

- There was a substantial degree of dropouts in both studies. This introduces bias, especially with the per protocol analysis of evaluable subjects. The primary analysis is ITT with LOCF methodology to reduce bias. The baselines of the three treatment groups were comparable in the two studies, and there were no specific covariates that would trigger adjustment in the data analysis.
- The comparison of post-treatment period evaluations in 190168-016C between active and vehicle is not adequate to support claims regarding maintenance of therapeutic effect because of post-randomization selection, dropouts and unbalanced baseline status at the time of entry into that phase. Thus, the post-treatment period efficacy data will not be further discussed.
- In the comment under Section 8.2, the issue of demonstration of advantages of having two formulations for marketing has been discussed. In summary, the studies were not designed or powered for pairwise comparisons between the two concentrations for statistical significance. The anticipation of the Applicant 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%.

### 9.3.2 Comparison of Efficacy Data between Phase 3 Studies

As 190168-017C did not have a post-treatment phase, only the treatment period data from 190168-016C are compared with those from 190168-017C.

#### Primary Parameter:

**Clinical Success Rate (Overall Lesional Assessment of none, minimal or mild)**

Week	190168-016C			190168-017C		
	Taz 0.1% N=221	Taz 0.05% N=218	Vehicle N=229	Taz 0.1% N=211	Taz 0.05% N=210	Vehicle N=214
1	13%; p 0.016	10%; p 0.190	7%	12%; p 0.002	7%; p 0.118	4%
	<u>p 0.243</u>			<u>p 0.114</u>		
2	22%; p 0.134	24%; p 0.044	16%	20%; p<0.001	16%; p 0.008	8%
	<u>p 0.648</u>			<u>p 0.176</u>		
4	35%; p<0.001	28%; p 0.034	20%	32%; p<0.001	24%; p 0.038	17%
	<u>p 0.098</u>			<u>p 0.043</u>		
6	34%; p 0.012	34%; p 0.008	24%	41%; p<0.001	35%; p 0.007	24%
	<u>p 0.967</u>			<u>p 0.166</u>		
12	39%; p<0.001	42%; p<0.001	25%	51%; p<0.001	41%; p 0.001	26%
	<u>p 0.648</u>			<u>p 0.025</u>		

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

#### Comments

1. Using a dichotomized outcome for OLA (success defined as none, minimal or mild), both tazarotene concentrations (0.1% and 0.05%) have shown superiority over vehicle cream independently in each of the two phase 3 studies. Multiple comparison adjustment procedure requires tazarotene cream 0.1% to show significance level of < 0.025 at Week 12, which has been fulfilled. This constitutes the evidence in support of effectiveness as agreed upon with the Agency in 1997.
2. In accordance to the Applicant's other criterion for effectiveness, the active creams have achieved ≥1% greater clinical success rates than vehicle cream at Week 12, except for tazarotene cream 0.1% in 190168-016C (14%).
3. In both studies, tazarotene cream 0.05% shows superiority over vehicle from Week 2 onwards, and tazarotene cream 0.1% shows superiority from Week 1 onwards (except for an interruption at Week 2 evaluation in 190168-016C). It has been questioned whether

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this is an advantage for the 0.1% cream. At the pre-IND/EOP2 meeting, the Agency did not recommend endpoints for "time-to" comparisons. Indeed, the primary endpoint was predefined as to be at Week 12. Thus, no analysis with direct pairwise comparison between the two concentrations was made in terms of "time-to" effects, which are dependent on other endpoints such as "clinical success" or "treatment success". In lieu of such analyses, it would appear that an earlier demonstration of superiority over vehicle by one week, using the dichotomized OLA, does suggest an advantage of the 0.1% cream.

4. The "clinical success" rates were similar in the two studies, except for the relatively lower rates for tazarotene 0.1% in 190168-016C at Weeks 8 and 12: 34% for Week 8 and 39% for Week 12 (41% and 51% for corresponding figures in 190168-17C). In view of the steeper slope for success in 190168-017C and those shown by tazarotene cream 0.05% in both studies, the modest changes after Week 4 for tazarotene cream 0.1% in 190168-016C remain to be explained.

5. It is appropriate that a dichotomized OLA as primary endpoint is able to demonstrate effectiveness for both formulations in both studies. Because of limitations in the interpretation of the clinical sign scores (see below), it might have been difficult to establish efficacy, had the clinical signs been used to provide the primary analyses.

**Secondary Parameters:**

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

190168-016C Lesions	Plaque Elevation			Scaling			Erythema		
	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
	<u>p 0.221</u>			<u>p 0.243</u>			<u>p 0.587</u>		
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
	<u>p 0.338</u>			<u>p 0.955</u>			<u>p 0.029</u>		
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
	<u>p 0.001</u>			<u>p 0.153</u>			<u>p 0.809</u>		
190168-017C Lesions	Plaque Elevation			Scaling			Erythema		
	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
	<u>p 0.026</u>			<u>p 0.004</u>			<u>p 0.030</u>		
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
	<u>p 0.022</u>			<u>p 0.055</u>			<u>p 0.022</u>		
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
	<u>p 0.001</u>			<u>p 0.071</u>			<u>p 0.046</u>		

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.

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

190168-016C Lesions	"Treatment Success"			% Body Area Involvement		
	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
	<u>p 0.161</u>			<u>p 0.570</u>		
Knee/elbow	118/221=53%; p<0.001	99/218=45%; p 0.001	70/229=31%			
	<u>p 0.067</u>					
Trunk/limb	113/211=51%; p<0.001	99/218=45%; p 0.003	74/229=32%			
	<u>p 0.178</u>					
190168-017C Lesions	"Treatment Success"			% Body Area Involvement		
	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
	<u>p 0.031</u>			<u>p 0.007</u>		
Knee elbow	132/211=63%; p<0.001	112/210=53%; p 0.002	84/214=39%			
	<u>p 0.073</u>					
Trunk/limb	120/211=57%; p<0.001	103/210=49%; p 0.014	81/214=38%			
	<u>p 0.135</u>					

"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. At Week 12, the reduction in clinical sign scores and surface area involvement, as well as "treatment success" rates (by overall or target lesion global evaluation), was greater across the board for all treatment arms in 190168-017C.

2. At Week 12, both studies are in agreement in showing superiority over vehicle for plaque elevation. For scaling and erythema, some differences between studies exist -

a. Scaling: tazarotene 0.1% was effective over vehicle in both studies. Tazarotene 0.05% was effective for knee/elbow lesions in both studies and overall scaling in 190168-016C, but not for trunk/limb lesions in both studies or overall scaling in 190168-17C.

b. Erythema: tazarotene 0.1% was effective for target lesion and overall erythema in 190168-017C but only for knee/elbow lesions in 190168-016C; tazarotene 0.05% was not effective for target lesions in 190168-016C or for overall erythema in either study, although it was effective for target lesions in 190168-017C.

Plaque elevation is the sine qua non in plaque psoriasis, and it is appropriate that both formulations significantly reduce it in both studies. Erythema may result from the irritation effect due to retinoid use and its reduction or lack thereof is difficult to interpret. Because the formulation is a cream containing 24% mineral oil, it is not surprising that the vehicle effect is substantial, resulting in difficulty for the demonstration of efficacy in scaling for the 0.05% cream. This should not be interpreted as lacking of efficacy for the lower concentration formulation, but rather that the vehicle contribution to efficacy is considerable. Tazarotene 0.05% does provide reduction above and beyond that from vehicle cream for target lesions and overall in each study.

3. "Treatment success" rates from overall global at Week 12 corroborate the "clinical success" rates in showing superiority of both formulations in both studies. The rates were also higher numerically in 190168-017C than in 190168-016C.

4. Reduction in body area involvement varied considerably between studies for all study arms. However, they were all in the same direction, with better reduction in 190168-017C. This is consistent with other data discussed above.

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### 9.3.3 Subset Analysis

The following gives analyses for the primary parameter "clinical success" (from OLA) by demographic subsets. These post-hoc analyses are not powered for significance, but intended to show large differences of treatment effects, if any would exist.

#### Age

**Clinical Success<sup>a</sup> by Age at Week 12 in Phase 3 Studies Pooled**

Age	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
≤65 years	167/370 (45.1%)	151/370 (40.8%)	95/387 (24.5%)
>65 years	27/62 (43.5%)	25/58 (43.1%)	17/56 (30.4%)
P-value <sup>b</sup>	0.922	0.967	

a Clinical success rates based upon an overall lesional assessment of none, minimal, or mild.  
 b Comparison of patients ≤65 years old vs patients >65 years old based on logistic regression for 2 x 2 tables; there were no significant age category-by-study-interactions.

The >65 age group did not show superiority for either formulation over vehicle (p=0.182 for the 0.01% cream and 0.178 for the 0.05% cream). This might simply be due to the small sample size, but the vehicle effect is also greater. There is no significant difference between the young and the old in the "clinical success" rates for either active cream.

#### Sex

**Clinical Success<sup>a</sup> by Sex at Week 12 in Phase 3 Studies Pooled**

Sex	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Males	115/271 (42.4%)	101/278 (36.3%)	57/267 (21.4%)
Females	79/161 (49.1%)	75/150 (50.0%)	55/176 (31.3%)
P-value <sup>c</sup>	0.159	0.004	0.021

a Clinical success rates based upon an overall lesional assessment of none, minimal, or mild.  
 b Comparison of females vs males based on logistic regression for 2 x 2 tables; there were no significant age category-by-study-interactions.

Both formulations were superior to vehicle (p<0.001) in both sexes. The females in general appear to have better "clinical success rates" than males, including the data in the vehicle group.

#### Race

**Clinical Success<sup>a</sup> by Race at Week 12 in Phase 3 Studies Pooled**

Sex	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Caucasian	164/372 (44.1%)	152/375 (40.5%)	99/380 (26.1%)
Black	6/ 13 (46.2%)	5/ 10 (50.0%)	4/ 17 (23.5%)
Asian	0/ 1 ( 0 %)	3/ 9 (33.3%)	0/ 6 ( 0 %)
Hispanic	23/ 44 (52.3%)	15/ 31 (48.4%)	9/ 38 (23.7%)
"Other"	1/ 2 (50.0%)	1/ 3 (33.3%)	0/ 2 ( 0 %)

a Clinical success rates based upon an overall lesional assessment of none, minimal, or mild.

The Caucasian and Hispanic groups showed superiority of both creams over vehicle. The Black, Asian and "Other" groups did not have sufficient sample size to demonstrate superiority for either formulation (p-values for 0.1% and 0.05% creams vs vehicle – Blacks: 0.255 and 0.219, Asians: 0.255 and 0.229, "Other": 0.999 and 0.999). It would be difficult to compare between ethnic groups because besides Caucasians, the sample sizes were too small.

### **9.3.4 Demonstration of Differences between Tazarotene 0.1% and 0.05% Creams**

The Applicant asserts that two formulations, if marketed, would allow flexibility for physicians and patients. Inherent in this assumption is that there is a difference between the two concentrations of tazarotene cream in safety and in efficacy. The safety aspects will be discussed in Section 10. The following are differences in efficacy shown in the two phase 3 trials:

- With the primary parameter, a dichotomized OLA cutoff between mild and moderate disease, tazarotene cream 0.1% achieved superiority over vehicle earlier than the 0.05% cream (Week 1 vs Week 2 for tazarotene 0.05%) in both studies. However, in one study, 190168-016C, this superiority was interrupted by a lesser response at Week 2 and reestablished from Week 4 onwards.
- With dichotomized OLA, head-to-head comparisons between the two formulations demonstrate superiority of tazarotene 0.1% cream at Weeks 4 and 12 in 190168-017C but do not reveal significant differences in 190168-016C. As discussed above, the lack of substantial improvement in success rates after Week 4 in the tazarotene 0.1% arm in 190168-016C is unexplained. Since the success rates in the tazarotene 0.05% group continued to show impressive improvement in this study, statistical superiority of the higher concentration could not be demonstrated for this endpoint in 190168-016C.
- Although not statistically significant in every case, at Week 12, tazarotene 0.1% is better than tazarotene 0.05% in reduction of clinical signs for target lesions and overall numerically in the phase 3 studies, with the exception of the following in 190168-016C:
  - (a) scaling in knee/elbow lesions (-0.76 for 0.1% cream vs -0.78 for 0.05% cream), &
  - (b) erythema in trunk/limb lesions (both -0.49).In addition, "treatment success" rates (by global) and reduction in percent body surface area involvement are all better numerically with tazarotene 0.1% at Week 12 than with tazarotene 0.05%. The differences were significant for overall global "treatment success" and reduction in body area involvement in 190168-017C.
- With overall global evaluation (dynamic global), tazarotene 0.1% cream had lower proportions of patients showing no change or worsening at the end of treatment (Week 12): 24%, vs 30% for the 0.05% cream, in 190168-016C; and 19%, vs 30% for the 0.05% cream, in 190168-017C.

The Applicant has been advised in previous meetings that the formulation with best efficacy should be marketed if there is not greater toxicity. The above data would suggest that the 0.1% concentration provides an overall better efficacy, as shown by the primary endpoint in 190168-017C (dichotomized OLA at Week 12), with confirmatory evidence from secondary parameters in both 190168-016C and 190168-017C.

#### Comments

1. The above comparisons between the two formulations do not uniformly reveal statistical significance between the two concentrations. However, significance is not necessarily relevant in dose-ranging, and the ICH guidance E4 allows for a trend as

evidence of difference. In this regard, the sum of available data does suggest a trend arguing for tazarotene 0.1% being a more effective product because of:

- (a) earlier onset of superiority vs vehicle,
- (b) greater degree of "clinical success" for most time points in both studies,
- (c) greater reduction in clinical sign scores and area of involvement, and
- (d) greater "treatment success" rates overall and for target lesions.

Some of these differences are manifested not only as a trend, but also statistically significant (see above).

2. An additional consideration is the adjustment for multiplicity. This will be addressed in the Biometrics review. It is important to note that the Applicant is applying for both products to be marketed, to be based independently on superiority over vehicle for each cream, and not on an "one or the other" approach pending the study outcome. However, the Applicant did not specify an "all-or-none" approach in conducting the phase 3 studies, whereby success for both formulations was required for the application. They have agreed to perform adjustments for multiplicity using Hochberg's step-up procedure or the Fisher protected least significant difference (LSD) test for comparisons between active and vehicle (3 comparisons). This procedure was set up with tazarotene 0.05% vs vehicle as the first comparison, and the second comparison (tazarotene 0.1% vs vehicle) requires a significance level of  $0.05/2=0.025$ , based on the assumption that  $p$  for 0.05% >  $p$  for 0.1%. Superiority of both formulations over vehicles was demonstrated even after adjustment.

#### 9.4 Conclusions on Efficacy

1. Superiority of tazarotene creams 0.1% and 0.05% vs vehicle has been demonstrated by two adequate and well-controlled studies.
2. There is a trend showing superiority of tazarotene cream 0.1% over the 0.05% formulation.
3. Treatment responses for the target lesions in the knee/elbow area and in the trunk/limb area appear to be comparable.
4. "Maintenance of therapeutic effect" post-treatment has not been demonstrated because of design problems of the post-treatment phase in 190168-016C.

#### 10 Overview of Safety

Dataset. The clinical studies conducted in support of the safety of tazarotene creams 0.1% and 0.05% are tabulated in Section 8.1 (page 7) of this review. In addition to dermal safety and PK studies, they consist of two phase trials, each enrolling approximately 220 patients per arm for tazarotene 0.05%, tazarotene 0.1% and vehicle.

Demographics. The demographics parameters are also shown in the Table in Section 8.1. Drug-demographic interactions will be discussed below (Section 10.2.4). Pediatric patients have not been included in the clinical development of tazarotene creams. It is noted that the phase 3 trials enrolled more male than female psoriasis patients (approximately 2:1), while the majority of subjects in the dermal safety and PK studies were females. In addition, the subjects in the phase 3 studies were mostly Caucasians (>85%). This is also true of the phase 1 trials except for the study for contact sensitization, in which the majority of subjects were Black.

Drug Exposure. The phase 3 trials used the study medication for the longest period of time (12 weeks). There was considerable dropout, and the actual exposure information is summarized in the following Table:

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Mean exposure (days)	70±30	67±31	71±30
Median exposure (days)	85	84	85
Range (days)	1-152	1-164	1-159
Week 0	432 (100%)	428 (100%)	443 (100%)
At least 1 week	396 (92%)	398 (93%)	405 (91%)
At least 2 weeks	382 (88%)	370 (86%)	377 (85%)
At least 4 weeks	353 (82%)	349 (82%)	360 (81%)
At least 8 weeks	298 (69%)	293 (69%)	319 (72%)
At least 12 weeks	267 (62%)	217 (51%)	271 (61%)
At least 14 weeks	14 (3%)	17 (4%)	22 (5%)

These data show that approximately 300 patients have been exposed to each active cream for at least 8 weeks. The mean exposure was 10 weeks for tazarotene 0.1% and 9.6 weeks for tazarotene 0.05%. With the active groups, there was an 18% dropout rate for the first 4 weeks, followed by 13% in the next 4 weeks. In the final 4 weeks of study, tazarotene 0.1% had a lower dropout rate (7% vs 18% with tazarotene 0.05%).

**Comment** Although the numbers shown above may fall slightly short of the ICH E1A Guidance recommended for studying exposure in long-term treatments, experience may be supplemented by:

- long-term use data of tazarotene gels for psoriasis (up to 12 months in Study R168-128-8606); a similar safety profile is expected from long-term use of tazarotene creams; and
- information from tazarotene cream 0.1% in studies on other indications: in one completed photodamage study (190168-025C), tazarotene 0.1% cream was used daily for 24 weeks in 53 of the 58 enrolled patients, making qd exposure to the highest strength of tazarotene cream to be at least 8 to 12 weeks in at least 320 patients. The safety database may be considered adequate.

The reasons for discontinuation are shown in the following Table:

Disposition	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Enrolled	432 (100%)	428 (100%)	443 (100%)
Discontinued	127 (29%)	159 (37%)	125 (28%)
Non-compliance	2 (0%)	7 (2%)	2 (0%)
Adverse event	16 (4%)	25 (6%)	27 (6%)
Lack of efficacy	8 (2%)	32 (8%)	28 (6%)
Concomitant therapy	56 (13%)	41 (10%)	20 (5%)
Relocated	5 (1%)	7 (2%)	2 (0%)
Improper entry	0	5 (1%)	2 (0%)
Lost to follow-up	3 (1%)	4 (1%)	6 (1%)
Other	28 (7%)	32 (8%)	30 (7%)
	9 (2%)	6 (1%)	8 (2%)

**Comment** Adverse event discontinuations constitute 44% (56/127) and 26% (41/159) of discontinuations in the tazarotene 0.1% and 0.05% groups respectively.

## 10.1 Significant/Potentially Significant Events

**10.1.1 Deaths** 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.

## 10.1.2 Other Significant/Potentially Significant Events

### Serious Adverse Events

- During the treatment period, serious adverse events were reported for 2.5% (11/432) of patients in the tazarotene 0.1% group, 1.2% (5/428) of patients in the tazarotene 0.05% group, and 1.4% (6/443) of patients in the vehicle group.
- During the post-treatment period of 190168-016C, 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, except for a severe skin infection in a patient receiving tazarotene 0.1% (2172-G16) in 190168-017C. They are summarized in the following Table:

Study	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
190168-016C: 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"
190168-017C:	H10 right elbow fracture G16 skin infection F39 congestive heart failure, acute renal failure, left ventricle thrombus D33 atypical chest pain	J01 thrombophlebitis	N10 fracture left arm K21 peri-rectal abscess

**Comment** Although pancreatitis is a known retinoid toxicity, this adverse event in patient 0168-N31 (190168-016C) was unlikely due to tazarotene (See section 8.2.1.4.3).

### Discontinuation due to Adverse Events

Adverse events leading to discontinuation have been discussed in the individual studies. Discontinuations due to adverse events during treatment period were dose-related with 13.0% (56/432), 9.6% (41/428), and 4.5% (20/443) of patients in the tazarotene 0.1%, tazarotene 0.05%, and vehicle groups, respectively. Such events were primarily dermatological and included pruritus, inflammation skin/dermatitis, psoriasis worsened, erythema, rash, skin irritation, skin burning, skin pain, peripheral edema, irritant contact dermatitis, fissure skin, hem skin, desquamation, and dry skin.

Since there was post-treatment period only in 190168-016C, there are no pooled data to analyze. The discontinuations were unlikely due to treatment effect persisting from the treatment period (See Section 8.2.1.4.3).

### 10.1.3 Overdosage exposure

Overdose of tazarotene cream(s) has not been studied in humans. The creams are intended for topical application, and excess application may lead to local irritation

effects. Oral ingestion may be expected to lead to symptoms of hypervitaminosis A or other retinoid toxicity.

**10.2 Other Safety Findings**  
**10.2.1 ADR Incidence Tables**

**Number (%) of Patients with Adverse Events Reported by >2% of Patients in Either Tazarotene Group During the Treatment Period of the Phase 3 Studies**

BODY SYSTEM preferred term	Tazarotene 0.1% N = 432	Tazarotene 0.05% N = 428	Vehicle N = 443	Among-group P-value <sup>a</sup>
Any adverse event	297 (69%)	268 (63%)	195 (44%)	< 0.001
<b>BODY AS A WHOLE</b>				
headache	18 ( 4%)	15 ( 4%)	21 ( 5%)	0.663
<b>METABOLIC AND NUTRITIONAL</b>				
hypertriglyceridemia	7 ( 2%)	10 ( 2%)	6 ( 1%)	0.543
<b>RESPIRATORY</b>				
infection	21 ( 5%)	26 ( 6%)	23 ( 5%)	0.734
<b>SKIN AND APPENDAGES</b>				
pruritus	101 (23%)	83 (19%)	51 (12%)	< 0.001
erythema	73 (17%)	58 (14%)	10 ( 2%)	< 0.001
burning skin	61 (14%)	51 (12%)	21 ( 5%)	< 0.001
irritation skin	42 (10%)	31 ( 7%)	8 ( 2%)	< 0.001
desquamation	16 ( 4%)	12 ( 3%)	6 ( 1%)	0.080
rash	15 ( 3%)	13 ( 3%)	3 ( 1%)	0.007
irritant contact dermatitis	13 ( 3%)	8 ( 2%)	1 ( 0%)	0.002
stinging skin	13 ( 3%)	5 ( 1%)	3 ( 1%)	0.019
dermatitis	12 ( 3%)	6 ( 1%)	1 ( 0%)	0.004
psoriasis worsened	11 ( 3%)	15 ( 4%)	9 ( 2%)	0.401
pain skin	11 ( 3%)	12 ( 3%)	7 ( 2%)	0.409
eczema	11 ( 3%)	3 ( 1%)	1 ( 0%)	0.004

<sup>a</sup> Among-group p-value based on the Fisher exact test.

**Number (%) of Patients with Treatment-Related Adverse Events Reported by >2% of Patients in Either Tazarotene Group During the Treatment Period of the Phase 3 Studies**

BODY SYSTEM preferred term	Tazarotene 0.1% N = 432	Tazarotene 0.05% N = 428	Vehicle N = 443	Among-group P-value <sup>a</sup>
Any treatment-related AE	226 (52%)	199 (46%)	89 (20%)	< 0.001
<b>SKIN AND APPENDAGES</b>				
pruritus	98 (23%)	80 (19%)	47 (11%)	< 0.001
erythema	69 (16%)	54 (13%)	10 ( 2%)	< 0.001
burning skin	59 (14%)	50 (12%)	21 ( 5%)	< 0.001
irritation skin	40 ( 9%)	31 ( 7%)	7 ( 2%)	< 0.001
desquamation	14 ( 3%)	11 ( 3%)	4 ( 1%)	0.039
stinging skin	13 ( 3%)	5 ( 1%)	3 ( 1%)	0.019
irritant contact dermatitis	12 ( 3%)	8 ( 2%)	1 ( 0%)	0.004
dermatitis	12 ( 3%)	5 ( 1%)	1 ( 0%)	0.004
pain skin	10 ( 2%)	11 ( 3%)	7 ( 2%)	0.587
psoriasis worsened	10 ( 2%)	10 ( 2%)	6 ( 1%)	0.480
eczema	10 ( 2%)	3 ( 1%)	0 ( 0%)	0.001
rash	9 ( 2%)	9 ( 2%)	2 ( 0%)	0.050

<sup>a</sup> Among-group p-value based on the Fisher exact test.

**Comments**

1. The p-values in the above two Tables are among-group comparisons using all three arms. Pairwise comparisons are only provided in this NDA when the among-group comparison was statistically significant. As head-to-head comparisons are important to determine the differences between the two tazarotene concentrations, this information was requested and provided by the Applicant in the submission of 3/22/00 (See Section 10.2.10 for comparisons between 0.05% and 0.1% creams).

2. Most of the "treatment-related" adverse events are those of skin and appendages.

### Severity of adverse events.

Most of the adverse events were of mild to moderate severity. The following gives the incidence of adverse events rated as "severe" in the treatment period. As only 190168-016C had a post-treatment period, there are no data for analysis by pooling, and the only severe dermal adverse event in this period was pruritus (2 in tazarotene 0.05% group and 1 in vehicle group), which is also a manifestation of psoriasis.

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
<b>Treatment Period</b>			
Patients with severe AEs	36/432 (8.3%)	20/428 (4.7%)	11/443 (2.5%)
Pruritus	11	7	3
Skin irritation	3	2	0
Erythema	5	5	1
Burning skin	2	4	1
Dry skin	2	0	0
Psoriasis worsened	2	0	0
Desquamation	1	1	0
Irritant contact dermatitis	1	0	0
Eczema	3	0	0
Allergic contact dermatitis	1	0	0
"Dermatitis"	1	0	0
Other	15 ("cardiovascular disease" 2, right heart failure 2, bronchitis 2, manic depression 1, lung ca 1, lung disease 1, skin ca 1, "infection" 1, kidney failure 1, tooth anomaly 1, bone fracture 1, lung edema 1)	9 (abdominal pain 1, arm pain 1, ventricular tachycardia 1, bloody diarrhea 1, pancreatitis 1, tooth disease 1, peripheral edema 1, thrombophlebitis 1, hypertriglyceridemia 1)	9 (chest pain 1, sepsis 1, gastrointestinal ca 1, 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, desquamation). Therefore, the significance of these retinoid adverse effects are hard to evaluate. The low incidence of severe local adverse events outside of the skin and appendages system in the vehicle group gives credence to their being true retinoid effects. Despite this, during the treatment period, only 36/297 patients with adverse events in the tazarotene 0.1% group and 20/268 in the tazarotene 0.05% group had severe adverse events, with a substantial proportion of these patients having severe events not related to treatment. The other severe adverse events were reported in 15/36 and 9/20 patients in tazarotene 0.1% and 0.05% groups respectively.

### 10.2.2 Laboratory Findings, Vital Signs, ECGs

The phase 3 studies included clinical laboratory testing with hematology, serum chemistry and urinalysis. Besides possibly triglyceride elevation, 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
<b>Treatment Period</b>	<b>N=432</b>	<b>N=428</b>	<b>N=443</b>
ALL	21 (4.9%)	15 (3.5%)	12 (2.7%)
Treatment-related	3 (0.7%)	8 (1.9%)	4 (0.9%)
<b>Post-treatment Period</b>	<b>N=221</b>	<b>N=221</b>	<b>N=221</b>
ALL	3 (2.2%)	2 (1.7%)	4 (2.9%)
Treatment-related	0	1 (0.9%)	2 (1.4%)

\*190168-016C only.

**Comment** The studies 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.

Since triglyceride elevation may be a potential adverse effect of retinoid use, changes in this parameter are shown as follows:

Week	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle	p-values*
<b>190168-016C</b>				
0	N=221, mean=177	N=217, mean=164	N=226, mean=184	0.382, 0.067, 0.338
4	N=183, mean Δ=-6.09	N=179, mean Δ=-5.81	N=187, mean Δ=-8.74	0.716, 0.514, 0.777
8	N=151, mean Δ=-1.74	N=150, mean Δ=+5.48	N=160, mean Δ=+0.36	0.903, 0.401, 0.487
12	N=146, mean Δ=-2.62	N=124, mean Δ=-0.42	N=151, mean Δ=-2.97	0.939, 0.746, 0.812
<b>190168-017C</b>				
0	N=210, mean=195	N=210, mean=194	N=212, mean=186	0.504, 0.688, 0.790
4	N=176, mean Δ=-0.86	N=177, mean Δ=-10.02	N=173, mean Δ=-10.47	0.329, 0.870, 0.256
8	N=164, mean Δ=-0.37	N=157, mean Δ=-3.58	N=167, mean Δ=-4.78	0.701, 0.628, 0.921
12	N=161, mean Δ=-2.48	N=144, mean Δ=-12.85	N=163, mean Δ=-0.11	0.849, 0.228, 0.309

\* p-values given are pairwise comparisons from t-test comparing least square means using mean square error from 2-way ANOVA in this order: 0.1% vs vehicle, 0.05% vs vehicle, 0.1% vs 0.05% (Fisher's protected LSD test).

Shift Table showing triglyceride value changes from baseline:

Wk/Base: line level:	Numbers of Low, Normal or High Triglyceride Values at Weeks 4, 8, or 12								
	Tazarotene 0.1% (N=432)			Tazarotene 0.05% (N=428)			Vehicle (N=443)		
	Low	Normal	High	Low	Normal	High	Low	Normal	High
4 Low	0	3	0	2	0	0	1	1	0
4 Normal	4	247	21	2	241	21	1	238	21
4 High	0	28	56	0	26	64	0	37	61
8 Low	0	3	0	0	2	0	1	1	0
8 Normal	1	211	22	2	196	27	2	209	26
8 High	0	25	53	0	24	56	0	23	65
12 Low	2	1	0	0	2	0	0	2	0
12 Normal	1	212	20	1	170	24	1	195	26
12 High	0	24	47	0	22	49	0	26	64

**Comment** Review of the listing for abnormal triglyceride values and the above summary Tables does not suggest consistent, clinically meaningful differences between the active and vehicle treatment groups.

There were no pertinent vital sign changes observed in the clinical studies. ECG was not part of the evaluation.

### 10.2.3 Special Studies

The phase 1 program contained 2 PK studies and 5 dermal safety studies (see Table under "Dataset" of Section 10).

#### 10.2.3.1 Pharmacokinetic Studies

The synopses, instead of study reports, of the PK studies were not submitted to the Clinical Data Section of the NDA. The following review is based on the reports submitted to the Human Pharmacokinetic Data Section (vol 1.11-1.15). The PK studies were done using the to-be-marketed formulations.

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### 10.2.3.1.1 First Bioavailability Study

#### 190168-024C An Open-Label, Single-Center, Pharmacokinetics Study Of Tazarotene 0.1% Cream Applied Once Daily For 14 Days In The Treatment Of Plaque Psoriasis [Started 8/7/98, Completed 10/13/98]

This study was designed to determine drug absorption in psoriasis when used under regular and under excess conditions and was conducted by \_\_\_\_\_

\_\_\_\_\_ Ten patients were planned with 3 blocks:

% Body Area with Psoriasis	QD Dose	Patient with Area Involvement of Psoriasis Shown on First Column
5%-9.9%	10 mg/cm <sup>2</sup>	1 <sup>st</sup> , 3 <sup>rd</sup>
	2 mg/cm <sup>2</sup>	2 <sup>nd</sup> , 4 <sup>th</sup>
10%-14.9%	10 mg/cm <sup>2</sup>	1 <sup>st</sup> , 3 <sup>rd</sup>
	2 mg/cm <sup>2</sup>	2 <sup>nd</sup> , 4 <sup>th</sup>
≥15%	10 mg/cm <sup>2</sup>	1 <sup>st</sup>
	2 mg/cm <sup>2</sup>	2 <sup>nd</sup>

Tazarotene cream 0.1% was applied each evening by investigational site personnel to all plaques, except for scalp and intertriginous areas. Patients were to shower/bathe in the morning, and non-medicated emollients were allowed. Sampling for plasma levels of tazarotene and "tazarotenic acid" were to be done:

- Prior to 1<sup>st</sup> dose on day 0, and at 3, 6, 9, 12, 16, 20, 24, 36, 48, 60 and 72 hrs post-dose
- Prior to 7<sup>th</sup> dose on day 8, and at 3, 6, 9, 12, 16, 20, and 24 hrs post-dose
- Prior to 10<sup>th</sup> dose on day 11, and the 12<sup>th</sup> dose on Day 13
- Prior to 14<sup>th</sup> dose on day 15, and at 3, 6, 9, 12, 16, 20, 24, 36, 48, 60 and 72 hrs post-dose

Nine Caucasian patients were enrolled, with 3 males and 6 females, aged 39-59 (mean 51). The mean percent psoriasis involvement was 14% at baseline. The Applicant considers the conduct of the study inadequate, and therefore blood samples and efficacy data were not analyzed at the time of NDA submission. The problems reported were:

1. Site personnel failed to re-calculate dose when patient's area of involvement changed;
2. Some doses not accurately weighed by site personnel;
3. Improper patient assignment;
4. Improper timing of blood draws.

At the time of the 120-day Safety Update, the data from analysis of the blood samples were presented (mean values and range):

**Bioavailability Data (on "Tazarotenic Acid") at Day 15 from 190168-024C**

	% BSA Involvement	Cmax (ng/mL)	Tmax (hr)	AUC <sub>24</sub> (ng.hr/mL)	T <sub>1/2</sub> (hr)
2 mg/cm <sup>2</sup>	10 (5-15)	0.4 (0.1-0.6)	8 (6-9)	8.3 (4.4-10.9)	NC
10 mg/cm <sup>2</sup>	17 (5-50)	1.9 (0.7-3.4)	7 (6-9)	26.6 (10.0-41.8)	20.3 (13.3-33.8)

BSA= Body surface area; NC=not calculable.

The highest exposure was seen in a patient dosed at 10 mg/cm<sup>2</sup> over 50% body area involvement (Cmax 6.5, AUC 89.3), and the second highest was in a patient dosed at 10 mg/cm<sup>2</sup> over 5% body area involvement (Cmax 3.4, AUC 39.3).

Only safety data were presented in the original NDA. Eight of the 9 patients enrolled reported adverse events during the study:-

headache 7, erythema 7, pruritus 6, burning skin 6, dry skin 4, desquamation 3, insomnia 2, fever 2, and 1 patient each for pain (head), pain (chest tightness), anemia, bilirubinuria, myalgia, dyspnea, alopecia, multiple macular eruption on normal skin, skin reaction (tenderness of psoriatic lesion), and dry eye.

Laboratory evaluations (hematology, blood chemistry, and urinalysis) showed no consistent, clinically significant, drug-related effects.

**Comment** This study was unsuccessful for the determination of bioavailability (contrast data from 190168-023C with substantially higher Cmax and AUC at Day 15). The safety data could not be stratified according to dosing because of application errors. The sample size is too small for interpretation of the adverse event information. It is noted that most patients had headache as adverse event (at least 7 of 9) in this study (only 4% in phase 3 trials). As patients had to be dosed at the study site every day, it is unclear whether this event is related to the treatment or the study site environment.

**10.2.3.1.2 Second Bioavailability Study**

**190168-023C An Open-Label, Multi-Center, Pharmacokinetics Study Of Tazarotene 0.1% Cream Applied Once Daily For 14 Days In The Treatment Of Plaque Psoriasis [Started 1/23/99, Completed 5/25/99]**

The study report for 023C is being reviewed by Biopharm. It was conducted as a replacement for study 024C with identical design. The Investigators were

Eleven Caucasian patients were enrolled and 9 completed the study. There were 4 males and 7 females, aged 23-68 (mean 45). The following PK data are presented (mean values and range):

**Bioavailability Data (on "Tazarotenic Acid") from 190168-023C**

	Cmax (ng/mL)	Tmax (hr)	AUC <sub>0-24</sub> (ng.hr/mL)	T½ (hr)	F (% dose)
Day 0					
2 mg/cm <sup>2</sup>	0.4 (0.1-0.8)	11 (9-12)	23.6	13.6	1.1
10 mg/cm <sup>2</sup>	0.5 (0.2-1.3)	11 (6-12)	45.6	19.2	0.6
Day 6					
2 mg/cm <sup>2</sup>	1.6 (0.1-4.0)	7 (6-9)	23.5 (1.3-56.6)	NA	2.0 (0.4-3.3)
10 mg/cm <sup>2</sup>	3.4 (0.4-9.6)	8 (6-12)	51.1 (8.0-141)	NA	1.5 (0.7-2.3)
Day 15					
2 mg/cm <sup>2</sup>	2.3 (0.1-6.9)	8 (6-12)	31.2 (1.0-88.3)	15.4	2.5 (0.4-4.0)
10 mg/cm <sup>2</sup>	3.1 (0.7-6.4)	7 (6-9)	46.4 (14.0-97.1)	31.3 (24.1-65.0)	1.8 (1.2-2.3)

The highest exposure was seen in a patient dosed at 10 mg/cm<sup>2</sup> over 25% body area involvement (Cmax 9.6, AUC 141), and the second highest was in a patient dosed at 2 mg/cm<sup>2</sup> over 36% body area involvement (Cmax 6.9, AUC 88.3).

One patient receiving tazarotene 10mg/cm<sup>2</sup> discontinued due to "treatment-related" hypertension and pruritus. Nine of 11 (82%) patients enrolled reported adverse events (4/5 in 2 mg/cm<sup>2</sup> group and 5/6 in 10 mg/cm<sup>2</sup> group) as follows:

irritant contact dermatitis 6, pruritus 5, headache 5, chills 4, arthritis 2, rash 2, 1 report each of face edema, flu syndrome, hypertension, tooth disorder, echymosis, dehydration, dizziness, burning skin, and urinary abnormality.

Overall, "treatment-related" adverse events were seen in 8 patients (72.7%). These were dermatological events:

- 3/5 (60.0%) of patients receiving tazarotene 2 mg/cm<sup>2</sup>; and
- 5/6 (83.3%) of patients receiving tazarotene 10 mg/cm<sup>2</sup>.

There were no significant changes in physical exams and vital signs from pre- to post-study. Clinical laboratory parameters were unremarkable.

**Comments**

1. Systemic exposure to "tazarotenic acid" (AUC and Cmax data) appears to be 1.3 to 2.5 fold higher after daily application of cream 0.1% at 10 mg/cm<sup>2</sup> when compared to 2 mg/cm<sup>2</sup>. The percent dose bioavailable is comparable.
2. The highest attainable levels of "tazarotenic acid" with 10 mg/cm<sup>2</sup> dosing (up to 9.6 ng/mL) are within the range previously seen after treatment with tazarotene gels and oral formulation. No evidence of systemic retinoid toxicity has been observed with this degree of exposure in previous studies or in 190168-023C. However, the exposure (AUC up to 141 ng.hr/mL) may attain that associated with preclinical teratogenicity (for rats at AUC 115 ng.hr/mL).
3. Detailed correlation of PK parameter with body area involvement should be reviewed by the Biopharm Reviewer. The following Table is a summary of the data derived from the study report, arranged in increasing area size to be treated. Although there may be a suggestion of proportionality, this is not perfect in terms of either dose or area size being treated. Many factors may be related to this, including especially the thickness of the plaques and the degree of inflammation.

**PK Data by Size of Treatment Area**

Patient Number and dose ca.	Treat area (cm <sup>2</sup> )	Day 1				Day 8				Day 15				
		% BSA	Dose (Gm)	Cmax	AUC	% BSA	Dose (Gm)	Cmax	AUC	% BSA	Dose (Gm)	Cmax	AUC	
3	2 mg	83C	5	1.81	<	<	7	2.81	.565	8.273	7	2.43	.515	8.673
6	10 mg	92E	5	9.50	.241	4.294	3	5.42	.419	8	3	5.65	.746	14.04
7	2 mg	128G	6	2.59	<	<	5	2.48	.109	1.270	4	1.68	.131	0.960
1	10 mg	147Z	8	15.5	.289	4.658	5	9.21	1.48	23.52	4	7.37	1.21	22.32
6	2 mg	325E	14	6.16	.232	3.737	15	6.78	2.05	32.24	14	6.98	3.05	40.72
11	2 mg	346G	20	6.73	.133	2.513	26	8.76	1.19	18.86	20	6.75	1.02	17.5
9	10 mg	257Z	14	29.6	.437	6.720	14	29.9	2.07	31.78	14	30.0	3.93	51.93
5	10 mg	492E	26	50.6	1.25	19.28	25	43.8	9.55	141.2	17	29.9	6.40	97.12
4	2 mg	773E	35	15.4	.836	13.34	35	15.4	4.01	56.64	36	15.7	6.85	88.26

Areas <200, Cmax >1 and AUC >20 are highlighted. Treat area = initial treatment area size. Cmax in ng/mL and AUC in ng.hr/mL.

4. The adverse event data from the two doses 2 mg/cm<sup>2</sup> and 10 mg/cm<sup>2</sup> appear to be similar.

**10.2.3.1.3 Therapeutic Drug Monitoring in Phase 3 Studies**

In the phase 3 trials, 190168-016C and -017C, supervised dosing and pre- and post-dose sampling were done to determine levels of tazarotene and "tazarotenic acid" after an evening of no dosing.

**Bioavailability Data of Phase 3 Trials**

	Tazarotene Levels (ng/mL)	"Tazarotenic Acid" Levels (ng/mL)
<b>190168-016C</b>		
tazarotene 0.05% group (N=32)	all undetectable	12 (38%) detectable, up to
tazarotene 0.1% group (N=38)	one Week 8 sample at 0.091	24 (63%) detectable, up to
<b>190168-017C</b>		
tazarotene 0.05% group (N=37)	all undetectable	19 (51%) detectable, up to
tazarotene 0.1% group (N=32)	two Week 4 samples: 0.091 & 0.0838	23 (72%) detectable, up to

**Comments** Low plasma levels would not be informative, since the time of sampling varied and could be up to 10 hours post-dose. The highest level attained was in a patient using tazarotene 0.1% cream. It is noted that patients in studies for other tazarotene formulations (gel and oral capsules) had achieved levels a log higher without apparent adverse effects.

Systemic availability data suggest dose-dependence and can be shown in the following Table:

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	Week 4 (Mean "Tazarotenic Acid" Values)					Week 8 (Mean "Tazarotenic Acid" Values)				
	Dose	%BSA	Cpre	Cpost	Time	Dose	%BSA	Cpre	Cpost	Time
<b>190168-016C</b>										
Tazarotene 0.05%	4.74	12	0.030	0.083	4.05	4.45	8	0.064	0.130	5.18
Tazarotene 0.1%	3.88	7	0.185	0.311	4.86	3.80	7	0.157	0.348	4.58
<b>190168-017C</b>										
Tazarotene 0.05%	2.26	10	0.028	0.040	4.38	2.08	10	0.023	0.043	4.48
Tazarotene 0.1%	2.13	11	0.072	0.155	3.92	2.43	11	0.047	0.111	3.97

Dose=dose of test drug in Gm. %BSA= percent body surface area involvement, Cpre=pre-dose plasma level, Cpost=post-dose plasma level, Time=time of sampling.

### 10.2.3.2 Dermal Safety Studies

Apart from the Formulation Selection study (190168-503C), all dermal safety studies were done using the to-be-marketed formulation.

#### 10.2.3.2.1 Study for Formulation Selection.

##### 190168-503C 21-Day Cumulative Irritation Study Of Five Tazarotene Creams At Three Different Concentrations (0.1%, 0.05% and 0.01%) In Healthy Subjects [Started 7/96, Completed 8/96]

This is a formulation selection study, and the to-be-marketed formulations were chosen on the basis of its outcome. It is a single-center, investigator-masked, randomized, incomplete-block study conducted by [REDACTED].

and was a standard 21-day cumulative irritancy testing using the following formulations:

- 5 tazarotene cream formulations, each at 3 concentrations (0.01%, 0.05% and 0.1%)
- vehicle cream
- tazarotene gels at 2 concentrations (0.05% and 0.1%)
- Retin-A<sup>®</sup> creams at 2 concentrations (0.05% and 0.1%)
- Renova<sup>®</sup> cream 0.05%.

Each subject received the vehicle cream and 8 of the 20 active test products, applied to semi-occlusive patches, and affixed with hypoallergenic tape to the same location on the back throughout the study. Approximately 24 hours later, the patches were removed and the reactions graded using an 8-point scale. This sequence of events (i.e., patch application, removal, evaluation, and reapplication) was repeated Monday through Friday until day 21.

#### Results:

There were 100 Caucasian subjects, with 16 males and 84 females, aged 18-65 (mean 40). The irritation score findings are:

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**Least Squares Mean  $\pm$  SE<sup>a</sup> Cumulative 21-Day Irritation Scores in 190168-503C**

Formulation (number)	Cumulative 21-day irritation score	Between group comparison <sup>b</sup>
vehicle cream (8891X)	0.263 $\pm$ 0.892	A
tazarotene cream 0.01% (8888X)	1.673 $\pm$ 1.496	A, B
tazarotene cream 0.01% (8879X)	3.557 $\pm$ 1.494	A, B, C
tazarotene cream 0.01% (8876X)	3.915 $\pm$ 1.475	B, C, D
tazarotene cream 0.01% (8882X)	5.644 $\pm$ 1.493	B, C, D, E
Retin-A <sup>®</sup> cream 0.05% (8174X)	7.600 $\pm$ 1.516	C, D, E, F
Renova <sup>®</sup> cream 0.05% (8895X)	8.845 $\pm$ 1.515	E, F
tazarotene cream 0.05% (8880X)	15.957 $\pm$ 1.494	G
Retin-A <sup>®</sup> cream 0.1% (8175X)	18.199 $\pm$ 1.474	G, H
tazarotene cream 0.05% (8889X)	19.929 $\pm$ 1.475	H, I
tazarotene cream 0.05% (8877X)	23.362 $\pm$ 1.496	I, J
tazarotene gel 0.05% (8607X-A)	23.887 $\pm$ 1.514	I, J
tazarotene cream 0.1% (8881X)	25.724 $\pm$ 1.514	J, K
tazarotene cream 0.05% (8883X)	27.110 $\pm$ 1.493	J, K, L
tazarotene gel 0.1% (8606X)	28.462 $\pm$ 1.494	K, L
tazarotene cream 0.1% (8890X)	30.566 $\pm$ 1.495	L, M
tazarotene cream 0.1% (8885X)	30.636 $\pm$ 1.494	L, M
tazarotene cream 0.1% (8878X)	33.904 $\pm$ 1.493	M, N
tazarotene cream 0.1% (8884X)	37.455 $\pm$ 1.475	N
tazarotene cream 0.05% (8886X)	50.415 $\pm$ 1.496	O
tazarotene cream 0.1% (8887X)	58.372 $\pm$ 1.492	P

<sup>a</sup> SE = standard error of least squares mean.

<sup>b</sup> Between-group comparison p-value from Fisher protected least significant difference test; formulations sharing a common letter were not statistically significantly different from each other ( $p > 0.05$ ).

**Adverse Event Data:** Overall, 21% (21/100) of subjects reported adverse events. Six subjects experienced mild or moderate treatment-related events: rash 3, cheilitis 2, and stomatitis 1. Adverse events of unlikely, unknown, or no relationship to treatment included respiratory infection 6, herpes simplex 4, diarrhea 3, migraine 2, pharyngitis 2, vomiting 2, and 1 each of abdominal pain, back pain, leg pain, malaise, stomach ulcer, swollen glands, paresthesia, burst blood vessel in eye, blurred vision, and vaginal monilia. One discontinued due to hospitalization for abdominal pain later diagnosed as gastric ulcer. This serious adverse event was considered not related to study drug.

**Applicant's Conclusion and Actions:** When comparing the cumulative irritation scores within each formulation type, there was a trend towards lower cumulative irritation scores as the concentration of tazarotene decreased. On the basis of these study findings, the current formulation type (8880X for 0.05% and 8881X for 0.1%) was selected for further development. One of the minor excipients was changed from \_\_\_\_\_ to sodium thiosulfate \_\_\_\_\_, and this formulation type was used in all subsequent studies.

**10.2.3.2.2 Irritancy Potential**

**190168-019C A Single-Center, Double-Blind, Randomized, Vehicle-Controlled, 21-Day Cumulative Irritation Study Of 0.01%, 0.025%, 0.05% And 0.1% Tazarotene Creams In Healthy Subjects [Started 6/1/98, Completed 6/29/98]**

This was a single-center, double-blind, vehicle-controlled, randomized, complete-block study to assess the irritation potential of tazarotene creams 0.01%, 0.025%, 0.05% and 0.1% compared with vehicle cream and sodium lauryl sulfate solution 0.5% conducted by \_\_\_\_\_. Each healthy subject received 6 formulations, applied to semi-occlusive patches and affixed with hypoallergenic tape to the same location on the back throughout the study. Approximately 24 hours later,

the patches were removed and the reactions graded using a 6-point scale: 0 = no signs of irritation, 0.5 = faint, minimal erythema, 1 = slight erythema, 2 = noticeable erythema with slight infiltration, 3 = erythema with marked edema, 4 = erythema with edema and blistering. This sequence of events (i.e., patch application, removal, evaluation, and reapplication) was repeated Monday through Saturday until day 21.

**Results:**

Forty subjects were enrolled: 9 males and 31 females aged 29-69 (mean 51). There were 27 Caucasians and 13 Blacks.

During the 21-day treatment period, the cumulative irritation scores were related to the concentration of tazarotene, with the irritation scores being significantly higher with increasing concentrations of tazarotene (0.01% < 0.025% < 0.05% < 0.1%).

**Least Squares Mean ± SE<sup>a</sup> Cumulative 21-Day Irritation Scores in 190168-019C**

Formulation	Cumulative 21-day irritation score	Between group comparison <sup>b</sup>
vehicle cream	4.38 ± 1.76	A
tazarotene cream 0.01%	11.58 ± 1.76	B
tazarotene cream 0.025%	27.57 ± 1.76	C
tazarotene cream 0.05%	35.06 ± 1.76	D
tazarotene cream 0.1%	45.09 ± 1.76	E
sodium lauryl sulfate solution 0.5%	29.11 ± 1.76	C, D

<sup>a</sup> SE = standard error of least squares mean; <sup>b</sup> Between-group comparison p-value from Tukey test, formulations sharing a common letter were not statistically significantly different from each other (p > 0.05).

**Comments**

- It is noted that the irritation scores of 190168-019C and 190168-503C are not comparable. In 190168-019C, a 6-point scale was used, but 190168-503C used an 8-point scale. However, the vehicle cream cumulative score in 190168-019C is 17 times that in 190168-503C. It is unclear whether the same vehicle formulation was used in the two studies. The scores for tazarotene 0.05% and 0.1% creams are approximately twice as high as those in 190168-053C. There has been a change in the excipient with \_\_\_\_\_ changed to sodium thiosulfate \_\_\_\_\_ but this appears to be unlikely to account for the difference. In the absence of other testing material that might have been used in common to both studies (e.g., other retinoid products), the differences in scores are unexplained.
- The study was done using semi-occlusive patches. This may be acceptable if the product is a known irritant.
- Tazarotene 0.05% cream is as irritant as sodium lauryl sulfate 0.5% solution, while the 0.1% cream has greater irritancy potential.

**Adverse Event Data:** Since the clinical signs of cutaneous irritation evaluated were edema, vesiculation, scaling, dry skin, cracking or crazing, burning or stinging, scabbing, papules, reaction spreading outside area of application, glazing, and tape response were expected in this study, they were not considered adverse events in safety data evaluation. In general, there was an increase in the incidence of signs of irritation as the concentration of tazarotene cream increased. Overall, 12.5% (5/40) of subjects reported adverse events. One experienced mild, treatment-related urticaria and discontinued study. Four other subjects experienced adverse events unrelated to the test products: dislocation of knee and pulled ligament with accompanying pain, sprained ankle, eyelid edema/erythema, and tape reaction at patch sites extending outside of patch area which led to study discontinuation. All of the events were mild to moderate in severity. There were no serious adverse events.

### 10.2.3.2.3 Sensitization Potential

#### 190168-020C A Single-Center, Double-Blind, Randomized, Vehicle-Controlled, 39-Day Contact Sensitization Study Of 0.01%, 0.025%, 0.05% And 0.1% Tazarotene Creams In Healthy Subjects [Started 6/8/98, Completed 7/10/98]

This was a single-center, double-blind, vehicle-controlled, randomized, complete-block study to assess the contact sensitization potential of tazarotene creams 0.01%, 0.025%, 0.05% and 0.1% compared with vehicle cream conducted by \_\_\_\_\_ on healthy subjects. Each subject received the 5 formulations, applied to semi-occlusive patches affixed with hypoallergenic tape to the same location on the back throughout the study. Approximately 48 hours later, patches were removed and skin responses graded using a 6-point scale. This sequence of events (i.e., patch application, removal, evaluation, and reapplication) was repeated Monday-Wednesday-Friday for a total of 9 applications over a 3-week induction period. After a 2-week rest period, one additional challenge 48-hr patch was evaluated (at 48 hrs and 72 hrs). Evaluation of each of the 5 test products was based on the 6-point irritation scale same as that in 190168-019C.

#### Results:

Of 230 subjects enrolled, 201 completed the study. There were 44 males and 186 females, aged 18 to 70 (mean 46 years). The racial distribution was: Caucasian 83, Black 145 and "other" 2. During induction, there were numerous skin responses with irritation graded as 0.5 to 4. Many subjects had the patches dropped due to excessive reactions. At challenge, there were no skin responses that were greater than grade 1. The investigator regarded all the test products as irritating, but none of the reactions were considered to be consistent with contact sensitization.

#### Comments

1. This study used semi-occlusive instead of occlusive patches. This may be acceptable if the drug being tested is a known irritant.
2. The data corroborate those of 190168-019C in confirming the irritant effect of tazarotene.
3. Interpretation of sensitization may be interfered by the irritant effect of tazarotene. However, the low level of skin responses at challenge ( $\leq 1$ ) suggests that the reactions were probably from irritation rather than from sensitization. This is also consistent with previous findings from sensitization studies on tazarotene gels. It may be concluded that tazarotene creams up to 0.1% concentration are of low sensitization potential.

**Adverse Event Data:** Only 7.8% (18/230) of subjects reported adverse events, none of which were considered related to treatment. Three subjects experienced headaches, 2 had an accidental injury, and 2 had periodontal abscesses. All other events were reported by a single subject. Three dermatologic reactions were noted: facial swelling with tooth abscess; focal skin edema and erythema; and sunburn to area around patches. One subject (2420-157) experienced the severe and serious adverse events of depression and overdose of multiple medications (not study drugs). All other events were rated mild or moderate.

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#### **10.2.3.2.4 Phototoxicity And Photoallergenicity**

##### **190168-021C A Single-Center, Double-Blind, Randomized, Vehicle-Controlled, 46-Day Phototoxicity And Photoallergy Study Of 0.01%, 0.025%, 0.05% And 0.1% Tazarotene Creams In Healthy Subjects [Started 5/26/98, Completed 7/10/98]**

This was a single-center, double-blind, vehicle-controlled, randomized, complete-block study to assess the phototoxic and photoallergic potentials of tazarotene creams 0.01%, 0.025%, 0.05% and 0.1% compared with vehicle cream conducted by \_\_\_\_\_ on healthy subjects. Each subject received each of the 5 formulations, applied to semi-occlusive 24-hr patches and affixed with hypoallergenic tape to duplicate sites on the back throughout the study. One set of treated sites served as control, while the second set was irradiated. Another site, adjacent to the irradiated, treated sites, was irradiated but not treated. For phototoxicity evaluations, upon patch removal, sites were irradiated (UVA 10 MED equivalents and UVA/UVB 0.5 MED) and assessments made 5 minutes, 20 minutes, 3, 24 and 48 hours following irradiation. For photoallergic evaluations, upon removal of the 24-hr induction patches, each site was examined for irritation. Designated sites were irradiated with 2MEDs of UVA/UVB and evaluated at 5 minutes and 24 hrs. This sequence was repeated for a total of 6 applications over the 3-week induction period. After a 2-week rest period, challenge patches were applied to fresh sites for 24 hrs and then irradiated (UVA 10 MED equivalents), with evaluation at 5 minutes, 20 minutes, 24 and 48 hours following irradiation. Evaluation was based on the same irritation scale as that in 190168-019C.

#### **Results:**

Of 30 subjects enrolled, 28 completed the study. There were 4 males and 26 females, aged 23 to 71 (mean 46 years). The racial distribution was: Caucasian 29, "other" 1.

- For phototoxicity. The initial gradings of the irradiated sites were generally "0.5" and a few "1", which fell to "0" by 24 to 48 hours. In the opinion of the investigator, none of the test products caused phototoxic reactions.
- For photoallergenicity. During the induction period, there were numerous "0.5" and "1" noted at the irradiated sites with all test products. During the challenge phase, the majority of irradiated sites were graded "0". In the opinion of the investigator, none of the test products caused photoallergic reactions.

**Adverse Event Data:** Overall, 23.3% (7/30) of subjects reported adverse events, none of which were considered related to treatment: headaches 2, asthenia 1, back pain 1, hypertension 1, paresthesia 1, bronchitis 1, laryngitis 1, and otitis media 1. Three events were rated severe: back pain, hypertension, and paresthesia. There were no serious adverse events.

#### **Comments**

1. Tazarotene creams 0.05% and 0.1% are of low phototoxicity and photoallergenicity potential with the electromagnetic spectrum tested.
2. Since tazarotene absorbs in the UVC and UVB spectra (373, 307, 269 nm), the challenge phase for photoallergenicity with UVA alone would be inadequate.
3. The 6-application procedure for photoallergenicity testing is a standard version of the photomaximization test (Kaidbey and Kligman. *Contact Dermatitis* 6: 161, 1980).

### 10.2.3.2.5 Photoallergenicity

#### 190168-032C A Single-Center, Double-Blind, Randomized, Vehicle-Controlled, 40-Day Photoallergy Study Of 0.05% And 0.1% Tazarotene Creams In Healthy Subjects [Started 7/12/99, Completed 8/27/99]

This study was performed as a repeat of the photoallergenicity part of 190168-021C to address its inadequacy by using both UVB and UVA in the challenge phase. Its protocol was otherwise identical to the photoallergenicity part of that study.

\_\_\_\_\_ also conducted this study. The irradiation at challenge consisted of UVA 10 MED equivalents, followed immediately by UVB 0.5 MED.

#### Results:

The 30 Caucasian subjects enrolled consisted of 2 males and 28 females, aged 26 to 70 (mean 52 years); 29 completed the study.

**Frequency of Irritation Scores During Induction and Challenge Phases of 190168-032C**

Irritation Score	Induction Phase						Challenge Phase					
	Tazarotene 0.1%		Tazarotene 0.05%		Vehicle		Tazarotene 0.1%		Tazarotene 0.05%		Vehicle	
	I	NI	I	NI	I	NI	I	NI	I	NI	I	NI
0	0	0	0	0	0	3	16	16	17	17	23	23
0.5	1	4	1	8	3	19	5	5	5	4	4	4
1	10	19	15	18	25	8	8	8	7	8	2	2
2	0	0	0	0	0	0	0	0	0	0	0	0
3	8	3	6	1	1	0	0	0	0	0	0	0
4	11	4	8	3	1	0	0	0	0	0	0	0

I=Irradiated, NI=Non-Irradiated.

During the induction period, there were numerous "0.5" and "1" noted at the irradiated and non-irradiated sites with all test products. There were also grades "3" and "4" with the active formulations at both kinds of sites, as well as one "3" and one "4" with vehicle at irradiated sites. For the active formulations, the "3" and "4" reactions were more frequent over irradiated vs non-irradiated sites.

During the challenge phase, the majority of irradiated sites were graded "0". There were both "0.5" and "1" grades with all formulations, the frequencies of these reactions being similar between irradiated and non-irradiated sites. In the opinion of the investigator, none of the test products caused photoallergic reactions.

#### Comments

1. Since the frequencies of reactions were similar between irradiated and non-irradiated sites at challenge, it is unlikely that they represented photoallergic reactions. It may be concluded that tazarotene creams are of low photoallergenic potential.
2. The greater frequencies of "3" and "4" reactions over irradiated sites of the active formulations is consistent with the well known irritant effect of retinoids aggravating acute damage from UV radiation.
3. The differences between the frequencies of "3" and "4" scores for 190168-021C and 190168-032C are unexplained. Both protocols were conducted by the same Investigator, and used the same procedures in the induction phase. Yet there were far more "3" and "4" reactions during induction in 190168-032C.

**Adverse Event Data:** Only one subject reported adverse event: kidney calculus, considered unrelated to treatment and severe. The subject was discontinued from study.

## 10.2.4 Drug-Demographic Interactions

The following analyses are based on data from the phase 3 trials:

### 10.2.4.1 Age

In the phase 3 studies, 42.6% (555/1303) of patients were <45 years old, 43.9% (572/1303) were from 45 to 65 years old, and 13.5% (176/1303) were >65 years old. The overall incidence of adverse events was similar in the 3 age subgroups: 56.4% (313/555) of patients <45 years old, 59.3% (339/572) of patients from 45 to 65 years old, and 61.4% (108/176) of patients >65 years old.

- In the <45 years old subgroup, patients receiving tazarotene 0.1% or 0.05% experienced significantly more burning skin, erythema, and skin irritation than vehicle patients ( $p \leq 0.021$ ).
- In the 45 to 65 years old subgroup, patients receiving tazarotene 0.1% or 0.05% experienced significantly more burning skin, erythema, skin irritation, pruritus, and rash than vehicle patients ( $p \leq 0.043$ ).
- In the >65 years old subgroup, patients receiving tazarotene 0.1% or 0.05% experienced significantly more erythema than vehicle patients ( $p \leq 0.008$ ).

In each subgroup, there were no statistically significant differences among the 3 treatments for adverse events in body systems other than "skin and appendages", except for pharyngitis and flu syndrome in the 45 to 65 years old subgroup ( $p \leq 0.031$ ).

There was no statistically significant difference in the overall incidence of adverse events between patients aged  $\leq 65$  years and patients aged >65 years with either tazarotene formulation (0.1% or 0.05%):

**Number (%) of Patients with Any Adverse Event During the Treatment Period of Phase 3 Studies**

Age Category	Tazarotene 0.1% N = 432	Tazarotene 0.05% N = 428	Total Tazarotene N = 860
$\leq 65$ years	255/370 (68.9%)	226/370 (61.1%)	481/740 (65.0%)
> 65 years	42/62 (67.7%)	42/58 (72.4%)	84/120 (70.0%)
P-value <sup>a</sup>	0.853	0.097	0.285

<sup>a</sup> Comparison of patients  $\leq 65$  years old vs patients > 65 years old based on chi-square test.

### 10.2.4.2 Sex

The phase 3 studies had 62.6% (816/1303) males and 37.4% (487/1303) females. Overall, adverse events were reported for a somewhat lower proportion of males than females, 55.4% (452/816) vs 63.2% (308/487), respectively.

- Males receiving tazarotene 0.1% or 0.05% experienced significantly more irritant contact dermatitis, erythema, skin irritation, and pruritus than vehicle patients ( $p \leq 0.031$ ). There were no statistically significant treatment-group differences in males for adverse events in body systems other than "skin and appendages".
- Females receiving tazarotene 0.1% or 0.05% experienced significantly more burning skin, erythema, and rash than vehicle patients ( $p \leq 0.017$ ). There were no statistically significant treatment-group differences in females for any single adverse event in body systems other than "skin and appendages". There was however a higher incidence of digestive complaints overall for females receiving tazarotene 0.1% (7.5%, 12/161) compared with tazarotene 0.05% (2.0%, 3/150) or vehicle (2.8%, 5/176). No single event appeared to account for this disparity.

**Number (%) of Patients with Any Adverse Event During the Treatment Period of Phase 3 Studies**

Sex	Tazarotene 0.1% N = 432	Tazarotene 0.05% N = 428	Vehicle N = 443
Males	173/271 (64%)	172/278 (62%)	107/267 (40%)
Females	124/161 (77%)	96/150 (64%)	88/176 (50%)

**Comment** Females tended to have higher incidences of adverse events in tazarotene 0.1% and vehicle groups.

### 10.2.4.3 Race

In the phase 3 studies, 86.5% (1127/1303) of patients were Caucasian, 3.1% (40/1303) were black, 1.2% (16/1303) were Asian, 8.7% (113/1303) were Hispanic, and 0.5% (7/1303) were "other" race. Overall, adverse events were reported for 58.0% (654/1127) of the Caucasians, 55.0% (22/40) of the blacks, 43.8% (7/16) of the Asians, 64.6% (73/113) of the Hispanics, and 57.1% (4/7) of the other race patients.

- In the largest Caucasian subgroup, there were significantly more total adverse events, and dermatological events, in the tazarotene groups compared with vehicle, and the incidence was generally higher with the 0.1% than the 0.05% concentration. Caucasians receiving tazarotene 0.1% or 0.05% experienced significantly more burning skin, irritant contact dermatitis, erythema, skin irritation, pruritus, and rash than vehicle patients ( $p \leq 0.020$ ). There were also statistically significant treatment-group differences for the adverse events of dyspepsia, peripheral edema, sinus infection, and pharyngitis, but no distinct dose-response pattern was seen.
- In the smaller subgroups of blacks, Asian, and other race, there were no statistically significant treatment-group differences for any individual adverse event. Hispanic patients receiving tazarotene 0.1% reported significantly more burning skin than patients receiving tazarotene 0.05% or vehicle ( $p \leq 0.034$ ). There were no other statistically significant treatment-group differences in the Hispanic subgroup.

**Number (%) of Patients with Any Adverse Event During the Treatment Period of Phase 3 Studies**

Race	Tazarotene 0.1% N = 432	Tazarotene 0.05% N = 428	Vehicle N = 443
Caucasians	254/372 (68%)	237/375 (63%)	163/380 (43%)
<b>Overall Non-Caucasians</b>	<b>43/60 (72%)</b>	<b>31/53 (58%)</b>	<b>32/63 (48%)</b>
Blacks	10/13 (77%)	4/10 (40%)	8/17 (43%)
Asians	1/1 (100%)	6/9 (67%)	0/6
Hispanics	31/44 (71%)	19/31 (61%)	23/38 (61%)
Other	1/2 (50%)	2/3 (67%)	1/2 (50%)

**Comment** Adverse event incidences appear to be comparable between Caucasians and non-Caucasians as a whole for each treatment group.

### 10.2.5 Drug-Disease Interactions

No formal analysis has been made for interaction between tazarotene cream use and concomitant diseases. Since this is a topical product, the expected interactions would be with conditions in the skin and appendages. However, one of the exclusion criteria was: "History or evidence of skin conditions (eg, eczema) other than psoriasis, that would have interfered with evaluation of the study medication." This would not have allowed a meaningful analysis of interaction by excluding conditions which might have caused interaction.

### 10.2.6 Drug-Drug Interactions

No special studies or analyses were performed to evaluate systemic drug-drug interactions. Over 70% of patients were receiving concomitant medications during the phase 3 studies. The most frequently reported drug categories ( $\geq 5\%$ ) were propionic acid derivatives (eg, ibuprofen), concomitant emollients and protectives, platelet aggregation inhibitors (excluding heparin, mainly acetylsalicylic acid), anilides (mainly paracetamol [acetaminophen]), soft paraffin and fat products (mostly emollients and topical OTC products), and HMG-CoA reductase inhibitors (eg, simvastatin, atorvastatin). Due to the low blood levels of "tazarotenic acid" from topical administration, no significant interactions of tazarotene cream with systemic drugs were

expected. There is no information regarding potential interactions of systemic or topical anti-psoriasis medications coadministered with tazarotene cream, as such drugs were prohibited during the phase 3 studies.

### 10.2.7 Withdrawal Phenomena/Abuse Potential

Tazarotene and other retinoids are not known to have abuse potential. Withdrawal phenomena with tazarotene are also not known. The NDA contains one study, 190168-016C, in which a 12-week post-treatment period was instituted to observe for changes in the psoriasis condition after stopping treatment. No specific symptomatology other than worsening of psoriasis was noted. The findings are similar to the observations in the post-treatment period of R168-120-8606 for tazarotene gels 0.05% and 0.1%.

### 10.2.8 Human Reproduction Data

As a retinoid, tazarotene is a teratogen. Although there are animal data attesting to the teratogenicity of tazarotene, at this time, there are no human data accurately documenting such evidence. Tazarotene creams have not been marketed, and there are no cases of pregnancy in clinical trials for psoriasis involving tazarotene creams.

Information from tazarotene gels. Since tazarotene gels 0.05% and 0.1% were approved for marketing (first in Europe in 1996), Allergan claims to have received 16 reports of pregnancy occurring in patients using the drug.

- Seven of the reports were from Allergan's global medical surveillance. Six reported no associated adverse events. All six patients stopped drug use upon learning pregnancy. Two were about 8 weeks pregnant and one 4 weeks pregnant. The Applicant has received no other information about these pregnancy outcomes. One was a case of trisomy 18 in a fetus from a pregnancy terminated at ten weeks gestation. The mother used etretinate ten years previously, and tazarotene gel (strength not mentioned) from approximately 2 months prior to becoming pregnant to about 2 weeks after conception.
- Nine reports were from clinical trials, and are shown in the following Table:

Study No/Pt No	Outcome	Treatment
190168-001/B02	Discontinued, delivered healthy baby	tazarotene gel 0.1% /Synalar cream 0.01%
190168-002/D36	Discontinued, delivered healthy baby	tazarotene gel 0.1%
190168-022/111	Discontinued, delivered healthy baby	tretinoin cream 0.1%
190168-022/171	Pregnancy found at exit visit and terminated	tazarotene gel 0.1% qod group
190168-022/166	Pregnancy found at exit visit, lost to follow-up	tazarotene gel 0.1% qod group
190168-022/111	Discontinued, pregnancy terminated	tazarotene gel 0.1% /hydrocortisone 1%
190168-029C/1087	Discontinued (1/2/00): planning pregnancy termination	tazarotene cream 0.1%
190168-031C/1301	Discontinued (2/15/00): pregnancy ongoing	tazarotene cream 0.1%
190168-031C/1384	Discontinued (12/16/99): planning pregnancy termination	vehicle cream

Studies 190 55-029C and 190168-031C are for acne indication of tazarotene cream 0.1%.

#### Comments

- Two of the reports from clinical trials involved use of products other than tazarotene: tretinoin 1, vehicle cream 1. There are only 7 reports associated with tazarotene use: 5 cases with tazarotene gel 0.1% and 2 cases with tazarotene cream 0.1%.
- The above data are not adequate to draw any conclusions because:
  - For the reports from global medical surveillance,
    - the extent of exposure (indication, degree of skin involvement and severity of disease) is unknown and cannot be correlated with the lack of adverse events in [redacted] and
    - the relationship of the trisomy 18 case to tazarotene use is unclear. Trisomy 18 is not a known teratogenic effect of retinoids.
  - For the 7 clinical trial cases involving tazarotene use, 3 of the pregnancy outcomes have not been determined and two pregnancy terminations did not have details of the products of conception. The two cases with healthy babies associated with use of tazarotene gel 0.1% lack details of exposure.





**Least Squares Mean  $\pm$  SE<sup>a</sup> Cumulative 21-Day Irritation Scores in 190168-019C**

Formulation	Cumulative 21-day irritation score	Between group comparison <sup>b</sup>
vehicle cream	4.38 $\pm$ 1.76	A
tazarotene cream 0.05%	35.06 $\pm$ 1.76	B
tazarotene cream 0.1%	45.09 $\pm$ 1.76	C
sodium lauryl sulfate solution 0.5%	29.11 $\pm$ 1.76	B

<sup>a</sup> SE = standard error of least squares mean, <sup>b</sup> Between-group comparison p-value from Tukey test; formulations sharing a common letter were not statistically significantly different from each other ( $p > 0.05$ ).

**6. Irritancy and Photo-irritancy Data from Induction Phase of 190168-032C:**

**Frequency of Irritation Scores During Induction Phase of 190168-032C**

Irritation Score	Tazarotene 0.1%		Tazarotene 0.05%		Vehicle	
	I	NI	I	NI	I	NI
0	0	0	0	0	0	3
0.5	1	4	1	8	3	19
1	10	19	15	18	25	8
2	0	0	0	0	0	0
3	8	3	6	1	1	0
4	11	4	8	3	1	0

I=Irradiated, NI=Non-irradiated.

**10.3. Safety Conclusions**

1. Exposure to each to-be-marketed formulation (0.05% and 0.1%) averaged approximately 10 weeks in the phase 3 studies for psoriasis (median approximately 12 weeks), with the following numbers completing 8 to 12 weeks of treatment: tazarotene 0.05% 217-293, and tazarotene 0.1% 267-298. Although these numbers may fall short of the ICH E1A Guidance recommended for studying exposure in long-term treatments, experience may be supplemented by long-term use data of tazarotene gels (up to 12 months in Study R168-128-8606) and information from tazarotene cream 0.1% in studies on other indications. The safety database may be considered adequate.

2. Similar to other topical retinoid products, tazarotene creams 0.05% and 0.1% are topical irritants. Despite the retinoid irritant effect, tazarotene creams 0.05% and 0.1% are relatively well tolerated, as most of the treatment-related adverse events only involved mild to moderate topical toxicity in the phase 3 trials.

3. The dermal safety studies presented for tazarotene creams 0.05% and 0.1% appear to be adequate.

4. Systemic bioavailability for tazarotene cream 0.1% is low (up to 4% administered dose) even when applied in excess (10 mg/cm<sup>2</sup>), but may attain levels (AUC up to 141 ng.hr/mL) leading to teratogenicity identified in preclinical studies (teratogenicity in rats at AUC 115 ng.hr/mL).

5. There are important differences between tazarotene creams 0.05% and 0.1% in the safety data, as evidenced by the:

- Incidences of serious adverse events, severe adverse events, laboratory adverse events and adverse event discontinuations as well as certain clinical adverse event data in the treatment period of phase 3 trials;
- Systemic bioavailability data from therapeutic drug monitoring in phase 3 trials;
- Data on irritancy potential from 190168-019C; and
- Irritancy and photo-irritancy data from the induction phase of 190168-032C.

### **11 Risk-Benefit Analysis**

1. Both tazarotene creams 0.05% and 0.1% have independently demonstrated efficacy in the treatment of plaque psoriasis.
2. The risks involved in use of tazarotene creams are primarily (a) local irritation and photo-irritation retinoid effects and (b) teratogenicity potential.
3. Because of the greater efficacy of tazarotene cream 0.1% (Section 9.3.4) and the lower irritancy as well as potentially lower systemic exposure from the use of tazarotene cream 0.05% (Section 10.2.10), the marketing of both formulations may provide the benefit of enhanced flexibility for physicians and patients. It would be appropriate to recommend starting treatment with tazarotene 0.05% and increase the strength as a second line of treatment, if tolerated.
4. As with tazarotene gels, the risks may be adequately addressed with labeling.
5. The benefits of tazarotene creams 0.05% and 0.1% outweigh their risks in the treatment of plaque psoriasis.

### **12 Labeling Review**

The draft labeling is modeled after the label for tazarotene 0.05% and 0.1% gels, with changes to reflect the sole proposed indication (psoriasis) and pertinent data.

This label is acceptable with the following recommended changes [additions highlighted by underlining and deletions marked by strikethrough ~~—————~~.]

**APPEARS THIS WAY  
ON ORIGINAL**

7 pages redacted from this section of  
the approval package consisted of draft labeling

**ALLERGAN**

Irvine, California 92612, USA

September 1999

(PM#) (copy code)

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Comments

1. Comments from the Biopharm Reviewer should be incorporated into the second paragraph of the Pharmacokinetics subsection under CLINICAL PHARMACOLOGY.
2. Comments from the Pharm/Tox Reviewer should be incorporated into (a) the teratogenicity information under CONTRAINDICATIONS, and (B) the Carcinogenesis, Mutagenesis, Impairment of Fertility subsection under PRECAUTIONS.
3. Although the post-treatment period data do not establish a claim for maintenance of therapeutic effect, these data should be provided in the label as useful information to the prescriber. They do show declines in the rates of success for the active creams.
4. For Dosage and Administration Section, the instructions are according to those in the phase 3 studies. The description for the amount applied (with a thin film) is the same as in the label for tazarotene gels. As the emphasis is on the "thin" film, it is not amenable to wording with size comparator (pea sized, etc.). Use of emollient at least an hour before application of tazarotene is based on instructions in phase 3 trials.

**13 Financial Disclosure and Pediatric Rule Issues**

**13.1 Financial Disclosure**

The Applicant has provided adequate information regarding financial interests and arrangements of clinical investigators in the phase 3 studies 190168-016C and -017C used to support this NDA. Measures in the trials appear sufficient to preclude bias from affecting the outcome of these studies.

**13.2 Pediatric Rule**

The Applicant is requesting a waiver for pediatric studies on neonates, infants and children, because plaque psoriasis is not prevalent in the population from birth to 11 years and tazarotene creams would not represent a substantial therapeutic benefit over existing anti-psoriatic therapies. The Applicant should address potential benefit of tazarotene creams in the treatment of plaque psoriasis in the adolescent pediatric population before a waiver can be recommended.

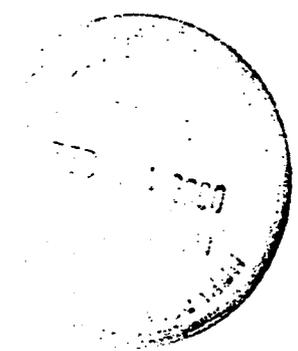
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February 3, 2000

Jonathan Wilkin, MD  
Director,  
Division of Dermatologic and Dental Drug Products  
HFD-540/Room N115  
Center for Drug Evaluation and Research  
Food and Drug Administration  
9201 Corporate Blvd., Building 2  
Rockville, MD 20850



REF: Tazorac® (tazarotene ) 0.05%, 0.1%  
NDA 21-184/120 Day Safety Update

*see medical  
office review of  
original NDA  
15/  
2/29/00*

Dear Doctor Wilkin:

Allergan is amending the above-referenced New Drug Application with the 120 Day Safety Update according to 21 CFR 314.50(d)(5)(vi)(b). Also, we are including information as was agreed between Allergan and FDA at the preNDA Meeting of June 14, 1999. The following information is included in this safety update:

Data required by 21 CFR 314.50(d)(5)(vi)(b):

- Case Report Forms for patients who discontinued due to an adverse event or death.

Data agreed to be included in the Safety Update from the preNDA Meeting:

- Re-challenge in the human photoallergy study with UVA irradiation, Study 190168-032C
- Provide plasma sample analysis from human pharmacokinetic study 190168-024C.

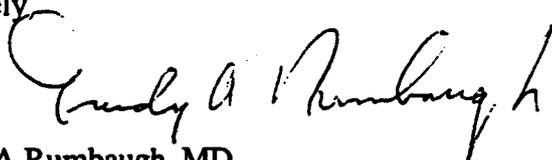
On the basis of this information, there will be no change to either the Integrated Summary of Safety or to the contraindications, warnings, precautions and adverse events as described in the draft labeling and as provided in the original NDA.

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NDA 21-184  
Page 2 of 2

We ask that this additional safety information be reviewed and filed to NDA 21-184, Tazorac® Cream. Should you have any questions or require further information, please call me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

A handwritten signature in black ink, appearing to read "Trudy A. Rumbaugh". The signature is written in a cursive style with a large initial "T" and "R".

Trudy A Rumbaugh, MD  
Director,  
Global Regulatory Affairs. Retinoids

**APPEARS THIS WAY  
ON ORIGINAL**