3 Chemistry/Manufacturing Controls The CMC Review is not available at this time. The drug products have the following formulations (percent w/w):

	Tazarotene 0.05%	Tazarotene 0.1%
Tazarotene	0.050	0.10
Benzyl Alcohol NF		
Sodium Thiosulphate USP		
EDTA Disodium USP		
Mineral Oil USP		
Medium Chain Triglycerides		
Carbomer 1342 NF		
Sorbitan Monooleate NF		
Carbomer 934P NF		
Sodium Hydroxide NF		
Purified water USP		

4 Animal Pharmacology/Toxicology Pharm/Tox Review is not available at this time.

5 Microbiology There is no Microbiology section in this NDA.

6 Human Pharmacokinetics/Pharmacodynamics Biopharm Review is not available at this time.

7 Human Clinical Experience

7.1 Foreign experience Tazarotene creams 0.05% and 0.1% have not been marketed anywhere. Tazarotene gels 0.05% and 0.1% are available in the U.S., Canada, the European Union and Latin America. To-date there are no marketing applications pending for tazarotene creams 0.05% or 0.1% in any country other than the U.S.

7.2 Post-Marketing Experience None

8 Clinical Studies

8.1 Introduction

In mid-1995, NDA 20-600 was filed for tazarotene gels 0.1% and 0.05% in the treatment of acne and psoriasis. Approval for marketing was obtained in June 1997. Subsequently, the Applicant developed cream formulations at the same concentrations. Based on the results of preclinical toxicology, pharmacology, and pharmacokinetic studies, 5 formulations of tazarotene cream were evaluated in a phase 1 study (Study 190168-503C). One tazarotene cream formulation type was selected for further development, modified slightly (a minor excipient was changed), and used in all subsequent studies. The cream formulation type chosen was associated with somewhat lower cumulative irritation scores than had been observed with a gel formulation at the same concentrations. The clinical studies in support of this NDA are listed in the following Table:

Study Number	Design	Treatment Dose	Exposure	Subject No	Mean Age (Range)	M:F	Race (C:non-C)
Phase 1 Formulation-Selection Study of Tazarotene Cream on Healthy Volunteers							
190168 -503C	single center, investigator-masked randomized, veh-controlled, (open label), incomplete block	5 tazarotene creams 0.01% 5 tazarotene creams 0.05% 5 tazarotene creams 0.1% vehicle cream tazarotene gel 0.05% tazarotene gel 0.1% Renova® cream 0.05% Retin-A® cream 0.05% Retin-A® cream 0.1%	15 applications over 21-days	100	40 (18-65)	16:84	100:0
Phase 1 Human Dermal Safety Studies of Tazarotene Cream on Healthy Volunteers							
190168 -019C for irritancy	single center, double-blind, randomized, veh-controlled, complete block	tazarotene cream 0.01% tazarotene cream 0.025% tazarotene cream 0.05% tazarotene cream 0.1% tazarotene vehicle cream sodium lauryl sulfate 0.5%	18 applications over 21 days	40	51 (29-69)	9:31	27:13
190168 -020C for sensitization	single center, double-blind, randomized, veh-controlled, complete block	tazarotene cream 0.01% tazarotene cream 0.025% tazarotene cream 0.05% tazarotene cream 0.1% tazarotene vehicle cream	10 applications over 39 days	230	46 (18-70)	44:186	83:147
190168 -021C for photoallergenicity & phototoxicity	single center, double-blind, randomized, veh-controlled, complete block	tazarotene cream 0.01% tazarotene cream 0.025% tazarotene cream 0.05% tazarotene cream 0.1% tazarotene vehicle cream	duplicate sites; 8 applications over 46 days	30	46 (23-71)	4:26	29:1
190168 -032C for photoallergenicity (repeat with UVB & UVA)	single center double-blind, randomized, veh-controlled, complete block	tazarotene cream 0.05% tazarotene cream 0.1% tazarotene vehicle cream	7 applications over 46 days	30	52 (26-70)	2:28	30:0
Phase 1 Human Pharmacokinetic Studies of Tazarotene Cream on Psoriasis Patients							
190168 -023C	multicenter, open-label stratified by % psoriatic involvement	tazarotene cream 0.1% 2 mg/cm^2 qd tazarotene cream 0.1% 10 mg/cm^2 qd	14 days 14 days	11	45 (23-68)	4:7	11:0
190168 -024C	single center, open-label, stratified by % psoriatic involvement	tazarotene cream 0.1% 2 mg/cm^2 qd tazarotene cream 0.1% 10 mg/cm^2 qd	14 days 14 days	9	51 (31-59)	3:6	9:0
Phase 3 Controlled Clinical Trials on Psoriasis Patients							
190168 -016C	multicenter, double-blind, randomized, veh-controlled	tazarotene cream 0.05% qd tazarotene cream 0.1% qd tazarotene vehicle cream qd	12 wks 12 wks 12 wks	218 221 229	49 (18-84) 50 (19-83) 48 (21-84)	146:72 135:86 151:78	193:25 189:32 199:30
190168 -017C	multicenter, double-blind, [illegible] veh-controlled	tazarotene cream 0.05% qd tazarotene cream 0.1% qd tazarotene vehicle cream qd	12 wks 12 wks 12 wks	210 211 214	48 (19-77) 47 (19-80) 47 (19-82)	132:78 136:75 116:98	182:28 183:28 181:33

veh=vehicle. C:non-C=Caucasians:non-Caucasians.

8.2 Indication #1 Plaque Psoriasis

Psoriasis is a chronic inflammatory disorder affecting the skin and, in some patients, psoriatic arthritis may be present. The most common form is a stable condition characterized by plaques which represent thickening of the skin, scaling and erythema.

Tazarotene is a retinoid which has been shown to be effective in the treatment of plaque psoriasis when administered in the gel formulations 0.05% and 0.1%.

The tazarotene creams 0.05% and 0.1% are actually line extensions of tazarotene gels. Allergan was advised of the options for their development at a teleconference dated 11/24/97 (See Section 1.12). The route of two adequate and well-controlled studies, each demonstrating superiority of both creams over vehicle, was chosen.

The Applicant's rationale for having two concentrations is as follows: As with the gel formulations, two concentrations may allow patients and physicians greater flexibility and utility. It was anticipated that the 0.1% concentration would provide an earlier onset of action and greater efficacy overall than the 0.05% concentration. For patients able to tolerate the higher dose, there may be benefit from earlier and better efficacy. Other patients may only tolerate the lower dose, but can still have substantial improvement which they may otherwise not achieve. While some physicians may be inclined to start patients on the lower concentration of tazarotene, others may wish to prescribe the higher dose to begin with, and titrate the patient to the lower dose once the disease has been brought under control.

Comment The marketing of two concentrations requires demonstration of efficacy of both and meaningful differences between the two. In previous interactions with the Agency, this issue has been brought up to the Applicant, but other than a discussion of multiplicity adjustment, no agreement has been reached on how the differences between the two concentrations need be demonstrated. In the last interaction at the pre-NDA meeting, the following guidance was provided:

- The Sponsor should give proper rationale for the dose (concentration, frequency and duration) selected for marketing. In general, the drug product showing best effectiveness and not worse in toxicity when compared to others should be selected. If more than one concentration is proposed, proper justification for having both should be provided.

In line with this guidance provided to the Applicant is the inherent assumption that the product with best efficacy should not be worse in safety. If the product with best efficacy does have greater toxicity, then there will be a place for the product with lesser efficacy (provided that this less efficacious product is still efficacious (superior over vehicle).

Therefore, this Reviewer regards the following essential in the consideration of a regulatory decision on the marketing of tazarotene 0.05% and 0.1% gels:

1. demonstration of superior efficacy vs vehicle for both;
2. establishment of (a) greater efficacy in one formulation and (b) better safety in the other.

The criteria for greater efficacy and better safety between the formulations have not been addressed in previous interactions with the applicant. However, the ICH E4 document "*Guideline for Industry. Dose-response information to support drug registration*" does provide some helpful points for consideration:

- "In principle, being able to detect a statistically significant difference in pair-wise comparisons between doses is not necessary if a statistically significant trend (upward slope) across doses can be established using all the data." As it may actually be difficult to demonstrate statistically significant differences between doses, the guideline proposes that the emphasis be on "the elucidation of the dose-response function, not individual pair-wise comparisons." Therefore, attempts will be made in this review to show statistical significance and elucidation of dose-response function.

- "In addition to seeking dose-response information from studies specifically designed to provide it, the entire database should be examined intensively for possible dose-response effects." Effort will be made in examining the dermal safety studies and PK data for differences in this review.

It should also be noted that -

1. The clinical trials were powered to demonstrate significant differences between actives and vehicle but not between the actives. In the phase 3 protocols, the powering was based on the following assumption: "Hochberg step-up multiple comparison procedure based on the first comparison (0.05% vs. vehicle). The two-sided alpha level used for this comparison was 0.05. It is assumed that the p-values corresponding to the 0.05% vs. vehicle and 0.1% vs. vehicle will be ordered p1 > p2." Thus, the assumption was simply p1 > p2, with the 0.05% superior over vehicle (and superiority of the 0.1% concentration would follow if indeed p1 > p2), but not necessarily statistical significance between the two actives.

2. The above discussion focuses on efficacy. Clinical trials are not powered to demonstrate differences in safety unless specifically designed to do that, which is not the case here. Thus, if there is a statistical difference in a clinically meaningful endpoint for safety, that will be a very important finding for consideration. For topical retinoids, the main concern is local irritation. Another consideration is systemic availability, which has been only studied formally for tazarotene cream 0.1%, although there are data on therapeutic drug monitoring in the phase 3 trials.

3. Similar analysis was used in the review of tazarotene gels 0.05% and 0.1% (in showing greater efficacy of 0.1% and better safety 0f 0.05% gels). Since the Agency offered the option of line extension to the Applicant in November, 1997, theoretically the Applicant only needed to demonstrate noninferiority of each cream formulation to the corresponding gel and superiority over vehicle in one study for marketing. However, this option would be predicated on the assumption of clinically meaningful differences between the approved tazarotene gels. Because of this, consistency in review methodology between the two NDA applications (tazarotene gels and creams) is especially important, when the current NDA for tazarotene creams does not use the line extension route. The two independent but identically designed (for the treatment period) studies in this NDA actually provide a better database and allow more rigorous approach in the direct comparison between the two strengths.

Therefore, although it is unrealistic to be specifically looking for statistical [illegible] by pairwise comparison, this review will include such comparison whenever possible, but will also examine the database as a whole for meaningful differences.

Formal dose-ranging studies have not been conducted. The concentrations were chosen on the basis of the approved gel formulations (0.05% and 0.1%). The Applicant addresses the frequency and duration aspects of dose-ranging as follows, basing the rationale on findings with tazarotene gels (Study R168-111-7997):

Dosing interval -

- Efficacy: once daily (QD) application was (a) similar to twice daily (BID) application for tazarotene gel 0.1% and (b) only slightly less effective for tazarotene 0.05%.
- Safety: irritation was less with QD than with BID application of tazarotene gels.

Duration -

[illegible] duration was based upon previous experience with tazarotene gels.

Comment The choice of concentration, dosing interval and duration for study is based on data for tazarotene gels. There are no previous efficacy data on tazarotene creams. This approach is similar to that used in the development of new dosage forms for other topical drug products and is acceptable. Originally, the planned phase 3 clinical studies included an arm of tazarotene cream 0.025% cream. Allergan eventually decided against testing this arm; previous data did not demonstrate efficacy of tazarotene gels with strength lower than 0.05% (Study R168-110-8225).

In the current submission, the Sponsor has presented two adequate and well controlled studies in patients with stable plaque psoriasis: 190168-016C and -017C.

8.2.1 Trial #1, Multicenter, Double-Blind, Randomized, Vehicle-Controlled Study of the Safety and Efficacy of 0.05% and 0.1% Tazarotene Creams Applied Once Daily for 12 Weeks, with a 12-Week Follow-Up, in the Treatment of Plaque Psoriasis (Study #190168-016C) [Initiated 12/29/97, completed 1/22/99]

8.2.1.1 Objectives: To assess the safety and efficacy of tazarotene creams 0.05% and 0.1% vs vehicle cream applied once daily for 12 weeks, with a 12-week follow-up period, in the treatment of plaque psoriasis.

8.2.1.2 Design: Multi-center, double-blind, randomized, vehicle-controlled, parallel-group study with a total of 624 patients to be enrolled in 3 arms (to yield 156 evaluable patients per arm) and once daily application of study cream in the evening for 12 weeks. Non-medicated emollients could be used as needed on all treated lesions, except 2 selected target lesions. The 3 arms were: tazarotene 0.05%, tazarotene 0.1% and vehicle creams. Patients entered a post-treatment period of 12 weeks following the end of the initial 12 weeks of treatment.

Schedule of Study Visits and Measurements

	Week 0	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
informed consent	X								
medical history	X								
baseline exam	X								
laboratory tests[a]	X			X[b]	X[b]	X			
urine pregnancy test[c]	X			X	X	X			
evaluate lesions	X	X	X	X	X	X	X	X	X
photographs[d]	X	X	X	X	X	X	X	X	X
dispense study med	X		X	X	X				
collect study med			X	X	X	X			

a hematology, blood chemistry, urinalysis
b additional blood samples drawn from patients at selected sites for determination of plasma tazarotenic acid levels
c if applicable
d at selected sites

8.2.1.3 Protocol Overview

8.2.1.3.1 Population and Procedures

8.2.1.3.1.1 Population

Inclusion criteria:

1. Male or female patients, 18 years or older who had plaque psoriasis.
2. Psoriasis involvement of at least 2% of the total body surface area (BSA).
3. Baseline overall assessment of all lesions to be treated ≥ 3 on a 6-point scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe).
4. One target lesion located on the elbow or knee and a second target lesion of similar severity located on the [illegible] elbow), or leg (excluding knee).
5. Minimum diameter of each target lesion 2.0 cm.
6. Baseline plaque elevation scores for each target lesion ≥ 2 on a 5-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe).
7. Normal menstrual cycle for female patients of childbearing potential prior to study entry (note: a female was considered of childbearing potential unless she was postmenopausal, without a uterus and/or both ovaries, or had bilateral tubal ligations).
8. A negative urine pregnancy test for female patients of childbearing potential at time of study entry.
9. Ability to follow study instructions and likely to complete all study requirements.

10. Anticipated acceptable blood and urine laboratory test results (note: acceptable test results were either those within the central laboratory's reference range or those "out-of-range" but acceptable to the investigator, consistent with inclusion/exclusion criteria).
11. Written informed consent.

Exclusion criteria:

1. Known sensitivity to any of the ingredients in the study medication.
2. History or evidence of skin conditions (eg, eczema) other than psoriasis, that would have interfered with evaluation of the study medication.
3. Anticipated need to use emollients on target lesions.
4. Spontaneously improving or rapidly deteriorating plaque psoriasis.
5. History or evidence of pustular or erythrodermic psoriasis.
6. Anticipated need to use topical or systemic therapies that might have altered the course of psoriasis.
7. Use of topical therapies that might have altered the course of psoriasis (eg, topical corticosteroids, topical retinoids, topical calcipotriene) within 2 weeks prior to study entry.
8. Use of oral retinoids (eg, etretinate, isotretinoin) within 8 weeks prior to study entry.
9. Use of systemic drugs other than retinoids (eg, methotrexate) that might have altered the course of psoriasis within 4 weeks prior to study entry.
10. PUVA treatment within 4 weeks prior to study entry.
11. UVB treatment within 2 weeks prior to study entry.
12. Required or desired excessive or prolonged exposure to ultra-violet light (eg, sunlight, tanning beds) during the study.
13. Uncontrolled systemic disease, including known positive HIV test.
14. Current evidence of chronic alcohol or drug abuse.
15. Evidence of active hepatitis B or C.
16. Anticipated need for surgery or hospitalization during the study.
17. Females who were pregnant, nursing, or planning a pregnancy.
18. Females of childbearing potential not using reliable means of contraception during the study.
19. Participation in another study (e.g., investigational drug or device study) within 30 days prior to entry into this study.
20. Condition or situation which, in the investigator's opinion, may have put the patient at significant risk, confounded the study results, or interfered significantly with the patient's participation in the study.

Early Termination of Therapy, Dropouts and Protocol Deviations

Patients could be discontinued from the study prior to completion of 12 weeks treatment and 12 weeks post-treatment for lack of efficacy, adverse events, protocol violations, pregnancy, or administrative reasons (eg, inability to continue, lost to follow-up). At the discretion of the investigator, any patient who experienced an adverse event or who had a response to treatment that affected his or her welfare, was discontinued from the study and received appropriate therapy. Investigators could also discontinue patients for reasons of medical prudence, unrelated to the study medication. Patients who were inadvertently enrolled despite significant deviation from protocol-specified criteria were discontinued from the study. Patients could voluntarily withdraw at anytime. Study medication could also be discontinued prior to 12 weeks if the psoriasis was completely cleared. Female patients of child-bearing potential who discontinued prematurely had a urine pregnancy test performed at the exit visit.

8.2.1.3.1.2 Procedures

The schedule of procedures has been given above (Section 8.2.1.2).

Application of Test Material:

The following instructions regarding use of the test medication are in the study protocol:

- Patients should apply a thin layer of the study medication to all psoriatic lesions
- Patients should avoid applying the study medication to normal (i.e., non-involved) skin. If the study medication accidentally gets on normal skin, patients should wash it off.
- Patients should avoid bringing the study medication in contact with their eyes, eyelids and mouth. If contact with these areas occurs, patients should rinse the area thoroughly with water.
- Patients should wash their hands after applying the study medication, unless they are treating their hands for psoriasis.
- If patients bathe or shower in the evening, they will be instructed to apply the study medication after they have allowed their skin to dry.
- If patients usually apply non-medicated emollients in the evening, they will be instructed to apply their own emollient (non-target lesions only) at least one hour before application of study medication.
- Patients should NOT apply their own emollient the evening prior to each study visit. However, they may apply their emollient after their study evaluation has been completed.

- Patients should avoid excessive sun exposure (e.g., sunlight, tanning booths) and should wear protective clothing when exposed to sunlight (e.g., hat, long-sleeved shirt, visor).
- Patients will be instructed to notify the investigator if their total disease appears to be "completely cleared". The patient will be instructed to return for an evaluation, and the investigator will determine whether treatment should be continued or stopped.
- Patients should store the study medication at room temperature and protect it from freezing. Storage instructions will be included on each medication label.
- Patients will be instructed to bring back all tubes of study medication (e.g., used, unused or partially used) at each visit. Additional study medication will be dispensed at each visit as needed.
- If at any visit prior to Week 12, the investigator determines that the patient's psoriasis has "completely cleared", all study medication should be returned.
- Patients will be instructed to fast 8 hours prior to blood collection for laboratory tests (hematology, blood chemistry and urinalysis).
- If repeat laboratory tests are required for lipids (e.g., triglyceride, cholesterol, HDL, or LDL), patients will be requested to fast for 12 hours prior to collection of blood.
- For therapeutic drug monitoring at selected sites, participating patients will have two additional study visits where non-fasting blood samples will be collected for the determination of "tazarotenic acid".

Prior/Concomitant Therapy and Compliance

Within 2 weeks prior to study entry, patients must not have used topical drugs that might alter the course of psoriasis (eg. topical corticosteroids, calcipotriene). Patients must not have used oral retinoids (eg, etretinate, isotretinoin) within 8 weeks prior to study entry, or systemic drugs other than retinoids (eg, methotrexate) that might alter the course of psoriasis within 4 weeks prior to study entry. Patients must not have had PUVA treatment within 4 weeks prior to study entry, or UVB treatment with 2 weeks prior to study entry. During the treatment and post-treatment periods, permissible medications included any therapy considered necessary for the patient's welfare that would not interfere with the response to treatment. Prohibited medications during the study included medicated emollients (eg, those containing corticosteroids), and medications or treatments that might alter the course of psoriasis, including calcipotriene, UVB, and PUVA.

Study medication usage was monitored. Patients were requested to bring back all tubes of study medication at each visit. At each return visit, patients were queried regarding use of concomitant medications. At selected sites, blood was drawn for plasma tazarotene and "tazarotenic acid" concentrations.

8.2.1.3.2 Evaluability Criteria

In the intent-to-treat (ITT) analysis, all patients randomized and dispensed study medication are considered evaluable, with last observation carried forward (LOCF) methodology. Per protocol analysis is also performed, with the following evaluability criteria for patient inclusion:

1) meeting specific entry criteria for the study
2) no major protocol violations
3) meeting visit-specific criteria such as proper (acceptable) use of concomitant medications or therapies. maintenance of specified drug regimen, acceptable level of compliance regarding use of medication
4) visits occurring within derived visit windows
5) at least one follow-up visit with evaluable data.

Comment The Applicant specifies in the protocol that per protocol analysis is the primary analysis. However, the Agency accepts the ITT analysis as the primary analysis. This has been discussed with the Applicant previously and both analyses have been presented for review.

8.2.1.3.3 Endpoints

Efficacy

The primary efficacy variable was based on a static global evaluation called "overall lesional assessment" (OLA). Each Investigator was given examples of the grades on photographs. The Applicant provided training sessions to familiarize the Investigators with this parameter, which consisted of the evaluation of clinical signs in all treated lesions as a whole, using a 6-point scale. The scores were:

0 None - no plaque elevation above normal skin level; may have residual non-erythematous discoloration; no psoriatic scale

1 Minimal - essentially flat with possible trace elevation; may have up to moderate erythema (red coloration); no psoriatic scale
2 Mild - slight but definite elevation of plaque above normal skin level; may have up to moderate erythema (red coloration); fine scales with some lesions partially covered
3 Moderate - moderate elevation with rounded or sloped edges to plaque; moderate erythema (red coloration); somewhat coarser scales with most lesions partially covered
4 Severe - marked elevation with hard, sharp edges to plaque; severe erythema (very red coloration); coarse, thick scales with virtually all lesions covered and a rough surface
5 Very severe - very marked elevation with very hard, sharp edges to plaque; very severe erythema (extreme red coloration); very coarse, thick scales with all lesions covered and a very rough surface

The primary endpoint was defined as "clinical success": an overall lesional assessment score of none, minimal, or mild at week 12.

Comment Overall lesional assessment is a static global evaluation previously discussed with the Agency and the cutoff for dichotomization between mild and moderate is acceptable.

Secondary efficacy measures were as follows:

Overall Plaque Elevation

Plaque elevation of all treated lesions was evaluated at baseline and each follow-up visit using a 5-point scale.

0 None - no evidence of plaque above normal skin level
1 Mild - slight but definite elevation above normal skin level
2 Moderate - moderate elevation with rounded or sloped edges to plaque
3 Severe - marked elevation with hard, sharp edges to plaque
4 Very severe - very marked elevation with very hard, sharp edges to plaque

Overall Scaling

Scaling of all treated lesions was evaluated at baseline and each follow-up visit using a 5-point scale.

0 None - no evidence of scaling on the lesions
1 Mild - mainly fine scales with some lesions at least partially covered
2 Moderate - somewhat coarser scales with most lesions at least partially covered
3 Severe - coarse, thick scales with virtually all lesions covered and rough surface
4 Very severe - very coarse, thick scales with all lesions covered and very rough surface

Overall Erythema

Erythema of all treated lesions was evaluated at baseline and each follow-up visit using a 5-point scale.

0 None - no evidence of erythema
1 Mild - light red coloration
2 Moderate - red coloration
3 Severe - very red coloration
4 Very severe - extreme red coloration

Body Surface Area Involvement

Body surface area of involvement (ie, psoriasis involvement expressed as a % of the total body surface area) was evaluated at baseline and each follow-up visit. The % psoriasis involvement was measured as accurately as possible using the patient's hand as a guide. An open hand with the fingers together and the thumb tucked to the side is approximately equal to 1% of the total body surface area.

Overall Global Response to Treatment

Overall global response to treatment of all treated lesions was compared to baseline at each follow-up visit using a 7-point scale.

0 Completely cleared - except for possible residual non-erythematous discoloration
1 Almost cleared - very significant clearance in disease, with only traces of disease remaining (approximately 90% improvement)
2 Marked response - significant improvement with some disease remaining (approximately 75% improvement)
3 Moderate response - intermediate improvement between slight and marked response (approximately 50% improvement)
4 Slight response - some improvement but significant disease remains (approximately 25% improvement)
5 Condition unchanged
6 Condition worsened

Target Lesions Plaque Elevation, Scaling and Erythema

Plaque elevation, scaling and erythema of each target lesion was evaluated at baseline and each follow-up visit using the 5-point scale outlined above for "overall" evaluation of the signs.

Target Lesion Response to Treatment
Response to treatment of each target lesion was compared to baseline at each follow-up visit using the 7-point scale for overall global response to treatment outlined above.

Comment Overall global response is a dynamic global evaluation previously used in the trials for tazarotene gels. The Applicant further defines "treatment success" based on a cutoff for dichotomization between slight and moderate response. For the studies in support of tazarotene creams, the Agency has previously advised Allergan to use a static global evaluation with dichotomization as the primary parameter.

Safety

Adverse events and laboratory tests were monitored. The lab tests included hematology, blood chemistry, and urinalysis tests at baseline and weeks 4, 8, and 12.

Other Measures

Patient Cosmetic Acceptability Questionnaire
At the termination of the treatment period, patients were asked to complete the cosmetic acceptability questionnaire. included as an attachment to the study protocol.

Photography
At selected sites, photographs of target lesions were taken at baseline and each follow-up visit. A central photography facility processed and labeled all photographs.

Drug Concentration Measurements
Therapeutic drug monitoring of tazatorene and "tazarotenic acid" was conducted at selected sites. At these sites, patients returned for 2 additional visits 1 to 4 days after the week 4 and week 8 visits. Patients were instructed not to apply the study medication the evening prior to such visits. Trough samples were collected in the morning, and the patients given a new pre-weighed tube of study medication. The tube was re-weighed after self application of the medication. Patients were not to wash or shower until after the second blood collection, approximately 2 to 10 hours later (post-application). Application of the study medication was resumed the following evening. Plasma samples were assayed for tazarotene and "tazarotenic acid" ——— method by Allergan's Pharmacokinetic and Drug Metabolism Department.

8.2.1.3.4 Statistical Considerations:

Sample size calculation: The sample size calculation was based on data from tazarotene gels, using the primary endpoint, the incidence of "clinical success" (i.e., proportion of patients with an overall lesional assessment score of none, minimal, or mild) at week 12, with the following assumptions:

- incidence of "clinical success" in the vehicle group of 22%, based on the average overall evaluation from the week 12 endpoint in tazarotene gel studies (Study R168-120-8606 and R168-121-8606)
- difference of 15% or greater in the incidence of clinical success (based on overall lesional assessment scores) between the active treatments and vehicle
- 25% attrition rate (Study R168-121-8606)
- Hochberg step-up procedure based on the second comparison (0.1% tazarotene vs vehicle) using a 2-sided type I error of 0.025, assuming that the tazarotene 0.05% group did not differ from vehicle at a 2-sided type I error of 0.05, and that the tazarotene 0.05% vs vehicle and tazarotene 0.1% vs vehicle were ordered P1 > P2.

Based on the above, with 156 evaluable patients per treatment group (208 patients per treatment group before attrition), the power to detect a 15% difference between the tazarotene 0.05% group and vehicle was computed to be 83%.

Randomization: Randomization was performed by Allergan, with patients assigned in ascending numerical order by the investigational sites. Within each site, patients were randomly assigned to tazarotene cream 0.05%, tazarotene cream 0.1%, or vehicle cream in a 2:2:2 ratio, based on a blocking factor of 6. The treatment codes for each site were also randomized, e.g., treatment for code "A" might have been tazarotene cream 0.1% for one investigator and vehicle cream for another. The randomization was generated by SAS 6.12 PROC PLAN using a single random seed.

Populations for Analysis: Analysis was based on ITT and per protocol populations (see Section 8.2.1.3.2). The Agency uses the ITT population for primary analysis.

Primary and Secondary Efficacy Endpoints: See Section 8.2.1.3.3.

Comments

1. The primary endpoint has been discussed between the Applicant and the Agency at the Pre-IND/EOP2 meeting and at subsequent teleconferences and agreed upon at a teleconference of 11/24/97. The Agency only expects statistical superiority over vehicle with the dichotomized endpoint "clinical success" (none, minimal or mild in OLA . The Applicant additionally defines a criterion for effectiveness as ≥15% difference between active treatment and vehicle in the "clinical success" rate.
2. As discussed above (under Section 8.2), there was no agreement reached between the Agency and Allergan regarding the efficacy criteria to support a difference between the two formulations. The hypothesis in the study protocol was success of both formulations in demonstration of superior over vehicle, and in multiplicity adjustment with "Hochberg step-up multiple comparison procedure based on the first comparison (0.05% vs. vehicle). The two-sided alpha level used for this comparison was 0.05. It is assumed that the p-values corresponding to the 0.05% vs. vehicle and 0.1% vs. vehicle will be ordered p1 > p2." Superiority over vehicle adjusted for multiplicity was an approach encouraged by the Agency in the Pre-IND, Pre-NDA and intervening meetings. This review will also look at pairwise comparisons between the two concentrations.

Statistical Methods:

Analysis of Categorical Variables

The homogeneity of continuous demographic and baseline data across treatment groups was assessed using 2-way analysis of variance (ANOVA). For categorical variables, the Cochran-Mantel-Haenszel (CMH) method was used. Treatment-by-investigator interactions were assessed using the pseudo-homogeneity test. For ordinal scaled variables (e.g. plaque elevation, scaling, erythema), baseline and changes from baseline were analyzed using the extended CMH method for ordinal data or ANOVA based on ranks. The stratification factor was the investigator. Within-group comparisons to baseline at each scheduled follow-up visit were performed by the Wilcoxon signed rank test. The incidence of patients with clinical success (i.e., an OLA score of none, minimal, or mild) was analyzed by CMH test, stratified by investigator. Global response to treatment was analyzed by the extended CMH test, stratified by investigator. Multiple comparisons between the active treatments and vehicle (3 comparisons) were performed using the Hochberg step-up procedure or the Fisher protected least significant difference (LSD) test.

Analysis of Continuous Variables

Percent body surface area of involvement was analyzed by the extended CMH test. Laboratory data were analyzed using shift tables and 2-way ANOVA with treatment, investigator, and interaction effects. Plasma tazarotenic acid concentrations were summarized using descriptive statistics. Time-to-event data were analyzed by life-table methods such as Kaplan-Meier, log-rank, or Cox proportional hazards model. The blocking or stratification factor was investigator.

8.2.1.4 Study Results

8.2.1.4.1 Demographics, Evaluability

Investigators: The Investigators were:

[redacted]

Comment: The Investigators were qualified.

Enrollment per center:-

	Taz 0.1%	Taz 0.05%	Vehicle	Total
[redacted]	13	12	13	38
	4	4	6	14
	13	14	14	41
	17	17	18	52
	20	20	20	60
	16	15	15	46
	7	8	7	22
	8	8	8	24
	6	6	6	18
	9	8	9	26
	8	7	8	23
	12	13	13	38
	4	4	5	13
	15	15	15	45
	18	17	17	52
	4	4	6	14
	14	13	14	41
	15	14	16	45
	10	11	10	31
	4	5	6	15
	4	3	3	10
Total	221	218	229	668

Enrollment and dropout information for the treatment period is as follows:

Disposition	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle	Total
Enrolled	221 (100%)	218 (100%)	229 (100%)	668 (100%)
Completed	145 (66%)	125 (57%)	155 (68%)	425 (64%)
Discontinued	76 (34%)	93 (43%)	74 (32%)	243 (36%)
Non-compliance	0	2 (1%)	0	2 (0%)
Personal	8 (4%)	15 (7%)	17 (7%)	40 (6%)
Lack of efficacy	5 (2%)	17 (8%)	15 (7%)	37 (6%)
Adverse event	36 (16%)	25 (12%)	11 (5%)	72 (11%)
Concomitant therapy	4 (2%)	5 (2%)	1 (0%)	10 (2%)
Relocated	0	4 (2%)	1 (0%)	5 (1%)
Improper entry	3 (1%)	4 (2%)	5 (2%)	12 (2%)
Lost to follow-up	15 (7%)	18 (8%)	18 (8%)	51 (8%)
"Other"	5 (2%)	3 (1%)	6 (3%)	14 (2%)

Comments

1. This study has a large proportion of dropout patients.

2. Discontinuations due to adverse events were dose-related with 16.3% (36/221), 11.5% (25/218), and 4.8% (11/229) of patients in the tazarotene 0.1%, tazarotene 0.05%, and vehicle groups, respectively. Such events were primarily dermatological and included pruritus, inflammation skin, psoriasis worsened, erythema, rash, irritation skin, burning skin, pain skin, peripheral edema, irritant contact dermatitis, fissure skin, hem skin, desquamation, and dry skin.
3. It appears that the tazarotene 0.1% group has fewer dropouts due to "personal" reasons and lack of efficacy than the tazarotene 0.05% and vehicle groups.

The patients discontinued under "other" are as follows:

Tazarotene 0.1% (N=5)	Tazarotene 0.05% (N=3)	Vehicle (N=6)
A46 lesions enlarged	A51 hepatitis C	F41 Investigator leaving Penn
C27 asthma requiring steroids	C13 "high labs"	G17"personal"
C52 "high labs"	M16 "abnormal labs"	J12 unable to obtain meds in time
N11 elevated triglycerides		J33 abnormal baseline labs
N27 noncompliant		M02 entry violation
		N16 elevated labs

Comment Most of the "other" reasons could have been grouped under those in the table on patient disposition.

The post-treatment period disposition is given below:

Disposition	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle	Total
Enrolled in treat period	221	218	229	668
Completed treat period	145	125	155	425
Enters post-treat period	134 (100%)	115 (100%)	140 (100%)	389 (100%)
Completed	94 (70%)	86 (75%)	101 (72%)	281 (72%)
Discontinued	40 (30%)	29 (25%)	39 (28%)	108 (28%)
Non-compliance	0	1 (1%)	0	1 (0%)
Personal	7 (5%)	5 (4%)	5 (4%)	17 (4%)
Lack of efficacy	1 (1%)	0	0	1 (0%)
Adverse event	3 (2%)	2 (2%)	4 (3%)	9 (2%)
Concomitant therapy	2 (2%)	3 (3%)	3 (2%)	8 (2%)
Relocated	1 (1%)	0	1 (1%)	2 (1%)
Lost to follow-up	1 (1%)	0	5 (4%)	6 (2%)
Other	3 (2%)	1 (1%)	3 (2%)	7 (2%)
Need for treatment	22 (16%)	17 (15%)	18 (13%)	57 (15%)

Comments
1. The most frequent reasons for premature discontinuation in the post-treatment period were a need for treatment (14.7%, 57/389) and personal reasons (4.4%, 17/389). No patient discontinued due to pregnancy.
2. There are several reasons why the post-treatment phase is not adequate:
a. There were 36 patients who completed the treatment period but declined entering post-treatment phase. This post-randomization selection introduces bias. Thus, the post-treatment period data cannot be considered adequate to support labeling claims.
b. Moreover, even if all those who completed treatment period entered the post-treatment phase, the subjects would have been selected on the basis of completion with its own bias.
c. The baselines of the treatment arms on entry to the post-treatment phase would be different because of the different treatment effects in the treatment phase. Thus, these groups are not really comparable in their psoriasis status. Any attempt to compare "maintenance of therapeutic effect" would lead to misleading conclusions.

Demographics: Demographics of the study subjects is shown as follows:

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Age mean & range	50 (19-83)	49 (18-84)	48 (21-84)
Sex M:F	135:86	146:72	151:78
Race C:B:A:H:O	189:8:1:23:0	193:1:3:19:2	199:9:2:19:0
Percent area involved	10% (2%-85%)	11% (2%-90%)	12% (2%-95%)
OLA mean & range	3.5 (3.0-5.0)	3.4 (3.0-5.0)	3.4 (3.0-5.0)

OLA=overall lesional assessment; C=Caucasian, B=black, A=Asian, H=Hispanic, O="other";

Comment The three treatment arms are comparable. There were also no significant differences between them with respect to Fitzpatrick skin type (data not shown).

Evaluability As discussed above, since the primary analysis is by ITT with LOCF methodology, all patients are considered evaluable. Because of the presence of substantial dropout, the per protocol analysis will also be examined.

8.2.1.4.2 Efficacy

All analyses are based on ITT population unless specified.

Treatment Period

Primary Parameter: "Clincial Success" (OLA of none, minimal or mild)

Clinical Success Rates for Tazarotene 0.1% and 0.05% Creams (ITT Analysis)

Week	Taz 0.1% (N=221)	Taz 0.05% (N=218)	Vehicle (N=229)
1	13%; p=0.016 (vs vehicle)	10%; p=0.190 (vs vehicle)	
	Taz 0.1% vs Taz 0.05%: p=0.243		7%
2	22%; p=0.134 (vs vehicle)	24%; p=0.044 (vs vehicle)	
	Taz 0.1% vs Taz 0.05%: p=0.648		16%
4	35%; p<0.001 (vs vehicle)	28%; p=0.034 (vs vehicle)	
	Taz 0.1% vs Taz 0.05%: p=0.098		20%
8	34%; p=0.012 (vs vehicle)	34%; p=0.008 (vs vehicle)	
	Taz 0.1% vs Taz 0.05%: p=0.967		24%
12	39%; p<0.001 (vs vehicle)	42%; p<0.001 (vs vehicle)	
	Taz 0.1% vs Taz 0.05%: p=0.648		25%

p-values based on stratified CMH test; Hochberg's step-up procedure requires p-values for tazarotene 0.1% to be ≤0.025 for statistical significance

Comments

1. ITT population is used in the analysis, as the outcome of interest in this study is superiority over vehicle. The hypothesis is not one of equivalence or noninferiority. As to the comparison between the two formulations, the aim is to show that the null hypothesis is not established, i.e., there is a difference, although there is no prior agreement that this difference be at the usual alpha level of 0.05.
2. The OLA is a static global evaluation. The Agency advised Allergan to support efficacy with analysis of OLA using dichotomization. The emphasis was not in a change from baseline. Although it is possible to look for evidence of worsening in individual patients by analyzing changes in the score from baseline, the global response to treatment (dynamic global) gives a direct measure of change, including worsening (See below, under Comments for "Treatment Success").
3. The clinical success rate of vehicle at Week 12 (25%) is consistent with the Applicant's assumption based on tazarotene gel studies (22%)
4. Both tazarotene 0.1% and 0.05% are superior to vehicle at the predefined endpoint (Week 12), even when adjusted for multiplicity.
5. The Applicant's own criterion of effectiveness (≥15% difference between active treatment and vehicle in the "clinical success" rate) is achieved at Week 12 by tazarotene 0.05% (42%-25%=17%) but not by tazarotene 0.1% (39%-25%=14%).
6. Pairwise comparison between the 0.1% and 0.05% creams did not reveal significant difference between the two formulations at any time point. Tazarotene 0.1% cream achieves superiority over vehicle earlier (Week 1; Week 2 for tazarotene 0.1%), but this was not consistent and interrupted by a lesser response at Week 2. It became consistent from Week 4 onwards. In addition, the hypothesis of ordered p-values (p for 0.05% > p for 0.1% cream) has not been consistent for this dichotomized OLA. Thus, a [illegible] difference between the two concentrations has not been established using this primary parameter.

Because of the substantial dropout rate, the per protocol analysis is also examined here:

Clinical Success Rates for Tazarotene 0.1% and 0.05% Creams (Per Protocol Analysis)

Week	Taz 0.1% (N=221)	Taz 0.05% (N=218)	Vehicle (N=229)
1	27/192=14%; p=0.010 (vs vehicle)	22/202=11%; p=0.172 (vs vehicle)	14/197=7%
	Taz 0.1% vs Taz 0.05%: p=0.185		
2	43/181=24%; p=0.137 (vs vehicle)	49/189=26%; p=0.065 (vs vehicle)	33/184=18%
	Taz 0.1% vs Taz 0.05%: p=0.803		
4	68/175=39%; p<0.001 (vs vehicle)	55/178=31%; p=0.048 (vs vehicle)	43/185=23%
	Taz 0.1% vs Taz 0.05%: p=0.078		
8	58/142=41%; p=0.014 (vs vehicle)	57/148=39%; p=0.023 (vs vehicle)	47/165=29%
	Taz 0.1% vs Taz 0.05%: p=0.934		
12	67/135=50%; p<0.001 (vs vehicle)	65/133=49%; p<0.001(vs vehicle)	50/164=31%
	Taz 0.1% vs Taz 0.05%: p=0.887		

Comments

1. This per protocol analysis is shown to compare with the ITT analysis, and not for demonstrating equivalence or noninferiority.
2. The per protocol analysis gives similar results as the ITT analysis, although the advantage of tazarotene 0.05% at Week 2 is no longer evident. Both formulations show ≥15% difference vs vehicle at Week 12.

Secondary Parameters:

A. Change from Baseline for Clinical Signs Plaque Elevation, Scaling & Erythema at Week 12

	Plaque Elevation			Scaling			Erythema		
Lesion	Taz 0.1% N=221	Taz 0.05% N=218	Vehicle N=229	Taz 0.1% N=221	Taz 0.05% N=218	Vehicle N=229	Taz 0.1% N=221	Taz 0.05% N=218	Vehicle N=229
Overall	-0.83; p<0.001	-0.75; p<0.001	-0.48	-0.73; p<0.001	-0.67; p 0.002	-0.46	-0.42; p 0.289	-0.40; p 0.534	-0.37
	p 0.221			p 0.243			p 0.587		
Knee elbow	-0.96; p<0.001	-0.91; p<0.001	-0.57	-0.76; p 0.044	-0.78; p 0.025	-0.62	-0.57; p 0.001	-0.44; p 0.322	-0.38
	p 0.338			p 0.955			p 0.029		
Trunk limb	-1.08; p<0.001	-0.83; p<0.001	-0.59	-0.84; p 0.012	-0.75; p 0.254	-0.66	-0.49; p 0.142	-0.49; p 0.212	-0.42
	p 0.001			p 0.153			p 0.809		

p-values with the score changes are comparisons between active with vehicle creams; p-values comparing tazarotene 0.1% and 0.05% are highlighted and underlined.

Comments

1. The tazarotene creams are superior over vehicle for overall plaque elevation and scaling but not erythema at Week 12. The lack of an overall effect on erythema is not surprising because of irritation effect from the retinoid.
2. Findings from the "target lesions" parallel those for overall clinical signs at Week 12. The following are exceptions: (a) tazarotene 0.05% ***not superior*** over vehicle for scaling at trunk/limb lesions and (b) tazarotene 0.1% ***superior*** over vehicle for erythema at knee/elbow lesions. These data are confirmed by the per protocol analysis.
3. There is no significant difference between the two tazarotene formulations for ***overall*** plaque elevation, scaling or erythema at Week 12.

For ***target*** lesion clinical signs: tazarotene 0.1% appears to be better than tazarotene 0.05% (a) for plaque elevation at the trunk/limb lesions and (b) for erythema at the knee/elbow lesions. These data are also confirmed by per protocol analysis. However, it is difficult to interpret these findings because of the potential need for multiplicity adjustment. The superior efficacy of tazarotene 0.1% vs tazarotene 0.05% for plaque elevation at trunk/limb lesions is probably real, because the higher concentration is consistently better since evaluation at Week 4:

	Tazarotene 0.01%	Tazarotene 0.05%	p-value
Week 1	-0.65	-0.45	0.006
Week 2	-0.83	-0.69	0.060
Week 4	-0.96	-0.73	0.003
Week 8	-1.04	-0.77	<0.001
Week 12	-1.08	-0.83	0.001

4. Although pairwise comparisons between the two formulations at Week 12 do not uniformly demonstrate statistical significance for clinical sign reductions, in all instances but one (knee/elbow lesion scaling), the p for 0.05% > p for 0.1% assumption appears to hold, with score reductions for tazarotene 0.1% ≥ those for tazarotene 0.05%. This is particularly evident for plaque elevation (see above; Comment 3). As the evaluation of plaque elevation is least affected by factors less relevant to the disease process itself, such findings do suggest an important difference and an advantage of tazarotene cream 0.1% in the reduction in clinical signs.
5. There does not appear to be evidence to support the conventional belief that knee/elbow lesions are more resistant to treatment than trunk/limb lesions from the above data.

B. "Treatment Success" and % Area with Psoriasis at Week 12

	"Treatment Success"			% Body Area Involvement		
Lesion	Taz 0.1% N=221	Taz 0.05% N=218	Vehicle N=229	Taz 0.1% N=221	Taz 0.05% N=218	Vehicle N=229
Overall	108/211=49%; p<0.001	93/218=43%; p 0.004	69/229=30%	-0.55; p 0.987	-0.24; p 0.536	+0.14
	p 0.161			p 0.570		
Knee-elbow	118/221=53%; p<0.001	99/218=45%; p 0.001	70/229=31%			
	p 0.067					
Trunk/limb	113/211=54%; p<0.001	99/218=45%; p 0.003	74/229=32%			
	p 0.178					

"Treatment Success" defined by overall global response of moderate or marked response, almost cleared or cleared. p-values with the active data are comparisons between active with vehicle creams; p-values comparing tazarotene 0.1% and 0.05% are highlighted and underlined

Comments
1. "Treatment success" is a dynamic global evaluation based on change from baseline with dichotomization cutoff between slight (25% improvement) and moderate (50% improvement). It confirms the data from "clinical success" using overall lesional assessment.
2. There is no significant difference between the two tazarotene cream formulations for "treatment success". However, for overall and for both target lesions, the rates of "treatment success" were consistently ordered with tazarotene 0.1% > tazarotene 0.05% > vehicle.
3. Other than "treatment success", the overall global response to treatment provides information on the proportion of patients whose psoriasis was unchanged or worsened:

Week 12	Taz 0.1% N=221	Taz 0.05% N=218	Vehicle N=229
Unchanged	39 (18%)	53 (24%)	88 (38%)
Worse	14 (6%)	12 (6%)	14 (6%)
Total	53 (24%)	65 (30%)	102 (44%)

Although this may not be statistically significant, there is clearly an order among the three arms in the proportions for "unchanged" and "unchanged and worse": tazarotene 0.1% < tazarotene 0.05% < vehicle.

4. There are no significant differences between the treatment arms regarding the changes in percent body area involvement by psoriasis. However, this is due to the great variability for this parameter; there is also a clear order among the treatment arms for the mean changes, with tazarotene 0.1% > tazarotene 0.05% > vehicle.

Post-Treatment Period

The post-treatment period data are essentially inadequate for the evaluation of efficacy because of the problem of bias introduced by post-randomization selection. In addition, comparison with a vehicle control is not valid, since the baselines on entry into the post-

treatment period are not balanced and therefore any comparison of subsequent data would not be interpretable. The data are presented here without further comments:

Primary Parameter:

Clinical Success Rates for Tazarotene 0.1% and 0.05% Creams (ITT Analysis)

Week	Taz 0.1% (N=134)	Taz 0.05% (N=115)	Vehicle (N=140)
16	36%; p 0.001	38%; p<0.001	22%
	p=0.677		
20	32%; p 0.003	32%; p 0.002	20%
	p=0.944		
24	31%; p 0.029	34%; p 0.003	21%
	p=0.506		

Clincial success=Overall Lesional Assessment of none, minimal or mild; p-values with data are comparisons between active with vehicle creams; p-values comparing tazarotene 0.1% and 0.05% are highlighted and underlined.

Secondary Parameters:

A. Change from Baseline for Clinical Signs Plaque Elevation, Scaling & Erythema at Week 24

	Plaque Elevation			Scaling			Erythema		
Lesion	Taz 0.1% N=134	Taz 0.05% N=115	Vehicle N=140	Taz 0.1% N=134	Taz 0.05% N=115	Vehicle N=140	Taz 0.1% N=134	Taz 0.05% N=115	Vehicle N=140
Overall	-0.63; p<0.001	-0.60; p 0.004	-0.42	-0.59; p 0.001	-0.51; p 0.038	-0.34	-0.39; p 0.269	-0.41; p 0.183	-0.33
	p 0.681			p 0.316			p 0.728		
Knee/elbow	-0.73; p 0.002	-0.73; p<0.001	-0.49	-0.61; p 0.028	-0.62; p 0.034	-0.45	-0.52; p 0.004	-0.44; p 0.119	-0.34
	p 0.924			p 0.869			p 0.164		
Trunk limb	-0.87; p<0.001	-0.75; p 0.021	-0.57	-0.79; p 0.009	-0.68; p 0.217	-0.56	-0.55; p 0.105	-0.52; p 0.156	-0.43
	p 0.153			p 0.095			p 0.752		

p-values with the score changes are comparisons between active with vehicle creams; p-values comparing tazarotene 0.1% and 0.05% are highlighted and underlined.

B. "Treatment Success" and % Area with Psoriasis at Week 24

	"Treatment Success"			% Body Area Involvement		
Lesion	Taz 0.1% N=134	Taz 0.05% N=115	Vehicle N=140	Taz 0.1% N=134	Taz 0.05% N=115	Vehicle N=140
Overall	38%; p 0.016	39%; p 0.007	27%	-0.86; p 0.449	-0.51; p 0.796	-0.04
	p 0.810			p 0.602		
Knee elbow	39%; p 0.004	40%; p 0.003	27%			
	p 0.964					
Trunk limb	40%; p 0.034	40%; p 0.027	31%			
	p 0.974					

Summary Comments on Efficacy Shown in Study 190168-016C

1. At week 12:

- Both formulations were superior to vehicle for the primary parameter, a dichotomized OLA with cutoff between "mild" and "moderate", even when adjusted for multiplicity.
- For the primary endpoint (OLA of mild, minimal or none at Week 12), there were no significant differences between tazarotene cream 0.1% and tazarotene cream 0.05%. There were small differences between them with respect to the reduction in area of involvement and clinical signs: plaque elevation, scaling and erythema (overall and for target lesions), as well as "treatment success" defined by a global response of "moderate or better". Patients using tazarotene 0.1% generally showed numerically greater response, albeit not statistically significant in most instances. There were also fewer patients showing no change or worsening with tazarotene cream 0.1% vs 0.05%.

2. No comments can be made on the data for the post-treatment period because of potentially serious bias arising from post-randomization selection.

8.2.1.4.3 Safety

Drug exposure is shown in the following Table:

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Mean exposure (days)	66±31	65±31	69±32
Median exposure (days)	85	83	85
Range (days)			
Week 0	221 (100%)	218 (100%)	229 (100%)
At least 1 week	203 (92%)	206 (95%)	207 (90%)
At least 2 weeks	193 (87%)	192 (88%)	195 (85%)
At least 4 weeks	179 (81%)	181 (83%)	186 (81%)
At least 8 weeks	142 (64%)	148 (68%)	155 (68%)
At least 12 weeks	126 (57%)	100 (46%)	134 (59%)
At least 14 weeks	6 (3%)	7 (3%)	13 (6%)

Serious Adverse Events

- There was one treatment-unrelated death that occurred during the post-treatment period of the study. Patient 2726-F31 died as a result of a head injury secondary to falling from a ladder. The patient had completed the 12-week treatment period, and the week 16 post-treatment visit.
- During the treatment period, serious adverse events were reported for 3.2% (7/221) of patients in the tazarotene 0.1% group, 1.8% (4/218) of patients in the tazarotene 0.05% group, and 1.7% (4/229) of patients in the vehicle group.
- During the post-treatment period, serious adverse events were reported for 1.5% (2/134) of patients in the tazarotene 0.1% group, 3.5% (4/115) of patients in the tazarotene 0.05% group, and 2.9% (4/140) of patients in the vehicle group.

None of the Serious AEs was considered to be related to the study medication. They are summarized in the following Table:

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Treatment Period	A40 mild heart attack J11 COPD/bronchitis worse M10 basal cell carcinoma S08 worsening bipolar disease R01 lung cancer L34 dizzy/nausea/vomit/angina V04 hospitalized for chest pain	N31 pancreatitis H15 bloody diarrhea, anemia H20 supraventricular tachy X02 abdominal pain; blood in urine	A49 mild heart attack E17 chest pain R37 rule out sepsis D31 rectal carcinoma
Post-Treatment Period	A26 lower leg cellulitis F31 head trauma	J39 heart attack M12 heart attack (by history) T14 hydronephrosis X02 blood in urine	N17 breast cancer A17 uterine cancer R12 carotid artery occlusion B09 "diabetic shock"

Comment Although unlikely in this case, pancreatitis in patient 0188-N31 is a known retinoid toxicity. This patient was a 40 year-old Caucasian male with a 10-year history of psoriasis, and was treated with 12% body surface area involvement. He had a history of Bufferin use for headaches. The patient said he was a social drinker, but the wife reported his drinking as 4-5 drinks per day. Baseline ALT was 53 U/L (normal <43), AST 86 U/L (normal <36), and GGT 171 U/L (normal <61). Retest one week later showed ALT of 59, AST 95 and GGT 227. He used tazarotene 0.05% cream for 51 days (according to case report form; listing states 36 days). Fifty-two days after start of medication, he was hospitalized for pancreatitis. Hospital nurse reported that he had delirium tremens. The patient was reportedly discharged from hospital after 37 days without sequelae.

Discontinuation due to Adverse Events

In the treatment period, adverse events leading to discontinuation have been discussed in Section 8.2.1.4.1. Discontinuations due to adverse events were dose-related with 16.3% (36/221), 11.5% (25/218), and 4.8% (11/229) of patients in the tazarotene 0.1%, tazarotene 0.05%, and vehicle groups, respectively in the treatment period. Such events were primarily dermatological and included pruritus, inflammation skin, psoriasis worsened, erythema, rash,

irritation skin, burning skin, pain skin, peripheral edema, irritant contact dermatitis, fissure skin, hem skin, desquamation, and dry skin.

In the post-treatment period, discontinuations due to adverse events occurred with 2.2% (3/134), 1.7% (2/115), and 2.9% (4/140) of patients in the tazarotene 0.1%, tazarotene 0.05%, and vehicle groups, respectively. These included:

- accidental injury, weight decrease, hepatitis, bilirubinemia, irritant contact dermatitis and abnormal liver function in the tazarotene 0.1% group;
- apnea, cardiovascular disease, duodenitis, fever, hydronephrosis, infection and weight increase in the tazarotene 0.05% group, and
- breast carcinoma, infection, breast neoplasm, irritant contact dermatitis, rash, psoriasis worsened and pruritus in the vehicle group.

These are unlikely to be due to treatment effect from the treatment period.

Adverse Event Incidence

Significantly more tazarotene patients reported adverse events than did vehicle patients during treatment. The majority of the events were considered by the investigators to be possibly, probably, or definitely related to study medication. The most frequently reported events were in the "skin and appendages" body system. There was a statistically significant dose-response pattern in the incidence of burning skin, irritant contact dermatitis, erythema, skin irritation, pruritus, rash and stinging skin.

Number (%) of Patients with Adverse Events, Reported by > 2% of Patients in Either Tazarotene Group During the Treatment Period

BODY SYSTEM preferred term	Tazarotene 0.1% N=221	Tazarotene 0.05% N=218	Vehicle N=229	Among-group P value[a]
Any adverse event	164 (74.2%)	143 (65.6%)	105 (45.9%)	<0.001 (<0.001, <0.001, 0.049)
BODY AS A WHOLE				
Headache	12 (5.4%)	11 (5.1%)	15 (6.6%)	0.796
Pain Arm	5 (2.3%)	3 (1.4%)	1 (0.4%)	0.209
METABOLIC AND NUTRITIONAL				
Peripheral edema	6 (2.7%)	3 (1.4%)	0 (0.0%)	0.027 (0.013, 0.115, 0.503)
RESPIRATORY				
Infection	11 (5.0%)	9 (4.1%)	11 (4.8%)	0.921
Pharyngitis	1 (0.5%)	5 (2.3%)	1 (0.4%)	0.189
SKIN AND APPENDAGES				
Pruritus	66 (29.9%)	53 (24.3%)	32 (14.0%)	< 0.001 (<0.001, 0.006, 0.199)
Erythema	38 (17.2%)	39 (17.9%)	3 (1.3%)	< 0.001 (<0.001, <0.001, 0.900)
Burning skin	39 (17.7%)	35 (16.1%)	13 (5.7%)	< 0.001 (<0.001, <0.001, 0.703)
Irritation skin	20 (9.1%)	16 (7.3%)	2 (0.9%)	< 0.001 (<0.001, <0.001, 0.603)
Rash	12 (5.4%)	10 (4.6%)	2 (0.9%)	0.011 (0.006, 0.018, 0.828)
Stinging skin	10 (4.5%)	5 (2.3%)	2 (0.9%)	0.049 (0.018, 0.274, 0.293)
Irritant contact dermatitis	9 (4.1%)	3 (1.4%)	0 (0.0%)	0.002 (0.002, 0.115, 0.083)
Psoriasis worsened	9 (4.1%)	9 (4.1%)	6 (2.6%)	0.592
Desquamation	5 (2.3%)	3 (1.4%)	3 (1.3%)	0.746
Pain skin	5 (2.3%)	7 (3.2%)	4 (1.8%)	0.566

a Among-group P value based on the Fisher exact test. Pairwise comparisons are given in parentheses when among group p-values are <0.05. (0.1% vs vehicle, 0.05% vs. vehicle, 0.1% vs 0.05%).

Number (%) of Patients with Adverse Events, Reported by > 2% of Patients in Either Tazarotene Group During the Post-treatment Period

BODY SYSTEM preferred term	Tazarotene 0.1% N=134	Tazarotene 0.05% N=115	Vehicle N=140	Among-group P value[a]
Any adverse event	51 (38.1%)	51 (44.3%)	59 (42.1%)	0.589
BODY AS A WHOLE				
Headache	3 (2.2%)	2 (1.7%)	4 (2.9%)	0.915
Flu syndrome	3 (2.2%)	0 (0.0%)	2 (1.4%)	0.329
MS				
Joint disease	3 (2.2%)	2 (1.7%)	0 (0.0%)	0.236
RESPIRATORY				
Infection	3 (2.2%)	2 (1.7%)	9 (6.4%)	0.105
SKIN AND APPENDAGES				
Pruritus	19 (14.2%)	13 (11.3%)	13 (9.3%)	0.437
Erythema	5 (3.7%)	4 (3.5%)	0 (0.0%)	0.036
Irritation skin	5 (3.7%)	1 (0.9%)	1 (0.7%)	0.162
Burning skin	4 (3.0%)	1 (0.9%)	0 (0.0%)	0.059
Psoriasis worsened	4 (3.0%)	3 (2.6%)	4 (2.9%)	>0.999

a Among-group P value based on the Fisher exact test.

The following Tables give the incidence of adverse events with at least possible attribution to treatment by the Investigator:

Number (%) of Patients with Treatment-Related Adverse Events, Reported by > 2% of Patients in Either Tazarotene Group During the Treatment Period

BODY SYSTEM preferred term	Tazarotene 0.1% N=221	Tazarotene 0.05% N=218	Vehicle N=229	Among-group P value[a]
Any treatment-related AE	127 (57.5%)	109 (50.0%)	49 (21.4%)	<0.001 (<0.001, <0.001, 0.117)
SKIN AND APPENDAGES				
Pruritus	65 (29.4%)	52 (23.9%)	28 (12.2%)	< 0.001 (<0.001, 0.002, 0.197)
Burning skin	39 (17.7%)	35 (16.1%)	13 (5.7%)	< 0.001 (<0.001, <0.001, 0.703)
Erythema	36 (16.3%)	35 (16.1%)	3 (1.3%)	< 0.001 (<0.001, <0.001, >0.999)
Irritation skin	19 (8.6%)	16 (7.3%)	1 (0.4%)	< 0.001 (<0.001, <0.001, 0.725)
Stinging skin	10 (4.5%)	5 (2.3%)	2 (0.9%)	0.049 (0.018, 0.274, 0.293)
Rash	8 (3.6%)	7 (3.2%)	2 (0.9%)	0.110
Irritant contact dermatitis	8 (3.6%)	3 (1.4%)	0 (0.0%)	0.005 (0.003, 0.115, 0.221)
Psoriasis worsened	8 (3.6%)	5 (2.3%)	4 (1.8%)	0.480
Pain skin	4 (1.8%)	7 (3.2%)	4 (1.8%)	0.552
Desquamation*	4 (1.8%)	2 (0.9%)	3 (1.3%)	0.779

a Among-group P value based on the Fisher exact test. *Desquamation added for completeness despite not >2% in either tazarotene group. Pairwise comparisons are given in parentheses when among group p-values are <0.05: (0.1% vs vehicle. 0.05% vs vehicle. 0.1% vs 0.05%).

Number (%) of Patients with Treatment-Related Adverse Events, Reported by > 2% of Patients in Either Tazarotene Group During the Post-Treatment Period

BODY SYSTEM preferred term	Tazarotene 0.1% N=134	Tazarotene 0.05% N=115	Vehicle N=140	Among-group P value[a]
Any treatment-related AE	25 (18.7%)	20 (17.4%)	12 (8.6%)	0.038
SKIN AND APPENDAGES				
Pruritus	16 (11.9%)	10 (8.7%)	8 (5.7%)	0.196
Burning skin	4 (3.0%)	1 (0.9%)	0 (0.0%)	0.059
Erythema	5 (3.7%)	4 (3.5%)	0 (0.0%)	0.036
Irritation skin	4 (3.0%)	1 (0.9%)	0 (0.0%)	0.059
Psoriasis worsened	3 (2.2%)	1 (0.9%)	2 (1.4%)	0.778
Desquamation*	0	0	0	N/A

a Among-group P value based on the Fisher exact test. *Desquamation added for completeness.

Adverse Event Severity

Most of the adverse events were of mild to moderate severity:

AE/	Tazarotene 0.1%			Tazarotene 0.05%			Vehicle		
Severity	mild	moderate	severe	mild	Moderate	severe	mild	moderate	severe
ALL*	66 (30%)	77 (35%)	21 (10%)	73 (34%)	53 (24%)	17 (8%)	56 (25%)	43 (19%)	6 (3%)
Headach	6 (3%)	6 (3%)	0	9 (4%)	2	0	8 (4%)	7 (3%)	0
Pain arm	2	3 (1%)	0	2	0	1	1	0	0
P edema	1	5 (2%)	0	1	1	1	0	0	0
Res-inf'n	7 (3%)	4 (2%)	0	8 (4%)	1	0	8 (4%)	3 (1%)	0
Ph'ngitis	1	0	0	3	2	0	0	1	0
Pruritus	28 (13%)	29 (13%)	9 (4%)	28 (13%)	18 (8%)	7 (3%)	20 (9%)	10 (4%)	2
Eryth	24 (11%)	12 (5%)	2	21 (10%)	13 (6%)	5 (2%)	1	2	0
Burning	16 (7%)	21 (10%)	2	19 (9%)	13 (6%)	3 (1%)	9 (4%)	3 (1%)	1
Irritation	8 (4%)	9 (4%)	3 (1%)	10 (5%)	4 (2%)	2	0	2	0
Rash	5 (2%)	7 (3%)	0	9 (4%)	1	0	2	0	0
Stinging	7 (3%)	3 (1%)	0	3 (1%)	2	0	2	0	0
ICD	4 (2%)	5 (2%)	0	2	1	0	0	0	0
Ps-worse	4 (2%)	4 (2%)	1	3 (1%)	6 (3%)	0	2	4 (2%)	0
Desqu'n	4 (2%)	0	1	2	0	1	2	1	0
Pain skin	3 (1%)	2	0	4 (2%)	3 (1%)	0	3 (1%)	1	0
Tr-rel AE*	56 (25%)	56 (25%)	15 (7%)	62 (28%)	36 (17%)	11 (5%)	28 (12%)	18 (8%)	3 (1%)
Pruritus	27 (12%)	29 (13%)	9 (4%)	28 (13%)	17 (8%)	7 (3%)	16 (7%)	10 (4%)	2
Burning	16 (7%)	21 (10%)	2	19 (9%)	13 (6%)	3 (1%)	9 (4%)	3 (1%)	1
Eryth	22 (10%)	12 (5%)	2	18 (8%)	12 (6%)	5 (2%)	1	2	0
Irritation	8 (4%)	8 (4%)	3 (1%)	10 (5%)	4 (2%)	2	0	1	0
Stinging	7 (3%)	3 (1%)	0	3 (1%)	2	0	2	0	0
Rash	3 (1%)	5 (2%)	0	6 (3%)	1	0	2	0	0
ICD	[illegible]	5 (2%)	0	2	1	0	0	0	0
Ps-worse	3 (1%)	4 (2%)	1	0	5 (2%)	0	1	3 (1%)	0
Pain skin	2	2	0	4 (2%)	3 (1%)	0	3 (1%)	1	0
Desqu'n	3 (1%)	0	1	1	0	1	2	1	0

Percentages only given when incidence greater than 1%. Headach=headache, P edema=peripheral edema, Res-inf'n=respiratory infection, Ph'ngitis=pharyngitis, Eryth=erythema, ICD=irritant contact dermatitis, Ps-worse=psoriasis worsened, Desqu'n= desquamation.

The following summarizes ALL of the adverse events rated as "severe":

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Treatment Period			
Patients with severe AEs	21/221 (9.5%)	17/218 (7.8%)	6/229 (2.6%)
Pruritus	9	7	2
Skin irritation	3	2	0
Erythema	2	5	0
Burning skin	2	3	1
Dry skin	1	0	0
Psoriasis worsened	1	0	0
Desquamation	1	1	0
Other	7 (cardiovascular disease 1, right heart failure 1, manic depression 1, bronchitis 1, lung ca 1, lung disease 1, skin ca 1)	7 (abdominal pain 1, arm pain 1, ventricular tachycardia 1, bloody diarrhea 1, pancreatitis 1, tooth disease 1, peripheral edema 1)	3 (chest pain 1, sepsis 1, gastrointestinal ca 1)

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Post-Treatment Period			
Patients with severe AEs	1/134 (0.7%)	6/115 (5.2%)	5/140 (3.6%)
Pruritus	0	2	1
Other	1 (accidental injury 1)	4 (headache 1, arm pain 1, cardiovascular disease 1, tooth caries 1)	6 (carcinoma 1, coronary occlusion 1, diabetes mellitus 1, thirst 1, breast ca 1, cystitis 1)

Comment It appears that the tazarotene formulations are fairly well tolerated, since most of the adverse events were reported to be mild or moderate in severity. In fact, some of the adverse events are also the very manifestations of the condition to be treated (pruritus, erythema, desquamation). Therefore, the significance of these retinoid adverse effects are hard to evaluate. The low incidence of severe local adverse events in the vehicle group gives credence to their being true retinoid effects. Despite this, during the treatment period, only 21/164 of the patients who experienced adverse events in the tazarotene 0.1% group and 17/143 in the tazarotene 0.05% group had severe adverse events, some of which were not treatment-related.

Clinical Laboratory Testing

There were no consistent clinically significant laboratory findings. Laboratory adverse events were defined as those events checked by the investigator "Yes, Lab AE" on the Adverse Event case report form. Incidence of laboratory adverse events are as follows:

AE	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Treatment period	N=221	N=218	N=229
ALL	9 (4.1%)	4 (1.8%)	6 (2.6%)
Treatment-related	1 (0.5%)	1 (3.5%)	2 (0.9%)
Post-Treatment Period	N=221	N=221	N=221
ALL	3 (2.2%)	2 (1.7%)	4 (2.9%)
Treatment-related	0	1 (0.9%)	2 (1.4%)

Comment The study did not predefine limits for laboratory parameters outside of which would one infer clinical significance. The study reports list all abnormal changes in laboratory findings except for low ⇒ low, high ⇒ high or reversion from baseline abnormality back to normal. "Laboratory adverse event" was a term assigned by the investigator when deemed appropriate. Such a listing was not provided in the original NDA but submitted on request on 6/7/00. Review of the abnormal lab values listing shows no consistent clinically significant laboratory findings.

Therapeutic Drug Monitoring

These data are reviewed by the Biopharm Reviewer. In summary, plasma tazarotene and "tazarotenic acid" (active metabolite of tazarotene) concentrations were determined for patients at 6 selected sites during the study (weeks 4 and 8). Patients were not selected on the basis of risk factors.

- Forty-one patients in the vehicle group provided samples. One patient (2678-L39) had a plasma tazarotene concentration of [redacted], which was above the lower limit of detection ([redacted]). This was considered to be a spurious finding. All plasma "tazarotenic acid" concentrations were below the lower limit of quantitation [redacted].
- Tazarotene concentrations were below the limit of detection for the 32 patients who provided samples in the tazarotene 0.05% group. Twelve of the 32 patients (38%) had detectable plasma "tazarotenic acid" concentrations, the highest being [redacted] ng/mL.
- Of the 38 patients who provided samples in the tazarotene 0.1% group, only 1 patient (1882-C02) had detectable tazarotene concentrations in the post-dose sample at week 8 ([redacted]). Twenty-four of the 38 patients (63%) had detectable plasma "tazarotenic acid" concentrations, the highest being [redacted].

Comment Since the body area involvement, quantity of medication applied, and time of sampling are important in the interpretation of the results, correlation between these parameters and plasma levels would be anticipated in the Biopharm review. This issue will be discussed greater detail in Section 10.2.3.1.3.

Comparison between Safety Data of Tazarotene Creams 0.05% and 0.1%

The above safety data demonstrate the following differences in the treatment period:

	Tazarotene 0.1%	Tazarotene 0.05%
Rate of discontinuation due to adverse events	16%	11%
Incidence of total adverse events	74%	66% (p=0.049)
Incidence of treatment-related adverse events	58%	50%
Incidence of "severe" adverse events	9.5%	7.8%
Proportion of patients with detectable "tazarotenic acid"	63% (up to 2.38 ng/mL)	38% (up to 0.64 ng/mL)

In addition, the incidences of individual treatment-related adverse events were all lower in the tazarotene 0.05% group except for skin pain, which is also one of the symptom of psoriasis itself.

Comment This study suggests an advantage of tazarotene cream 0.05%, because of a significantly lower incidence of adverse events. As the trial was not powered for demonstration of superiority of one concentration over the other for safety, a significant difference in the incidence of total adverse events would appear to suggest a true advantage. This is supported by the (a) potentially lower systemic bioavailability, and (b) differences in (i) rates of discontinuation due to adverse events, (ii) incidence for individual local adverse events, and (iii) incidence of "severe" adverse events, even though the data may not reach statistical significance.

8.2.1.5 Reviewer's Comments/Conclusions

1. This study demonstrates superiority of tazarotene 0.05% and tazarotene 0.1% cream over vehicle in the treatment of plaque psoriasis using dichotomized OLA criterion..
2. Both formulations appear to be fairly well tolerated, and adverse events are primarily of the skin and appendages.
3. Post-treatment efficacy data are not evaluable because of bias introduced by post-randomization selection and the different status on entry into that phase due to the prior treatment effect.
4. There appears to be a dose-dependent effect in (a) reduction in plaque elevation, especially for trunk/limb lesions (significant) favoring tazarotene cream 0.1%, and (b) (i) rates of all adverse events (significant), individual local adverse events, severe adverse events, and discontinuation due to adverse events and (ii) systemic bioavailability favoring tazarotene cream 0.05%.

8.2.2 Trial #2. Multicenter, Double-Blind, Randomized, Vehicle-Controlled Study of the Safety and Efficacy of 0.05% and 0.1% Tazarotene Creams Applied Once Daily for 12 Weeks, with a 12-Week Follow-Up, in the Treatment of Plaque Psoriasis (Study #190168-017C) [Initiated 12/30/97, completed 10/16/98]

8.2.2.1 Objectives: To assess the safety and efficacy of tazarotene creams 0.05% and 0.1% vs vehicle cream applied once daily for 12 weeks in the treatment of plaque psoriasis.

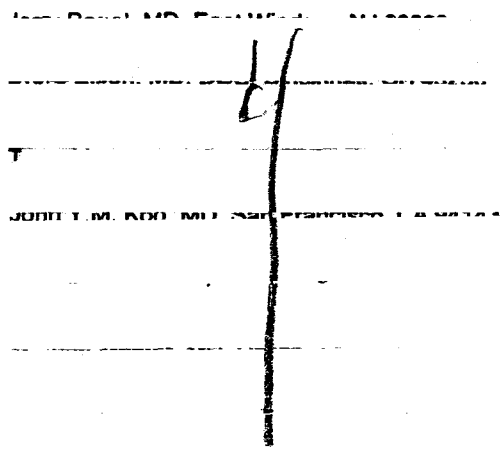
8.2.2.2 Design Identical to 190168-016C minus post-treatment phase

8.2.2.3 Protocol Overview Identical to 190168-016C minus post-treatment phase

8.2.2.4 Study Results

8.2.2.4.1 Demographics, Evaluability

Investigators: The Investigators were:



Comment The Investigators were qualified.

Enrollment per center:-

	Taz 0.1%	Taz 0.05%	Vehicle	Total
	10	11	12	33
	20	20	19	59
	16	16	16	48
	18	19	20	57
	4	4	4	12
	7	7	6	20
	9	10	10	29
	10	10	10	30
	16	16	16	48
	15	14	15	44
	10	9	10	29
	8	9	9	26
	16	14	14	44
	18	17	18	53
	19	19	19	57
	11	11	12	34
	4	4	4	12
	211	210	214	635

Enrollment and dropout information for the treatment period is as follows:

Disposition	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle	Total
Enrolled	211 (100%)	210 (100%)	214 (100%)	635 (100%)
Completed	160 (76%)	144 (69%)	163 (76%)	467 (73%)
Discontinued	51 (24%)	66 (31%)	51 (24%)	168 (27%)
Non-compliance	2 (1%)	5 (2%)	2 (1%)	9 (1%)
Personal	8 (4%)	10 (5%)	10 (5%)	28 (4%)
Lack of efficacy	3 (1%)	15 (7%)	13 (6%)	31 (5%)
Adverse event	20 (10%)	16 (8%)	9 (4%)	45 (7%)
Concomitant therapy	1 (0%)	2 (1%)	1 (0%)	4 (1%)
Relocated	0	1 (0%)	1 (0%)	2 (0%)
Improper entry	0	0	1 (0%)	1 (0%)
Lost to follow-up	13 (6%)	14 (7%)	12 (6%)	39 (6%)
"Other"	4 (2%)	3 (1%)	2 (1%)	9 (1%)

Comments

= large proportion of dropout patients.

2. Discontinuations due to adverse events were dose-related with 9.5% (20/211), 7.6% (16/210), and 4.2% (9/214) of patients in the tazarotene 0.1%, tazarotene 0.05%, and vehicle groups, respectively. Such events were generally dermatological and included irritation, burning, erythema, dermatitis, and pruritus in the tazarotene 0.1% group; burning, pruritus, irritation, and erythema in the tazarotene 0.05% group; and pruritus and erythema in the vehicle group.

3. It appears that the tazarotene 0.1% group has fewer dropouts due to lack of efficacy than the tazarotene 0.05% and vehicle groups.

The patients discontinued under "other" are as follows:

Tazarotene 0.1% (N=4)	Tazarotene 0.05% (N=3)	Vehicle (N=2)
A11 elevated triglycerides	J13 refuses blood draw	P36 abnormal baseline labs
G35 abnormal baseline labs	K23 wrong tube dispensed	S10 abnormal baseline labs
P23 abnormal baseline labs	P31 abnormal baseline labs	
P25 abnormal baseline labs		

Comment Most of the "other" reasons could have been grouped under those in the Table on patient disposition (entry criteria violation).

Demographics: Demographics of the study subjects is shown as follows:

Variable	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Age mean & range	47 (19-80)	48 (19-77)	47 (19-82)
Sex M:F	136:75	132:78	116:98
Race C:B:A:H:O	183:5:0:21:2	182:9:6:12:1	181:8:4:19:2
Percent area involved	10% (2%-70%)	12% (2%-80%)	11% (2%-80%)
OLA mean & range	3.7 (3.0-5.0)	3.7 (3.0-5.0)	3.7 (3.0-5.0)

OLA=overall lesional assessment; C=Caucasian, B=black, A=Asian, H=Hispanic, O="other";

Comment The three treatment arms are comparable. There were also no significant differences between them with respect to Fitzpatrick skin type (data not shown).

Evaluability As discussed above, since the primary analysis is by ITT with LOCF methodology, all patients are considered evaluable. Because of the presence of substantial dropout, the per protocol analysis will also be examined.

8.2.2.4.2 Efficacy

All analyses are based on ITT population unless specified.

Primary Parameter: "Clincial Success" (OLA of none, minimal or mild)

Clinical Success Rates for Tazarotene 0.1% and 0.05% Creams (ITT Analysis)

Week	Taz 0.1% (N=211)	Taz 0.05% (N=210)	Vehicle (N=214)
1	12%; p=0.002 (vs vehicle)	7%; p=0.118 (vs vehicle)	
	Taz 0.1% vs Taz 0.05%: p=0.114		4%
2	20%; p<0.001 (vs vehicle)	16%; p=0.008 (vs vehicle)	
	Taz 0.1% vs Taz 0.05%: p=0.176		8%
4	32%; p<0.001 (vs vehicle)	24%; p=0.038 (vs vehicle)	
	Taz 0.1% vs Taz 0.05%: p=0.043		17%
8	41%; p<0.001 (vs vehicle)	35%; p=0.007 (vs vehicle)	
	Taz 0.1% vs Taz 0.05%: p=0.166		24%
12	51%; p<0.001 (vs vehicle)	41%; p=0.001 (vs vehicle)	
	Taz 0.1% vs Taz 0.05%: p=0.025		26%

Comments

1. The clinical success rate of vehicle at Week 12 (26%) is consistent with the Applicant's assumption based on tazarotene gel studies (22%)
2. Both tazarotene 0.1% and 0.05% are superior to vehicle at the predefined endpoint [illegible] owing for multiplicity adjustment.
3. Tazarotene 0.1% cream is superior to tazarotene 0.05% cream at Weeks 4 and 12. In fact, it is numerically better since Week 1. Tazarotene 0.1% achieves superiority over vehicle earlier (Week 1; Week 2 for tazarotene 0.05%), which is an advantage. An analysis for superiority using the ITT population is appropriate because there is no hypothesis of equivalence or noninferiority involved.

4. The Applicant's own criterion of effectiveness (≥15% difference between active treatment and vehicle in the "clinical success" rate) is achieved at Week 12 by tazarotene 0.05% (41%-26%=15%) and by tazarotene 0.1% (51%-26%=25%).

Because of the substantial dropout rate, the per protocol analysis is also examined here:

Clinical Success Rates for Tazarotene 0.1% and 0.05% Creams (Per Protocol Analysis)

Week	Taz 0.1% (N=211)	Taz 0.05% (N=210)	Vehicle (N=214)
1	20/183=11%; p=0.006 (vs vehicle)	15/186=8%; p=0.082 (vs vehicle)	7/190=4%
	Taz 0.1% vs Taz 0.05%: p=0.283		
2	40/178=23%; p<0.001 (vs vehicle)	31/179=17%; p=0.018 (vs vehicle)	15/177=9%
	Taz 0.1% vs Taz 0.05%: p=0.172		
4	62/165=38%; p<0.001 (vs vehicle)	46/166=28%; p=0.088 (vs vehicle)	34/176=19%
	Taz 0.1% vs Taz 0.05%: p=0.027		
8	74/150=49%; p<0.001 (vs vehicle)	61/149=41%; p=0.016 (vs vehicle)	47/168=28%
	Taz 0.1% vs Taz 0.05%: p=0.125		
12	87/147=59%; p<0.001 (vs vehicle)	74/148=50%; p<0.001(vs vehicle)	52/169=31%
	Taz 0.1% vs Taz 0.05%: p=0.090		

Comments The per protocol analysis gives similar results as the ITT analysis, although the advantage of tazarotene 0.1% at Week 12 is no longer evident. In addition, the superiority of tazarotene 0.05% vs vehicle from Week 2 is interrupted by a non-significant comparison at Week 4. Both formulations show ≥15% difference vs vehicle at Week 12.

Secondary Parameters:

A. Change from Baseline for Clinical Signs Plaque Elevation, Scaling & Erythema at Week 12

	Plaque Elevation			Scaling			Erythema		
Lesion	Taz 0.1% N=211	Taz 0.05% N=210	Vehicle N=214	Taz 0.1% N=211	Taz 0.05% N=210	Vehicle N=214	Taz 0.1% N=211	Taz 0.05% N=210	Vehicle N=214
Overall	-1.08; p<0.001	-0.90; p<0.001	-0.61	-1.03; p<0.001	-0.80; p 0.359	-0.70	-0.78; p<0.001	-0.62; p 0.066	-0.47
	p 0.026			p 0.004			p 0.030		
Knee/elbow	-1.21; p<0.001	-1.04; p<0.001	-0.68	-1.13; p<0.001	-0.98; p 0.048	-0.76	-0.82; p<0.001	-0.66; p 0.007	-0.44
	p 0.022			p 0.055			p 0.022		
Trunk/limb	-1.25; p<0.000	-0.98; p 0.002	-0.69	-1.06; p 0.003	-0.90; p 0.229	-0.79	-0.82; p<0.001	-0.65; p 0.039	-0.46
	p 0.001			p 0.071			p 0.046		

p-values with the score changes are comparisons between active with vehicle creams; p-values comparing tazarotene 0.1% and 0.05% are highlighted and underlined.

Comments

1. Tazarotene 0.1% cream is superior over vehicle for overall plaque elevation, scaling and erythema at Week 12, while tazarotene 0.05% cream is superior for overall plaque elevation, but not scaling or erythema. Per protocol analysis shows tazarotene 0.05% crea- superior to vehicle for overall plaque elevation (-1.04 vs -0.71, p= [illegible] (-0.83 vs -0.57, p=0.009), but not scaling (-0.58 vs -0.54, p=[illegible].
2. Findings from the "target lesions" parallel those for overall clinical signs at Week 12. The following are exceptions: (a) tazarotene 0.05% ***not superior*** over vehicle for scaling at trunk/limb lesions despite its being ***superior*** at knee/elbow lesions; and (b) tazarotene 0.05% ***superior*** over vehicle for erythema at knee/elbow as well as trunk/limb lesions. These data are confirmed by the per protocol analysis.
3. Tazarotene 0.1% is superior to tazarotene 0.05% for ***overall*** plaque elevation, scaling and erythema at Week 12. For target lesions: tazarotene 0.1% appears to be

better than tazarotene 0.05% for plaque elevation and erythema, but not for scaling at both the knee/elbow and trunk/limb lesions. Per protocol analysis, however, only shows superiority of tazarotene 0.1% vs tazarotene 0.05% with plaque elevation and erythema at trunk/limb lesions; other comparisons between the two formulations at Week 12 do not reach statistical significance. It appears that per protocol analysis has excluded dropouts with less favorable data particularly in the tazarotene 0.05% group, narrowing the differences between the two active formulations.
4. There does not appear to be evidence to support the conventional belief that knee/elbow lesions are more resistant to treatment than trunk/limb lesions from the above data.

B. "Treatment Success" and % Area with Psoriasis at Week 12

	"Treatment Success"			% Body Area Involvement		
Lesion	Taz 0.1% N=211	Taz 0.05% N=210	Vehicle N=214	Taz 0.1% N=211	Taz 0.05% N=210	Vehicle N=214
Overall	124/211=59%; p<0.001	100/210=48%; p 0.020	79/214=37%	-0.82; p 0.004	-0.59; p 0.930	-0.37
	p 0.031			p 0.007		
Knee/elbow	132/211=63%; p<0.001	112/210=53%; p 0.002	84/214=39%			
	p 0.073					
Trunk/limb	120/211=57%; p<0.001	103/210=49%; p 0.014	81/214=38%			
	p 0.135					

"Treatment Success" defined by overall global response of moderate or marked response, almost cleared or cleared. p-values with the actual data are comparisons between active with vehicle creams; p-values comparing tazarotene 0.1% and 0.05% are highlighted and underlined.

Comments
1. "Treatment success" is a dynamic global evaluation based on change from baseline with dichotomization cutoff between slight (25% improvement) and moderate (50% improvement). It confirms the data from "clinical success" using overall lesional assessment.
2. Although tazarotene cream 0.05% is superior to vehicle for overall "treatment success" and at the "target lesions" at Week 12, tazarotene cream 0.1% is significantly better than the lower strength cream for overall "treatment success", albeit not specifically at the "target lesions" at Week 12.
3. Other than "treatment success", the overall global response to treatment provides information on the proportion of patients whose psoriasis was unchanged or worsened:

Week 12	Taz 0.1% N=211	Taz 0.05% N=210	Vehicle N=214
Unchanged	29 (14%)	51 (24%)	71 (33%)
Worse	11 (5%)	12 (6%)	11 (5%)
Total	40 (19%)	63 (30%)	82 (38%)

Although this may not be statistically significant, there is clearly an order among the three arms in the proportions for "unchanged" and "unchanged and worse": tazarotene 0.1% < tazarotene 0.05% < vehicle.
4. Tazarotene cream 0.1% is superior to tazarotene cream 0.05% and vehicle in percent reduction in body area involvement by psoriasis at Week 12.

Summary Comments on Efficacy Shown in Study 190168-017C
1. At week 12:
- Both formulations were superior to vehicle for the primary parameter, a dichotomized OLA with cutoff between "mild" and "moderate", even when adjusted for multiplicity.
- Tazarotene cream 0.1% was superior to tazarotene cream 0.05% for the dichotomized OLA, reductions in overall plaque elevation, overall scaling and overall erythema, and percent body area involvement, as well as "treatment success" defined by a global response of "moderate or better". There were also fewer patients showing no change or worsening with tazarotene cream 0.1% vs 0.05%.

2. Tazarotene cream 0.1% achieved superiority over vehicle at Week 1, one week earlier than tazarotene cream 0.05%.

8.2.2.4.3 Safety

Drug exposure is shown in the following Table:

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Mean exposure (days)	73±29	69±31	73±28
Median exposure (days)	85	85	85
Range (days)			
Week 0	211 (100%)	210 (100%)	214 (100%)
At least 1 week	193 (92%)	192 (91%)	198 (93%)
At least 2 weeks	189 (90%)	178 (85%)	182 (85%)
At least 4 weeks	174 (83%)	168 (80%)	174 (81%)
At least 8 weeks	156 (74%)	145 (69%)	164 (77%)
At least 12 weeks	141 (67%)	117 (56%)	137 (64%)
At least 14 weeks	8 (4%)	10 (5%)	9 (4%)

Serious Adverse Events

There were no deaths during the study. Serious adverse events were reported for 1.9% (4/211) of patients in the tazarotene 0.1% group, 0.5% (1/210) of patients in the tazarotene 0.05% group, and 0.9% (2/214) of patients in the vehicle group. No serious adverse event was considered to be related to study medication, except a severe skin infection in a patient receiving tazarotene 0.1% (2172-G16). They are summarized in the following Table:

Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
H10 right elbow fracture	J01 thrombophlebitis	N10 fracture left arm
G16 skin infection		K21 peri-rectal abscess
F39 congestive heart failure, acute renal failure. L ventricle thrombus		
D33 atypical chest pain		

Discontinuation due to Adverse Events

Adverse events leading to discontinuation have been discussed in Section 8.2.2.4.1. Discontinuations due to adverse events were dose-related with 9.5% (20/211), 7.6% (16/210), and 4.2% (9/214) of patients in the tazarotene 0.1%, tazarotene 0.05%, and vehicle groups, respectively. Such events were primarily dermatological and included irritation, burning, erythema, dermatitis, and pruritus in the tazarotene 0.1% group; burning, pruritus, irritation, and erythema in the tazarotene 0.05% group; and pruritus and erythema in the vehicle group.

Adverse Event Incidence

Significantly more tazarotene patients reported adverse events than did vehicle patients. The majority of the events were considered by the investigators to be possibly, probably, or definitely related to study medication. The most frequently reported adverse events were in the "skin and appendages" body system. There was a statistically significant dose-response pattern in the incidence of burning skin, dermatitis, eczema, erythema, skin irritation, and pruritus. Adverse events related to the other body systems were reported at lower rates, and there were no significant differences among the active and control groups.

Number (%) of Patients with Adverse Events, Reported by >2% of Patients in Either Tazarotene Group

BODY SYSTEM preferred term	Tazarotene 0.1% N=211	Tazarotene 0.05% N=210	Vehicle N=214	Among-group P value[a]
Any adverse event	133 (63.0%)	125 (59.5%)	90 (42.1%)	<0.001 <0.001, <0.001, 0.460
BODY AS A WHOLE				
Flu syndrome	1 (0.5%)	5 (2.4%)	2 (0.9%)	0.188
Headache	6 (2.8%)	4 (1.9%)	6 (2.8%)	0.856
METABOLIC AND NUTRITIONAL				
Hypertriglyceridemia	3 (1.4%)	9 (4.3%)	5 (2.3%)	0.192
RESPIRATORY				
Infection	10 (4.7%)	17 (8.1%)	12 (5.6%)	0.342
SKIN AND APPENDAGES				
Pruritus	35 (16.6%)	30 (14.3%)	19 (8.9%)	0.050 0.019, 0.095, 0.590
Erythema	35 (16.6%)	19 (9.1%)	7 (3.3%)	< 0.001 < 0.001, 0.015, 0.028
Burning skin	22 (10.4%)	16 (7.6%)	8 (3.7%)	0.025 0.008, 0.095, 0.395
Irritation skin	22 (10.4%)	15 (7.1%)	6 (2.8%)	0.005 0.002, 0.045, 0.302
Dermatitis	12 (5.7%)	6 (2.9%)	1 (0.5%)	0.003 0.001, 0.066, 0.228
Desquamation	11 (5.2%)	9 (4.3%)	3 (1.4%)	0.077
Eczema	11 (5.2%)	3 (1.4%)	0 (0.0%)	< 0.001 <0.001, 0.121, 0.030
Pain skin	6 (2.8%)	5 (2.4%)	3 (1.4%)	0.560
Irritant contact dermatitis	4 (1.9%)	5 (2.4%)	1 (0.5%)	0.194
Psoriasis worsened	2 (1.0%)	6 (2.9%)	3 (1.4%)	0.302

a Among-group P value based on the Fisher exact test. Pairwise comparisons are given in parentheses when among group p-values are <0.05: (0.1% vs vehicle, 0.05% vs. vehicle, 0.1% vs 0.05%).

The following Table gives the incidence of adverse events with at least possible attribution to treatment by the Investigator:

Number (%) of Patients with Treatment-Related Adverse Events, Reported by >2% of Patients in Either Tazarotene Group

BODY SYSTEM preferred term	Tazarotene 0.1% N=211	Tazarotene 0.05% N=210	Vehicle N=214	Among-group P value[a]
Any treatment-related AE	99 (46.9%)	90 (42.9%)	40 (18.7%)	<0.001 <0.001, <0.001, 0.402
METABOLIC AND NUTRITIONAL				
Hypertriglyceridemia	1 (0.5%)	6 (2.9%)	3 (1.4%)	0.131
SKIN AND APPENDAGES				
Pruritus	33 (15.6%)	28 (13.3%)	19 (8.9%)	0.096
Erythema	33 (15.6%)	19 (9.1%)	7 (3.3%)	< 0.001 <0.001, 0.013, 0.040
Irritation skin	21 (10.0%)	15 (7.1%)	6 (2.8%)	0.008 0.003, 0.045, 0.384
Burning skin	20 (9.5%)	15 (7.1%)	8 (3.7%)	0.055
Dermatitis	12 (5.7%)	5 (2.4%)	1 (0.5%)	0.004 0.002, 0.119, 0.085
Desquamation	10 (4.7%)	9 (4.3%)	1 (0.5%)	0.010 0.005, 0.010, >0.999
Eczema	10 (4.7%)	3 (1.4%)	0 (0.0%)	0.001 <0.001, 0.121, 0.050
Pain skin	6 (2.8%)	4 (1.9%)	3 (1.4%)	0.536
Irritant contact dermatitis	4 (1.9%)	5 (2.4%)	1 (0.5%)	0.194
Psoriasis worsened	2 (1.0%)	5 (2.4%)	2 (0.9%)	0.448

a Among-group P value based on the Fisher exact test. Pairwise comparisons are given in parentheses when among group p-values are <0.05: (0.1% vs vehicle, 0.05% vs. vehicle, 0.1% vs 0.05%).

Adverse Event Severity

Most of the adverse events were of mild to moderate severity:

AE/ Severity	Tazarotene 0.1% (N=211)			Tazarotene 0.05% (N=210)			Vehicle (N=214)		
	mild	moderate	severe	Mild	moderate	severe	mild	moderate	severe
ALL*	65 (31%)	51 (24%)	15 (7%)	69 (33%)	53 (25%)	3 (1%)	52 (24%)	32 (15%)	5 (2%)
Flu	1	0	0	1	4 (2%)	0	1	1	0
Headach	4 (2%)	2	0	3 (1%)	1	0	5 (2%)	1	0
Trigly**	1	1	0	6 (3%)	2	1	2	2	0
Res-infr	7 (3%)	3 (1%)	0	16 (8%)	1	0	10 (5%)	2	0
Pruritus	14 (7%)	19 (9%)	2	20 (10%)	10 (5%)	0	10 (5%)	8 (4%)	1
Eryth	18 (9%)	14 (7%)	3 (1%)	13 (6%)	6 (3%)	0	3 (1%)	3 (1%)	1
Burning	11 (5%)	11 (5%)	1	7 (3%)	8 (4%)	1	5 (2%)	2	1
Irritation	15 (7%)	7 (3%)	0	12 (6%)	3 (1%)	0	5 (2%)	1	0
Derm'titis	9 (4%)	2	1	4 (2%)	2	0	1	0	0
Desqu'n	9 (4%)	2	0	8 (4%)	1	0	3 (1%)	0	0
Eczema	6 (3%)	2	3 (1%)	1	2	0	0	0	0
Pain skin	4 (2%)	2	0	2	3 (1%)	0	2	0	1
ICD	2	1	1	2	3 (1%)	0	1	0	0
Ps-worse	1	0	1	3 (1%)	3 (1%)	0	2	1	0
Tr-relAE*	51 (24%)	37 (18%)	10 (5%)	56 (27%)	33 (16%)	1	25 (12%)	12 (6%)	2
Trigly**	0	0	0	4 (2%)	2	0	1	1	1
Pruritus	13 (6%)	19 (9%)	1	19 (9%)	9 (4%)	0	10 (5%)	8 (4%)	1
Eryth	17 (8%)	13 (6%)	3 (1%)	14 (7%)	5 (2%)	0	3 (1%)	3 (1%)	1
Irritation	15 (7%)	6 (3%)	0	12 (6%)	3 (1%)	0	5 (2%)	1	0
Burning	9 (4%)	11 (5%)	0	7 (3%)	7 (3%)	1	5 (2%)	2	1
Derm'titis	9 (4%)	2	1	3 (1%)	2	0	1	0	0
Desqu'n	9 (4%)	1	0	8 (4%)	1	0	1	0	0
Eczema	5 (2%)	2	3 (1%)	1	2	0	0	0	0
Pain skin	4 (2%)	2	0	2	2	0	2	0	1
ICD	2	1	1	2	3 (1%)	0	1	0	0
Ps-worse	1	0	1	2	3 (1%)	0	1	1	0

*Not graded: 2 in tazarotene 0.1% group, 1 in vehicle group. Flu=Flu syndrome, Headach=headache, Trigly =triglyceride level elevation, Res-inf=respiratory infection, Eryth=erythema, Derm'titis=dermatitis, Desqu'n=desquamation, ICD=irritant contact dermatitis, Ps-worse=psoriasis worsened.

The following summarizes ALL of the adverse events rated as "severe":

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Patients with severe AEs	15/211 (7.1%)	3/210 (1.4%)	5/214 (2.3%)
Pruritus	2	0	1
Irritant contact dermatitis	1	0	0
Erythema	3	0	1
Burning skin	0	1	1
Dry skin	1	0	0
Psoriasis worsened	1	0	0
Eczema	3	0	0
Allergic contact dermatitis	1	0	0
"Dermatitis"	1	0	0
Other	8 ("Infection" 1, kidney failure 1, "cardiovascular disease" 1, right heart failure 1, tooth anomaly 1, bone fracture 1, bronchitis 1, lung edema 1)	2 (hypertriglyceridemia 1, thrombophlebitis 1)	6 (abscess 1, abdominal pain 1, bone fracture 1, edema 1, skin pain 1, skin fissure 1)

Comment "It appears that the tazarotene formulations are fairly well tolerated, since most of the adverse events were reported to be mild or moderate in severity. In fact, some of the adverse events are also the very manifestations of the condition to be treated (pruritus, erythema, irritant contact dermatitis). Despite this, only [illegible] of the patients who experienced adverse events in the tazarotene 0.1% group and 3/125 in the tazarotene 0.05% group had severe adverse events, some of which were unlikely treatment-related.

Clinical Laboratory Testing

There were no consistent clinically significant laboratory findings. Laboratory adverse events were defined as those events checked by the investigator "Yes, Lab AE" on the Adverse Event case report form. Incidence of laboratory adverse events are as follows:

AE	Tazarotene 0.1% (N=211)	Tazarotene 0.05% (N=210)	Vehicle (N=214)
ALL	12 (5.7%)	12 (5.7%)	8 (3.7%)
Treatment-relate	2 (0.9%)	7 (3.3%)	3 (1.4%)

Comment The study did not predefine limits for laboratory parameters outside of which would one infer clinical significance. The study reports list all abnormal changes in laboratory findings except for low ⇒ low, high ⇒ high or reversion from baseline abnormality back to normal. "Laboratory adverse event" was a term assigned by the Investigator when deemed appropriate. Such a listing was not provided in the original NDA but submitted on request on 6/7/00. Review of the abnormal lab values listing shows no consistent clinically significant laboratory findings.

Therapeutic Drug Monitoring

These data are reviewed by the Biopharm Reviewer. In summary, plasma tazarotene and "tazarotenic acid" (active metabolite of tazarotene) concentrations were determined for patients at 5 selected sites during the study (weeks 4 and 8). Patients were not selected on the basis of risk factors.

- All plasma tazarotene and "tazarotenic acid" concentrations were below the lower limit of quantitation [redacted] for the 36 patients who provided samples in the vehicle group.
- Tazarotene concentrations were below the limit of detection for the 37 patients who provided samples in the tazarotene 0.05% group. Nineteen of the 37 patients (51.4%) had detectable plasma "tazarotenic acid" concentrations, the highest being [redacted] L.
- Of the 32 patients who provided samples in the tazarotene 0.1% group, only 2 patients (2137-K17 and 2762-M20) had detectable concentrations in their post-dose sample at week 4, 0.0912 and 0.0838 ng/mL, respectively. Twenty-three patients (71.9%) had detectable plasma "tazarotenic acid" concentrations, the highest being [redacted].

Comment Since the body area involvement, quantity of medication applied, and time of sampling are important in the interpretation of the results, correlation between these parameters and plasma levels would be anticipated in the Biopharm review. This issue will be discussed greater detail in Section 10.2.3.1.3.

Comparison between Safety Data of Tazarotene Creams 0.05% and 0.1%

The above safety data demonstrate the following differences:

	Tazarotene 0.1%	Tazarotene 0.05%
Rate of discontinuation due to adverse events	9.5%	7.6%
Incidence of total adverse events: treatment-related AE	63%/47%	60%/43%
Incidence of "severe" adverse events	7.1	1.4%
Incidence of erythema	17%	9% (p=0.028)
Incidence of treatment-related erythema	16%	9% (p=0.040)
Incidence of eczema	5.2%	1.4% (p=0.030)
Incidence of treatment-related eczema	4.7%	1.4% (p=0.050)
Proportion of patients with detectable "tazarotenic acid"	72% (up to [redacted]	51% ([redacted]

In addition, the incidences of individual local adverse events were all lower in the tazarotene 0.05% group except for psoriasis worsened and irritant contact dermatitis.

Comment This study suggests an advantage of tazarotene cream 0.05%, because of a [redacted] lower incidence of the adverse events erythema and eczema (ALL and treatment-related). As the trial was not powered for demonstration of superiority of one concentration over the other for safety, a significant difference in the incidence of these adverse events would appear to suggest a true advantage. This is supported by the (a) potentially lower systemic bioavailability, and (b) differences in (i) rates of discontinuation due to adverse events, (ii) incidence for other individual local adverse events, and (iii) incidence of "severe" adverse events, even though the data may not reach statistical significance.

8.2.2.5 Reviewer's Comments/Conclusions

1. This study demonstrates superiority of tazarotene 0.05% and tazarotene 0.1% cream over vehicle in the treatment of plaque psoriasis using dichotomized OLA criterion.
2. Both formulations appear to be fairly well tolerated, and adverse events are primarily of the skin and appendages.
3. There appears to be a dose-dependent effect in (a) reduction in overall plaque elevation, scaling and erythema, (b) discontinuation due to adverse events and (c) certain local adverse event incidences.
4. There appears to be a dose-dependent effect in (a) primary and secondary efficacy endpoints favoring tazarotene cream 0.1%, and (b) (i) rates of the adverse events erythema and eczema (significant), other individual local adverse events, severe adverse events, and discontinuation due to adverse events and (ii) systemic bioavailability favoring tazarotene cream 0.05%.

9 Overview of Efficacy

9.1 Clinical Development Plan for Tazarotene Creams

Although tazarotene gels 0.05% and 0.1% are products approved for the treatment of plaque psoriasis, the current application for tazarotene creams 0.05% and 0.1% is based on safety and efficacy data from two adequate and well controlled studies and not comparisons with approved products. These trials were modeled on those that supported the marketing of tazarotene gels, but the endpoints and success criteria have been modified after extensive discussion with the Agency. In addition, the Applicant had been advised not to have percent surface area restriction in enrollment in order to parallel real conditions in clinical practice. Thus, unlike in the tazarotene gel studies, the trials for tazarotene creams did not restrict surface area, and consequently the label does not contain wording limiting use according to percent surface area involvement. Although the tazarotene creams could be considered line extensions from the tazarotene gels, because of these differences, they were pursued as independent drug products with two adequate and well controlled studies using comparison with placebo cream. Multiple comparison adjustments have been built into the study protocols.

9.2 Dose-ranging

Formal dose-ranging studies have not been conducted. The concentrations were chosen on the basis of the approved gel formulations (0.05% and 0.1%). The Applicant addresses the frequency and duration aspects of dose-ranging as follows: with tazarotene gel, once daily (QD) application was similar in efficacy to twice daily (BID) application for the 0.1% concentration and only slightly less effective for the 0.05% concentration (Study R168-111-7997). Irritation was less with QD than with BID application of tazarotene gel, and thus QD dosing was selected for the phase 3 studies with tazarotene cream as well. The 12-week treatment duration was based upon previous experience with tazarotene gels.

The Applicant's rationale for having two concentrations is as follows: As with the gel formulations, two concentrations might allow patients and physicians greater flexibility and utility. It was anticipated that the 0.1% concentration would provide an earlier onset

of action and greater efficacy overall than the 0.05% concentration, while the lower concentration would yield greater tolerability. These aspects will be addressed below (Section 9.3.4 and 10.2.10).

Comment It has been questioned whether the study design of the phase 3 trials would support the anticipation of the Applicant, i.e. that the 0.1% concentration would provide an earlier onset of action and greater efficacy overall than the 0.05% concentration, while the lower concentration would yield greater tolerability. In the comment under Section 8.2, this issue has been discussed. In summary, the studies were not designed for pairwise comparisons between the two concentrations for statistical significance. The anticipation was to have superiority of both formulations over vehicle cream demonstrated even with multiplicity adjustment, and p-values (active vs vehicle) ordered such that p for 0.05% > p for 0.1%. Thus, a demonstration of significance in efficacy and/or safety parameters with direct pairwise comparison of the two concentrations would be a very important finding.

9.3 Phase 3 Clinical Trials

Because of previous work with tazarotene gels, at the pre-IND meeting, the Applicant proposed direct entry into phase 3 without efficacy data from earlier phases involving tazarotene creams. The Agency found this acceptable at the pre-IND/EOP2 meeting. The evidence for effectiveness in the current marketing application is based entirely on the two phase 3 studies 190168-016C and -017C. Their design is shown in the following Table:

Study No.	Site(s)	Treatment Dose/Duration	Enrolled Pt #s	Design
190168-016C	21	tazarotene 0.01% cream qd x 12 wks; no treatment 12 wks	221	double-blind, randomized
		tazarotene 0.05% cream qd x 12 wks; no treatment 12 wks	218	multi-center, comparative.
		vehicle cream qd x 12 wks; no treatment 12 wks	229	parallel-group trial
190168-017C	17	tazarotene 0.01% cream qd x 12 wks	211	double-blind, randomized
		tazarotene 0.05% cream qd x 12 wks	210	multi-center, comparative
		vehicle cream qd x 12 wks	214	parallel-group trial

9.3.1 Adequacy of Phase 3 Trials

Design and Conduct of 190168-016C and -017C

- Both trials were multi-center, randomized, double-blind, parallel-group, vehicle-controlled studies with subjects assigned to tazarotene 0.1%, tazarotene 0.05% or vehicle at a ratio of 1:1:1. Besides the addition of a post-treatment period in 190168-016C to observe for "maintenance effect" of tazarotene, the trials were identical in design. The selection criteria were appropriate. Selection of doses was based on experience with tazarotene gels 0.1% and 0.05%. Use of non-medicated emollients was allowed except on "target lesions", was to precede dosing of study medication by at least 1 hour, and was not allowed the evening prior to a study visit. The evaluation parameters have been discussed with the Agency and found to be acceptable.

- The randomization scheme is acceptable and the Investigators were qualified. Enrollment per center varied from 10 to 60. Audit is being conducted by DSI for selected centers but results are not yet available. The data analysis plan has been discussed with the Agency at the pre-NDA meeting. All changes to the analysis plan were made prior to breaking the double-masked randomization code, except for the additional analyses advised by the Agency at the pre-NDA meeting (correlation of OLA with clinical signs and multiplicity adjustment).