then the interaction was considered quantitative in nature and was not examined further. Is this acceptable to the FDA?

   Agency response: The sponsor's plan to conduct a sensitivity analysis when at least one center favors the vehicle seems reasonable. In addition, a sensitivity analysis should be performed if some centers show extremely favorable results for the active test treatment. When deleting centers to check the robustness of the results, keep in mind that the sample sizes of the deleted centers can influence the conclusions.

2. Are the age categories acceptable to the Agency? (This was addressed by the medical reviewer.)

3. Does the Agency have any other questions or comments concerning the ISS and/or ISE analysis plans?

Agency response:

a. In addition to the analyses submitted by the sponsor where treatment success is defined as improvement from baseline by at least one grade, the sponsor should submit analyses based on the following definitions of treatment success:

1) A severity score of 0 (none) at study endpoint.
2) A severity score of 0 or 1 at study endpoint.
3) Improvement from baseline by at least two grades.

b. The submission should include the analysis results of Study 037C, which would be helpful for checking inter- and intra-rater variability.

c. The submission should include the planned random treatment allocation list, and a list of the subjects enrolled in the trial and time of enrollment.

d. Efficacy, safety, and demographic data should be provided as SAS data sets export files.

e. The Integrated Summary of Efficacy Biostatistics Analysis Plan refers to 'treatment-by-study' interaction. This reviewer assumes that the author intended to say 'treatment-by-investigator', which is the phrase used in the study synopses of Studies 033C and 034C.

Summary of clinical studies

The clinical studies which were performed on topical tazarotene formulations in support of this supplement were as follows.

Study #	Study type	Study design	Treatment	# pts
190168-013	Pilot	Single center, paired comparison	Tazarotene gel 0.1% and vehicle, to forearms for 12 weeks	10
190168-036C	Histologic safety	Double blind, multicenter	Tazarotene cream 0.1% or vehicle, QD to face x 24 weeks	50
190168-038C	Pharmaco-kinetic	Single center, open label	Tazarotene cream 0.1% to 15% BSA over 33 days	24

190168-037C	Reliability of photonumeric guidelines	Single center	No treatment	40
190168-025C	Dose ranging	Single blind, multicenter, randomized	Tararotene creams 0.01%, 0.025%, 0.05%, 0.1% Tretinoin cream 0.05% Vehicle QD to face x 24 weeks	349
190168-033C	Phase 3	Double blind, multicenter, randomized	Tazarotene cream 0.1% or vehicle, QD to face x 24 weeks, followed by open label period	563
190168-034C	Phase 3	Double blind, multicenter, randomized	Tazarotene cream 0.1% or vehicle, QD to face x 24 weeks	568

The study dates were as follows.

Study number	Study initiation	Study completion
13C	9/8/97	12/12/97
25C	7/10/98	4/8/99
33C	9/30/99	8/31/00
34C	9/29/99	9/21/00
36C	1/24/00	9/11/00
37C	9/9/00	9/9/00

Study 190168-036C: Histological safety

This was a double blind, multicenter, randomized, vehicle controlled, parallel group study of the safety and histological effects of tazarotene cream 0.1% in patients with photodamaged facial skin. Applications of tazarotene cream 0.1% or its vehicle were made to the face once daily for up to six months. Histological evaluations were made of punch biopsies taken in the 'crow's feet' area of the face at baseline and at 24 weeks. The biopsies were evaluated primarily for keratinocytic atypia and melanocytic atypia.

The results were that tazarotene cream 0.1% did not appear to be associated with the formation or worsening of keratinocytic or melanocytic atypia. There was a trend towards a positive effect by tazarotene on the distribution and the distribution severity (a derived variable based on distribution and severity) of keratinocytic

atypia as compared to the vehicle. There was also a trend towards a positive effect by tazarotene on the distribution of melanocytic atypia as compared with the vehicle, and there was a significant positive effect on the distribution/severity of melanocytic atypia as compared with the vehicle. There were significantly greater increases in epidermal thickness and in the number of granular layers with tazarotene than with the vehicle. Tazarotene did not appear to be associated with changes in other epidermal variables such as the appearance of the stratum corneum, melanocytic number, melanin prominence and distribution, mucin, or inflammation, nor did it appear to be associated with changes in dermal variables such as presence of abnormal elastin, inflammation, papillary edema, melanin distribution, and mucin. Tazarotene was associated with significantly greater proportions of patients who showed an increase from baseline in epidermal edema distribution.

The only adverse events that were significantly higher in the tazarotene group than in the vehicle group were desquamation and erythema.

Study 190168-038C: Pharmacokinetics

This study was designed to characterize the pharmacokinetics of tazarotene cream 0.1% under conditions of standard use and exaggerated use in patients with photodamaged skin. Applications were made daily for 27 days to the face only in 8 patients, and to 15% of the body surface area, including the face, in 16 patients. Pre-dose and post-dose blood samples were collected on days 0, 8, 15, 22, and 29 for determination of the primary metabolite, tazarotenic acid.

Results showed that the highest mean plasma concentrations of tazarotenic acid after application to the face only were 0.236 +/- 0.255 ng/ml, and after applications to 15% BSA were 1.75 +/- 0.53 ng/ml.

Adverse events of the skin and appendages were reported by all patients. The most common events were erythema, rash, desquamation, pruritus, dry skin, acne, excoriated skin, and skin irritation. No serious adverse events occurred and no patients discontinued due to adverse events.

Study 190168-037C: Rater reliability

The objective of this study was to evaluate the inter-rater and intra-rater reliability of Allergan's Photonumeric Guidelines for fine wrinkling and mottled hyperpigmentation in subjects with facial photodamage. This was a single center study which evaluated the ratings of the same subjects by different raters (inter-rater) and the ratings of the same subjects by the same raters at two different time points (intra-rater). The medical monitor, a dermatologist, selected at least 2 subjects to each represent the following severity categories for fine wrinkling and mottled hyperpigmentation: minimal,

mild, moderate, and severe.

All raters were dermatologists, and were provided with the same training on the usage of the Photonumeric Guidelines and with booklets on the details of the scales and assessments for fine wrinkling and mottled hyperpigmentation. The subjects selected were evaluated independently by each of 10 raters twice on the same day. The order of presentation of the subjects to the raters was randomized separately for each round of evaluation, and the two evaluations were at least one hour apart. The subjects were also rated for the severity of lentigines, elastosis, irregular depigmentation, tactile roughness, coarse wrinkling, and telangiectasia, without the use of photonumeric guidelines. Pore size was also evaluated.

Severity was rated on a scale of 0=none, 1=minimal, 2=mild, 3=moderate, and 4=severe.

The sponsor's assessment was that the statistical analyses of the results showed a high degree of inter-rater agreement and a very good degree of intra-rater agreement for fine wrinkling and mottled hyperpigmentation.

Study 190168-025C: Dose ranging

The investigators for this study were as follows.

Sewon Kang, M.D. University of Michigan Medical Center Ann Arbor, Michigan	Jean-Paul Ortonne, M.D. Nice, France
James Leyden, M.D. Broomall, PA	Tania Phillips, M.D. Boston University Medical Center Boston, MA
Nicholas Lowe, M.D. Santa Monica, CA	Gerald Weinstein, M.D. University of California Irvine, CA

1) Study objectives: This was to determine the safety and efficacy of tazarotene cream 0.01%, 0.025%, 0.05%, and 0.1%, as compared with the vehicle cream and tretinoin emollient cream 0.05%, when applied once daily for 24 weeks in the treatment of photodamaged facial skin. It was also designed to determine the concentration of tazarotene cream to be used in the two Phase 3 studies, and to determine the most responsive efficacy variables to be used in those studies.

2) Study design: This was a multicenter, investigator-blinded,

randomized, parallel group study.

3) Patient selection: Patients were male and female, 18 years or older, with skin types I, II, III, or IV. The baseline severity for either mottled hyperpigmentation or fine wrinkling was at least moderate, based on a scale of 0=none, 1=minimal, 2=mild, 3=moderate, 4=severe, and 5=very severe. Patient exclusions were similar to those in the Phase 3 studies.

4) Treatment regimen: Applications were made once daily to the face for 24 weeks.

5) Efficacy parameters: These were as follows.

   a. Clinical signs: The clinical signs of photodamage were evaluated at weeks 2, 4, 8, 12, 16, 20, and 24, and at two weeks post-treatment; these were fine wrinkling, mottled hyperpigmentation, lentigines, elastosis, irregular depigmentation, tactile roughness, coarse wrinkling, telangiectasia, actinic keratoses, and an overall integrated assessment of photodamage. Grading of clinical signs was made on the following scale.

0	none
1	minimal
2	mild
3	moderate
4	severe
5	very severe

In addition, pore size was graded on the following scale.

0	barely visible
1	very small
2	small
3	medium
4	large

b. Global response to treatment: A comparison of the patient's photodamage at each visit was made with the photodamage at baseline, using the following scale.

0	complete response; complete resolution of photodamage
1	almost complete response; very significant improvement in photodamage (approximately 90% improvement)
2	marked response; significant improvement in photodamage (approximately 75% improvement)
3	moderate response; intermediate improvement, between slight and marked (approximately 50% improvement)
4	slight response; some improvement, but significant photodamage remains (approximately 25% improvement)
5	no response
6	condition worsened

Photographs taken at baseline were used to assist the investigators in the evaluation of photodamage at subsequent visits.

c. Patient's overall assessment of photodamage: At each return visit the patients rated their overall response to treatment on the following scale.

1	much improved
2	somewhat improved
3	no change
4	somewhat worse
5	much worse

d. Other studies: At one center, computerized analysis of variables denoting the surface topography of the periorbital region (crow's feet) was conducted, using silicone skin surface replicas obtained at baseline and week 24. At another center punch biopsies were taken at baseline and week 24 from the crow's feet area of some patients, and examined histologically for changes in the epidermis and dermis.

Photographs were taken at baseline and at weeks 12, 24, and 26.

7) Safety evaluation: The patients were monitored for adverse events, and the severity and drug relationship of events were recorded.

Blood samples were collected at weeks 4 and 24 at two centers for the determination of plasma tazarotenic acid. The patients were not to apply the medication the evening prior to blood collection. Samples were taken prior to and at 3 to 10 hours post-application.

Results were as follows.

1) Enrollment and demographic characteristics: 349 patients were enrolled in the study. There were no significant differences among the treatment groups with respect to demographic characteristics, and, except for lentigines, the baseline signs of photodamage were similar in the different treatment groups.

2) Clinical signs: Analyses were based on the ITT population, defined as all patients randomized. The results were reported as the percentage of patients that improved by at least one grade from baseline, as follows.

Fine wrinkling Improvement by one grade over baseline at week 24					
Taz 0.1% N=58	Taz 0.05% n=58	Taz 0.025% n=58	Taz 0.01% n=59	Tret 0.05% n=58	Vehicle n=58
53.4%	48.3%	34.5%	45.8%	53.4%	19.0%

Fine wrinkling p values - pairwise comparisons				
Taz 0.1% vs Taz 0.05%	Taz 0.1% vs Taz 0.025%	Taz 0.1% vs Taz 0.01%	Taz 0.1% vs Tret 0.05%	Taz 0.1% vs vehicle
0.547	0.032	0.372	0.978	< 0.001

Mottled hyperpigmentation Improvement by one grade over baseline at week 24					
Taz 0.1% N=58	Taz 0.05% n=58	Taz 0.025% n=58	Taz 0.01% n=59	Tret 0.05% n=58	Vehicle n=58
86.2%	81.0%	69.0%	72.9%	84.5%	67.2%

Mottled hyperpigmentation p values - pairwise comparisons				
Taz 0.1% vs Taz 0.05%	Taz 0.1% vs Taz 0.025%	Taz 0.1% vs Taz 0.01%	Taz 0.1% vs Tret 0.05%	Taz 0.1% vs vehicle
0.475	0.031	0.074	0.816	0.019

Lentigines Improvement by one grade over baseline at week 24					
Taz 0.1% N=58	Taz 0.05% n=58	Taz 0.025% n=58	Taz 0.01% n=59	Tret 0.05% n=58	Vehicle n=58
73.2%	77.2%	68.4%	71.2%	85.5%	49.1%

Lentigines p values - pairwise comparisons				
Taz 0.1% vs Taz 0.05%	Taz 0.1% vs Taz 0.025%	Taz 0.1% vs Taz 0.01%	Taz 0.1% vs Tret 0.05%	Taz 0.1% vs vehicle
0.621	0.582	0.853	0.098	0.010

Elastosis Improvement by one grade over baseline at week 24					
Taz 0.1% N=58	Taz 0.05% n=58	Taz 0.025% n=58	Taz 0.01% n=59	Tret 0.05% n=58	Vehicle n=58
54.9%	43.1%	44.0%	28.8%	43.1%	30.6%

Elastosis p values - pairwise comparisons				
Taz 0.1% vs Taz 0.05%	Taz 0.1% vs Taz 0.025%	Taz 0.1% vs Taz 0.01%	Taz 0.1% vs Tret 0.05%	Taz 0.1% vs vehicle
0.087	0.297	< 0.001	0.172	0.002

Irregular depigmentation Improvement by one grade over baseline at week 24					
Taz 0.1% N=58	Taz 0.05% n=58	Taz 0.025% n=58	Taz 0.01% n=59	Tret 0.05% n=58	Vehicle n=58
68.6%	72.2%	57.9%	51.4%	65.6%	54.3%

Irregular depigmentation p values - pairwise comparisons				
Taz 0.1% vs Taz 0.05%	Taz 0.1% vs Taz 0.025%	Taz 0.1% vs Taz 0.01%	Taz 0.1% vs Tret 0.05%	Taz 0.1% vs vehicle
0.967	0.203	0.103	0.519	0.177

Tactile roughness Improvement by one grade over baseline at week 24					
Taz 0.1% N=58	Taz 0.05% n=58	Taz 0.025% n=58	Taz 0.01% n=59	Tret 0.05% n=58	Vehicle n=58
61.1%	64.3%	54.5%	65.5%	61.1%	63.6%

Tactile roughness p values - pairwise comparisons				
Taz 0.1% vs Taz 0.05%	Taz 0.1% vs Taz 0.025%	Taz 0.1% vs Taz 0.01%	Taz 0.1% vs Tret 0.05%	Taz 0.1% vs vehicle
0.632	0.514	0.378	0.733	0.688

Coarse wrinkling Improvement by one grade over baseline at week 24					
Taz 0.1% N=58	Taz 0.05% n=58	Taz 0.025% n=58	Taz 0.01% n=59	Tret 0.05% n=58	Vehicle n=58
14.0%	10.5%	10.9%	10.2%	10.5%	3.6%

Coarse wrinkling p values - pairwise comparisons				
Taz 0.1% vs Taz 0.05%	Taz 0.1% vs Taz 0.025%	Taz 0.1% vs Taz 0.01%	Taz 0.1% vs Tret 0.05%	Taz 0.1% vs vehicle
0.586	0.663	0.476	0.615	0.051

Telangiectasia Improvement by one grade over baseline at week 24					
Taz 0.1% N=58	Taz 0.05% n=58	Taz 0.025% n=58	Taz 0.01% n=59	Tret 0.05% n=58	Vehicle n=58
25.5%	31.5%	16.0%	26.9%	24.5%	20.0%

Telangiectasia p values - pairwise comparisons				
Taz 0.1% vs Taz 0.05%	Taz 0.1% vs Taz 0.025%	Taz 0.1% vs Taz 0.01%	Taz 0.1% vs Tret 0.05%	Taz 0.1% vs vehicle
0.473	0.219	0.738	0.998	0.484

Pore size Improvement by one grade over baseline at week 24					
Taz 0.1% N=58	Taz 0.05% n=58	Taz 0.025% n=58	Taz 0.01% n=59	Tret 0.05% n=58	Vehicle n=58
41.4%	46.6%	42.1%	42.4%	35.7%	30.9%

Pore size p values - pairwise comparisons				
Taz 0.1% vs Taz 0.05%	Taz 0.1% vs Taz 0.025%	Taz 0.1% vs Taz 0.01%	Taz 0.1% vs Tret 0.05%	Taz 0.1% vs vehicle
0.591	0.966	0.927	0.433	0.185

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3) Other efficacy parameters. In the Global Response to treatment, the percentage of subjects who had a 50% or greater improvement at week 24 were as follows.

Global Response 50% or greater improvement from baseline at week 24					
Taz 0.1% N=58	Taz 0.05% n=58	Taz 0.025% n=58	Taz 0.01% n=59	Tret 0.05% n=58	Vehicle n=58
67.2%	51.7%	36.2%	40.7%	55.2%	22.8%

Global Response p values - pairwise comparisons				
Taz 0.1% vs Taz 0.05%	Taz 0.1% vs Taz 0.025%	Taz 0.1% vs Taz 0.01%	Taz 0.1% vs Tret 0.05%	Taz 0.1% vs vehicle
0.036	< 0.001	< 0.001	0.130	< 0.001

Baseline and post-treatment facial biopsies were obtained from 31 patients at one center; these consisted of 4 on tazarotene 0.1%, 16 on the other tazarotene concentrations combined, 7 on tretinoin 0.05%, and 4 vehicle patients. Findings in the active treatment groups were an increase in epidermal thickness, decreased melanin, a more compact stratum corneum, and increase in the granular cell layer. Optical analysis of skin surface replicas found no among group differences.

4) Pharmacokinetic data: Plasma tazarotenic acid levels were determined in 15 vehicle patients and 65 tazarotenic acid patients. All plasma levels in the vehicle patients were below the limit of detection of — ng/mL. The highest individual plasma tazarotenic acid concentration in the tazarotene patients was — ng/mL. The mean concentration ranged from 0.0163 ng/mL in the 0.05% patients to 0.0964 ng/mL in the 0.1% patients. Post-dose concentrations were significantly higher than pre-dose concentrations, but the post-dose levels at week 4 were not significantly different from those at week 24, indicating that drug accumulation did not occur.

5) Safety evaluation: Adverse events of the skin and appendages reported by 2% or more of patients were as follows.

	Tazarotene 0.1%	Tazarotene 0.05%	Tazarotene 0.025%	Tazarotene 0.01%	Tretinoin 0.05%	Vehicle
Desquamation	38%	47%	22%	14%	22%	9%
Erythema	29%	33%	22%	12%	12%	9%
Burning skin	29%	38%	16%	5%	19%	5%
Pruritus	21%	10%	9%	3%	3%	0
Dry skin	19%	24%	24%	17%	22%	9%
Irritation skin	17%	12%	12%	3%	7%	2%
Irritant contact dermatitis	12%	9%	12%	3%	9%	0
Stinging	10%	5%	2%	3%	9%	0
Papules	7%	5%	5%	2%	5%	7%
Rash	7%	7%	2%	0	2%	2%
Acne	5%	12%	3%	7%	7%	10%
Herpes simplex	3%	0	2%	2%	0	0
Seborrhea	3%	3%	0	0	0	0
Fissure	3%	0	0	2%	5%	0
Excoriation	2%	0	5%	0	2%	2%
Skin tightness	2%	3%	0	2%	0	2%
Skin reaction	2%	2%	0	3%	3%	2%
Hyperkeratosis	0	2%	3%	0	0	0

Reviewer's comments on Study 025C: There is no validation for the clinical endpoints other than fine wrinkling and mottled hyperpigmentation; this is discussed further in the comments on the Phase 3 studies. The results of this study have not been reviewed by our biostatisticians. It is doubtful that the p values have been adjusted for multiplicity. It is noted that the 0.05% tazarotene occasionally out-trends the 0.1 % tazarotene.

Phase 3 studies

The Phase 3 studies were performed with the same formulation as the approved Tazorac Cream 0.1%. Study 190168-033C was initiated on 9/30/99; the double blind portion ended on 8/31/00, and the open portion ended on 3/16/01, with an updated study report submitted on 10/29/01. Study 190168-034C was initiated on 9/29/99 and ended on 9/21/00.

I. Study 190168-033C

The investigators for the study were as follows.

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William Coleman, M.D. Metairie, LA	Nicholas Lowe, M.D. Clinical Research Specialists Santa Monica, CA
George Fisher, M.D. West Florida Clinical Research Center, Inc Pensacola, FL	Tania Phillips, M.D. Department of Dermatology Boston University School of Medicine Boston, MA
Toni Funicella, M.D. Dermresearch, Inc. Austin, TX	Nancy Silvis, M.D. Dermatology Clinic University of Arizona Tuczon, AZ
Alice Gottlieb, M.D. Clinical Research Center Robert Wood Johnson Medical School New Brunswick, NJ	Leonard Swinyer, M.D. Dermatology Research Center Salt Lake City, UT
Michael Heffernan, M.D. Division of Dermatology Washington University School of Medicine St. Louis, MO	David Tashijian, M.D. Central California Medical Research Fresno, CA
James Leyden, M.D. Skin Study Center Broomall, PA.	Kenneth Washenik, M.D. Department of Dermatology NYU Medical Center New York, NY
	David Wilson, M.D. Education and Research Foundation Lynchburg, VA

1) Study title: A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Comparison of the Safety and Efficacy of Tazarotene Cream 0.1% Applied Once Daily for 24 Weeks Followed by Treatment with Tazarotene Cream 0.1% (Open-Label) for 28 Weeks in Patients with Photodamaged Facial Skin.

2) Study objectives: This was to determine the safety and efficacy of tazarotene cream 0.1% versus vehicle cream applied once daily for 24 weeks in the treatment of photodamaged skin.

3) Study design: This was a multicenter, double blind, randomized, comparison of tazarotene cream 0.1% with its vehicle for 24 weeks, followed by open label treatment with tazarotene cream 0.1% for 28 weeks.

4) Inclusion criteria: These were as follows.

a. Males and females at least 18 years of age, with skin types I, II, III, or IV.
b. A baseline severity of at least mild for fine wrinkling and mottled hyperpigmentation, with one of these signs at least moderate in severity, based on a scale of 0=none, 1=minimal, 2=mild, 3=moderate and 4=severe.
c. Prior to study entry, a normal menstrual cycle and a negative urine pregnancy test for women of childbearing potential.

5) Exclusion criteria: These were as follows.

a. Known sensitivity to any of the ingredients in the study medication.
b. History or evidence of other skin conditions or significant illness that would interfere with the evaluation of the study medication.
c. Use of topical or systemic therapies that might interfere with the evaluation of the study medication.
d. History of basal cell or squamous cell carcinoma on the face within 3 months prior to study entry.
e. Use of topical glycolic acid, alpha-hydroxy acid, salicylic acid, lactic acid, beta-hydroxy acid, or vitamin A, C, or E containing products within 14 days prior to study entry.
f. Use of systemic retinoids within 6 months prior to study entry.
g. Use of topical retinoids within one month prior to study entry.
h. Use of vitamin A supplements > 5,000 IU per day or vitamin E supplements > 400 IU per day within one week prior to study entry and during the study.
i. Patients who are planning a cosmetic or therapeutic procedure on the face during the study, e.g., chemical peel, laser resurfacing, dermabrasion.
j. Patients who underwent a cosmetic or therapeutic procedure on the face within 4 months prior to study entry.
k. Anticipated need for surgery or hospitalization during the study.
l. Uncontrolled systemic disease.
m. Known HIV positive patients.
n. Current evidence of chronic alcohol or drug abuse.
o. Females who are pregnant, nursing, or planning a pregnancy during the study, or think they may be pregnant at the start of the study, or who are unable or unwilling to use reliable forms of contraception during the study.
p. Patients who require or desire excessive or prolonged exposure to ultraviolet light, e.g., sunlight, tanning beds, during the study.

q. Patients who are unwilling to use a sunscreen with an SPF of at least 15 during the study.
r. Concurrent involvement in another investigational study or participation within 30 days prior to the start of the study.
s. Patient has any condition or is in a situation which, in the investigator's opinion, may put the patient at significant risk, could confound the study results, or interfere significantly with the patient's participation in the study.

6) Treatment regimen: During the double blind period, applications of tazarotene cream 0.1% or its vehicle were made once daily to the face for 24 weeks. Patients were randomly assigned to the treatment groups.

The patients were required to use a sunscreen with an SPF of at least 15 during the study, were to avoid excessive sun exposure, and were to use protective measures, such as a hat or visor, when exposed to sunlight. Patients were allowed to use their own non-medicated facial moisturizers.

Following the double blind period the patients were entered into the open label phase, during which all patients applied tazarotene cream 0.1% to the face once daily for 28 weeks.

7) Efficacy parameters, double blind phase: These were as follows.

a. Clinical signs: The clinical signs were evaluated at weeks 2, 4, 8, 12, 16, 20, and 24; these were fine wrinkling, mottled hyperpigmentation, lentigines, elastosis, irregular depigmentation, tactile roughness, coarse wrinkling, and telangiectasia. The sponsor considered fine wrinkling and mottled hyperpigmentation to be the primary efficacy variables. A photonumeric guideline illustrating each fine wrinkling and mottled hyperpigmentation grade was provided to assist the investigators in determining the fine wrinkling and mottled hyperpigmentation scores. The sponsor's secondary variables were lentigines and elastosis, and 'other' variables were irregular depigmentation, tactile roughness, coarse wrinkling, pore size, and telangiectasia. No photonumeric guidelines were provided for the secondary and other parameters.

It is noted that although the sponsor considered these clinical signs to be efficacy endpoints, the Agency has stated that only the primary endpoints, namely, fine wrinkling and mottled hyperpigmentation are considered to be valid endpoints. The endpoints listed as secondary and 'other' have not been validated, as was stated in the review of the proposed Phase 3 protocol.

Grading of clinical signs was made as follows.

1) Primary efficacy variables.

a) Fine wrinkling.

Fine wrinkling	
0	none
1	minimal
2	mild
3	moderate
4	severe

b) Mottled hyperpigmentation.

Mottled hyperpigmentation	
0	none
1	minimal
2	mild
3	moderate
4	severe

2) Secondary variables.

a) Lentigines.

Lentigines	
0	none
1	minimal
2	mild
3	moderate
4	severe

b) Elastosis.

Elastosis	
0	none
1	minimal

2	mild
3	moderate
4	severe

3) Other variables.

a) Irregular depigmentation.

Irregular depigmentation	
0	none
1	minimal
2	mild
3	moderate
4	severe

b) Tactile roughness.

Tactile roughness	
0	none
1	minimal
2	mild
3	moderate
4	severe

c) Coarse wrinkling.

Coarse wrinkling	
0	none
1	minimal
2	mild
3	moderate
4	severe

d) Telangiectasia.

Telangiectasia	
0	none
1	minimal
2	mild
3	moderate
4	severe

e) Pore size.

Pore size	
0	barely visible
1	very small
2	small
3	medium
4	large

An overall integrated assessment of photodamage (OIA) was made at each return visit on the following scale.

OIA	
0	none
1	minimal
2	mild
3	moderate
4	severe
5	very severe

In addition, actinic keratoses were counted.

b. Global response to treatment: A comparison of the patient's photodamage at each visit was made with the photodamage at baseline, using the following scale.

Global response	
0	complete response; complete resolution of photodamage
1	almost complete response; very significant improvement in photodamage (approximately 90% improvement)
2	marked response; significant improvement in photodamage (approximately 75% improvement)
3	moderate response; intermediate improvement, between slight and marked (approximately 50% improvement)
4	slight response; some improvement, but significant photodamage remains (approximately 25% improvement)
5	no response
6	condition worsened

Photographs taken at the screening visit were used to assist the investigators in the evaluation of photodamage at subsequent visits.

c. Patient's overall assessment of photodamage: At each return visit the patients rated their overall response to treatment on the following scale.

Patient assessment	
1	much improved
2	somewhat improved
3	no change
4	somewhat worse
5	much worse

8) Safety evaluation, double blind phase. The patients were monitored for signs and symptoms of adverse events. The severity, action taken, and relationship to the study drug were recorded on the case

report forms.

Plasma determinations of tazarotenic acid were done at five sites at baseline and at weeks 2, 12, 24, 36, and 52. At these visits the date and time of the last study application was recorded. The patients then applied the study medication under supervision from a pre-weighed tube of medication, which was re-weighed after application. Blood samples were taken at 3 to 10 hours after this application.

The sponsor's presentation of the study results is as follows.

A. Double blind phase

Two analysis populations were defined: a safety population and an ITT population. The safety population consisted of all randomized and treated patients, and was used for all analyses of safety data. The ITT population was defined as all randomized patients, and was used for all efficacy analyses.

1) Baseline and demographic characteristics: 563 patients were enrolled in the study, of which 283 were assigned to tazarotene cream 0.1% and 280 were assigned to the vehicle. The demographic characteristics, skin types, and baseline severity of the signs of photodamage in the ITT population were as follows.

Demographic characteristics Study 33C		
	Tazarotene	Vehicle
# pts	283	280
Age (mean)	56.2	56.2
Gender		
Male	30 (11%)	31 (11%)
Female	253 (89%)	249 (89%)
Race		
Caucasian	268 (95%)	270 (96%)
Black	0	0
Asian	6 (2%)	3 (1%)
Hispanic	7 (3%)	5 (2%)
Other	2 (0.7%)	2 (0.7%)

Skin type Study 33C			
Category	Description	Tazarotene	Vehicle
I	Always burns easily; rarely tans	32 (11%)	45 (16%)
II	Always burns easily; tans minimally	71 (25%)	74 (26%)
III	Burns moderately; tans gradually	123 (44%)	98 (35%)
IV	Burns minimally; always tans well	57 (20%)	63 (23%)
V	Rarely burns; tans profusely	0	0
VI	Never burns; deeply pigmented	0	0

Fine wrinkling at baseline Study 33C		
	Tazarotene n=283	Vehicle n=280
0-None	0	0
1-Minimal	0	0
2-Mild	54 (19%)	41 (15%)
3-Moderate	169 (60%)	171 (61%)
4-Severe	60 (21%)	68 (24%)
Mean	3.0	3.1

Mottled hyperpigmentation at baseline Study 33C		
	Tazarotene n=283	Vehicle n=280
0-None	0	0
1-Minimal	0	1 (0.4%)
2-Mild	93 (33%)	106 (38%)
3-Moderate	158 (56%)	150 (54%)

4-Severe	32 (11%)	23 (8%)
Mean	2.8	2.7

Lentigines at baseline Study 33C		
	Tazarotene n=283	Vehicle n=280
0-None	19 (7%)	25 (9%)
1-Minimal	55 (19%)	57 (20%)
2-Mild	83 (29%)	93 (33%)
3-Moderate	110 (39%)	96 (34%)
4-Severe	16 (6%)	9 (3%)
Mean	2.2	2.0

Elastosis at baseline Study 33C		
	Tazarotene n=283	Vehicle n=280
0-None	61 (22%)	67 (24%)
1-Minimal	61 (22%)	59 (21%)
2-Mild	90 (32%)	68 (24%)
3-Moderate	56 (20%)	71 (25%)
4-Severe	15 (5%)	15 (5%)
Mean	1.7	1.7

Tactile roughness at baseline Study 33C		
	Tazarotene n=283	Vehicle n=280
0-None	65 (23%)	70 (25%)
1-Minimal	93 (33%)	87 (31%)
2-Mild	72 (25%)	76 (27%)
3-Moderate	37 (13%)	26 (9%)

4-Severe	16 (6%)	21 (8%)
Mean	1.5	1.4

Coarse wrinkling at baseline Study 33C		
	Tazarotene n=283	Vehicle n=280
0-None	21 (7%)	18 (6%)
1-Minimal	57 (20%)	68 (24%)
2-Mild	94 (33%)	81 (29%)
3-Moderate	83 (29%)	87 (31%)
4-Severe	28 (10%)	26 (9%)
Mean	2.1	2.1

Telangiectasia at baseline Study 33C		
	Tazarotene n=283	Vehicle n=280
0-None	33 (12%)	25 (9%)
1-Minimal	103 (36%)	105 (38%)
2-Mild	90 (32%)	87 (31%)
3-Moderate	52 (18%)	50 (18%)
4-Severe	5 (2%)	13 (5%)
Mean	1.6	1.7

Pore size at baseline Study 33C		
	Tazarotene n=283	Vehicle n=280
0-Barely visible	16 (6%)	13 (5%)
1-Very small	62 (22%)	59 (21%)
2-Small	105 (37%)	88 (31%)

3-Medium	91 (32%)	109 (39%)
4-Large	9 (3%)	11 (4%)
Mean	2.1	2.2

Irregular depigmentation at baseline Study 33C		
	Tazarotene n=283	Vehicle n=280
0-None	127 (45%)	136 (49%)
1-Minimal	69 (24%)	54 (19%)
2-Mild	51 (18%)	56 (20%)
3-Moderate	31 (11%)	32 (11%)
4-Severe	5 (2%)	2 (0.7%)
Mean	1.0	1.0

Overall assessment at baseline Study 33C		
	Tazarotene n=282	Vehicle n=280
None	0	0
Minimal	1 (0.4%)	0
Mild	60 (21%)	53 (19%)
Moderate	147 (52%)	159 (57%)
Severe	60 (21%)	61 (22%)
Very severe	14 (5%)	7 (3%)

2) Patient disposition: The number of patients that discontinued, and the reasons for discontinuation, were as follows.

Discontinuations Study 33C		
	Tazarotene n=283	Vehicle n=280
Lack of efficacy	0	0

Adverse events	20	1
Lost to followup	4	2
Relocated	2	1
Personal reasons	7	9
Improper entry	0	2
Non-compliance	1	1
Other	1	1
Total completed	248 (88%)	263 (94%)
Total discontinued	35 (12%)	17 (6%)

3) Efficacy parameters: Clinical signs.

a. The percentages of patients who had an improvement in their score of at least one grade at endpoint, were as follows.

Patients with clinical improvement of one grade or more Study 33C			
	Tazarotene n=283	Vehicle n=280	p value
Fine wrinkling	40.3%	16.1%	< 0.001
Mottled hyperpigmentation	59.0%	17.9%	< 0.001
Lentigines	50.2%	15.7%	< 0.001
Elastosis	20.5%	4.6%	< 0.001
Tactile roughness	44.2%	34.6%	0.005
Coarse wrinkling	13.1%	5.7%	0.002
Telangiectasia	14.8%	11.8%	0.283
Pore size	27.2%	9.6%	< 0.001
Irregular depigmentation	19.8%	9.3%	< 0.001

b. The percentages of patients with a baseline score of 2 or more, who had an improvement in their score of at least two grades at endpoint, were as follows.

Patients with clinical improvement of two grades or more Study 33C			
	Tazarotene	Vehicle	p value

Fine wrinkling	5.3%	1.4%	0.011
Mottled hyperpigmentation	17.3%	0.7%	< 0.001
Lentigines	19.6%	2.0%	< 0.001
Elastosis	0.6%	0	0.359
Tactile roughness	44.8%	35.0%	0.004
Coarse wrinkling	2.0%	1.0%	0.505
Telangiectasia	3.4%	2.7%	0.463
Pore size	5.9%	1.9%	0.045
Irregular depigmentation	16.1%	4.4%	0.011

c. The percentages of patients with a baseline score of 2 or more, who had a score of 0 at endpoint, were as follows.

Patients with score of 0 Study 33C			
	Tazarotene	Vehicle	p value
Fine wrinkling	0.4%	0	0.332
Mottled hyperpigmentation	2.8%	0	0.005
Lentigines	2.4%	0	0.034
Elastosis	0	0	-
Tactile roughness	26.4%	22.8%	0.080
Coarse wrinkling	0	0	-
Telangiectasia	0.7%	0	0.248
Pore size	1.5%	1.0%	0.720
Irregular depigmentation	4.6%	2.2%	0.508

d. The percentages of patients with a baseline score of 2 or more, who had a score of 0 or 1 at endpoint, were as follows.

Patients with score of 0 or 1 Study 33C			
	Tazarotene	Vehicle	p value
Fine wrinkling	7.1%	2.1%	0.005
Mottled hyperpigmentation	27.9%	6.8%	< 0.001

Lentigines	37.8%	8.1%	< 0.001
Elastosis	14.3%	2.6%	< 0.001
Tactile roughness	69.6%	57.7%	0.011
Coarse wrinkling	8.3%	3.1%	0.040
Telangiectasia	16.3%	8.7%	0.024
Pore size	15.6%	4.8%	< 0.001
Irregular depigmentation	29.9%	10.0%	< 0.001

4) Efficacy parameters: Overall assessments.

a. Overall assessments: At endpoint, the percentage of patients with an improvement of one grade in the overall integrated assessment (OIA) of photodamage, and the percentage of patients that had a 50% or greater improvement in the global response to treatment were as follows.

Results of OIA and Global Response Study 33C			
	Tazarotene n=283	Vehicle n=280	p value
OIA *	32.6%	8.2%	< 0.001
Global response **	36.8%	3.2%	< 0.001
* improvement by one grade at endpoint ** 50% or more improvement at endpoint			

b. Actinic keratoses: The mean change at endpoint in the number of actinic keratoses was - 0.1 in the tazarotene group and - 0.2 in the vehicle group (p=0.294).

c. Patient's overall assessment of photodamage: The overall assessment of photodamage at endpoint was as follows.

Patient assessment of photodamage Study 33C		
	Tazarotene n=281	Vehicle n=277
Much improved	37%	6%
Somewhat improved	43%	26%
No change	16%	66%
Somewhat worse	3%	2%
Much worse	1%	0

d. Subgroup analyses. Analyses of the improvement in fine wrinkling and mottled hyperpigmentation by one point from baseline were done by age categories, sex, race, and severity at baseline, as follows. (Subgroup analyses of changes in the other clinical signs are not provided.)

Fine wrinkling: analysis by age Improvement of one grade or more at endpoint Study 33C			
	Tazarotene n=283	Vehicle n=280	p value
< 40 years	28% (5/18)	11% (2/19)	0.232
40 - 65 years	44% (89/202)	16% (32/200)	< 0.001
> 65 years	32% (20/63)	18% (11/61)	0.098

Mottled hyperpigmentation: analysis by age Improvement of one grade or more at endpoint Study 33C			
	Tazarotene n=283	Vehicle n=280	p value
< 40 years	39% (7/18)	21% (4/19)	0.295
40 - 65 years	60% (121/202)	18% (35/200)	< 0.001
> 65 years	62% (39/63)	18% (11/61)	< 0.001

Fine wrinkling: analysis by sex Improvement of one grade or more at endpoint Study 33C			
	Tazarotene n=283	Vehicle n=280	p value
Male	30% (9/30)	7% (2/31)	0.022
Female	42%(105/253)	17% (43/249)	< 0.001

Mottled hyperpigmentation: analysis by sex Improvement of one grade or more at endpoint Study 33C			
	Tazarotene n=283	Vehicle n=280	p value
Male	60% (18/30)	10% (3/31)	< 0.001
Female	59%(149/253)	19% (47/249)	< 0.001

Fine wrinkling: analysis by race Improvement of one grade or more at endpoint Study 33C			
	Tazarotene n=283	Vehicle n=280	p value
White	39% (105/268)	16% (43/270)	< 0.001
Non-white	60% (9/15)	20% (2/10)	0.099

Mottled hyperpigmentation: analysis by race Improvement of one grade or more at endpoint Study 33C			
	Tazarotene n=283	Vehicle n=280	p value
White	59% (157/268)	18% (49/270)	< 0.001
Non-white	67% (10/15)	10% (1/10)	0.012

Fine wrinkling: analysis by baseline severity Improvement of one grade or more at endpoint Study 33C			
	Tazarotene n=283	Vehicle n=280	p value
Mild	19% (10/54)	10% (4/41)	0.261
Moderate	43% (72/169)	13% (22/171)	< 0.001
Severe	53% (32/60)	28% (19/68)	0.004

Mottled hyperpigmentation: analysis by baseline severity Improvement of one grade or more at endpoint Study 33C

	Tazarotene n=283	Vehicle n=280	p value
Mild	59% (32/54)	17% (7/41)	< 0.001
Moderate	57% (97/169)	18% (30/171)	< 0.001
Severe	63% (38/60)	19% (13/68)	< 0.001

5) Pharmacokinetic data: Plasma samples for pharmacokinetic analyses were collected from 60 patients on tazarotene cream 0.1% and 65 patients on the vehicle. The plasma tazarotenic acid concentrations in the tazarotene treatment group were as follows.

Plasma tazarotenic acid concentrations Study 33C			
	Week 2 n=55	Week 12 n=54	Week 24 n=50
Mean	0.092	0.108	0.108
Maximum			

6) Safety assessment. The adverse events of the skin and appendages which occurred in 1% or more of the patients were as follows.

Adverse events - skin and appendages 1% or more of patients Study 33C		
	Tazarotene n=283	Vehicle n=280
Desquamation	106 (38%)	5 (2%)
Erythema	86 (30%)	5 (2%)
Burning sensation	84 (30%)	0
Dry skin	43 (15%)	8 (3%)
Irritant contact dermatitis	31 (11%)	5 (2%)
Pruritus	29 (10%)	3 (1%)
Stinging	12 (4%)	0
Acne	11 (4%)	10 (4%)
Rash	10 (4%)	4 (1%)
Skin hypertrophy	9 (3%)	5 (2%)
Skin irritation	8 (3%)	2 (1%)
Herpes simplex	7 (3%)	2 (1%)
Skin edema	4 (1%)	3 (1%)
Skin laceration	4 (1%)	1 (0.4%)
Skin pain	4 (1%)	0
Sun-induced erythema	3 (1%)	1 (0.4%)
Papules	3 (1%)	1 (0.4%)
Vesiculobullous rash	3 (1%)	1 (0.4%)
Skin erosion	3 (1%)	0
Allergic contact dermatitis	2 (1%)	2 (1%)
Skin tightness	2 (1%)	1 (0.4%)
Skin benign neoplasm	2 (1%)	0
Skin discoloration	2 (1%)	0

The following adverse events of the skin and appendages in the tazarotene group were denoted as severe: desquamation in 3, erythema in 1, burning in 2, dry skin in 2, skin irritation in 1, and vesiculobullous rash in 1. There were no severe adverse events of the skin and appendages in the vehicle group.

No vehicle treated patients discontinued from the study due to adverse events of the skin and appendages. The following 18 patients treated with tazarotene discontinued from the study because of adverse events of the skin and appendages.

Subjects discontinued due to adverse events of the skin Study 33C	
Subject #	Adverse event
0084-1378	Mild to moderate burning, peeling
0084-1383	Severe dryness and burning
0084-1398	Moderate to severe burning, mild peeling and swelling, moderate erythema
1964-1414	Moderate eye and skin irritation
1964-1415	Moderate acne rosacea
2234-1127	Severe irritation
2234-1129	Severe peeling
2234-1465	Mild skin discoloration
2420-1012	Mild erythema, peeling, pain
2420-1013	Mild burning, scaling, erythema
2420-1029	Moderate burning, scaling, erythema, edema
3157-1493	Moderate peeling, erythema
3242-1306	Mild irritant dermatitis
3242-1563	Mild scaling and erythema
3242-1566	Mild irritation
3244-1547	Moderate erythema and swelling around eyes
3245-1207	Mild erythema and burning
3275-1482	Moderate erythema, burning, pruritus

B. Open label phase.

A total of 511 subjects continued into the 28 week open label phase. The patients were evaluated at weeks 28, 36, 44 and 52, using the same parameters for safety and efficacy as in the double blind phase. (The open label phase has regulatory utility only for assessment of safety, not for efficacy).

1) Efficacy parameters. The percentages of subjects that had an improvement of at least one grade from baseline (week 0) were as follows. (The subject population was observed cases.)

Improvement of one grade or more from baseline Open label phase - Study 33C		
	Tazarotene/ tazarotene *	Vehicle/ tazarotene **
No of pts Week 24 Week 52	 248 241	 263 248
Fine wrinkling Week 24 Week 52	 45% 66%	 17% 50%
Mottled hyperpigmentation Week 24 Week 52	 64% 87%	 18% 75%
Lentigines Week 24 Week 52	 55% 72%	 16% 55%
Elastosis Week 24 Week 52	 23% 33%	 5% 21%
Tactile roughness Week 24 Week 52	 48% 52%	 35% 45%
Coarse wrinkling Week 24 Week 52	 15% 27%	 6% 14%
Telangiectasia Week 24 Week 52	 17% 25%	 12% 21%
Pore size Week 24 Week 52	 30% 42%	 10% 34%
Irregular depigmentation Week 24 Week 52	 21% 32%	 10% 26%
* tazarotene cream in double blind phase/tazarotene cream in open phase ** vehicle in double blind phase/tazarotene in open phase		

2) Safety parameters. The adverse events of the skin and appendages occurring in 1% or more of patients during the open label phase were as follows.

Adverse events - skin and appendages 1% or more of patients Open label phase - Study 033C	
	Tazarotene n=511
Desquamation	124 (24%)
Burning sensation	61 (12%)
Erythema	55 (11%)
Dry skin	48 (9%)
Irritant contact dermatitis	38 (7%)
Pruritus	23 (5%)
Stinging	18 (4%)
Skin hypertrophy	14 (3%)
Acne	12 (2%)
Rash	11 (2%)
Skin irritation	9 (2%)
Herpes simplex	8 (2%)
Papules	6 (1%)
Vesiculobullous rash	5 (1%)
Rosacea	4 (1%)

Three patients had adverse events of the skin and appendages which were considered to be severe; these were vesiculobullous rash in 1, burning in 1, and melanoma in 1.

Plasma determinations of tazarotenic acid were done at weeks 36 and 52 in 106 patients at five centers. Of the 106 patients, 48 patients had been in the tazarotene treatment group during the double blind phase and 58 patients had been in the vehicle group. The mean tazarotenic acid concentrations at weeks 36 and 52 were 0.112 ng/mL and 0.097 ng mL, respectively. The single highest concentration during the open label period was 0.705 ng/mL; this was at week 36 in a patient who had been on tazarotene during the double blind period. Plasma levels of tazarotenic acid were similar at weeks 36 and 52, and were similar to levels during the double blind period.

Reviewer's evaluation of Study 33C

1. Efficacy - double blind phase. As stated by the Division at the End of Phase 2 meeting, there is no known primary efficacy variable for 'photodamage' per se, and the validity of an overall evaluation of photodamage such as the sponsor's 'overall integrated assessment of photodamage' has not been determined. We stated that the clinical signs of photodamage should be the primary endpoints, and that these will be acceptable as individual indications if the product is shown to be effective for the particular signs.

Nine clinical signs were evaluated in this study, Of the nine signs, fine wrinkling and mottled hyperpigmentation were considered by the sponsor to be primary efficacy variables; lentigines and elastosis were considered secondary variables, and irregular depigmentation, tactile roughness, coarse wrinkling, telangiectasia, and pore size were 'other' variables.

The protocol for Study 33C was reviewed by the Agency subsequent to the End of Phase 2 meeting. In the comments, which were conveyed to the sponsor, the Agency stated that the primary efficacy parameters (i.e., fine wrinkling and mottled hyperpigmentation) are acceptable, but that the inter- and intra- observer consistency should be addressed. It was also stated that the validation for the measurement of the secondary and 'other' parameters should be presented. Study 37C was submitted to address inter- and intra- rater reliability. This study is supportive of the primary efficacy variables, but does not provide clinical validation of the scoring scales for the secondary and 'other' endpoints.'

The clinical signs which are designated as primary efficacy variables by the sponsor in the Phase 3 protocol, namely, fine wrinkling and mottled hyperpigmentation, are considered to be the primary endpoints for claims approval. Secondary endpoints are usually used to support the primary endpoints. Other endpoints should be accompanied by demonstration of clinical validity and adequate scoring scales. Ideally, they should be agreed upon in advance and considered in the statistical plan.

The additional clinical signs, designated as secondary and other variables by the sponsor, have not been accompanied by demonstration of clinical validity or adequate scoring scales for approval as novel claims. In particular, pore size and elastosis are not considered to be accompanied by adequate clinical validation. The sponsor has not demonstrated the method by which pore size was assessed during the clinical trial. The labels ' small, medium, large' are not standard terminology which would be immediately clinically relevant across the physician population. There is essentially no literature which addresses this issue.

Therefore, the evaluation of the results by this reviewer is

restricted to the changes in fine wrinkling and mottled hyperpigmentation found with treatment.

At the pre-NDA meeting, the sponsor proposed a definition of treatment success as a one grade improvement from baseline. We requested that in addition they perform analyses based on the following definitions of treatment success:

1) *A severity score of 0 (none) at endpoint.*
2) *A severity score of 0 (none) or 1 (minimal) at endpoint.*
3) *Improvement from baseline by at least two grades at endpoint.*

The sponsor has provided these analyses. In accordance with our discussion on photodamage endpoints, it was felt by this reviewer that the most appropriate method of analysis is a comparison of the proportion of subjects with an improvement of at least two grades from baseline.

The results of Study 33C show that tazarotene cream 0.1% was significantly superior to the vehicle for fine wrinkling and mottled hyperpigmentation in the proportion of subjects with an improvement of two grades or more from baseline.

The results of the other methods of analysis showed that tazarotene cream 0.1% was also significantly superior to the vehicle for fine wrinkling and mottled hyperpigmentation in:

a. *the proportion of subjects with a clinical improvement of one grade at endpoint, and*
b. *the proportion of subjects with a baseline score of at least 2 that had a score of 0 or 1 at endpoint.*

Few patients with a baseline score of 2 or more had a score of 0 at endpoint; this was significant only for mottled hyperpigmentation.

2. Safety. In the double blind (24 week) portion of the study the predominant adverse reactions were desquamation, erythema, and burning in 30-38% of subjects, with dry skin, irritation, and pruritus in 10-15% of subjects. Severe adverse events of the skin and appendages in the tazarotene group were as follows: desquamation in 3, erythema in 1, burning in 2, dry skin in 2, skin irritation in 1, and vesiculobullous rash in 1. There were no severe adverse events of the skin and appendages in the vehicle group.

The adverse events of the skin and appendages were similar in the open label portion of the study (24-52 weeks), but were less frequent and less severe.

Plasma levels of tazarotenic acid were similar throughout the double

blind and open label phases of the study, indicating no drug accumulation.

II. Study 190168-034C

The investigators for the study were as follows.

Debra Breneman, M.D. University Dermatology Consultants University of Cincinnati Cincinnati, OH	David Pariser, M.D. Virginia Clinical Research Norfolk, VA
Suzanne Bruce, M.D. Houston, TX	Owen Reynolds, M.D. Opthalmic Research Associates North Andover, MA
Vincent Falanga, M.D. Roger Williams Medical Center Providence, RI	Ronald Savin, M.D. Savin Dermatology Center New Haven, CT
C. William Hanke, M.D. Carmel Medical Center Carmel, IN	Joel Shavin, M.D. Gwinnett Clinical Research Center Snellville, GA
Sewon Kang, M.D. University of Michigan Medical Center Ann Arbor, MI	Stacy Smith, M.D. Therapeutics, Inc La Jolla, CA
Gerald Kreuger, M.D. University of Utah Health Sciences Center Salt Lake City, UT	Emil Tanghetti, M.D. Center for Dermatology and Laser Surgery Sacramento, CA
Bruce Miller, M.D. Oregon Medical Research Center Portland OR	Guy Webster, M.D. Thomas Jefferson University Medical College Philadelphia, PA
	Gerald Weinstain, M.D. University of California, Irvine Irvine, CA

The conduct of this study was the same as for Study 190168-33C, with the exceptions that no open label period was included and no monitoring for plasma drug levels was done. The inclusion and exclusion criteria, treatment regimen, efficacy parameters and safety evaluations were the same as for Study 190168-33C.

Results were as follows.

1) Baseline and demographic characteristics: 568 patients were enrolled in the study, of which 284 were assigned to tazarotene cream 0.1% and 284 were assigned to the vehicle. The demographic characteristics, skin types, and baseline severity of the signs of photodamage in the ITT population were as follows.

Demographic characteristics Study 34C		
	Tazarotene	Vehicle
# pts	284	284
Age (mean)	53.7	53.9
Gender		
Male	35 (12%)	45 (16%)
Female	249 (88%)	239 (84%)
Race		
Caucasian	279 (98%)	276 (97%)
Black	0	0
Asian	0	2 (1%)
Hispanic	5 (2%)	5 (2%)
Other	0	1 (0.4%)

Skin type Study 34C			
Skin type	Description	Tazarotene	Vehicle
I	Always burns easily; rarely tans	34 (12%)	26 (9%)
II	Always burns easily; tans minimally	72 (25%)	76 (27%)
III	Burns moderately; tans gradually	118 (42%)	117 (41%)
IV	Burns minimally; always tans well	60 (21%)	65 (23%)
V	Rarely burns; tans profusely	0	0
VI	Never burns; deeply pigmented	0	0

Fine wrinkling at baseline Study 34C		
	Tazarotene n=284	Vehicle n=284
0-None	0	0
1-Minimal	0	0
2-Mild	61 (22%)	58 (20%)
3-Moderate	148 (52%)	145 (51%)
4-Severe	75 (26%)	81 (29%)
Mean	3.1	3.1

Mottled hyperpigmentation at baseline Study 34C		
	Tazarotene n=284	Vehicle n=284
0-None	0	0
1-Minimal	0	0
2-Mild	84 (30%)	110 (39%)
3-Moderate	167 (59%)	136 (48%)
4-Severe	33 (12%)	38 (13%)
Mean	2.8	2.8

Lentigines at baseline Study 34C		
	Tazarotene n=284	Vehicle n=284
0-None	6 (2%)	12 (4%)
1-Minimal	51 (18%)	59 (21%)
2-Mild	104 (37%)	109 (38%)
3-Moderate	104 (37%)	89 (31%)
4-Severe	19 (7%)	15 (5%)
Mean	2.3	2.1

Elastosis at baseline Study 34C		
	Tazarotene n=284	Vehicle n=284
0-None	39 (14%)	38 (13%)
1-Minimal	92 (32%)	99 (35%)
2-Mild	81 (29%)	70 (25%)
3-Moderate	54 (19%)	58 (20%)
4-Severe	18 (6%)	19 (7%)
Mean	1.7	1.7

Tactile roughness at baseline Study 34C		
	Tazarotene n=284	Vehicle n=284
0-None	44 (16%)	53 (19%)
1-Minimal	105 (37%)	97 (34%)
2-Mild	98 (35%)	90 (32%)
3-Moderate	36 (13%)	38 (13%)
4-Severe	1 (0.4%)	6 (2%)
Mean	1.5	1.5

Coarse wrinkling at baseline Study 34C		
	Tazarotene n=284	Vehicle n=284
0-None	22 (8%)	31 (11%)
1-Minimal	66 (23%)	66 (23%)
2-Mild	93 (33%)	84 (30%)
3-Moderate	70 (25%)	73 (26%)
4-Severe	33 (12%)	30 (11%)
Mean	2.1	2.0

Telangiectasia at baseline Study 34C		
	Tazarotene n=284	Vehicle n=284

0-None	23 (8%)	33 (12%)
1-Minimal	118 (42%)	103 (36%)
2-Mild	92 (32%)	89 (31%)
3-Moderate	44 (16%)	55 (19%)
4-Severe	7 (3%)	4 (1%)
Mean	1.6	1.6

Pore size at baseline Study 34C		
	Tazarotene n=284	Vehicle n=284
0-Barely visible	16 (6%)	22 (8%)
1-Very small	72 (25%)	66 (23%)
2-Small	104 (37%)	112 (39%)
3-Medium	83 (29%)	75 (26%)
4-Large	9 (3%)	9 (3%)
Mean	2.0	1.9

Irregular depigmentation at baseline Study 34C		
	Tazarotene n=284	Vehicle n=284
0-None	105 (37%)	94 (33%)
1-Minimal	79 (28%)	86 (30%)
2-Mild	67 (24%)	73 (26%)
3-Moderate	32 (11%)	30 (11%)
4-Severe	1 (0.4%)	1 (0.4%)
Mean	1.1	1.2
Overall assessment at baseline Study 34C		
	Tazarotene n=284	Vehicle n=284
None	0	0
Minimal	0	1 (0.4%)
Mild	54 (19%)	57 (20%)
Moderate	163 (57%)	154 (54%)

Severe	57 (20%)	63 (22%)
Very severe	10 (4%)	9 (3%)

2) Patient disposition: The number of patients that discontinued, and the reasons for discontinuation, were as follows.

Discontinuations Study 34C		
	Tazarotene n=284	Vehicle n=284
Lack of efficacy	0	4
Adverse events	10	4
Lost to followup	2	5
Relocated	1	2
Personal reasons	13	18
Non-compliance	0	1
Concomitant therapy	1	0
Other	2	0
Total completed	255 (90%)	250 (88%)
Total discontinued	29 (10%)	34 (12%)

3) Efficacy parameters: Clinical signs.

a. The percentages of patients who had an improvement in their score of at least one grade at endpoint, were as follows.

Clinical signs Patients with clinical improvement of at least one grade Study 34C			
	Tazarotene n=284	Vehicle n=284	p value
Fine wrinkling	58.1%	22.5%	< 0.001
Mottled hyperpigmentation	81.7%	39.4%	< 0.001
Lentigines	54.6%	23.9%	< 0.001
Elastosis	28.5%	10.9%	< 0.001
Tactile roughness	44.4%	37.3%	0.055
Coarse wrinkling	14.4%	10.2%	0.075

Telangiectasia	15.5%	13.0%	0.333
Pore size	39.8%	18.0%	< 0.001
Irregular depigmentation	22.5%	13.4%	0.002

b. The percentages of patients with a baseline score of 2 or more, who had an improvement in their score of at least two grades at endpoint, were as follows.

Clinical signs Patients with clinical improvement of at least two grades Study 34C			
	Tazarotene	Vehicle	p value
Fine wrinkling	13.4%	4.9%	< 0.001
Mottled hyperpigmentation	28.2%	9.5%	< 0.001
Lentigines	19.8%	5.2%	< 0.001
Elastosis	7.8%	2.7%	0.016
Tactile roughness	19.3%	24.6%	0.765
Coarse wrinkling	5.1%	2.1%	0.142
Telangiectasia	4.9%	5.4%	0.858
Pore size	9.2%	3.1%	0.002
Irregular depigmentation	18.0%	5.8%	0.005

c. The percentages of patients with a baseline score of 2 or more, who had a score of 0 at endpoint, were as follows.

Clinical signs Patients with score of 0 Study 34C			
	Tazarotene	Vehicle	p value
Fine wrinkling	1.4%	1.4%	0.619
Mottled hyperpigmentation	4.6%	1.8%	0.030
Lentigines	4.4%	0.5%	0.015
Elastosis	4.6%	0.7%	0.024
Tactile roughness	11.9%	19.4%	0.161
Coarse wrinkling	3.1%	1.1%	0.219
Telangiectasia	1.4%	0.7%	0.511

Pore size	5.1%	1.5%	0.007
Irregular depigmentation	9.0%	2.9%	0.041

d. The percentages of patients with a baseline score of 2 or more, who had a score of 0 or 1 at endpoint, were as follows.

Clinical signs Patients with score of 0 or 1 Study 34C			
	Tazarotene	Vehicle	p value
Fine wrinkling	19.7%	7.4%	< 0.001
Mottled hyperpigmentation	42.6%	17.6%	< 0.001
Lentigines	37.9%	14.1%	< 0.001
Elastosis	22.2%	6.1%	< 0.001
Tactile roughness	54.1%	44.8%	0.043
Coarse wrinkling	10.2%	4.3%	0.020
Telangiectasia	17.5%	16.9%	0.906
Pore size	26.5%	13.3%	< 0.001
Irregular depigmentation	41.0%	23.1%	0.003

4) Efficacy parameters: Overall assessments.

a. Overall assessments: At endpoint, the percentage of patients with an improvement of one grade in the overall integrated assessment (OIA) of photodamage, and the percentage of patients that had a 50% or greater improvement in the global response to treatment were as follows.

Results of OIA and Global Response Study 34C			
	Tazarotene n=284	Vehicle n=284	p value
OIA *	53.5%	16.5%	< 0.001
Global response **	65.5%	18.9%	< 0.001
* improvement by one grade at endpoint ** 50% or more improvement at endpoint			

The global response above was calculated for 278 and 281 patients in the active and vehicle groups, respectively, rather than for the

ITT population of 284 patients in each group.

b. Actinic keratoses: The mean change at endpoint in the number of actinic keratoses was - 0.2 in the tazarotene group and - 0.32 in the vehicle group (p=0.690).

c. Patient's overall assessment of photodamage: The overall assessment of photodamage at endpoint was as follows.

Patient assessment of photodamage Study 34C		
	Tazarotene n=278	Vehicle n=280
Much improved	48%	12%
Somewhat improved	41%	34%
No change	9%	53%
Somewhat worse	1%	1%
Much worse	0.4%	0

d. Subgroup analyses. Analyses of the improvement in fine wrinkling and mottled hyperpigmentation by one point from baseline were done by age categories, sex, race, and severity at baseline, as follows. (Subgroup analyses of the changes in other clinical signs are not provided.)

Fine wrinkling: analysis by age Improvement of one grade or more at endpoint Study 34C			
	Tazarotene n=284	Vehicle n=284	p value
< 40 years	67% (16/24)	19% (5/26)	0.001
40 - 65 years	59%(123/209)	24% (50/209)	< 0.001
> 65 years	51% (26/51)	18% (9/49)	< 0.001

Mottled hyperpigmentation: analysis by age Improvement of one grade or more at endpoint Study 34C			
	Tazarotene n=284	Vehicle n=284	p value
< 40 years	88% (21/24)	58% (15/26)	0.028
40 - 65 years	81%(170/209)	37% (77/209)	< 0.001
> 65 years	80% (41/51)	41% (20/49)	< 0.001

Fine wrinkling: analysis by sex Improvement of one grade or more at endpoint Study 34C			
	Tazarotene n=284	Vehicle n=284	p value
Male	66% (23/35)	24% (11/45)	< 0.001
Female	57%(142/249)	22% (53/239)	< 0.001

Mottled hyperpigmentation: analysis by sex Improvement of one grade or more at endpoint Study 34C			
	Tazarotene n=284	Vehicle n=284	p value
Male	74% (26/35)	40% (18/45)	0.003
Female	83%(206/249)	39% (94/239)	< 0.001

Fine wrinkling: analysis by race Improvement of one grade or more at endpoint Study 34C			
	Tazarotene n=284	Vehicle n=284	p value
White	59% (164/279)	23% (63/276)	< 0.001
Non-white	20% (1/5)	13% (1/8)	> 0.999

Mottled hyperpigmentation: analysis by race Improvement of one grade or more at endpoint Study 34C			
	Tazarotene n=284	Vehicle n=284	p value
White	82% (228/279)	40%(109/276)	< 0.001
Non-white	80% (4/5)	38% (3/8)	0.266

Fine wrinkling: analysis by baseline severity Improvement of one grade or more at endpoint Study 34C			
	Tazarotene n=284	Vehicle n=284	p value
Mild	44% (27/61)	21% (12/58)	0.007
Moderate	66% (98/148)	21% (31/145)	< 0.001
Severe	53% (40/75)	26% (21/81)	< 0.001

Mottled hyperpigmentation: analysis by baseline severity Improvement of one grade or more at endpoint Study 34C			
	Tazarotene n=284	Vehicle n=284	p value

Mild	85% (52/61)	43% (25/58)	< 0.001
Moderate	82% (121/148)	43% (63/145)	< 0.001
Severe	79% (59/75)	30% (24/81)	< 0.001

5) Safety assessment. The adverse events of the skin and appendages which occurred in 1% or more of the patients were as follows.

Adverse events - skin and appendages Occurring in 1% or more of patients Study 34C		
	Tazarotene n=284	Vehicle n=284
Desquamation	118 (42%)	6 (2%)
Erythema	104 (37%)	9 (3%)
Burning sensation	59 (21%)	1 (0.4%)
Dry skin	47 (17%)	7 (3%)
Skin irritation	46 (16%)	1 (0.4%)
Pruritus	25 (9%)	4 (1%)
Irritant contact dermatitis	16 (6%)	1 (0.4%)
Rash	9 (3%)	3 (1%)
Stinging	7 (3%)	1 (0.4%)
Acne	5 (2%)	8 (3%)
Dermatitis	5 (2%)	2 (1%)
Allergic contact dermatitis	4 (1%)	1 (0.4%
Excoriated skin	3 (1%)	0
Skin tightness	3 (1%)	0
Papules	2 (1%)	1 (0.4%)
Vesiculobullous rash	2 (1%)	1 (0.4%)
Herpes simplex	2 (1%)	0
Seborrhea	2 (1%)	0
Skin erosion	2 (1%)	0
Skin reaction	2 (1%)	0

The following adverse events of the skin and appendages in the

tazarotene group were denoted as severe: desquamation in 2, erythema in 2, burning in 1, dry skin in 1, severe irritation in 1, irritant contact dermatitis in 1, urticaria in 1, and eyelid edema in 1. There were no severe adverse events of the skin and appendages in the vehicle group.

Eight tazarotene patients and 2 vehicle patients discontinued from the study due to adverse events of the skin and appendages; these were as follows.

Subjects discontinued due to adverse events of the skin Study 34C	
Subject #	Adverse event
Tazarotene 0.1%	
0188-2209	Moderate skin irritation
0272-2168	Irritant contact dermatitis
0432-2140	Mild to moderate facial peeling
1565-2551	Moderate burning, scaling, and erythema
2930-2414	Moderate burning, dryness, erythema; severe lid edema
2930-2420	Moderate peeling, erythema
3160-2274	Moderate dryness, peeling, erythema
3160-2275	Mild eye edema
Vehicle	
1565-2291	Mild vesiculobullous rash (fever blister)
2930-2438	Mild erythema, skin eruption

Reviewer's evaluation of Study 34C

1. Efficacy. Reference is made to the Reviewer's Evaluation of Study 33C for a discussion of the primary efficacy variables and the appropriate analyses; the evaluation of the results of Study 034C is in accordance with that of Study 033C.

The results of Study 34C show that tazarotene cream 0.1% was significantly superior to the vehicle for both fine wrinkling and mottled hyperpigmentation in the proportion of subjects that had an improvement of two or more points over baseline. This was considered by this reviewer to be the primary efficacy endpoint.

The results of the other methods of analysis showed that tazarotene cream 0.1% was significantly superior to the vehicle for fine

wrinkling and mottled hyperpigmentation in:

a. *the proportion of subjects with an improvement of one grade at endpoint, and*
b. *the proportion of subjects with a baseline score of at least 2 that had a score of 0 or 1 at endpoint.*

Tazarotene cream 0.1% was significantly superior to the vehicle for mottled hyperpigmentation, but not for fine wrinkling, in the proportion of patients with a baseline score of 2 or more that had a score of 0 at endpoint.

2. Safety. As in Study 33C, the predominant adverse events were desquamation, erythema, and burning, which occurred in 21-42% of subjects, with dry skin, irritation, and pruritus in 9-22% of subjects. Severe adverse events of the skin and appendages in the tazarotene group were as follows: desquamation in 2, erythema in 2, burning in 1, dry skin in 1, urticaria in 1, and eyelid edema in 1. There were no severe adverse events of the skin and appendages in the vehicle group.

Labeling review

The clinical labeling review is deferred, as consultation is needed with Biostatistics on the clinical data included in the proposed labeling, particularly concerning values that reflect the results in the observed population, rather than the ITT population.

Summary and evaluation

This NDA is for Tazorac (tazarotene) cream 0.1% for the proposed indication [redacted] Tazorac cream 0.1% has been approved for the treatment of psoriasis and acne.

1. Efficacy. Two pivotal clinical studies (033C and 034C) were performed for a determination of safety and effectiveness. The protocol was the same for both studies except that an open label period was included and plasma drug monitoring was done in Study 033C, but not in Study 034C. Both studies were double blind, multicenter, parallel group comparisons of Tazorac cream with its vehicle in subjects with clinical signs of photoaging of the facial skin. Applications were made once daily for 24 weeks. Study 033C had an additional open label treatment phase of 28 weeks. For the evaluation of efficacy, grading of the individual clinical signs was done on a five point scale, overall assessments of photodamage were made, and an investigator's global assessment of response to treatment was performed. Study 033C enrolled 563 patients and Study 034C enrolled 568 patients.

As stated by the Division at the End of Phase 2 meeting, there is no known primary efficacy variable for 'photodamage' per se, and the validity of an overall evaluation of photodamage such as the sponsor's 'overall integrated assessment of photodamage' has not been determined. We stated that the clinical signs of photodamage should be the primary endpoints, and that these will be acceptable as individual indications if the product is shown to be effective for the particular signs.

Nine clinical signs were evaluated in these studies, Of the nine signs, fine wrinkling and mottled hyperpigmentation were considered by the sponsor to be primary efficacy variables; lentigines and elastosis were considered secondary variables, and irregular depigmentation, tactile roughness, coarse wrinkling, telangiectasia, and pore size were 'other' variables.

The protocol for Study 33C was reviewed by the Agency subsequent to the End of Phase 2 meeting. In the comments, which were conveyed to the sponsor, the Agency stated that the primary efficacy parameters (i.e., fine wrinkling and mottled hyperpigmentation) are acceptable, but that the inter- and intra- observer consistency should be addressed. It was also stated that the validation for the measurement of the secondary and 'other' parameters should be presented. Study 37C was submitted to address inter- and intra- rater reliability. This study is supportive of the primary efficacy variables, but does not provide clinical validation of the scoring scales for the secondary and 'other' endpoints.'

The clinical signs which are designated as primary efficacy variables by the sponsor in the Phase 3 protocol, namely, fine wrinkling and mottled hyperpigmentation, are considered to be the primary endpoints for claims approval.

The additional clinical signs, designated as secondary and other variables by the sponsor, have not been accompanied by demonstration of clinical validity or adequate scoring scales for approval as novel claims. In particular, pore size and elastosis are not considered to be accompanied by adequate clinical validation. The sponsor has not demonstrated the method by which pore size was assessed during the clinical trial. The labels ' small, medium, large' are not standard terminology which would be immediately clinically relevant across the physician population. There is essentially no literature which addresses this issue.

Therefore, the evaluation of the results by this reviewer is restricted to the changes in fine wrinkling and mottled hyperpigmentation.

At the pre-NDA meeting, the sponsor proposed a definition of treatment success as a one grade improvement from baseline. We requested that in addition they perform analyses based on the following definitions of

treatment success:

1) *A severity score of 0 (none) at endpoint.*
2) *A severity score of 0 (none) or 1 (minimal) at endpoint.*
3) *Improvement from baseline by at least two grades at endpoint.*

The sponsor has provided these analyses in those subjects with a grade of 2 (mild) or more at baseline. In accordance with our discussion on photodamage endpoints, it was felt by this reviewer that the most appropriate method of analysis is a comparison of the proportion of subjects with an improvement of at least two grades from baseline.

The results of both Studies 033C and 034C show that tazarotene cream 0.1% was significantly superior to the vehicle for fine wrinkling and mottled hyperpigmentation in the proportion of subjects with an improvement of at least two grades from baseline.

The results of the other methods of analysis showed that in both studies tazarotene cream 0.1% was also significantly superior to the vehicle for fine wrinkling and mottled hyperpigmentation in:

a. *the proportion of subjects with a clinical improvement of one grade at endpoint, and*
b. *the proportion of subjects with a baseline score of at least 2 that had a score of 0 or 1 at endpoint.*

Few patients with a baseline score of 2 or more had a score of 0 at endpoint; this was significant only for mottled hyperpigmentation in both studies.

On the basis of these results it is felt that the effectiveness for the indications fine wrinkling and mottled hyperpigmentation has been adequately demonstrated.

2. Safety. In both studies the most frequent adverse events were desquamation, erythema, burning, and dry skin. The incidence and severity of these events were lower in the extended open label treatment phase of Study 33C.

Plasma determinations of tazarotenic acid, the primary metabolite of tararotene, were done throughout the double blind and open phases of Study 33C. It was found that the levels were similar in the first 24 week period and in the second 28 period, indicating that drug accumulation did not occur.

<u>Conclusions</u>: It is felt that the safety and effectiveness of Tazorac cream 0.1% for the proposed labeling indications have not been adequately demonstrated. There is an adequate demonstration of safety and effectiveness for the indications fine wrinkling and mottled hyperpigmentation.

Recommendations: It is recommended that the application not be approved. The application is approvable with revision of the labeling indications, together with revisions of other sections of the proposed labeling, for the indications fine wrinkling and mottled hyperpigmentation.

/S/

Phyllis A. Huene, M.D.

cc: NDA 21-184/S-002
HFD-540/Wilkin
HFD-540/Walker
HFD-540/Huene
HFD-540/Alosh
HFD-540/Fritsch
HFD-540/Jacobs
HFD-540/DeCamp

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/s/

Phyllis Huene
4/22/02 12:59:33 PM
MEDICAL OFFICER

Susan Walker
4/22/02 03:47:08 PM
MEDICAL OFFICER
Concur with findings and recommendations

Jonathan Wilkin
4/28/02 05:24:31 PM
MEDICAL OFFICER
Even though there are no patient assessments of the individual indications, I concur that this application is (only) approvable for fine wrinkling and mottled hyperpigmentation.