

Table 5c.(cont.): Acne Study R 168-221
Total Lesions

----- Age=> 25 Years -----				Week	0	4	8	12
Drug	Tazarotene 0.1%	Diff from baseline (0)	n	25	24	23	22	
			Mean	62.3	-17.8	-23.1	-27.4	
			Std Dev	29.2	16.6	17.2	15.0	
	Tazarotene 0.05%	Diff from baseline (0)	n	43	41	41	38	
			Mean	54.9	-12.1	-19.1	-20.9	
			Std Dev	13.9	14.9	16.8	19.4	
Vehicle	Diff from baseline (0)	n	36	34	33	30		
		Mean	57.8	-10.5	-15.9	-18.9		
		Std Dev	22.5	18.1	15.9	18.7		
Drug	Tazarotene 0.1%	% Diff	Mean	.	-28.2	-41.2	-49.8	
			Std Dev	.	25.6	24.6	23.6	
			Tazarotene 0.05%	% Diff	Mean	.	-22.1	-35.4
	Std Dev	.			26.3	28.8	33.6	
	Vehicle	% Diff			Mean	.	-18.4	-28.7
			Std Dev	.	33.0	27.9	34.1	

Statistical Review and Evaluation

MAY 14 1996

NDA/ Drug Class: 20-600 / 1S

Name of Drug: Tazarotene Gel, 0.05%, 0.1% (Zorac™),

Applicant: Allergan, Inc.
P.O. Box 19534
2525 Dupont Drive
Irvine, CA 92713-9534

Type of Report: Clinical/Statistical

Indication: Plaque type Psoriasis and Acne Vulgaris

Documents Reviewed: Volumes 1.1, 1.2, 1.73 through 1.156 (Clinical Data) and diskettes containing SAS data sets from the sponsor

Medical Officer: Dr. Hon S. Ko (HFD-540)

Introduction

According to the sponsor the "improvement in psoriatic patients appears to occur in association with restoration of normal cutaneous morphology and the reduction of" two inflammatory markers: ICAM-1 and HLA-DR." There is also a diminution of markers of epidermal hyperplasia and abnormal differentiation such as keratinocyte transglutaminase, involucrin, and keratin 16."

The sponsor also suggests that tazarotene "is thought to act against several of the factors that contribute to acne vulgaris. Animal and *in vitro* studies" are claimed to "show that tazarotene inhibits corneocytic accumulation in rhino mouse skin (*in vivo*) and cross-linked envelope formation in cultured human keratinocytes (*in vitro*). The primary mechanisms of action in humans are believed to be the normalizing of keratinization and a decrease in the coherence of follicular keratinocytes. Both mechanisms contribute to a comedolytic effect against existing comedones and prevention of the development of new microcomedones." Tazarotene is also said by the sponsor to be active against inflammatory acne.

The sponsor conducted five studies to provide evidence of the effectiveness and safety of 0.05% and 0.10% tazarotene gel in the treatment of plaque type psoriasis and two studies in the treatment of acne vulgaris.

Phase I and II studies:

Several different phase I dermal safety tolerance studies, and phase II dose ranging studies were performed, some using apparently slightly different formulations and concentrations of the gel than that used here. However, as detailed reports and data sets were not available to this reviewer, they will be ignored. This report will focus on the clinical efficacy studies, or more exactly, a subset of these studies.

Phase III studies:

The designs are summarized in the following table:

**Table 1a. Phase III Clinical Studies
Stable Plaque Psoriasis**

<u>Study no</u>	<u>design</u>	<u>objective</u>	<u>duration of study</u>	<u>No. enrolled*</u>
R168-120-8606	multicenter, double blind, randomized, parallel-group (psoriasis)	safety/efficacy & duration of therapeutic effect vs vehicle od	12-week treatment, post-tr: 12 weeks	<u>T.1%</u> <u>T.05%</u> <u>V</u> 108 108 108
R168-121-8606		safety/efficacy vs vehicle od	12-week treatment	<u>T.1%</u> <u>T.05%</u> <u>V</u> 112 111 113
R168-125-8606	multicenter, investigator- masked randomized, parallel-group (psoriasis)	safety/efficacy & duration of therapeutic effect od vs Lidex cream .05% bid	12-week treatment, post-tr: 12 weeks	<u>T.1%</u> <u>T.05%</u> <u>L</u> 116 117 115
R168-126-8606		safety/efficacy & duration of therapeutic effect od vs Lidex cream .05% bid	12-week treatment, post-tr: 12 weeks	<u>T.1%</u> <u>T.05%</u> <u>L</u> 110 111 110
R168-145-8606		safety/efficacy & duration of therapeutic effect od vs Dovonex ointment .005% bid	12-week treatment, post-tr: 12 weeks	<u>T.1%</u> <u>T.05%</u> <u>D</u> 122 124 123

*T=Tazarotene, V=vehicle, L=Lidex cream and D=Dovonex ointment.

**Table 1b. Phase III Clinical Studies
Acne Vulgaris**

<u>Study no</u>	<u>design</u>	<u>objective</u>	<u>duration of study</u>	<u>No. enrolled*</u>
R168-220-7997	multicenter, double blind, randomized, parallel-group (acne)	safety/efficacy vs vehicle od	12-week treatment	<u>T.1%</u> <u>T.05%</u> <u>V</u> 150 148 148
R168-221-8606		safety/efficacy vs vehicle od	12-week treatment	<u>T.1%</u> <u>T.05%</u> <u>V</u> 149 149 149

*T=Tazarotene, V=vehicle, L=Lidex cream and D=Dovonex ointment.

One problem in comparing these studies is the exact formulation of tazarotene used. Note that in the sponsors reports the various formulations are labeled as follows (the NA refers to the active controlled trials, with no vehicle comparator):

Table 2. Tazarotene and Vehicle Formulations

Study	Tazarotene	Tazarotene	Vehicle
	0.1%	0.05%	
R168-120-8606	8606X	8607X	8608X
R168-121-8606	8606X	8607X-A	8608X
R168-125-8606	8606X	8607X-A	NA
R168-126-8606	8606X	8607X-A	NA
R168-145-8606	8606X	8607X-A	NA
R168-220-8606	7997X	8225X	8006X
R168-221-8606	8606X	8607X-A	8608X

So both the tazarotene and vehicle formulations, used in the R168-220-8606 acne study, differ from the formulations used in the other studies, as apparently does the tazarotene 0.05% formulation used in the R168-120-8606 study. The sponsor (personal communication) has said these changes are minor, but for the goals of good science, the formulations used in all studies should agree (and be the formulation proposed for marketing).

Results:

I. Stable Plaque Psoriasis

A. Study R168-120-8606:

1. Study Design, Objectives, Patient Enrollment, Inclusion/exclusion Criteria, Patient Demographics:

Sponsors' protocol coded Study#R168-120-8606: **Safety, Efficacy and Duration of Therapeutic Effect of Once-Daily Tazarotene (AGN 190168) 0.1% Gel or 0.05% Gel versus Vehicle Gel in Stable Plaque Psoriasis.**

The objective of this study was to evaluate the safety, efficacy and duration of therapeutic effect of Tazarotene 0.1% and 0.05% gels versus vehicle gel applied once daily in the treatment of stable plaque psoriasis. The study was a 24-week, randomized, multicenter (nine U.S. centers), double-blind, parallel-group, vehicle-controlled trial comparing the efficacy and safety of Tazarotene with those of the vehicle. The study included a 12-week treatment period followed by a 12 post-treatment follow-up. A total of 324 patients were enrolled, 217 males and 107 females, aged 12-83 years. Of these 242 completed the 12-week treatment phase (15 dropped out due to lack of efficacy, 27 due to adverse events, 39 were dropped for administrative reasons, and one patient was disqualified). Of these, 241 entered the 12-week

post-treatment period, with 95 completing this phase (one was terminated by an adverse event, 22 for administrative reasons, and 123, due to the need for psoriasis treatment).

Among the selection criteria for patients were the following:

1. "total area of psoriatic involvement not over 20% of total body surface area"
2. "one of two target lesions (selected for evaluation) had to be located on elbow or knee; the other on trunk or limbs and was of similar severity"
3. "minimum size of each target lesion 2 cm in diameter"
4. "score for baseline plaque elevation of each selected target psoriatic lesion greater than or equal to 2 (from a 0-4 scale in half point increments: 0=none, 1=mild, 2=moderate, 3=severe and 4=very severe)"

Subjects were randomly assigned to Tazarotene 0.1%, 0.05% or vehicle in blocks of six patients. Subjects were instructed to apply their treatment daily (every evening) to all psoriatic plaques for 12 weeks, or less if a global response of "completely cleared" was achieved. Subjects were to bathe/shower in the morning and refrain from using tar shampoos. Non-medicated shampoos were allowed as often as needed. Emollient was allowed as needed, but only on non-target lesions and at least one hour after application of study medication. Emollient was not allowed on the evening prior to a visit and until the visit was completed. Visits were scheduled as listed in table 3 below:

Table 3. Operations of Experiment

Visit	Weeks	History & Consent	Baseline Exam	Lab Screen	Pregnancy Test**	Evaluate Sites	Tubes of Study Med to dispense	Emollient Bottles to dispense
<u>Treatment Phase</u>								
1	0	x	x	xx	x	x	2	1
2	1			x	x	x	2	
3	2			x	x	x	3	
4	4			xx	x	x	5	1
5	8			xx	x	x	5	1
6	12			xx	x	x		1
<u>Posttreatment Phase*</u>								
7	16			xxx	x	x		1
8	20				x	x		1
9	24				x	x		

*Posttreatment phase started at the end of week-12 or when treatment was discontinued because of global response = 5 (completely cleared).

**Pregnancy tests done if applicable. Lab screen: x = CBC, chemistry panel and urinalysis; xx = with additional blood for drug level and metabolites at 3 investigational sites; xxx = if week-12 result outside normal range or unacceptable to investigator (CBC, chemistry or urinalysis), the test was repeated until normal or explained.

"Patients could voluntarily withdraw from the study at any time they chose. Any patient who experienced an adverse event that was possibly related to the study treatment, or who had an unacceptable response to treatment that affected his or her welfare was removed from the study and received appropriate therapy at discretion of the investigator."

Demographics:

The following table summarizes the demographics of the subjects.

Table 4. Demographics

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Age (Yrs)	48±14	46±15	46±15
Sex			
M	71	69	72
F	34	37	35
Race			
White	95	89	98
Hispanic	8	13	7
Black	2	2	1
Oriental	0	0	0
"other"	0	2	1
% Body area with psoriasis	7±6	7±5	7±5
Duration of psoriasis (Yrs)	16±12	17±11	19±15
Total patient no	105	106	107

The sponsor reported that there were no statistically significant differences among treatments with respect to age, sex, race (white versus other), percent of psoriatic involvement, or duration of psoriasis.

2. Efficacy Assessments

After discussion with the medical officer it was decided to use reduction in scores of erythema, plaque elevation, and scaling as aspects of the primary response for deciding efficacy, along with their sum, and the physicians' assessments of global response to treatment. Those variables are scored as follows:

1. Plaque elevation of each target lesion.
2. Scaling of each target lesion.
3. Erythema of each target lesion.

For the preceding, their responses were all scored in ½-point increments: from 0 = none, 1 = mild, 2 = moderate, 3 = severe, to 4 = very severe.

4. Sum of plaque elevation, scaling and erythema, i.e., sum of scores for 1, 2 and 3 above, ranging from 0 to 12.

5. Target lesion response to treatment at postbaseline visit (for each target lesion).

These responses were scored as follows:

0 = lesion unchanged or worsened	1 = poor = 1-24% improvement
2 = fair = 25-49% improvement	3 = good = 50-74% improvement
4 = excellent = 75-99% improvement	5 = complete clearance (100%).

Using these variables, overall treatment success was defined by the Medical Officer as achieving all of the following:

1. Statistically significant reduction in at least two of erythema, plaque elevation, and scaling.
2. Statistically significant reduction in the sum of erythema, plaque elevation, and scaling.
3. Physicians' assessment of global response to treatment.

Note that since all of these need to be achieved for the conclusion of efficacy, no adjustment for multiple comparisons is needed (i.e. we are dealing with H_E , not U_E).

Table 5. Patient Disposition

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Treatment period			
Enrolled	108 (3)*	108 (2)	108 (1)
Completed study	81	80	81
Not completed	27	28	27
lack of efficacy	4	5	6
adverse event	13	11 (1)	3
not meeting entry criteria	1 (1)	0	0
"other"***	9 (2)	12 (1)	18 (1)
Posttreatment period			
Started	80	80	81
Completed follow-up	35	37	23
Not completed	45	43	58
need for treatment	39	35	49
adverse event	1	0	0
"other"***	5	8	9

*Numbers in parentheses indicate unevaluable patient numbers.***Other" refers to discontinuation besides disqualification or termination (AE or lack of efficacy) in treatment period and to those exiting due to administrative reasons (e.g., missed visits) in posttreatment period.

Thus, according to the sponsor, six patients were "unevaluable". Three of these were in the tazarotene 0.1% gel group: one was an entry criteria violation (previous treatment washout period), another for a concomitant therapy, and the third because of no evaluable postbaseline visit. One patient in the vehicle group had a concomitant therapy, and two patients in the tazarotene 0.05% treatment group had no post-baseline visit.

3. Efficacy Results (by the Sponsor and checked by the reviewer):

For convenience the sponsors' "fully evaluable" subset of patients is used. Note that the sponsor claims that results using a modified intent-to-treat group, and a last observation carried forward group give essentially the same results. The following table, table 6a., displays means of erythema and scaling over the treatment period. Note that the week 0 results compare baseline scores of erythema and scaling, each with an original scale from 0 (none) to 4 (very severe). The remaining weeks compare change from baseline for these scales.

**Table 6a. Change from Baseline Response for Target Lesion Mean Response
(At Baseline, week=0, Compares Original Scores)**

Week	n	Erythema*:			Scaling*:		
		Tazarotene 0.1%	Tazarotene 0.05%	Vehicle	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
		Mean (STD)	Mean (STD)	n Mean STD	Mean (STD)	Mean (STD)	Mean STD
		p-value of diff	p-value of diff		p-value of diff	p-value of diff	
		-----	-----		-----	-----	
		p-value of diff	p-value of diff		p-value of diff	p-value of diff	
0	105	2.35 (0.58)	2.30 (0.63)	106 2.23 (0.58)	2.42 (0.61)	2.41 (0.64)	2.46 (0.54)
		0.393	0.327		0.958	0.523	
			0.067			0.559	
1	96	-0.15 (0.54)	-0.21 (0.53)	97 -0.22 (0.48)	-0.44 (0.56)	-0.43 (0.66)	-0.30 (0.57)
		0.433	0.968		0.798	0.108	
			0.407			0.063	
2	94	-0.45 (0.63)	-0.33 (0.66)	100 -0.31 (0.54)	-0.66 (0.77)	-0.64 (0.72)	-0.38 (0.64)
		0.056	0.899		0.739	0.008	
			0.074			0.003	
4	96	-0.65 (0.75)	-0.53 (0.73)	102 -0.43 (0.64)	-0.87 (0.69)	-0.83 (0.82)	-0.48 (0.73)
		0.149	0.288		0.630	<0.001	
			0.012			<0.001	
8	86	-0.86 (0.86)	-0.77 (0.86)	90 -0.56 (0.84)	-1.01 (0.83)	-1.05 (0.87)	-0.67 (0.82)
		0.325	0.077		0.731	0.001	
			0.006			0.004	
12	81	-0.98 (0.81)	-0.92 (0.92)	85 -0.55 (0.77)	-1.25 (0.85)	-1.12 (0.92)	-0.66 (0.85)
		0.464	0.004		0.266	<0.001	
			<0.001			<0.001	

* Original scores are means from the subjects' two target lesions, scaled at 0 (none) to 4 (very severe).

Note that in reading this tables and similar later tables, the first line lists sample sizes, means, and standard deviations. The next two lines have p-values corresponding to the ANOVA contrasts, on the untransformed scores or differences, testing treatment group differences. From right to left, the second line displays the results for comparing the mean of the 0.1% tazarotene group to the mean of the 0.05% tazarotene group and the mean of the vehicle with the 0.05% tazarotene group mean. The third line has the p-value for comparing mean of the 0.1% tazarotene treatment group to that of the vehicle group. For example, from table 6a above for erythema at the fourth week the p-values corresponding to the tests of difference between the tazarotene 0.1% group and the tazarotene 0.05% group, and the tazarotene 0.05% group and vehicle are both not statistically significant ($p \leq 0.149$ and $p \leq 0.288$ respectively). However, for erythema the difference between the tazarotene 0.1% group and vehicle is statistically significant ($p \leq 0.012$).

Thus, by inspecting the p-values in table 6a. above, we see that for both scaling and erythema, by the 12th week, both the tazarotene 0.1% group and the tazarotene 0.05% group are statistically significantly better than vehicle.

Similarly, for plaque elevation and total score we get the following:

Table 6b. Change from Baseline Response for Target Lesion Mean Response (At Baseline, week=0, Compares Original Scores)

Week	n	Plaque Elevation*:				Sum of Scores [‡] :					
		Tazarotene 0.1%		Tazarotene 0.05%		Tazarotene 0.1%		Tazarotene 0.05%		Vehicle	
		Mean (STD)	n	Mean (STD)	n	Mean (STD)	n	Mean (STD)	n	Mean (STD)	n
0	105	2.51 (0.48)	106	2.52 (0.44)	107	2.50 (0.54)	7.27 (1.30)	7.23 (1.36)	7.19 (1.26)		
				p-value of diff				p-value of diff			
				0.799				0.763			0.805
				0.945				0.583			
1	96	-0.61 (0.61)	97	-0.66 (0.64)	99	-0.30 (0.49)	-1.20 (1.31)	-1.30 (1.49)	-0.81 (1.28)		
				p-value of diff				p-value of diff			
				0.517				0.643			0.008
				<0.001				0.028			
2	94	-0.95 (0.74)	100	-0.84 (0.71)	100	-0.40 (0.56)	-2.07 (1.64)	-1.81 (1.71)	-1.09 (1.43)		
				p-value of diff				p-value of diff			
				0.199				0.149			0.001
				<0.001				<0.001			
4	96	-1.11 (0.72)	97	-1.05 (0.70)	102	-0.65 (0.70)	-2.64 (1.75)	-2.41 (1.87)	-1.56 (1.75)		
				p-value of diff				p-value of diff			
				0.427				0.277			<0.001
				<0.001				<0.001			
8	86	-1.27 (0.81)	89	-1.31 (0.71)	90	-0.69 (0.78)	-3.14 (2.16)	-3.14 (2.10)	-1.93 (2.15)		
				p-value of diff				p-value of diff			
				0.836				0.872			<0.001
				<0.001				<0.001			
12	81	-1.43 (0.84)	82	-1.38 (0.85)	85	-0.74 (0.88)	-3.66 (2.22)	-3.42 (2.37)	-1.95 (2.25)		
				p-value of diff				p-value of diff			
				0.604				0.372			<0.001
				<0.001				<0.001			

* Original scores are means from the subjects' two target lesions.

[‡] Sum of erythema, scaling, and plaque elevation mean target lesion scores ranging from 0 to 12.

And again, by inspecting the p-values in table 6b., above, we see that for both plaque elevation and total scores, both tazarotene treatment groups display a statistically significant reduction in scores from the 1st through the 12th weeks. Although after the first week, the decrease in both plaque elevation and total score is numerically larger for the tazarotene 1.0% than for the tazarotene 0.05% group, the difference between dose levels of tazarotene is never statistically significant.

Finally, for the physicians' global assessment of response to treatment we get the following, table 7.:

Table 7. Global Evaluation of Response to Treatment

Week	n	Tazarotene 0.1%		Tazarotene 0.05%		Vehicle	
		Mean (STD)		Mean (STD)		n	Mean STD
1	95	1.27 (0.94)	0.499	97	1.19 (0.92)	99	0.81 (0.91)
					<0.001		
2	94	1.77 (1.20)	0.034	100	1.45 (1.17)	100	1.00 (0.91)
					<0.001		
4	95	1.99 (1.27)	0.305	96	1.77 (1.30)	102	1.24 (1.14)
					<0.001		
8	84	2.29 (1.36)	0.083	89	1.99 (1.39)	90	1.37 (1.27)
					<0.001		
12	79	2.65 (1.42)	0.217	81	2.23 (1.58)	84	1.55 (1.48)
					<0.001		

Scoring scale: 0=unchanged or worsened 3=50-74% improvement
 1=1-24% improvement 4=75-99% improvement
 2=25-49% improvement 5=Completely cleared

Again, by inspecting the p-values in table 7. above we see that both tazarotene treatment groups show a statistically significantly better score for global response to treatment at all weeks after the first. Thus for this particular study, by the decision rule given by the medical officer, both of these dosages are statistically significantly better than vehicle (see table 6a., 6b, & 7.), and seem to show efficacy. Note that the difference between the tazarotene 0.1% group and the tazarotene 0.05% group are statistically significant at the second week. This, coupled with the numerical superiority of the tazarotene 0.1% group over the tazarotene 0.05% group at each time point, is evidence that the tazarotene 0.1% group is superior to the tazarotene 0.05% group. However, by the decision rule established by the medical officer, it is not sufficient to show the superiority of the tazarotene 0.1% group over the tazarotene 0.05% group.

For the 12-week follow-up period, the sponsor included similar tests for plaque elevation, scaling, erythema, total of the preceding three variables, and the global response to treatment during the follow-up period. However, these were defined in terms of the difference of the particular follow-up week from the 12th week score. That is at each of the 16th, 20th, and 24th weeks, the difference from the 12th week was computed. So the null hypothesis of no difference in these differences is just that the changes from say the 16th week to the 12th week are the same across treatment group. Since the 12th week values already differ according to treatment effect, equal changes only indicate constant change over time, not any measure directly interpretable as indicative of treatment effect. Further, these variables are bounded, so we would expect to see a non-constant change, no matter what the treatment effect. That is, there will be some tendency to reject the null hypothesis no matter what the true

treatment effects. Thus it is this reviewer's opinion that this part of the sponsors' analysis is of very limited value.

For completeness, the means are also presented for the initial 12 week treatment period, broken down by body part:

Table 8. Changes in Mean from Baseline

I. Target Lesion	Reduction of Plaque Elevation	Trunk/Arm/Leg					Knee/Elbow				
		wk- 1	wk- 2	wk- 4	wk- 8	wk-12	wk- 1	wk- 2	wk- 4	wk- 8	wk-12
Tazarotene 0.1%	<u>0.63*</u>	<u>0.99</u>	<u>1.13</u>	<u>1.24</u>	<u>1.39</u>	<u>0.59</u>	<u>0.92</u>	<u>1.10</u>	<u>1.29</u>	<u>1.47</u>	
Tazarotene 0.05%	<u>0.71</u>	<u>0.81</u>	<u>1.08</u>	<u>1.38</u>	<u>1.41</u>	<u>0.60</u>	<u>0.88</u>	<u>1.03</u>	<u>1.28</u>	<u>1.35</u>	
Vehicle	0.28	0.41	0.70	0.69	0.77	0.31	0.39	0.60	0.70	0.71	
	Scaling										
Tazarotene 0.1%	<u>0.52</u>	<u>0.72</u>	<u>0.93</u>	<u>1.00</u>	<u>1.25</u>	<u>0.36</u>	<u>0.60</u>	<u>0.81</u>	<u>1.01</u>	<u>1.25</u>	
Tazarotene 0.05%	<u>0.48</u>	<u>0.67</u>	<u>0.90</u>	<u>1.12</u>	<u>1.13</u>	<u>0.37</u>	<u>0.62</u>	<u>0.77</u>	<u>0.98</u>	<u>1.11</u>	
Vehicle	0.30	0.42	0.54	0.67	0.68	0.30	0.35	0.42	0.67	0.62	
	Erythema										
Tazarotene 0.1%	0.16	0.49	0.65	<u>0.90</u>	<u>1.01</u>	0.15	0.41	<u>0.65</u>	<u>0.83</u>	<u>0.96</u>	
Tazarotene 0.05%	0.25	0.36	0.57	0.82	<u>0.96</u>	0.16	0.29	0.51	0.75	<u>0.87</u>	
Vehicle	0.19	0.32	0.46	0.57	0.59	0.25	0.31	0.42	0.56	0.50	
	Total Scores										
Tazarotene 0.1%	<u>1.30</u>	<u>2.20</u>	<u>2.71</u>	<u>3.14</u>	<u>3.65</u>	1.10	<u>1.93</u>	<u>2.56</u>	<u>3.12</u>	<u>3.68</u>	
Tazarotene 0.05%	<u>1.45</u>	<u>1.83</u>	<u>2.55</u>	<u>3.31</u>	<u>3.51</u>	1.14	<u>1.79</u>	<u>2.81</u>	<u>3.01</u>	<u>3.33</u>	
Vehicle	0.76	1.14	1.70	1.93	2.05	0.86	1.04	1.44	1.93	1.82	
II. Overall						wk- 1	wk- 2	wk- 4	wk- 8	wk-12	
Investigator's Global (mean)		Tazarotene 0.1%				<u>1.27</u>	<u>1.17</u>	<u>1.99</u>	<u>2.29</u>	<u>2.65</u>	
		Tazarotene 0.05%				<u>1.19</u>	<u>1.45</u>	<u>1.77</u>	<u>1.99</u>	<u>2.23</u>	
		Vehicle				0.81	1.00	1.24	1.37	1.55	

*Figures underlined are significantly different from those of vehicle (p<0.05). **Figures highlighted show significant difference among 0.1% gel and 0.05% gel treatment groups (p<0.02).

Again, for both dose levels of tazarotene, table 8, shows statistically significant reductions in plaque elevation, scaling, erythema, and total, as well as a statistically significant increase in the investigator's global evaluation or treatment efficacy.

Note the following table, table 9, gives the change from the beginning of the post-treatment period of the indicated response. This was the primary response supplied by the sponsor for these measurements. In fact, it is difficult to see how it has any real value in interpreting these results. One can add it to the corresponding twelve-week value to compute the unadjusted change from baseline, but the tests provided are still based on the difference from the twelfth week. It is this reviewer's claim that this part of the table is of minimal value in interpreting the results of this experiment. But for completeness, it is included. The part of the table dealing with the investigator's global assessment is, however, still readily interpretable.

Table 9. Post-treatment, follow-up Period:

I. Mean Scores for Reduction	Trunk/Arm/Leg			Knee/Elbow		
	week-16	week-20	week-24	week-16	week-20	week-24
Plaque Elevation						
Tazarotene 0.1%	1.21	1.17	1.10	<u>1.19*</u>	<u>1.12</u>	<u>1.01</u>
Tazarotene 0.05%	<u>1.39</u>	<u>1.32</u>	<u>1.24</u>	<u>1.31</u>	<u>1.19</u>	<u>1.11</u>
Vehicle	0.99	0.92	0.89	0.82	0.80	0.74
Scaling						
Tazarotene 0.1%	1.05	0.96	0.98	0.89	0.83	0.85
Tazarotene 0.05%	1.08	1.01	0.89	<u>1.09</u>	<u>0.95</u>	0.81
Vehicle	0.96	0.92	0.82	0.75	0.67	0.68
Erythema						
Tazarotene 0.1%	0.99	0.95	0.91	<u>0.94</u>	0.87	0.77
Tazarotene 0.05%	<u>1.13</u>	<u>1.02</u>	<u>1.05</u>	0.88	0.79	0.74
Vehicle	0.81	0.72	0.66	0.66	0.64	0.59
Total Scores						
Tazarotene 0.1%	3.24	3.08	2.99	<u>3.01</u>	<u>2.82</u>	2.63
Tazarotene 0.05%	<u>3.61</u>	<u>3.35</u>	3.18	<u>3.28</u>	<u>2.93</u>	2.66
Vehicle	2.75	2.55	2.37	2.22	2.11	2.01
II. Overall Disease Parameters						
Investigator's Global (mean)			<u>week-12</u>	<u>week-16</u>	<u>week-20</u>	<u>week-24</u>
Tazarotene 0.1%			<u>2.83</u>	<u>2.15</u>	1.86	1.58
Tazarotene 0.05%			<u>2.41</u>	<u>2.28</u>	1.91	1.88
Vehicle			1.74	1.71	1.48	1.42

*Figures underlined are significantly different from those of vehicle ($p < 0.05$). **Figures highlighted show significant difference among 0.1% gel and 0.05% gel treatment groups ($p < 0.05$).

Note again from table 9. that the investigator global mean shows that both levels of tazarotene are statistically significantly better than vehicle at the end of treatment, i.e. the 12th & 16th week, but not at any later date.

Subgroup analyses are presented later.

B. Study R168-121-8606:

Sponsor's protocol Study#R168-121-8606: **Safety, Efficacy and Duration of Therapeutic Effect of Once-Daily Tazarotene (AGN 190168) 0.1% Gel or 0.05% Gel versus Vehicle Gel in Stable Plaque Psoriasis.**

1. Study Design, Objectives, Patient Enrollment, Patient Demographics:

As in the preceding study, the objective of this study was to evaluate the safety, efficacy and duration of therapeutic effect of Tazarotene 0.1% and 0.05% gels versus vehicle gel applied once daily in the treatment of stable plaque psoriasis. The study was a 12-week, randomized, multicenter (10 U.S. centers), double-blind, parallel-group, vehicle-controlled trial

comparing the efficacy and safety of Tazarotene with those of vehicle. The design was almost identical to the study above, except that there was no untreated follow-up period. A total of 336 patients were enrolled, 218 males and 118 females, aged 16-87 years. Of these 243 completed the 12 week treatment phase (16 dropped out due to lack of efficacy, 40 due to adverse events, 33 were dropped for administrative reasons, and 4 patients were disqualified).

- The primary difference in response measures is that the investigator's assessment of global response to treatment was a 6-point scale, having "lesion unchanged" and "lesion worsened" separated out (these two having the same score in R168-120-8606).

Demographics:

The following table summarizes the demographics of the patients. Overall, there seems to be no particularly large difference among groups.

Table 10. Demographics

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Total patient no	104	104	109
Age (Yrs)	50±16	48±15	49±14
Sex M	69	66	70
F	35	38	39
Race White	92	95	91
Hispanic	9	8	9
Black	1	0	5
Oriental	2	1	4
"other"	0	0	0
% Body area with psoriasis	10±6	8±6	8±5
Duration of psoriasis (Yrs)	18±12	19±12	21±14

The sponsor reported that there were no statistically significant differences among treatments with respect to age, sex, race (white versus other), percent of psoriatic involvement, or duration of psoriasis.

2. Efficacy Assessments

Table 11. Patient Disposition

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Enrolled	112 (8)*	111 (7)	113 (4)
Completed study	69	86	88
Not completed	43	25	25
lack of efficacy	4	8	4
adverse event	21	10 (2)	9
not meeting entry criteria	2 (2)	0	2 (2)
"other"***	16 (6)	7 (5)	10 (2)

*Numbers in parentheses indicate unevaluable patient numbers.***Other refers to discontinuation besides disqualification or termination (AE or lack of efficacy) in treatment period.

According to the sponsor, 19 patients were "unevaluable." Eight of these were in the tazarotene 0.1% gel group: 6 because they had no evaluable post-baseline visit, and two for entry violations. Seven patients were labeled "unevaluable" in the tazarotene 0.05% treatment group: five, because they had no evaluable post-baseline visit, and two for noncompliance. Four patients in the vehicle group were labeled "unevaluable": two because they had no post-baseline visit and two because of an entry violation.

Again, for convenience the sponsor's "fully evaluable" subset of patients is used. Note that the sponsor claims that results using a modified intent-to-treat group, and a last observation carried forward group give essentially the same results. The following table displays means of erythema and scaling over the treatment period. Note that the week 0 results compare baseline scores of erythema and scaling. The remaining weeks compare change from baseline for these scales.

3. Efficacy Results (by the Sponsor and checked by the reviewer):

The following table 12a shows the effect of treatment differences on erythema and scaling. /, plaque elevation, and total scores.

Table 12a. Change from Baseline Response for Target Lesion Mean Response (At Baseline, week=0, Compares Original Scores)

Week	n	Erythema:			Scaling:		
		Tazarotene 0.1%	Tazarotene 0.05%	Vehicle	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
		Mean (STD)	Mean (STD)	Mean (STD)	Mean (STD)	Mean (STD)	Mean (STD)
		p-value of diff		p-value of diff		p-value of diff	
		----- p-value of diff-----		----- p-value of diff-----		----- p-value of diff-----	
0	104	2.65 (0.60)	104 2.59 (0.61)	109 2.61 (0.61)	2.00 (0.58)	2.57 (0.72)	2.61 (0.60)
			0.504	0.941		0.330	0.516
			0.548			0.736	
1	103	-0.03 (0.43)	101 -0.14 (0.47)	102 -0.10 (0.34)	-0.35 (0.56)	-0.38 (0.67)	-0.20 (0.54)
			0.083	0.367		0.831	0.023
			0.404			0.038	
2	92	-0.19 (0.55)	102 -0.33 (0.50)	105 -0.25 (0.48)	-0.68 (0.77)	-0.62 (0.74)	-0.30 (0.64)
			0.062	0.413		0.338	<0.001
			0.276			<0.001	
4	85	-0.48 (0.64)	98 -0.45 (0.62)	102 -0.28 (0.61)	-0.90 (0.69)	-0.75 (0.77)	-0.44 (0.73)
			0.793	0.048		0.180	0.002
			0.031			<0.001	
8	77	-0.78 (0.78)	94 -0.66 (0.74)	97 -0.47 (0.77)	-1.07 (0.83)	-0.82 (0.87)	-0.59 (0.94)
			0.316	0.061		0.091	0.040
			0.006			<0.001	
12	72	-0.95 (0.95)	94 -0.82 (0.84)	91 -0.52 (0.80)	-1.26 (0.85)	-1.02 (0.99)	-0.62 (0.96)
			0.443	0.012		0.189	0.003
			0.002			<0.001	

* Original scores are means from the subjects' two target lesions, scaled at 0 (none) to 4 (very severe).

As noted in table 12a., above, when reading these the first line lists sample sizes,

means, and standard deviations. The p-values correspond to the ANOVA contrasts testing treatment group differences, with the second line comparing the 0.1% tazarotene group to the 0.05% tazarotene group and the vehicle with the 0.05% tazarotene group. The third row is the p-value for comparing the 0.1% tazarotene treatment group to vehicle.

Thus, by inspecting the p-values above we see that for both scaling and erythema, by the 12th week both the tazarotene 0.1% group and the tazarotene 0.05% group are statistically significantly better than vehicle. Note that by week 1, and for all following weeks, both dose levels of tazarotene are statistically significantly better than vehicle.

The following table 12b shows the effect of treatment differences on plaque elevation, and total scores:

Table 12b. Change from Baseline Response for Target Lesion Mean Response (At Baseline, week=0, Compares Original Scores)

Week	Plaque Elevation:						Sum of Scores:					
	Tazarotene 0.1%		Tazarotene 0.05%		Vehicle		Tazarotene 0.1%		Tazarotene 0.05%		Vehicle	
	n	Mean (STD)	n	Mean (STD)	n	Mean (STD)	n	Mean (STD)	n	Mean (STD)	n	Mean (STD)
0	104	2.61 (0.55)	104	2.57 (0.60)	109	2.59 (0.54)		7.93 (1.51)		7.73 (1.64)		7.85 (1.55)
		0.663		0.731		0.923		0.385		0.604		0.718
1	103	-0.54 (0.61)	101	-0.53 (0.57)	102	-0.26 (0.41)		-0.92 (1.31)		-1.05 (1.28)		-0.56 (0.97)
		0.737		<0.001		<0.001		0.543		0.009		0.001
2	92	-0.85 (0.58)	102	-0.80 (0.65)	105	-0.31 (0.50)		-1.73 (1.64)		-1.75 (1.49)		-0.86 (1.30)
		0.264		<0.001		<0.001		0.802		<0.001		<0.001
4	85	-1.06 (0.61)	98	-0.98 (0.68)	102	-0.40 (0.61)		-2.43 (1.75)		-2.19 (1.63)		-1.13 (1.66)
		0.241		<0.001		<0.001		0.232		<0.001		<0.001
8	77	-1.22 (0.78)	94	-1.08 (0.73)	97	-0.59 (0.79)		-3.06 (2.16)		-2.56 (1.97)		-1.65 (2.29)
		0.204		<0.001		<0.001		0.123		<0.001		0.001
12	72	-1.34 (0.89)	94	-1.20 (0.87)	91	-0.66 (0.87)		-3.55 (2.22)		-3.04 (2.36)		-1.80 (2.47)
		0.240		<0.001		<0.001		0.221		<0.001		<0.001

So, reviewing the p-values in table 12b. above, it may be noted that for the specific level of plaque elevation and the total score defined as the sum of scores for scaling, erythema, and plaque elevation by the first week and all following weeks in the treatment period, both the tazarotene 0.1% group and the tazarotene 0.05% groups are statistically significantly better than vehicle.

Table 13. Global Evaluation of Response to Treatment

Global Evaluation of Response to Treatment							
Week	n	Tazarotene 0.1%		Tazarotene 0.05%		Vehicle	
		Méan (STD)	n	Mean (STD)	n	Mean	STD
1	102	1.77 (0.89)	101	1.95 (0.92)	102	1.57 (0.79)	
			0.207		<0.001		
				0.033			
2	90	2.24 (1.00)	101	1.45 (1.17)	100	1.00 (0.91)	
			0.034		<0.001		
				<0.001			
4	80	2.86 (1.10)	96	1.77 (1.30)	102	1.24 (1.14)	
			0.305		<0.001		
				<0.001			
8	73	3.03 (1.41)	93	1.99 (1.39)	90	1.37 (1.27)	
			0.083		0.003		
				<0.001			
12	69	3.23 (1.57)	93	2.23 (1.58)	84	1.55 (1.48)	
			0.217		<0.001		
				<0.001			

Scoring scale: 0=worsened
 1=unchanged
 2=1-24% improvement
 3=25-49% improvement
 4=50-74% improvement
 5=75-99% improvement
 6=Completely cleared

Again, by inspecting the p-values above, we see that from week one, both tazarotene treatment groups show a statistically significantly better score for global response to treatment. (The superiority of the tazarotene 0.05% group to the tazarotene 0.1% group at the first week is just a minor blip in the general trend.) Thus, for this particular study, by the decision rule given by the medical officer, both of these dosages are statistically significantly better than vehicle, and seem to show efficacy.

The sponsor included similar tests for the 12 week follow-up period. However, in this case, note that the change from the initial score at the beginning of the twelve week period is not a useful response variable for analysis. This is because the initial scores already show the effect of treatment. So this part of the sponsors analysis is of limited value. For convenience, only means are presented for the follow-up period. This gives some idea of trend over time. For completeness, the means are also presented for the initial 12 week treatment period:

Table 14. Response Variable Means

I. Mean Scores for	Trunk/Arm/Leg					Knee/Elbow				
	wk- 1	wk- 2	wk- 4	wk- 8	wk-12	wk- 1	wk- 2	wk- 4	wk- 8	wk-12
Reduction of Plaque Elevation										
Tazarotene 0.1%	<u>0.63*</u>	0.93	<u>1.11</u>	<u>1.26</u>	<u>1.41</u>	<u>0.44</u>	<u>0.78</u>	<u>1.00</u>	<u>1.19</u>	<u>1.28</u>
Tazarotene 0.05%	<u>0.56</u>	<u>0.93</u>	<u>1.08</u>	<u>1.15</u>	<u>1.29</u>	<u>0.50</u>	<u>0.67</u>	<u>0.89</u>	<u>1.04</u>	<u>1.12</u>
Vehicle	0.26	0.36	0.44	0.61	0.71	0.26	0.26	0.37	0.56	0.62
Scaling										
Tazarotene 0.1%	<u>0.45</u>	<u>0.77</u>	<u>0.96</u>	<u>1.08</u>	<u>1.30</u>	0.25	<u>0.60</u>	<u>0.84</u>	<u>1.05**</u>	<u>1.23</u>
Tazarotene 0.05%	<u>0.46</u>	<u>0.75</u>	<u>0.86</u>	<u>0.89</u>	<u>1.11</u>	0.30	<u>0.49</u>	<u>0.64</u>	<u>0.74</u>	<u>0.92</u>
Vehicle	0.22	0.36	0.44	0.62	0.86	0.18	0.24	0.45	0.56	0.58
Erythema										
Tazarotene 0.1%	0.07	<u>0.17</u>	<u>0.49</u>	<u>0.85</u>	<u>1.08</u>	0	0.21	0.45	0.71	<u>0.82</u>
Tazarotene 0.05%	0.19	<u>0.37</u>	0.42	0.60	<u>0.83</u>	0.09	0.28	<u>0.48</u>	<u>0.71</u>	<u>0.81</u>
Vehicle	0.10	0.27	0.29	0.47	0.54	0.09	0.24	0.28	0.47	0.50
Total Scores										
Tazarotene 0.1%	<u>1.15</u>	<u>1.88</u>	<u>2.57</u>	<u>3.18</u>	<u>3.80</u>	0.68	<u>1.58</u>	<u>2.28</u>	<u>2.98</u>	<u>3.33</u>
Tazarotene 0.05%	<u>1.21</u>	<u>2.04</u>	<u>2.35</u>	<u>2.63</u>	<u>3.23</u>	<u>0.89</u>	<u>1.45</u>	<u>2.02</u>	<u>2.46</u>	<u>3.06</u>
Vehicle	0.59	0.99	1.17	1.71	1.92	0.53	0.74	1.09	1.60	2.16
II. Overall Disease Parameters					<u>wk- 1</u>	<u>wk- 2</u>	<u>wk- 4</u>	<u>wk- 8</u>	<u>wk-12</u>	
Investigator's Global (mean)					Tazarotene 0.1%	<u>1.77</u>	<u>2.24</u>	<u>2.86</u>	<u>3.03</u>	<u>3.23</u>
					Tazarotene 0.05%	<u>1.95</u>	<u>2.39</u>	<u>2.53</u>	<u>2.70</u>	<u>2.85</u>
					Vehicle	1.57	1.67	1.83	2.13	1.69

*Figures underlined are significantly different from those of vehicle (p<0.05). **Figures highlighted show significant difference among 0.1% gel and 0.05% gel treatment groups (p<0.05).

So, again by the 12th week, both levels of tazarotene are statistically significantly different from vehicle for each measure of each target lesion as well as the global evaluation of response to treatment. In fact, except for erythema, these differences are apparent for both lesions from the second week of treatment.

Again, subgroup analyses are presented later.

C. Study R168-125-8606:

1. Study Design, Objectives, Patient Enrollment, Patient Demographics:

Sponsor's protocol Study#R168-125-8606: **Safety, Efficacy and Duration of Therapeutic Effect of Once-Daily Tazarotene (AGN 190168) 0.1% Gel or 0.05% Gel versus Lidex® 0.05% Cream applied Twice daily in Stable Plaque Psoriasis**

The objective of this study was to evaluate the safety, efficacy and duration of therapeutic effect of Tazarotene 0.1% and 0.05% gels applied once daily in the treatment of stable plaque psoriasis versus Lidex (fluocinonide) 0.05% cream applied twice daily. Similar in design to the R168-120-8606 study, except for using an active control, the study was a 24-week, randomized, multicenter (10 U.S. centers), investigator-masked, parallel-group, active-controlled trial. The study included a 12 week treatment period followed by a 12 week post-treatment follow-up. 348 patients were enrolled, 200 males and 148 females, aged 12-88

years. Of these, 275 completed the 12 week treatment phase (7 dropped out due to lack of efficacy, 37 due to adverse events, 27 were dropped for administrative reasons, and 2 patients were disqualified).

Again, the design of this study was very similar to that of R168-120-8606, with the primary exception that Lidex (fluocinonide) 0.05% cream was to be applied twice daily instead of tazarotene vehicle applied once daily. Thus, the study had to be treatment masked so as to not allow the investigator to know how the study medications were applied.

Demographics:

The following table summarizes the demographics. Overall, there seems to be no particularly large difference among groups.

Table 15. Demographics

	Tazarotene 0.1%	Tazarotene 0.05%	Lidex cream 0.05%
Total patient no	112	115	113
Age (Yrs)	44±14	47±15	46±16
Sex			
M	66	59	70
F	46	56	43
Race			
White	103	107	103
Hispanic	2	4	5
Black	3	2	2
Oriental	2	1	1

Again, the sponsor reported that there were no statistically significant differences among treatments with respect to age, sex, race (white versus other), percent of psoriatic involvement, or duration of psoriasis.

2. Efficacy Analysis (by the sponsor and checked by the reviewer):

Again this 24-week clinical study was divided into two study periods: a 12 week treatment period during which patients applied one of the three treatments to their psoriatic lesions; and a 12 week post-treatment period during which patients could only apply emollient cream to their non-target psoriatic lesions.

Table 16. Patient Disposition

Treatment period	Tazarotene 0.1%	Tazarotene 0.05%	Lidex cream 0.05%
Enrolled	116 (4)*	117 (2)	115 (2)
Completed study	79	89	107 (1)
Not completed	37	28	8
lack of efficacy	3	4	0
adverse event	21 (1)	14	2
not meeting entry criteria	1 (1)	1 (1)	0
"other"***	12 (2)	9 (1)	6 (1)

Posttreatment period			
Started	79/45*	89/42	107 (1)/70 (1)
Completed follow-up	57/35	57/31	59/42
Not completed	22/10	32/11	48/28
need for treatment	18/8	21/7	39/23
adverse event	0	7/1	3/1
not meeting entry criteria	0	0	1 (4)/1 (1)
"other"	4/2	4/3	5/3

*Numbers in parentheses indicate unevaluable patient numbers. ***"Other" refers to discontinuation besides disqualification or termination (AE or lack of efficacy) in treatment period and to those exiting due to administrative reasons (e.g., missed visits) in posttreatment period. *Figures in posttreatment period are given as: total patient number/number of patients who had "Treatment Success" at entry of the posttreatment period.

The response variable means are summarized in table 17.

Table 17. Response Variable Means

Baseline		Reduction in Scores									
		wk-0	wk-1	wk-2	wk-4	wk-8	wk-12	wk-16	wk-20	wk-24	
Plaque elevation											
T/A/L	Taz 0.1%	2.4	0.7	1.0	1.1	1.4	1.4	1.4	1.1	1.0	
	Taz 0.05%	2.4	<i>0.5*</i>	0.9	1.1	1.3	1.3	1.0	0.9	0.9	
	Lidex	2.3	0.6	1.0	1.3	1.4	1.5	1.3	1.1	0.9	
K/E	Taz 0.1%	2.4	0.7	1.0	1.2	1.4	1.5	<u>1.3</u>	1.1	1.0	
	Taz 0.05%	2.5	0.5	1.0	1.2	1.3	1.3	<u>1.2</u>	0.9	0.9	
	Lidex	2.5	0.7	1.1	1.3	1.4	1.4	1.0	0.9	0.8	
Scaling											
T/A/L	Taz 0.1%	2.4	0.7	1.0	<u>1.0</u>	1.3	1.3	<u>1.3</u>	1.1	<u>1.0</u>	
	Taz 0.05%	2.3	<i>0.5</i>	<i>0.7</i>	<u>1.0</u>	<i>1.1</i>	<i>1.1</i>	<u>1.1</u>	0.9	<u>0.9</u>	
	Lidex	2.4	0.8	1.1	1.4	1.6	1.6	1.3	1.2	1.1	
K/E	Taz 0.1%	2.5	<i>0.6</i>	<i>0.9</i>	<u>1.0</u>	1.3	1.3	<u>1.3</u>	1.1	1.0	
	Taz 0.05%	2.5	<i>0.5</i>	<i>0.8</i>	<u>1.1</u>	<i>1.2</i>	<i>1.2</i>	<u>1.2</u>	1.0	0.9	
	Lidex	2.5	0.8	1.2	1.3	1.5	1.4	1.0	0.9	0.9	
Erythema											
T/A/L	Taz 0.1%	2.4	<i>0.2</i>	<i>0.4</i>	<i>0.5</i>	<i>0.9</i>	<i>0.9</i>	<u>1.2</u>	<u>1.1</u>	<u>1.1</u>	
	Taz 0.05%	2.4	<i>0.2</i>	<i>0.3</i>	<i>0.5</i>	<i>0.8</i>	<i>0.8</i>	0.9	0.8	<u>0.7</u>	
	Lidex	2.4	0.6	0.9	1.2	1.4	1.4	1.1	1.0	0.8	
K/E	Taz 0.1%	2.2	<i>0.2</i>	<i>0.4</i>	<i>0.6</i>	<i>0.7</i>	<i>0.8</i>	<u>1.0</u>	<u>0.9</u>	<u>0.9</u>	
	Taz 0.05%	2.3	<i>0.2</i>	<i>0.4</i>	<i>0.5</i>	<i>0.8</i>	<i>0.9</i>	<u>1.0</u>	0.8	<u>0.7</u>	
	Lidex	2.3	0.5	0.8	1.1	1.2	1.2	0.8	0.7	<u>0.6</u>	
Sum of Scores											
T/A/L	Taz 0.1%	7.2	<i>1.6</i>	2.4	<u>2.7</u>	3.6	3.7	3.9	3.4	3.1	
	Taz 0.05%	7.1	<i>1.2</i>	<u>2.0</u>	<u>2.6</u>	<i>3.1</i>	<i>3.2</i>	2.9	<u>2.6</u>	<u>2.5</u>	
	Lidex	7.2	2.0	3.0	3.9	4.3	4.5	3.7	3.3	2.8	
K/E	Taz 0.1%	7.2	<i>1.5</i>	<i>2.3</i>	<u>2.9</u>	<i>3.4</i>	3.6	<u>3.7</u>	3.0	3.0	
	Taz 0.05%	7.3	<i>1.3</i>	<i>2.1</i>	<u>2.9</u>	<i>3.2</i>	3.4	<u>3.3</u>	2.7	2.5	
	Lidex	7.3	2.0	3.1	3.7	4.1	4.1	2.9	2.6	2.3	
Overall Global (mean)											
			<u>wk-1</u>	<u>wk-2</u>	<u>wk-4</u>	<u>wk-8</u>	<u>wk-12</u>		<u>wk-16</u>	<u>wk-20</u>	<u>wk-24</u>
	Taz 0.1%		<u>2.4</u>	<u>3.0</u>	<u>3.3</u>	3.6	3.5		<u>3.5</u>	<u>3.2</u>	<u>3.1</u>
	Taz 0.05%		<u>2.1</u>	<u>2.7</u>	<u>3.2</u>	<u>3.4</u>	<u>3.3</u>		2.9	2.7	2.8
	Lidex		2.7	3.3	3.6	3.8	3.8		2.9	2.6	2.5

*Bold italics indicate superiority of Lidex over Tazarotene ($p < 0.05$). Underlined figures show superiority of Tazarotene over Lidex ($p < 0.05$). Highlighted figures indicate a difference between 0.1% and 0.05% gels ($p < 0.05$). T/A/L=trunk/arm/leg lesions; K/E=knee/elbow lesions; Taz=Tazarotene.

During the 12 week treatment period, all three treatments were associated with statistically significant decreases from baseline. These are not shown, since this result may be due to regression effects. At most time points during the treatment period, Lidex (fluocinonide) 0.05% cream was numerically better than either dose level of tazarotene. For either lesion, for scaling, erythema, and the sum of scores, it was often statistically significantly better than either dose level of tazarotene. However during the 12 week follow-up period fluocinonide 0.05% cream was numerically generally inferior to tazarotene 0.1% gel. Fluocinonide 0.05% cream was statistically significantly inferior to either dose level of tazarotene at week 16 for all lesion measures at knees or elbows. Further, fluocinonide 0.05% cream was statistically significantly inferior to tazarotene 0.1% gel for erythema at knees or elbows. Further, from table 16. above, it is clear that more patients dropped out of the post-treatment Lidex group due to the need for treatment. Although the results are not individually statistically significant, there is a clear trend over time for the tazarotene 0.1% gel to be superior post treatment to Lidex (fluocinonide) 0.05% cream. The results comparing tazarotene 0.05% gel to the fluocinonide 0.05% cream are more problematical.

D. Study R168-126-8606:

Sponsor's protocol Study#R168-126-8606: **Safety, Efficacy and Duration of Therapeutic Effect of Once-Daily Tazarotene (AGN 190168) 0.1% Gel or 0.05% Gel versus Lidex® 0.05% Cream applied Twice daily in Stable Plaque Psoriasis**

1. Study Design, Objectives, Patient Enrollment, Patient Demographics:

As with the preceding study, R168-125-8606, the objective of this study was to evaluate the safety, efficacy and duration of therapeutic effect of Tazarotene 0.1% and 0.05% gels applied once daily in the treatment of stable plaque psoriasis versus Lidex (fluocinonide) 0.05% cream applied twice daily. Similar in design to the R168-120-8606 study, except for using an active control, the study was a 24-week, randomized, multicenter (9 U.S. centers), investigator-masked, parallel-group, active-controlled trial. The study included a 12 week treatment period followed by a 12 post-treatment follow-up. 331 patients were enrolled, 211 males and 120 females, aged 19-91 years. Of these, the sponsor reported that 243 completed the 12 week treatment phase (7 dropped out due to lack of efficacy, 48 due to adverse events, 32 were dropped for administrative reasons, and 1 patients were disqualified).

Patient demographics are summarized in the following table:

Demographics

Table 18. Demographics

	Tazarotene 0.1% 107	Tazarotene 0.05% 107	Lidex cream 0.05% 108
Total patient no			
Age (Yrs)	50±14	49±16	50±16
Sex - M	73	62	70
F	34	45	38
Race White	104	101	102
Hispanic	2	5	4
Black	1	0	1
Oriental	0	1	1
"other"	0	0	0
% Body area with psoriasis	7±5	6±5	7±4
Duration of psoriasis (Yrs)	20±14	20±13	17±11

Once again, the sponsor reported that there were no statistically significant differences among treatments with respect to age, sex, race (white versus other), percent of psoriatic involvement, or duration of psoriasis. So, again, these treatment groups appear to be relatively homogeneous.

2. Efficacy Results (by the Sponsor and checked by the reviewer)

Table 18 below tabulates the disposition of the patients:

Table 19. Patient Disposition

Treatment period	Tazarotene 0.1%	Tazarotene 0.05%	Lidex cream 0.05%
Enrolled	110 (3)*	111 (4)	110 (2)
Completed study	74	74	95
Not completed	36	37	15
lack of efficacy	1	1	5
adverse event	25	21	2
not meeting entry criteria	0	0	1 (1)
"other"***	10 (3)	15 (4)	7 (1)
Posttreatment period			
Started	74/30*	74/29	95/60
Completed follow-up	39/20	34/21	51/40
Not completed	35/10	40/8	44/20
need for treatment	28/7	27/5	38/16
adverse event	3	5/2	0
"other"	4/3	8/1	6/4

*Numbers in parentheses indicate unevaluable patient numbers.***Other refers to discontinuation besides disqualification or termination (AE or lack of efficacy) in treatment period and to those exiting due to administrative reasons (e.g., missed visits) in posttreatment period. *Figures in posttreatment period are given as: total patient number/number of patients who had "Treatment Success" at entry of the posttreatment period.

Again, this study was very similar in design to that of R168-120-8606, with the primary exception that Lidex 0.05% cream was to be applied twice daily. Thus, the study had to be

treatment masked so as to not allow the investigator to know how the study medications were applied.

Response variable means are summarized as follows:

Table 20. Response Variable Means

		<u>Baseline</u>	<u>Reduction in Scores</u>							
		<u>wk-0</u>	<u>wk-1</u>	<u>wk-2</u>	<u>wk-4</u>	<u>wk-8</u>	<u>wk-12</u>	<u>wk-16</u>	<u>wk-20</u>	<u>wk-24</u>
Plaque elevation										
T/A/L	Taz 0.1%	2.5	0.6	1.0	1.2*	<u>1.5</u>	1.6	1.4	1.1	1.0
	Taz 0.05%	2.4	0.5	0.9	1.1	<u>1.0</u>	1.2	1.2	1.1	1.0
	Lidex	2.4	0.6	1.0	1.3	1.6	1.6	1.3	1.0	0.9
K/E	Taz 0.1%	2.5	0.6	0.9	1.2	1.5	1.4	1.1	1.0	0.9
	Taz 0.05%	2.5	0.4	0.9	1.0	1.1	1.2	1.2	1.1	1.0
	Lidex	2.5	0.5	0.9	1.2	1.3	1.3	1.2	0.9	0.8
Scaling										
T/A/L	Taz 0.1%	2.5	0.6	0.9	1.1	<u>1.5</u>	1.6	1.2	1.1	1.0
	Taz 0.05%	2.4	0.3	0.8	0.9	<u>0.9</u>	1.1	1.0	1.1	1.0
	Lidex	2.4	0.8	1.1	1.4	1.6	1.6	1.3	1.0	0.9
K/E	Taz 0.1%	2.6	0.5	0.8	1.0	1.3	1.2	1.0	0.9	0.8
	Taz 0.05%	2.7	0.4	0.7	0.9	1.0	1.1	1.2	1.1	0.9
	Lidex	2.6	0.7	1.1	1.3	1.5	1.4	1.2	1.0	0.8
Erythema										
T/A/L	Taz 0.1%	2.2	0	0.2	0.4	0.7	0.9	1.2	0.9	0.9
	Taz 0.05%	2.3	0	0.3	0.6	0.5	0.9	1.0	1.2	1.0
	Lidex	2.4	0.4	0.8	1.2	1.4	1.5	1.2	1.0	0.9
K/E	Taz 0.1%	2.1	0	0.3	0.5	0.7	0.9	1.0	0.7	0.7
	Taz 0.05%	2.1	0.1	0.2	0.5	0.5	0.7	0.8	0.8	0.6
	Lidex	2.2	0.4	0.7	1.0	1.1	1.1	1.0	0.8	0.8
Sum of scores										
T/A/L	Taz 0.1%	7.2	1.2	2.1	2.7	3.8	4.1	3.8	3.2	2.9
	Taz 0.05%	7.2	0.8	2.0	2.6	2.5	3.2	3.2	3.4	3.0
	Lidex	7.2	1.8	2.8	3.9	4.5	4.7	3.8	3.1	2.7
K/E	Taz 0.1%	7.1	1.0	2.0	2.7	3.5	3.5	3.1	2.6	2.5
	Taz 0.05%	7.3	0.9	1.9	2.3	2.6	3.0	3.3	3.1	2.5
	Lidex	7.3	1.6	2.8	3.5	3.9	3.7	3.3	2.7	2.4
Overall Global (mean)			wk-1	wk-2	wk-4	wk-8	wk-12	wk-16	wk-20	wk-24
Taz 0.1%			1.8	2.4	2.8	3.2	3.4	2.9	2.5	2.2
Taz 0.05%			1.8	2.4	2.5	2.5	2.9	2.9	2.8	2.6
Lidex			2.2	2.9	3.4	3.6	3.6	3.1	2.6	2.3

*Bold italics indicate superiority of Lidex over Tazarotene ($p < 0.05$). Underlined figures show superiority of Tazarotene over Lidex ($p < 0.05$). Highlighted figures indicate a difference between 0.1% and 0.05% gels ($p < 0.05$). T/A/L=trunk/arm/leg lesions; K/E=knee/elbow lesions; Taz=Tazarotene.

Again, at most time points during the treatment period, fluocinonide 0.05% cream was numerically better than either dose level of tazarotene. For either lesion, for scaling, erythema, and the sum of scores, it was often statistically significantly better than either dose level of tazarotene. Unlike the preceding study, in this study, with due allowance to variation,

fluocinonide 0.05% cream was numerically generally indistinguishable from either dose level of tazarotene gel during the 12 week follow-up period. However, from table 19 above, it is apparent that more patients dropped out of the post-treatment fluocinonide 0.05% cream group due to the need for treatment. Still, in this study, there is no immediately clear pattern comparing fluocinonide 0.05% cream to either dose level of tazarotene.

E. Study R168-145-8606:

Sponsor's protocol Study#R168-145-8606: Safety, Efficacy and Duration of therapeutic Effect of Once-Daily Tazarotene (AGN 190168) 0.1% Gel or Once-Daily 0.05% Gel versus Twice daily Calcipotriol 0.005% Ointment in Plaque Psoriasis: an Investigator-Masked Study.

1. Study Design, Objectives, Patient Enrollment, Patient Demographics:

The objective was to evaluate the safety, efficacy and duration of therapeutic effect of once-daily Tazarotene 0.1% and 0.05% gels versus twice-daily Dovonex (calcipotriol) 0.005% ointment in the treatment of stable plaque psoriasis. The rationale of this study was the same as those of Studies R168-125-8606 and R168-126-8606. Instead of Lidex cream, Dovonex ointment was used as active control in this study.

This trial had 12 centers in the United Kingdom and 3 in Germany. Because of the small number of patients in two of the German centers, the applicant pooled the German centers as one for analysis. There were also 3 British centers with fewer than 10 patients each but the Applicant lumped the 12 centers as one. This might be justifiable because of geographic proximity and the relative homogeneity of population as well as clinical practice within each country. Further, although two target lesions were studied, there was no requirement that one had to be on the trunk/arm/leg region and the other on knee/elbow.

Demographics

Table 21. Demographics

	Tazarotene 0.1%	Tazarotene 0.05%	Dovonex [™]
Total patient no	95	95	88
Age (Yrs)	43±15	46±15	49±16
Sex			
M	56	66	72
F	39	29	60
Race			
White	92	90	86
Asian	3	5	1
Black	0	0	1
% Body area with psoriasis	8±6	8±6	8±5
Duration of psoriasis (Yrs)	not given	not given	not given

The sponsor reported that there were no statistically significant differences among treatments with respect to age, sex, race (white versus other), or percent of psoriatic involvement. Thus, these treatment groups appear to be relatively homogeneous.

2. Efficacy Results (Provided by the Sponsor):

Table 22., below, gives the disposition of the patients.

Table 22. Patient Disposition

Treatment Period	Tazarotene 0.1%	Tazarotene 0.05%	Dovonex 0.005%
Enrolled	123 (28)*	122 (27)	124 (36)
Completed study	70 (18)	63 (16)	92 (26)
Not completed	53	59	32
lack of efficacy	20	27 (3)	11 (2)
adverse event	24 (6)	22 (5)	5 (3)
entry criteria violation	1 (1)	0	1
"other"***	8 (3)	10 (3)	15 (5)
Posttreatment Period			
Started	70 (18)	63 (17)	92 (26)
Completed follow-up	31 (8)	29 (9)	37 (12)
Not completed	39	34	55
need for treatment	30 (5)	29 (8)	51 (11)
adverse event	0	0	0
"other"***	9 (5)	5	4 (3)

*Numbers in parentheses indicate unevaluable patient numbers. ***"Other" refers to discontinuation besides disqualification or termination (AE or lack of efficacy) in treatment period.

As this study did not distinguish the anatomical location of the 2 target lesions, their data were combined and averaged in the analyses for this study. Again, this study had a 12 week treatment period followed by a 12 week, post-treatment follow-up period. Also, though not displayed here, there were large treatment by center interactions during the first week. Unless one wanted to go into a subgroup analysis, it seems best to ignore the results from the first week.

Table 23. Response Variable Means

	Baseline	Reduction in Scores						
	wk-0	wk-1	wk-4	wk-8	wk-12	wk-16	wk-20	wk-24
Plaque elevation (Average Scores from 2 target lesions)								
Taz 0.1%	2.5	0.6	1.2	1.4	1.3	1.3	1.3	1.1
Taz 0.05%	2.5	0.6	0.9 *	1.0	1.2	1.4	1.2	1.1
Dovonex	2.4	0.7	1.3	1.6	1.7	1.3	1.2	1.2
Scaling (Average Scores from 2 target lesions)								
Taz 0.1%	2.5	0.7	1.1	1.2	1.3	1.2	1.1	0.9
Taz 0.05%	2.4	0.4	0.7	0.8	1.0	1.2	1.1	0.9
Dovonex	2.3	1.1	1.4	1.6	1.7	1.2	1.1	1.0
Erythema (Average Scores from 2 target lesions)								
Taz 0.1%	2.3	0.1	0.4	0.7	0.8	0.9	0.9	0.8
Taz 0.05%	2.2	0.1	0.2	0.4	0.7	0.8	0.8	0.5
Dovonex	2.2	0.2	0.6	0.8	1.1	1.0	0.9	0.8
Sum of scores (Average Scores from 2 target lesions)								
Taz 0.1%	7.3	1.5	2.7	3.2	3.4	3.3	3.3	2.9
Taz 0.05%	7.0	1.1	1.7	2.2	2.9	3.3	3.0	2.4
Dovonex	6.9	2.0	3.2	3.9	4.4	3.5	3.2	3.0

Table 23.(cont.) Response Variable Means

	<u>Baseline</u>						<u>Reduction in Scores</u>																	
	<u>wk-0</u>						<u>wk-1</u>		<u>wk-4</u>		<u>wk-8</u>		<u>wk-12</u>		<u>wk-16</u>		<u>wk-20</u>		<u>wk-24</u>					
<u>Global "Treatment Success"(% pts)</u>							<u>wk-1</u>	<u>wk-4</u>	<u>wk-8</u>	<u>wk-12</u>							<u>wk-16</u>	<u>wk-20</u>						
Taz 0.1%							7	26	33	41							33	26						
27																								
Taz 0.05%							3	16	29	44							45	35						
24																								
Dovonex							9	35	52	63							47	36						
36																								
<u>Overall Global* (pt nos)</u>	<u>wk-1</u>						<u>wk-4</u>						<u>wk-8</u>						<u>wk-12</u>					
<u>Treatment Period</u>	5	4	3	2	1	0/-1 (n)	5	4	3	2	1	0/-1 (n)	5	4	3	2	1	0/-1 (n)	5	4	3	2	1	0/-1 (n)
Taz 0.1%	0	0	5	8	33	24 (71)	1	2	15	17	14	21 (70)	1	7	12	16	11	14 (61)	1	14	9	8	9	17 (58)
Taz 0.05%	0	0	2	7	36	24 (69)	1	3	7	12	22	22 (67)	2	12	4	8	13	24 (63)	3	11	10	2	4	24 (54)
Dovonex	0	0	5	15	30	8 (58)	0	5	14	15	11	10 (55)	3	15	10	15	3	8 (54)	6	17	8	4	6	8 (49)
	<u>wk-16</u>						<u>wk-20</u>						<u>wk-24</u>											
<u>Posttreatment Period</u>	5	4	3	2	1	0/-1 (n)	5	4	3	2	1	0/-1 (n)	5	4	3	2	1	0/-1 (n)						
Taz 0.1%	1	6	6	10	7	10 (40)	0	7	3	5	9	14 (38)	1	5	3	3	8	14 (34)						
Taz 0.05%	4	6	4	3	5	9 (31)	4	5	2	3	8	10 (32)	1	7	12	16	11	14 (26)						
Dovonex	8	9	4	2	7	14 (44)	5	7	3	3	8	15 (41)	4	7	3	1	7	16 (38)						

*Bold italics indicate superiority of Devonex over Tazarotene (p<0.05). Underlined figures show superiority of Tazarotene over Devonex (p<0.05). Highlighted figures indicate a difference between 0.1% and 0.05% gels (p<0.05). T/A/L=trunk/arm/leg lesions; K/E=knee/elbow lesions; Taz=Tazarotene. *Global Scores: 5=cleared, 4=75-99% improvement, 3=50-74% improvement, 2=25-49% improvement, 1=0-24% improvement, 0=no change, -1=worsened. Global scores of 2 centers were excluded for analysis because of "inconsistent choice of baseline".

At most time points during the treatment period or the follow-up period calcipotriol 0.005% ointment was numerically better than either dose level of tazarotene. However, from table 22 above, it is apparent that nearly twice as many patients dropped out of calcipotriol 0.005% ointment post-treatment group than either tazarotene dose group. This may suggest a differential post treatment advantage for the tazarotene groups, however, the table above suggests that for those that continued in the follow-up study there was an advantage to calcipotriol 0.005% ointment.

II. Acne Vulgaris

A. Study R168-220-7997:

Sponsor's protocol Study#R168-220-7997: **Safety and Efficacy of Tazarotene (AGN 190168) in the Treatment of Acne Vulgaris: 0.1% Gel and 0.05% Gel versus Vehicle Gel**

1. Study Design, Objectives, Patient Enrollment, Inclusion/exclusion Criteria, Patient Demographics:

The objective was to evaluate the safety and efficacy of once-daily Tazarotene 0.1% and 0.05% gels versus vehicle gel in the treatment of acne vulgaris. This study was a 12-week, randomized, multicenter (9 centers), double-blind, parallel-group, vehicle-controlled trial comparing the efficacy and safety of Tazarotene with those of vehicle when applied once daily in patients having acne vulgaris. Patients were restricted to be 14 years or older, with mild to moderate facial acne vulgaris. Among other restrictions, patients were required to have a minimum of 10 but no more than 60 facial inflammatory lesions (sum of papules and pustules) and a minimum of 25 but no more than 200 facial non-inflammatory lesions (sum of open and closed comedones).

Again, the formulation used in this study for the tazarotene 0.1% gel is labeled 7997X, for the tazarotene 0.05% gel is labeled 8225X, while vehicle is labeled 8006X. It is not clear if these are different formulations or different productions of the same formulation. However, only the vehicle label agrees with those used in the other studies. The labeled versions of tazarotene used in the R168-221-8606 protocol agree with those in the R168-120-8606 study. This report assumes that any such possible differences in formulation are irrelevant. However, as a matter of good science, the formulations used in all studies should be identical.

Demographics

Table 24. Demographics

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Total patient no	122	124	129
Age (Yrs)	20±7	22±8	20±7
Sex			
M	63	61	76
F	59	63	53
Race			
White	71	83	84
Hispanic	32	25	29
Black	16	15	16
Oriental	1	0	0
"other"	2	1	0

The sponsor reported that there were no statistically significant differences in age, sex, race distribution, or baseline number of lesions across treatment groups.

2. Efficacy Assessments:

The following parameters were evaluated:

1. Lesion counts: Open comedones, closed comedones, papules, pustules and nodules were counted at weeks 0, 4, 8 and 12.
 - a) Total non-inflammatory lesion count=sum of open and closed comedones.
 - b) Total inflammatory lesion count=sum of papules, pustules and nodules
 - c) Total lesion count=sum of a and b
2. Global evaluation of response to treatment at postbaseline visits according to the following scale: 5=cleared; 4=excellent=75-99% improvement; 3=good=50-74% improvement; 2=fair=25-49% improvement; 1=poor=1-24% improvement; and 0=unchanged or worse.

Under the direction of the medical officer we shall take treatment success as being determined by each of the following:

1. reduction of either inflammatory or noninflammatory lesion counts
2. reduction of total lesion counts
3. significant change in the global evaluation of response.

Again, these criteria do not need a multiple comparisons adjustment.

According to the sponsor, similar results come from using the intent-to-treat and the group of patients who completed the entire study, i.e. the "fully evaluable" subset of patients. For convenience, this analysis used this "fully evaluable" group.

Table 25. Patient Disposition

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Enrolled	150 (28)*	148 (24)	148 (19)
Completed study	111 (1)	103 (1)	119
Not completed	39	45	29
lack of efficacy	0	1 (1)	3 (1)
adverse event	13 (10)	12 (7)	2 (2)
not meeting entry criteria	3 (3)	4 (4)	3 (3)
"other"***	23 (14)	28 (11)	21 (13)

*Numbers in parentheses indicate unevaluable patient numbers. ***"Other" refers to discontinuation besides disqualification or termination (AE or lack of efficacy) in treatment period and to those exiting due to administrative reasons (e.g., missed visits) in posttreatment period.

Unevaluability was based on the following reasons:

	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>
Lacking evaluable postbaseline visit data	18	15	11
concomitant medication violation	4	2	3
selection criteria violation	3	4	3
other protocol violations*	3	3	2

*other protocol violations primarily involved dosing changes or violation in visits which made the data unevaluable.

3. Efficacy Results:

Table 26 following displays the mean baseline score, and the percent change from baseline for non-inflammatory lesions, inflammatory lesions, and total lesions. Again, in reading this table, the first line lists sample sizes, means, and standard deviations. The next two lines have p-values corresponding to the ANOVA contrasts, on the untransformed scores or differences, testing treatment group differences. From right to left, the second line displays the results for comparing the mean of the 0.1% tazarotene group to the mean of the 0.05% tazarotene group and the mean of the vehicle with the 0.05% tazarotene group mean. The third line has the p-value for comparing mean of the 0.1% tazarotene treatment group to that of the vehicle group. For example, from table 26 for inflammatory lesions at the fourth week the p-values corresponding to the tests of difference between the tazarotene 0.1% group and the tazarotene 0.05% group, and the tazarotene 0.05% group and vehicle are both not statistically significant ($p \leq 0.282$ and $p \leq 0.061$ respectively). Similarly the difference between the tazarotene 0.1% group and vehicle is not statistically significant ($p \leq 0.454$).

Table 26. Percent Change From Baseline (Except at Baseline)

Total Non-Inflammatory Lesions:										Total Inflammatory Lesions:							
		Tazarotene 0.1%			Tazarotene 0.05%			Vehicle				Tazarotene 0.1%		Tazarotene 0.05%		Vehicle	
Week	n	Mean (STD)	n	Mean (STD)	n	Mean (STD)	n	Mean (STD)	STD	Mean (STD)	Mean (STD)	Mean (STD)	Mean (STD)	Mean (STD)	Mean (STD)	Mean (STD)	
		p-value of diff			p-value of diff			p-value of diff				p-value of diff		p-value of diff			
		----- p-value of diff-----			----- p-value of diff-----			----- p-value of diff-----				----- p-value of diff-----		----- p-value of diff-----			
0	122	61.9 (39.8)	124	55.5 (33.3)	129	59.8 (38.1)				20.5 (10.8)	19.7 (10.2)				23.3 (13.2)		
		0.299			0.511			0.367				0.087					
		0.695						0.425									
4	112	-31.8 (28.7)	118	-25.3 (36.3)	127	-16.4 (57.4)				-16.1 (45.4)	-21.5 (40.5)				-16.7 (41.7)		
		0.050			0.087			0.282				0.061					
		<0.001						0.454									
8	102	-46.2 (31.8)	97	-42.6 (32.0)	118	-31.0 (33.4)				-28.6 (42.7)	-37.9 (30.1)				-32.6 (47.5)		
		0.160			0.006			0.310				0.493					
		<0.001						<0.711									
12	105	-54.9 (33.8)	100	-45.3 (35.6)	117	-34.6 (36.7)				-42.5 (40.6)	-39.4 (40.0)				-29.6 (46.6)		
		0.002			0.032			0.224				0.082					
		<0.001						0.003									
Total Lesions:																	
		Tazarotene 0.1%			Tazarotene 0.05%			Vehicle									
Week	n	Mean (STD)	n	Mean (STD)	n	Mean (STD)	n	Mean (STD)	STD	Mean (STD)	Mean (STD)	Mean (STD)	Mean (STD)	Mean (STD)	Mean (STD)	Mean (STD)	
		p-value of diff			p-value of diff			p-value of diff									
		----- p-value of diff-----			----- p-value of diff-----			----- p-value of diff-----									
0	122	82.4 (44.5)	124	75.2 (37.5)	129	83.0 (44.2)											
		0.208			0.216												
		0.971															
4	112	-28.5 (25.9)	118	-24.8 (31.1)	127	-19.3 (36.7)											
		0.194			0.076												
		0.002															
8	102	-42.2 (30.1)	97	-41.5 (28.0)	118	-31.9 (29.8)											
		0.487			0.008												
		<0.001															
12	105	-52.4 (31.7)	100	-43.8 (32.6)	117	-33.4 (34.1)											
		0.005			0.017												
		<0.001															

From the table 26 it can be seen that at both the 8th week and 12th week both dosages of tazarotene are associated with a statistically significant reduction in noninflammatory lesions and in total lesions. Further, there is evidence that by the 12th week the tazarotene 0.1% dosage is associated with a statistically significant reduction in inflammatory lesions, whereas there is no such conclusion for the 0.05% dosage. By the 12th week, the tazarotene 0.1% gel means are also statistically significantly lower than the tazarotene 0.05% means in both noninflammatory and total lesions.

Table 27. Global Evaluation of Response to Treatment

Global Evaluation of Response to Treatment:									
		Tazarotene 0.1%			Tazarotene 0.05%			Vehicle	
		p-value of diff			p-value of diff				
Week	n	Mean	(STD)	n	Mean	(STD)	n	Mean	STD
4	112	1.84	(1.14)	118	1.63	(1.14)	127	1.48	(1.21)
					0.102			0.152	
					0.002				
8	102	2.33	(1.30)	97	2.20	(1.19)	118	1.91	(1.28)
					0.212			0.061	
					0.002				
12	105	2.74	(1.37)	100	2.42	(1.28)	117	2.03	(1.40)
					0.020			0.010	
					<0.001				

Scoring scale: 0=unchanged or worsened 3=50-74% improvement
 1=1-24% improvement 4=75-99% improvement
 2=25-49% improvement 5=Completely cleared

It is to be noted from table 27 that, by week 12, both dosages of tazarotene gel show a statistically significant difference from vehicle, in the investigator's global evaluation of response to treatment. Further, by week 12, there is a small, but statistically significant, superiority of the tazarotene 0.1% gel over the 0.5% gel with this response measure.

B. Study R168-221-8606:

Sponsor's protocol Study#R168-221-8606: Safety and Efficacy of Tazarotene (AGN 190168) in the Treatment of Acne Vulgaris: 0.1% Gel and 0.05% Gel versus Vehicle Gel

1. Study Design, Objectives, Patient Enrollment, Patient Demographics:

Again, the objective was to evaluate the safety and efficacy of once-daily Tazarotene 0.1% and 0.05% gels versus vehicle gel in the treatment of acne vulgaris. This study was a 12-week, randomized, multicenter (9 centers), double-blind, parallel-group, vehicle-controlled trial comparing the efficacy and safety of Tazarotene with those of vehicle when applied once daily in patients having acne vulgaris. Patients were restricted to be 12-45 years of age, with mild to moderate facial acne vulgaris. Among other restrictions, patients were required to have a minimum of 10 but no more than 60 facial inflammatory lesions (sum of papules and pustules)

and a minimum of 25 but no more than 200 facial non-inflammatory lesions (sum of open and closed comedones). The design of the study was virtually identical to the preceding R168-220-7997 study.

Demographics

Table 28. Patient Demographics

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Total patient no	133	129	136
Age (Yrs)	20±7	22±8	21±9
Sex			
M	63	54	60
F	70	75	76
Race			
White	118	116	118
Hispanic	1	2	3
Black	12	11	12
Oriental	1	0	3
"other"	1	0	0

For the preferred analysis population, as used here, the sponsor reported that there were no statistically significant differences among treatments with respect to sex, race, and baseline number of lesions. There was statistically significant difference in age ($p \leq 0.047$). However, this is treated as an artifact of the experiment, and will be ignored.

2. Efficacy Analyses (Provided by the Sponsor):

The patient disposition follows:

Table 29. Patient Disposition

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Enrolled	149 (16)*	149 (20)	149 (13)
Completed study	120	118	115
Not completed	29	31	34
lack of efficacy	0	0	5
adverse event	9 (7)	10 (9)	2 (1)
not meeting entry criteria	1 (1)	3 (3)	5 (5)
"other"***	19 (8)	18 (8)	22 (7)

*Numbers in parentheses indicate unevaluable patient numbers. ***"Other" refers to discontinuation besides disqualification or termination (AE or lack of efficacy) in treatment period and to those exiting due to administrative reasons (e.g., missed visits) in posttreatment period.

Unevaluability was based on the following reasons:

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Lacking postbaseline visit data	12	14	6
concomitant medication violation	1	0	2
selection criteria violation	1	3	5
other protocol violations*	2	3	0

*other protocol violations primarily involved dosing changes or violation in visits which made the data unevaluable.

The results for the primary response variables follow:

Table 30. Percent Change From Baseline (Except at Baseline)

Total Non-Inflammatory Lesions:						Total Inflammatory Lesions:												
Tazarotene 0.1%			Tazarotene 0.05%			Vehicle			Tazarotene 0.1%			Tazarotene 0.05%			Vehicle			
Week	n	Mean (STD)	n	Mean (STD)	n	Mean	STD	Mean (STD)	n	Mean (STD)	n	Mean	STD	Mean (STD)	n	Mean	STD	
p-value of diff			p-value of diff			p-value of diff			p-value of diff			p-value of diff			p-value of diff			
-----			-----			-----			-----			-----			-----			
0	133	52.1 (29.8)	129	52.4 (30.0)	136	49.6	(25.4)	22.4	(12.1)	22.3	(12.0)	21.2	(10.7)	0.697	0.489	0.520	0.663	0.828
				0.761														
4	128	-19.0 (33.3)	126	-15.4 (33.6)	132	-7.7	(36.6)	-16.8	(39.7)	-13.8	(40.9)	-11.7	(40.0)	0.212	0.016	0.433	0.172	0.572
				<0.001														
8	116	-35.9 (31.8)	117	-30.5 (32.3)	121	-19.0	(46.1)	-40.4	(28.7)	-31.2	(47.1)	-24.9	(47.5)	0.151	0.002	0.442	0.009	0.064
				<0.001														
12	117	-42.9 (33.1)	115	-37.8 (30.7)	110	-27.1	(36.4)	-46.8	(27.8)	-36.6	(44.4)	-28.0	(50.8)	0.035	0.001	0.185	0.009	0.188
				<0.001														
Total Lesions:																		
Tazarotene 0.1%			Tazarotene 0.05%			Vehicle												
Week	n	Mean (STD)	n	Mean (STD)	n	Mean	STD	Mean (STD)	n	Mean (STD)	n	Mean	STD	Mean (STD)	n	Mean	STD	
p-value of diff			p-value of diff			p-value of diff			p-value of diff			p-value of diff						
-----			-----			-----			-----			-----						
0	133	74.5 (36.5)	129	73.7 (37.9)	136	70.7	(31.0)	0.905	0.778	0.684								
				0.684														
4	128	-18.9 (27.8)	126	-15.7 (27.2)	132	-9.5	(31.3)	0.232	0.032	<0.001								
				<0.001														
8	116	-37.6 (25.1)	117	-31.5 (27.2)	121	-21.0	(42.3)	0.084	0.006	<0.001								
				<0.001														
12	117	-44.6 (26.2)	115	-38.7 (27.4)	110	-27.4	(44.4)	0.051	0.002	<0.001								
				<0.001														

As before, from the table 30, it can be seen that by the 4th week of treatment, both dosages of tazarotene are associated with a statistically significant reduction in noninflammatory lesions and in total lesions. Further, by the 8th week of treatment, there is evidence that the tazarotene 0.1% dosage is associated with a statistically significant reduction in inflammatory lesions, whereas there is no such conclusion for the 0.05% dosage. At the 12th week of treatment, the tazarotene 0.1% gel mean is also statistically significantly lower than the tazarotene 0.05% gel mean in noninflammatory lesions.

Table 31. Global Evaluation of Response to Treatment

Global Evaluation of Response to Treatment:
Tazarotene 0.1% Tazarotene 0.05% Vehicle

p-value of diff p-value of diff
----- p-value of diff-----

Week	n	Mean (STD)	n	Mean (STD)	n	Mean	STD
4	128	2.05 (1.15)	126	1.83 (1.15)	132	1.72 (1.11)	
			0.073		0.179		
			0.002				
8	116	2.90 (1.20)	117	2.60 (1.35)	121	2.25 (1.28)	
			0.154		0.008		
			<0.001				
12	117	3.26 (1.30)	115	2.93 (1.39)	110	2.50 (1.51)	
			0.039		0.010		
			<0.001				

Scoring scale: 0=worsened 4=50-74% improvement
1=unchanged 5=75-99% improvement
2=1-24% improvement 6=Completely cleared
3=25-49% improvement

It may be noted that by week 12, both dosages of tazarotene gel show a statistically significant difference from vehicle, in the investigator's global evaluation of response to treatment. Further, by week 12, there is a small, but statistically significant, superiority of the tazarotene 0.1% gel over the 0.5% gel with this response measure. (Note that the larger scores here than in the preceding experiment are due to the slightly different scale for the global evaluation. Adjusting for this, the scores are quite comparable across studies.)

Subset Analysis

The Applicant analyzed the two vehicle-controlled trials for differences in response among subsets with respect to age, sex and race. The data are summarized in the following Table:

Table 32. Psoriasis Subgroups

		<u>Superiority at Endpoint: week-12 (R168-120-8606/R168-121-8606)*</u>						
		<u>Age</u>			<u>Sex</u>		<u>Race</u>	
		<u><45</u>	<u>45-65</u>	<u>>65</u>	<u>Males</u>	<u>Females</u>	<u>whites</u>	<u>nonwhites</u>
Plaque Elevation	Taz 0.1%	+/+	+/+	-/-	+/+	+/+	+/+	+/±
	Taz 0.05%	+/+	+/+	-/-	+/+	+/+	+/+	-/+
Scaling	Taz 0.1%	+/+	+/+	-/-	+/±	+/±	+/±	±/-
	Taz 0.05%	+/±	+/±	-/-	±/-	+/+	+/+	-/±
Erythema	Taz 0.1%	+/±	±/±	-/-	+/+	+/±	+/+	±/-
	Taz 0.05%	±/-	±/±	-/-	-/±	+/±	±/-	-/±

*+=Significantly superior over vehicle, -=not superior, ±=superior in trunk/arm/leg lesions only, ±=superior in knee/elbow lesions only. Highlighted signs show superiority of 0.1% gel over 0.05% gel.

To summarize the results in table 32, at the 12th week of treatment, most of the

subgroups displayed a statistically significant difference between each dose level and vehicle at both target lesions. Note that the 0.1% gel was found to be statistically significantly better 0.05% gel for scaling in males and whites in the R168-121-8606 study. No subset analysis of the data has been performed for the 3 active-controlled psoriasis trials. According to the medical officer, they would not be necessary to support the claim of maintenance effect.

- In the acne trials, the age range was quite limited in both studies. Hence the results are not broken down by age group.

Table 33. Acne Subgroups

		<u>Superiority at Endpoint: week-12 (R168-220-7997/R168-221-8606)*</u>			
		<u>Sex</u>		<u>Race</u>	
		<u>Males</u>	<u>Females</u>	<u>whites</u>	<u>nonwhites</u>
<u>Total Inflammatory Lesions</u>	Taz 0.1%	-/+	-/-	+/+	-/-
	Taz 0.05%	-/-	-/-	-/-	-/-
<u>Total Noninflammatory Lesions</u>	Taz 0.1%	+/+	+/+	+/+	+/-
	Taz 0.05%	-/-	-/-	-/+	-/-
<u>Total Lesions</u>	Taz 0.1%	+/+	+/+	+/+	+/-
	Taz 0.05%	-/-	-/-	-/+	-/-

*+=Significantly superior over vehicle, -=not superior. Highlighted signs show superiority of 0.1% gel over 0.05% gel.

Unlike the psoriasis studies, from table 33, the majority of the subgroups do not continue to show statistically significant differences at all response variables. Still, though the actual means are not displayed above, usually the results are consistent with the tazarotene 0.1% group being numerically slightly better than the tazarotene 0.05% group. In turn, the tazarotene 0.05% group is generally slightly better than the vehicle group. In several instances, the results for blacks are not consistent with this pattern, but due to the small number of black patients, it was felt this was just an artifact of the experiment.

Safety Data

A. Adverse Events

The sponsor separately tabulated adverse events that the sponsor indicated were treatment related from those that the sponsor claimed were not treatment related. Separating the five psoriasis studies from the two acne studies we get tables 34-37. The adverse events were primarily those indicative of local irritation (pruritus, burning, erythema, or desquamation).

Tables 34. & 35. summarize the adverse events labeled as the psoriasis trials. An event was listed if it occurred more than once in some treatment group. Events that occurred at most once in a treatment group were deleted from the table.

Table 34. Adverse Events Related to Treatment

Psoriasis Trials

Event	Tazarotene 0.1% 568	Tazarotene 0.05% 569	Tazarotene Vehicle 221	Lidex 0.05% 225	Devonex 0.005% 122
All Patients	568	569	221	225	122
All Patient Events	321	260	46	27	12
	56.5%	45.7%	20.8%	12.0%	9.8%
Pruritus	127	102	24	6	7
	22.4%	17.9%	10.9%	2.7%	5.7%
Burning Skin	106	86	10	12	
	18.7%	15.1%	4.5%	5.3%	
Erythema	93	79	4	1	4
	16.4%	13.9%	1.8%	0.4%	3.3%
Irritation Skin	76	52	1	1	
	13.4%	9.1%	0.5%	0.4%	
Pain Skin	43	26	1		1
	7.6%	4.6%	0.5%		0.8%
Psoriasis Worsened	32	30	9	4	
	5.6%	5.3%	4.1%	1.8%	
Desquamation	29	18			1
	5.1%	3.2%			0.8%
Rash	29	19	2		
	5.1%	3.3%	0.9%		
Dermatitis Contact	25	17	1	1	
	4.4%	3.0%	0.5%	0.4%	
Inflammation Skin	11	6	4		2
	1.9%	1.1%	1.8%		1.6%
Stinging Skin	10	7	2	4	
	1.8%	1.2%	0.9%	1.8%	
Skin Dry	5	8	3		
	0.9%	1.4%	1.4%		
Insomnia	4				
	0.7%				
Reaction Skin	4				
	0.7%				
Chills	3				
	0.5%				
Edema Skin Focal	3	2			
	0.5%	0.4%			
Hem Skin	3	7	1		
	0.5%	1.2%	0.5%		
Sweat	3				
	0.5%				
Cellulitis	2				
	0.4%				
Discharge Skin	2	4	2		1
	0.4%	0.7%	0.9%		0.8%
Excoriation	2	2	1		
	0.4%	0.4%	0.5%		
Fissure Skin	2	8	1		
	0.4%	1.4%	0.5%		
Rash Maculopapular	2	2			
	0.4%	0.4%			
Rash Vesic Bull	1	4			
	0.2%	0.7%			
Hypertriglyceridem	1	3	1		
	0.2%	0.5%	0.5		
Vasodilat	1	3			
	0.2%	0.5%			
Edema Peripheral		2	1		1
		0.4%	0.5		0.8%

Table 34. (cont.) Adverse Events Related to Treatment

Psoriasis Trials

Event	Tazarotene 0.1%	Tazarotene 0.05%	Tazarotene Vehicle	Lidex 0.05%	Devonex 0.005%
Erosion Skin		2 0.4%	1 0.5		
Skin Tightness		2 0.4%			
Alopecia				1 0.4	

It may be noted that 57% of the subjects reported treatment related adverse events in the tazarotene 0.1% group, versus 46% in the tazarotene 0.05% group, and 27% in the tazarotene vehicle group. Similarly 12% of the Lidex patients and 10% of the Devonex patients showed adverse events labeled by the sponsor as treatment related. The most frequent adverse events in the tazarotene treatment groups were pruritus, burning, erythema, irritation, worsening of psoriasis, desquamation, and rash. The most frequent adverse event in the vehicle group was pruritus. The sponsor reported in all the vehicle and active controlled phase 3 trials there were no treatment related serious adverse events.

"Adverse events during the psoriasis trials caused the termination of 18% of the patients treated with tazarotene 0.1%, 14% with tazarotene 0.05%, 5% with tazarotene vehicle, 2% with Lidex, and 3% with Devonex. The majority of these terminations were due to signs and symptoms of local irritation. Burning resulted in the termination of 5% of the tazarotene 0.1% group, 3% of the tazarotene 0.05% group, 0.5% of the tazarotene vehicle group, none of the Lidex group, and 1% of the Devonex group. Pruritus resulted in the termination of 4% of the patients in each of tazarotene groups, 1% of the tazarotene vehicle group, none of the Lidex group, and 2% of the Devonex group. Worsening of psoriasis resulted in the termination of 4% of the tazarotene 0.1% group, 2% of the tazarotene 0.05% group, 3% of the tazarotene vehicle group, 0.4% of the Lidex group, and none of the Devonex group."

Table 35 lists all adverse events, labeled by the sponsor as not being treatment related, and were reported by at least 1% of the patients in some treatment group:

Table 35. Adverse Events Sponsor Claims Not Related to Treatment Psoriasis Trials

	Tazarotene 0.1%	Tazarotene 0.05%	Tazarotene Vehicle	Lidex 0.05%	Devonex 0.005%
All Patients	568	569	221	225	122
All Patient Events	219	242	99	108	19
	38.6%	42.5%	44.8%	48.0%	15.6%
Infection	43	43	24	23	1
	7.6%	7.6%	10.9%	10.2%	0.8%
Psoriasis Worsened	25	26	11	11	
	4.4%	4.6%	5.0%	4.9%	
Headache	20	26	12	12	
	3.5%	4.6%	5.4%	5.3%	
Pruritus	15	13	3	1	
	2.6%	2.3%	1.4%	0.4%	
Rhinitis	13	13	4	11	
	2.3%	2.3%	1.8%	4.9%	
Pharyngitis	12	12	4	4	6
	2.1%	2.1%	1.8%	1.8%	4.9%
Flu Synd	10	11	7	10	2
	1.8%	1.9%	3.2%	4.4%	1.6%
Pain Skin	9	3	1		
	1.6%	0.5%	0.5%		
Hypertriglyceridem	7	10	2	3	
	1.2%	1.8%	0.9%	1.3%	
Injury Accidental	7	5	4	1	
	1.2%	0.9%	1.8%	0.4%	
Erythema	6	6	4		
	1.1%	1.1%	1.8%		
Pain Back	6	7	7	5	1
	1.1%	1.2%	3.2%	2.2	0.8%
Tooth Disorders	6	3	2	7	
	1.1%	0.5%	0.9%	3.1%	
Infection Sinus	5	10	1	4	1
	0.9%	1.8%	0.5%	1.8%	0.8%
Arthritis	2	7	4	5	
	0.4%	1.2%	1.8%	2.2%	
Rash	1	6	2		
	0.2%	1.1%	0.9%		
Infection-Urin Tract	2	5	8	4	
			3.6%	1.8%	
Hematuria	5	4	4	3	
	0.9%	0.7%	1.8%	1.3%	
Bronchitis			3		
			1.4%		
Bursitis	2		3		
	0.4%		1.4%		
Edema Peripheral	4	2	3		
	0.7%	0.4%	1.4%		
Eosinophila	3	2	3		
	0.5%	0.4%	1.4%		
Myalgia			6		
			2.7%		
Cough Inc	2	3		4	
	0.4	0.5		1.8	
Liver Func Abnorm		1	2	3	
		0.2	0.9	1.3	
Nausea	2	2		3	
	0.4	0.4		1.3	
Pain	4	2	2	3	1
	0.7	0.4	0.9	1.3	0.8%

Again, note the large number of adverse events related to irritation of the skin. Looking at this table, one might suspect the proportions reported by the sponsor of treatment related

adverse events are, if anything, an underestimate of the true proportion.

Table 36 summarizes the adverse events in the acne trials. Again, an event was listed if it occurred more than once in some treatment group. Events that occurred at most once in a treatment group were deleted from the table.

Table 36. Adverse Events Sponsor Indicates Related to Treatment Acne Trials

	Tazarotene 0.1%	Tazarotene 0.05%	Tazarotene Vehicle
All Patients	299	297	297
All Patient Events	139	123	45
	46.5%	41.4%	15.2%
Desquamation	84	60	6
	28.1%	20.2%	2.0%
Burning Skin	74	57	8
	24.7%	19.2%	2.7%
Skin Dry	59	59	14
	19.7%	19.9%	4.7%
Erythema	53	33	
	17.7%	11.1%	
Pruritus	36	31	21
	12.0%	10.4%	7.1%
Irritation Skin	16	8	4
	5.4%	2.7%	1.3%
Stinging Skin	9	10	1
	3.0%	3.4%	0.3%
Pain Skin	5	1	
	1.7%	0.3%	
Discolor Skin	3		
	1.0%		
Fissure Skin	3	1	
	1.0%	0.3%	
Cheilitis	2	1	
	0.7%	0.3%	
Skin Tightness	2	3	
	0.7%	1.0%	
Acne Worsened		2	3
		0.7%	1.0%

It may be noted that 47% of the subjects reported treatment related adverse events in the tazarotene 0.1% group, versus 41% in the tazarotene 0.05% group, and 15% in the vehicle group. The most frequent adverse events in the tazarotene treatment groups were desquamation, burning, dryness, erythema, pruritus, and irritation. The most frequent adverse event in the vehicle group was pruritus. Again, the sponsor reported that in all the vehicle and active controlled phase 3 trials there were no treatment related serious adverse events.

Adverse events during the two acne vulgaris trials caused the termination of 7% of the patients treated with tazarotene 0.1%, 7% with tazarotene 0.05%, and 1% with tazarotene vehicle. The majority of these terminations were due to signs and symptoms of local irritation. "Burning resulted in the termination of 4% of the patients in each of tazarotene group, and 0.7% of the tazarotene vehicle group. Erythema resulted in the termination of 4% of the tazarotene 0.1% group and 3% of the tazarotene 0.05% group. Desquamation resulted in the termination of 3% of the tazarotene 0.1% group and 4% of the tazarotene 0.05% group." No patients in the

vehicle group were terminated because of erythema or desquamation.

For completeness, table 37., lists all adverse events labeled as not being related to treatment and further are reported by at least 1% of the patients in any of the acne treatment groups:

**Table 37. Adverse Events Sponsor Claims Not Related to Treatment
Acne Trials**

	Tazarotene 0.1%	Tazarotene 0.05%	Tazarotene Vehicle
All Patients	299	297	297
All Patient Events	79	78	84
Infection	26.4%	26.3%	28.3%
Headache	19	22	24
	6.4%	7.4%	8.1%
Pharyngitis	16	14	13
	5.4%	4.7%	4.4%
Rhinitis	8	6	9
	2.7%	2.0%	3.0%
Flu Synd	7	2	14
	2.3%	0.7%	4.7%
Infection Ear	5	8	6
	1.7%	2.7%	2.0%
Injury Accidental	4	3	4
	1.3%	1.0%	1.3%
Sinusitis	4	2	1
	1.3%	0.7%	0.3%
Infection Ear	1	6	5
	0.3%	2.0%	1.7%
Infection Urin Tract		3	
		1.0%	
Cheilitis	2	3	
	0.7%	1.0%	
Skin Tightness	2	1	
	0.7%	0.3%	
Acne Worsened		3	
		1.0%	
Sinusitis	2	2	6
	0.7%	0.7%	2.0%
Cough Inc	1		1
			1.7%

Unlike the situation with the psoriasis studies, it may be noted for this table that there are few adverse events related to the skin.

Conclusions (Which may be conveyed to the Sponsor):

1. A total of seven randomized, multicenter studies were provided to support the claim of efficacy of Tazarotene Gel (Zorac™), at concentrations of 0.05% and 0.1% for the treatment of moderate stable plaque type psoriasis and general acne vulgaris. Of the five studies for stable plaque type psoriasis, two were double-blind vehicle-controlled and three were investigator masked active controlled studies. The two studies provided to support the claim of efficacy in the treatment of acne vulgaris were both double-blinded and vehicle-controlled.
2. One of the acne studies, R168-220-8606, used a different formulation of tazarotene for both the 0.1% and 0.05% concentrations, as well as for the vehicle (see table 2.). Further, it appears that the formulation used for the tazarotene 0.05% concentration in the R168-120-8606 psoriasis study was apparently slightly different from that used in the remaining five studies. The sponsor has said (personal communication) that the differences are inconsequential, but for purposes of good science it would have been preferable to use the same formulation in each study (and, of course, that to be the formulation proposed for marketing!).
3. It seems that the Sponsor would like to have both formulations of Tazarotene gel approved for the treatment of stable plaque psoriasis. This is supposed to be supported by the two vehicle-controlled trials. In addition, it seems that the Sponsor wished to make the claim that the therapeutic effect of Tazarotene is maintained in a 12-week posttreatment period to some degree more than alternative treatments. The three comparative studies with active controls were at least partly designed to address this issue.
4. The two vehicle controlled-studies for psoriasis had one major difference between them: a 12 week posttreatment period, which was only present in the R168-120-8606 study. By the twelfth week of treatment in the R168-120-8606 study, tazarotene 0.1% displayed a statistically significant reduction of erythema, scaling, plaque elevation, and total score at the target lesions (From table 6, $p \leq 0.001$ for all four responses.) Similarly by the twelfth week in the R168-121-8606 study, tazarotene 0.1% displayed a statistically significant reduction of erythema, scaling, plaque elevation, and total score at the target lesions (From table 12, $p \leq 0.002$ for all four responses.) Otherwise, these two studies gave almost identical findings. The mean global scores were higher in the second study because the grading added one level (no change and worsened split to 2 scores) to the scale so that the mean scores appeared to be 1 point higher approximately. Results are similar for tazarotene 0.05%, i.e., for all four measures in both studies, by the 12th week, all four comparisons were statistically significant (From table 6, $p \leq 0.004$ for all four responses, and from table 12, $p \leq 0.012$ for all four responses.) For scaling, plaque elevation, and total score, both Tazarotene gels were statistically significantly better than vehicle from week one or two. However,

it took 8-12 weeks for them to be statistically significantly better than vehicle for erythema.

5. For the physicians' global evaluation of response to treatment, both dosages were statistically significantly better than vehicle in both studies (from table 7 and 13, $p \leq 0.001$). The differences in means between the two studies are due to the fact the global evaluation is scaled from 0-5 in the R168-120-8606 study, and from 0-6 in the R168-121-8606 study. There appear to be no statistically significant differences between the two gels in efficacy parameters except for scaling at week-8 (knee/elbow; 0.1% gel superior; R168-121-8606) and erythema at week-2 (trunk/arm/leg, 0.05% gel superior; R168-121-8606). These differences are presumably artifacts of the experiment. Thus, it is this reviewer's opinion that the sponsor has demonstrated efficacy in the treatment of stable plaque psoriasis.

6. The 3 active controlled-studies had very similar protocols that included a 12-week treatment and a 12-week posttreatment period. From table 17, for study R168-125-8606, there is some statistically significant evidence that at least for some lesions (particularly knees/elbows) and for some time points (particularly week 16), both tazarotene gels are superior during the 12 week follow-up period to fluocinonide 0.05% cream. This is not confirmed in the other study using fluocinonide cream, R168-126-8606, nor in the study using calcipotriol 0.005% ointment (see tables 20 & 23).

7. There were two phase III studies for the treatment of facial acne which had almost identical protocols. The primary difference was that the global score in the R168-220-7997 study had is a 5 point scale, while in R168-221-8606 t "no change" and "worsened" are split into 2 scores, producing a 6-point scale.

8. The two studies gave similar trends in lesion reduction and global evaluation of response to treatment. For both noninflammatory lesions and inflammatory lesions, as well as total lesions, in both studies the differences in reduction of lesions between tazarotene 0.1% gel and vehicle were statistically significant (see table 26 and 30, for both studies, for all three responses all $p \leq .009$). Using the tazarotene 0.1% gel, from these tables we would estimate the overall reduction in inflammatory lesions after 12 weeks of treatment as 43-47%, and in noninflammatory lesions as 43-55%. With tazarotene 0.05% gel, the reduction in noninflammatory was statistically significant (from table 26, $p \leq 0.032$, and from table 30, $p \leq .001$). Differences in inflammatory lesions were not statistically significant (from table 26, $p \leq 0.082$, and from table 30, $p \leq .188$) Similarly, the reduction in total lesions was statistically significant (from table 26, $p \leq 0.017$, and from table 30, $p \leq .001$): After 12 weeks of treatment we would estimate the reduction in noninflammatory lesions as 38-45%, and 39-44% in total lesions. Further, both dosages were statistically significantly better than vehicle in terms of the 12th week physician's global evaluation of response to treatment (from table 27 and 31, for both dosages, at end of treatment at the 12th week, all $p \leq 0.010$).

Thus, both dosages have demonstrated efficacy relative to vehicle. However, tazarotene 0.1% gel is statistically significantly better than tazarotene 0.05% gel in reducing noninflammatory lesions, and almost for total lesions.

9. In the psoriasis trial at least 57% of the subjects reported treatment related adverse events in the tazarotene 0.1% group, versus 46% in the tazarotene 0.05% group, and 27% in the tazarotene vehicle group (table 34). The large number of similar events that the sponsor has labeled as being not related to treatment (table 35) suggests these are underestimates of treatment related adverse events. In the acne trial, 47% of the subjects reported treatment related adverse events in the tazarotene 0.1% group, versus 41% in the tazarotene 0.05% group, and 15% in the vehicle group (table 36). These were predominately desquamation, burning, dryness, erythema, pruritus, and other skin irritations.

10. Thus, it is this reviewer's opinion that the sponsor has demonstrated that both tazarotene 0.05% gel and tazarotene 0.1% gel are statistically significantly more effective than its vehicle for the treatment of stable plaque psoriasis and for acne vulgaris. The active control studies seem to have been designed to show that at least one dosage is tazarotene gel is longer acting than either fluocinonide 0.05% cream or calcipotriol 0.005% ointment for the treatment of stable plaque type psoriasis. However this claim is not confirmed.

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cc:
Archival NDA: 20-600
HFD-540/Division File
HFD-540/Dr. Wilkin
HFD-540/Dr. Ko
HFD-540/Mr. Cross
HFD-725/Dr. Harkins
HFD-725/Dr. Srinivasan
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This review has 40 pages, and 37 tables.
Chron.

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