8.1.3.4.3 Safety Comparison

8.1.3.4.3.1 Adverse Events See Appendix IV. Adverse events of skin and appendages are listed in the following Table:

	Tazarotene 0.1%	Tazarotene 0.05%	Lidex cream 0.05%
Total patients enrolled	116 (100%)	117 (100%)	115 (100%)
Patients with adverse events	97 (84%)/79 (68%)	95 (81%)/65 (56%)	65 (55%)/14 (12%)
Dermatologic adverse events	90 (78%)/79 (68%)	80 (68%)/65 (56%)	25 (22%)/13 (11%)
pruritus	40 (34%)/34 (29%)	24 (21%)/24 (21%)	4 (3%)/2 (2%)
erythema	35 (30%)/32 (28%)	26 (22%)/23 (20%)	1 /1
burning/stinging	33 (28%)/30 (26%)	27 (23%)/25 (21%)	10 (9%)/9 (8%)
psoriasis worsened	14 (12%)/2 (2%)	18 (15%)/7 (6%)	10 (9%)/1
desquamation	13 (11%) /11 (9%)	7 (6%)/7 (6%)	0
contact dermatitis, irritant	11 (9%)/9 (8%)	11 (9%)/9 (8%)	2 /1
skin pain	11 (9%) /8 (7%)	3 (3%)/3 (3%)	1
irritation	10 (9%)/8 (7%)	7 (6%)/6 (5%)	1 /1
rash/maculopapular & vesiculobullous rash	5 (4%)/5 (4%)	7 (6%)/5 (4%)	2 (2%)
sweat	4 (3%)/1	1	1
"skin disorder"	2 (2%)/1	0	0
"dermatitis"/"eczema"	1 /1	2 (2%)	0
dry skin	1	3 (3%)/3 (3%)	0
furunculosis	1	1	1
alopecia	1	0	1 /1
infestation	1	0	1
herpes simplex	1	0	0
nail disorder	1	0	0
urticaria	1	0	0
skin fissure	0	2 (2%)/2 (2%)	0
skin laceration	0	2 (2%)	0
skin focal edema	0	1	1
acne	0	1	0
sun-induced erythema/photodermatitis	0	2	0
skin hemorrhage	0	1 /1	0
seborrhea	0	1	0
skin tightness	0	1 /1	0
skin atrophy	0	0	1 /1
skin neoplasm	0	0	1

*Incidence of "Treatment-related" adverse events is listed after a slash (/) from the total incidence.

Termination of study due to adverse events were as follows:

Treatment period	Tazarotene 0.1%	Tazarotene 0.05%	Lidex
Total patients terminated for AE	21 (18%)	14 (12%)	2 (2%)
pruritus	8 (7%)	4 (3%)	0
burning/stinging	7 (6%)	3 (7%)	0
erythema	6 (5%)	0	0
psoriasis worsened	4 (3%)	3 (3%)	1
skin pain	3 (3%)	1	0
desquamation	3 (3%)	1	0
sweat	2 (2%)	0	0
contact dermatitis, irritant	1	2 (2%)	0
skin inflammation	1	2 (2%)	0
hypercholesterolemia	1	0	0
liver function abnormality*	1	0	0
infection/chills	1	0	0
myocardial infarction	1	0	0
irritation	1	0	0
nervousness/ineffective treatment	1	0	0
rash	0	2 (2%)	0

dry skin	0	1	0
photodermatitis	0	1	0
chest pain	0	1	0
Ca colon	0	0	1

Posttreatment period - 10 subjects were terminated for adverse events:
Tazarotene 0.5% gel: psoriasis worsened 5, irritation 1, rash 1.
Lidex: psoriasis worsened 3.

*Patient who had high alcohol intake and was on methadone and Xanax, had elevation of liver enzymes during the study and was terminated as having an adverse event:

	Baseline (2/9/94)	4/11/94	6/1/94
SGPT	78	202	117
SGOT	52	94	93
GGT	47	66	39

There were no pregnancies reported during this study. One patient died of myocardial infarction (Patient , tazarotene 0.1%, 45, Indian male).

8.1.3.4.3.2 Laboratory Studies

A. CBC, chemistry and urinalysis - no consistent, significant abnormalities.
B. Therapeutic drug monitoring -see Section 10.

8.1.3.5 Conclusions

Tazarotene gels qd were inferior to Lidex 0.05% cream bid during the actual treatment period for stable plaque psoriasis. However, in the posttreatment period, tazarotene gels performed better than Lidex cream for knee/elbow target lesions at week-16 (see Table below). Tazarotene 0.1% gel was also better than the 0.05% gel in some efficacy variables during the treatment treatment period and in the posttreatment period (see Table below). Their safety profiles were similar. The commonest adverse events were pruritus, burning/stinging, irritation, erythema and psoriasis worsened. However, this trial had problems in design (not double dummy trial and possibly unintentional unblinding due to corticosteroid effect) and caution must be exercised in interpreting the data.

Table 8.1.3.5 Summary of Findings in R168-125-8606

	SUPERIORITY OF		
	Taz* 0.1% vs Lidex	Taz* 0.05% vs Lidex	Taz 0.1% vs Taz 0.05%
1° Variables at Treatment Endpoint			
↓ plaque elevation	-/-	-/-	-/-
↓ scaling	-/-	[illegible]/-	-/-
↓ erythema	[illegible]	[illegible]	-/-
↓ sum of scores	[illegible]/-	[illegible]/-	-/-
Global (treatment success)	-	[illegible]	-
Onset of Action*			
week-1	[illegible] -	[illegible] -	PST/P. -
week-2	[illegible] -	[illegible]	ST/-. -
week-4	[illegible]	[illegible]	-/-. -
week-8	[illegible] -	[illegible]	-/-. -
Duration of Effect*			
week-16	-/PSET. -	-/PSET. -	PSET/-. -
week-20	-/E. -	-/-. -	ET/-. -
week-24	E/E. G	-/-. -	ET/E. -
Safety			
All/ "treatment-related" AE* rates (%)	84/68 vs 55/12	81/56 vs 55/12	84/68 vs 81/56

T=tazarotene, AE=adverse event, P=↓ plaque elevation, S=↓ scaling, E=↓ erythema, T=↓ total of scores, G=global treatment success.
Letters given under "Onset of Action" and "Duration of Effect" are for variables with an among group comparison showing $p<0.05$.
Parameters are given for Trunk/arm /leg lesionsbefore the slash (/) and for knee/elbow lesions after the slash.
Global "treatment success" is given after the target lesion parameters after a period (.) when applicable. -=Not significant ($p>0.05$).
Significant inferiority is represented by highlighting in shaded areas.

8.1.4 Trial #4. Study#R168-126-8606: Safety, Efficacy and Duration of Therapeutic Effect of Tazarotene (AGN 190168) 0.1% or 0.05% Gel applied Once Daily versus Lidex® 0.05% Cream applied Twice daily in Stable Plaque Psoriasis.

8.1.4.1 Objective/Rationale Same as in Study#R168-125-8606

8.1.4.2 Design Same as in Study#R168-125-8606

8.1.4.3 Protocol Same as in Study#R168-125-8606

8.1.4.4 Results

8.1.4.4.1 Patient Disposition, Comparability

Three hundred and thirty-one patients were enrolled into the study among 9 Investigators. The Investigators and enrollment are as follows:

Investigator	Center no.	Total	Tazarotene 0.1%	Tazarotene 0.05%	Lidex cream 0.05%
Cole	1424	20	6	7	7
Greenspan	1425	36	12	12	12
Kantor	2184	36	12	12	12
Krusinski	2181	48	16	16	16
Maloney	1566	48	16	16	16
Medansky	1381	36	12	12	12
Miller	1421	36	12	12	12
Moore	2179	36	12	12	12
Weinstein	0188	35	12	12	11
		331	110	111	110

Comment

1. The following drug-by-investigator interactions were found:
   Knee/elbow lesions: plaque elevation at wk-4 & -8; scaling at wk-1 & -2; sum of scores for erythema, scaling and plaque elevation at wk-1 and -4.
   However, these interactions were sporadic and did not materially alter the outcome of or conclusions derived from the data.
2. Dr. Cole's data were combined with Dr. Weinstein's because of low numbers and because of geographical proximity (Southern California).

Completion Status

	Tazarotene 0.1%	Tazarotene 0.05%	Lidex cream 0.05%
Treatment period			
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.

Unevaluability was primarily due to lack of evaluable postbaseline visit (5 subjects) except for the following patients:

(Lidex). Entry criteria violation (target lesion <2 cm).
(tazarotene 0.1%). Discontinued at week-10 for noncompliance.
(tazarotene 0.05%). Discontinued at week-3 for noncompliance.
(Lidex). Discontinued at week-13 for noncompliance.

Three patients achieved complete clearing (global) before the end of the treatment period. Both were in the Lidex group. Duration of drug exposure was:

	Tazarotene 0.1%	Tazarotene 0.05%	Lidex
Enrolled	110	111	110
Exposed for ≥8weeks	81	87	101
Completed treatment	74	74	95
Exposed for ≥12 weeks	68	71	90
Exposed for ≥14 weeks	4	5	7

Comments

1. The small number of unevaluables (2-4 per arm) would not be expected to affect the analyses substantially.
2. Pertinent comments in Study R168-125-8606 on patient participation in the posttreatment period also apply here.

Comparability of Treatment Groups

		Tazarotene 0.1%	Tazarotene 0.05%	Lidex cream 0.05%
Total patient no		**107**	**107**	**108**
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

Comment The 3 arms were comparable at baseline.

8.1.4.4.2 Efficacy Parameters

8.1.4.4.2.1 Main Variables

Table 8.1.4.4.2.1 Primary Efficacy Variables in R168-126-8606

Clinical Signs		Baseline wk-0	Reduction in Scores wk-1	wk-2	wk-4	wk-8	wk-12	wk-16	wk-20	wk-24
		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%	2.5	0.6	1.0	***1.2****	[illegible]	1.6	1.4	1.1	1.0
	Taz 0.05%	2.4	0.5	0.9	***1.1***	[illegible]	***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	[illegible]	0.9	***1.1***	[illegible]	[illegible]	1.2	1.1	1.0
	Taz 0.05%	2.4	[illegible]	***0.8***	***0.9***	[illegible]	[illegible]	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***	[illegible]	3.5	3.1	2.6	2.5
	Taz 0.05%	7.3	***0.9***	***1.9***	***2.3***	[illegible]	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 Evaulations	wk-1	wk-2	wk-4	wk-8	wk-12	wk-16	wk-20	wk-24
I. Global "Treatment Success"(% pts)								
Taz 0.1%	***4***	***18***	***28***	[illegible]	***45***	41	29	22
Taz 0.05%	***4***	***13***	***18***	[illegible]	***38***	40	35	31
Lidex	13	33	51	60	61	47	30	25
II. Overall Global (mean)								
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 ($p<0.05$). [illegible] 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.

8.1.4.4.2.2 Other efficacy measures

Patient comparison with past therapy and cosmetic acceptability were not reported. Reduction in Psoriasis Disability Index (PDI) and Dermatology Life Quality Score (DQLS), percent body surface involved, overall clinical severity, pain and pruritus are given below:

Table 8.1.4.4.2.2 Other Efficacy Variables in R168-125-8606

	Baseline	Reduction in Scores or Percentage							
	wk-0	wk-1	wk-2	wk-4	wk-8	wk-12	wk-16	wk-20	wk-24
PDI									
Taz 0.1%	27.9	Only values for end of				*-0.4*			0.2
Taz 0.05%	27.4	treatment and posttreatment				*-0.6*			1.2
Lidex	28.7	periods were given				4.7			2.7
DQLS									
Taz 0.1%	20.3	Only values for end of				*-2.8*			0.4
Taz 0.05%	22.0	treatment and posttreatment				*-1.2*			1.7
Lidex	21.5	periods were given				8.1			4.0
Overall Clinical Severity									
Taz 0.1%	2.5	*0.3*	*0.6*	*0.7*	*1.0*	*1.1*	0.8	0.6	0.6
Taz 0.05%	2.5	*0.2*	*0.5*	*0.6*	*0.6*	*0.8*	0.9	0.8	0.6
Lidex	2.6	0.5	0.8	1.1	1.2	1.3	1.0	0.7	0.6
Percent Body Surface Area involved									
Taz 0.1%	6.5	0	0.1	*0.2*	*0.5*	*1.6*	1.2	1.0	0.7
Taz 0.05%	6.0	0	*0.2*	*0.2*	*0.4*	*0.2*	*0.5*	0.8	0.8
Lidex	6.7	0.1	0.4	1.1	2.6	1.9	1.7	1.1	1.1
Pain									
Taz 0.1%	0.7	*0*	*0*	*0*	0.3	0.3	0.3	0.1	0.2
Taz 0.05%	0.7	*0.1*	*0.1*	*0.2*	*0.1*	0.3	0.5	0.4	0.5
Lidex	0.8	0.5	0.5	0.6	0.6	0.5	0.4	0.4	0.3
Pruritus									
Taz 0.1%	1.8	*0.3*	*0.2*	*0*	*0.3*	*0.5*	0.7	0.5	0.6
Taz 0.05%	1.9	*0.3*	*0.2*	*0.2*	*0.2*	*0.4*	0.7	0.5	0.5
Lidex	1.9	0.7	1.1	1.3	1.2	1.3	0.7	0.7	0.6

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.

8.1.4.4.2.3 Duration of Therapeutic Effect in Posttreatment Period

The changes in efficacy variables have been shown in 8.1.4.4.2.1 and 8.1.4.4.2.2. In view of the unbalanced baseline conditions of the treatment groups, two additional analyses were made, by using patients who had "treatment success" or having "overall clinical severity" of <2 at the end of the treatment period:

A. "Treatment success" in subjects having end-of-treatment "treatment success"

	Tazarotene 0.1%				Tazarotene 0.05%				Lidex 0.05%			
	wk-12	wk-16	wk-20	wk-24	wk-12	wk-16	wk-20	wk-24	wk-12	wk-16	wk-20	wk-24
Trunk/arm/leg	N=45	N=39	N=39	N=38	N=30	N=25	N=26	N=27	N=75	N=68	N=64	N=68
% "success"	*100*	*79*	*54*	*45*	*100*	*84*	*62*	*59*	*100*	*71*	*52*	*41*
Knee/elbow	N=37	N=32	N=32	N=32	N=30	N=26	N=27	N=27	N=58	N=53	N=50	N=52
% "success"	*100*	*66*	*53*	*44*	*100*	*77*	*63*	*48*	*100*	*70*	*50*	*38*
Overall	N=30	N=28	N=26	N=26	N=29	N=24	N=24	N=25	N=60	N=55	N=52	N=54
% "success"	*100*	*79*	*50*	*38*	*100*	*75*	*58*	*52*	*100*	*71*	*42*	*35*

None of the success rates showed statistical significance between treatment groups.

Table 8.1.4.5 Summary of Findings in R168-126-8606

	SUPERIORITY OF		
	Taz* 0.1% vs Lidex	Taz* 0.05% vs Lidex	Taz 0.1% vs Taz 0.05%
1° Variables at Treatment Endpoint			
↓ plaque elevation	-/-	[redacted]/-	-/-
↓ scaling	-/-	[redacted]/-	0.006/-
↓ erythema	[redacted]/-	[redacted]	—/-
↓ sum of scores	[redacted]/-	[redacted]/-	-/-
Global (treatment success)	-	-	-
Onset of Action*			
week-1	[redacted]	[redacted]	S/-. -
week-2	[redacted]	[redacted]	-/-. -
week-4	[redacted]	[redacted]	-/-. -
week-8	[redacted]	[redacted]	PS/T. -
Duration of Effect*			
week-16	-/-. -	-/-. -	-/-. -
week-20	-/-. -	-/-. -	-/-. -
week-24	-/-. -	-/-. -	-/-. -
Safety			
All "treatment-related" AE* rates (%)	71/61 vs 49/12	71/54 vs 49/12	71/61 vs 71/54

*Taz=tazarotene, AE=adverse event, P=↓ plaque elevation, S=↓ scaling, E=↓ erythema, T=↓ total of scores, G=global treatment success, -=not significant (p>0.05).
Letters given under "Onset of Action" and "Duration of Effect" are for variables with an among group comparison showing p<0.05.
Parameters are given for Trunk/arm /leg lesionsbefore the slash (/) and for knee/elbow lesions after the slash.
Global "treatment success" is given after the target lesion parameters after a period (.) when applicable.
[redacted]

8.1.5 Trial #5. 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.

8.1.5.1 Objective/Rationale

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.

8.1.5.2 Design Similar to that of Study#R168-125-8606

8.1.5.3 Protocol Similar to that of Study#R168-120-8606 with the following differences:

	R168-120-8606	E168-145-8606
Location of study	U.S.	U.K. and Germany
Lower age limit	12	age of legal consent
Target lesions	trunk/limbs + knee/elbow	No site-specific requirement
Normal menstrual cycle prior to entry	needed	only needed negative pregnancy test
Washout period for topical drugs	2 weeks	1 week
Emollients	as needed	not allowed for ≥1 hr after application
Tar shampoos for scalp	not allowed	allowed
Low potency topical corticosteroid	not allowed	allowed for face/flexural/genital psoriasis
Global	5 grades	6 grades (split no change/worsened)
Visits	has wk-2 visit	no wk-2 visit; additional lab test at wk-24
"Need for treatment" overall severity	score of ≥2	score of >2

8.1.5.4 Results

8.1.5.4.1 Patient Disposition, Comparability

Three hundred and sixty-nine patients were enrolled into the study among 9 Investigators. The Investigators and enrollment are as follows:

Investigator	Center no.	Total	Tazarotene 0.1%	Tazarotene 0.05%	Dovonex
Ashton	2241	34	11	11	12
Camp	2242	13	4	4	5
Cunliffe	2154	16	6	5	5
Friedmann	2243	35	12	12	11
Griffiths	2248	5	2	2	1
Kennedy	2250	3	1	1	1
Kingston	2251	8	4	2	2
Leigh	2244	29	10	10	9
Marks	1968	30	10	10	10
Rees	2245	28	9	10	9
Sim-Davis	2246	48	13	15	20
White	2247	50	17	16	17
Altmeyer	2240	61	22	20	19
Happle	2249	4	1	2	1
Luger	2252	5	1	2	2
		369	123	122	124

Comment

1. All of Dr. White's (50 patients) and almost half (14 patients) of Professor Marks' patients were rendered unevaluable on the basis of "Good Clinical Research Practice" violation. The nature of the violations has not been presented.
2. The German centers were combined as one for analysis because of low numbers in two of them.
3. Regarding the primary variables, there were treatment by center interactions for reduction of scores for scaling and erythema. The U.K. and German centers had the following differences in the analyses: erythema (U.K.: significant differences between Dovonex and the 0.05% gel at weeks-4, 8 and 12, and between the 2 gels at week-8; German: no difference) and scaling (U.K.: significant differences between Dovonex and either gel at weeks-1, 4, 8 and 12 and between the 2 gels at week-4; German: significant differences between Dovonex and the 0.05% gel at week-1 and between the 2 gels at week-0 and -1). It is to be noted that the sizes of the U.K. and German "centers" were disproportionate (U. K. 299 and German 70) which may have affected the significance levels reached in analyses by center. The drug-"center" interactions were sporadic (as occurring in the analyses for pain, pruritus and

overall lesional severity) but did not appear to materially affect the outcome and conclusions of analyses.

Completion Status

	Tazarotene 0.1%	Tazarotene 0.05%	Dovonex 0.005%
Treatment Period			
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 (16)	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.

Patients classified as unevaluable were due to the following reasons:

	Tazarotene 0.1%	Tazarotene 0.05%	Dovonex 0.005%
Treatment Period			
Good clinical research practice violation	27	26	33
Dr. White	17	16	17
Prof Marks	4	4	6
other investigators	6	6*	10*
Entry violation	1	0	1
Did not use medication	0	0	2
Suspected steroid user	0	1	0
Total	28	27	36
Posttreatment Period	All unevaluables were due to "good clinical research practice violation".		

*One case of each under "other investigators" was in Germany. The remainder were all in the U. K.

Thirteen patients achieved complete clearing (global) before the end of the treatment period (tazarotene 0.1%=2, tazarotene 0.05%=4, Dovonex=7). Duration of drug exposure was:

	Tazarotene 0.1%	Tazarotene 0.05%	Dovonex
Enrolled	123	122	124
Exposed for up to 8 weeks	88 (72%)	91 (75%)	106 (85%)
Exposed for up to 12 weeks	79 (64%)	67 (55%)	96 (77%)
Completed treatment	70 (57%)	63 (52%)	92 (74%)

Comments

1. The large number of unevaluables after randomization is undesirable. It is unclear as to how this might have affected outcome of the data analysis, as the majority of these unevaluables came from 2 centers (both in the U. K.).
2. There was a greater proportion of patients in the Dovonex arm who completed treatment. The dropout rates for lack of efficacy and for adverse events were both higher in the tazarotene groups than in the Dovonex group.
3. Pertinent comments in Study R168-125-8606 on patient participation in the

posttreatment period also apply here.
4. The Applicant has included an intent-to-treat analysis (ITT) in addition to the preferred analysis. The ITT analysis was defined in the same way as in study R168-120-8606. However, in practice it had excluded almost just as many patients as in the preferred analysis (only 7 more patients included). This is misleading use of terms and unacceptable. This review is based on the preferred analysis unless specified. This "ITT" analysis is not expected to differ substantially from the preferred analysis in view of the small difference in patient numbers.

Comparability of Treatment Groups

	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

Comment The 3 arms were comparable at baseline.

8.1.5.4.2 Efficacy Parameters

8.1.5.4.2.1 Main Variables

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.

Table 8.1.5.4.2.1 Main Variables in R168-145-8606

I. Clinical Signs	Baseline wk-0	Reduction in Scores wk-1	wk-4	wk-8	wk-12	wk-16	wk-20	wk-24
Plaque elevation								
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								
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								
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								
Taz 0.1%	7.3	*1.5*	*2.4*	*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

II. Overall Assessment	wk-1	wk-4	wk-8	wk-12	wk-16	wk-20	wk-24
Global "Treatment Success"(% pts)							
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	3

Overall Global* (pt nos)

Treatment Period	wk-1 5	4	3	2	1	0/-1	(n)	wk-4 5	4	3	2	1	0/-1	(n)	wk-8 5	4	3	2	1	0/-1	(n)	wk-12 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)

Posttreatment Period	wk-16 5	4	3	2	1	0/-1	(n)	wk-20 5	4	3	2	1	0/-1	(n)	wk-24 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 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 ($p\leq 0.05$).

**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 (Ashton & Sim-Davis) were excluded for analysis because of "inconsistent choice of baseline".

8.1.5.4.2.2 Other efficacy measures

Patient comparison with past therapy and cosmetic acceptability were not reported. Reduction in percent body surface involved, overall clinical severity, pain and pruritus are given below. Psoriasis Disability Index (PDI) and Dermatology Life Quality Score (DQLS) showed no statistically significant differences between treatment groups in the treatment period or the posttreatment period.

Table 8.1.5.4.2.2 Other Efficacy Variables in R168-145-8606

	Baseline	Reduction in Scores or Percentage						
	wk-0	wk-1	wk-4	wk-8	wk-12	wk-16	wk-20	wk-24
Overall Clinical Severity								
Taz 0.1%	2.4	0.3	0.6	0.8	0.8	0.9	0.9	0.6
Taz 0.05%	2.3	0.2	0.3	0.5	0.6	0.8	0.7	0.5
Dovonex	2.2	0.4	0.7	0.9	1.1	0.8	0.7	0.7
Percent Body Surface Area involved								
Taz 0.1%	8.5	-0.3	0.1	0.4	0.6	1.4	1.7	1.4
Taz 0.05%	8.3	-0.1	-0.1	0	0.5	2.1	2.5	1.9
Dovonex	7.7	0.1	0.2	1.2	2.2	2.2	1.9	1.7
Pain								
Taz 0.1%	0.4	-0.3	-0.4	-0.1	0.1	0	0.2	0.1
Taz 0.05%	0.4	0.1	0	0	0.1	0.1	0	-0.1
Dovonex	0.4	0.2	0.3	0.2	0.3	0.2	0.2	0.2
Pruritus								
Taz 0.1%	1.5	0.2	-0.2	0.2	0.4	0.7	0.5	0.6
Taz 0.05%	1.6	0.2	-0.2	-0.1	0.2	0.7	0.5	0.5
Dovonex	1.4	0.6	0.7	0.8	0.8	0.7	0.7	0.6

T/A/L=trunk/arm/leg lesions; K/E=knee/elbow lesions; Taz=tazarotene.

Comment The Applicant performed intragroup comparisons but not between-group comparisons with these parameters. Thus, any significance between the treatment arms for these variables cannot be ascertained. However, the data above does not suggest that any better maintenance of therapeutic effect than that given by Dovonex.

8.1.5.4.2.3 Duration of Therapeutic Effect in Posttreatment Period

The changes in efficacy variables have been shown in 8.1.5.4.2.1 and 8.1.5.4.2.2. No attempt at subset analysis based on equivalent "treatment success" at the beginning of posttreatment period was presented.

A. "Treatment failure" in subjects having end-of-treatment "overall clinical severity" of <2

	Tazarotene 0.1%			Tazarotene 0.05%			Dovonex		
	Failure*	Censured	Total	Failure	Censured	Total	Failure	Censured	Total
	32 (61%)	20 (39%)	52	23 (51%)	22 (49%)	45	41 (65%)	22 (35%)	70
Median time to retreatment		week-20			week-22**			week-19	

*Failure defined as overall clinical severity (OCS) reaching ≥2 in posttreatment period or termination by investigator for another treatment.
**Underlined figures show superiority of tazarotene over Dovonex ($p<0.05$).

B. Exit from study due to "need for treatment" in posttreatment period

Timepoint	Tazarotene 0.1% N=70	Tazarotene 0.05% N=63	Dovonex N=92
Exit at wk-16 (wk-12 to 16)	20 (29%)	19 (30%)	35 (38%)
at wk-20 (wk-16 to 20)	9 (13%)	8 (13%)	14 (15%)
at wk-24 (wk-20 to 24)	1 (1%)	2 (3%)	2 (2%)
Total	30 (43%)	29 (46%)	38 (55%)

Comment The "need for treatment" rate was slightly higher in the Dovonex group and median time to retreatment slightly shorter. Interpretation of such data is

desquamation	12 (1%)	13 (2%)	0	0	0
	13 (1%)	8	1	0	0
kin	6	7	0	0	0
focal edema	7	2	0	0	0
"skin inflammation"	3	4	0	0	2
"dermatitis"	0	1	1	0	0
contact dermatitis, irritant	6	3	1	0	0
sweat	2	0	0	0	0
rash, vesiculobullous	1	3	1	0	0
skin fissure	1	2	0	0	0
rash, maculopapular	1	2	0	0	0
skin tightness	1	1	0	0	0
acne	1	0	0	0	0
skin discharge	1	0	0	0	0
skin laceration	1	0	0	0	0
skin excoriation	1	0	0	0	0
alopecia	1	0	0	0	0
urticaria	1	0	0	0	0
"skin disorder"	1	0	0	0	0
contact dermatitis, allergic	1	0	0	0	0
acne worsened	0	2	2	0	0
skin hemorrhage	0	2	0	0	0
photodermatitis	0	1	0	0	0
skin atrophy	0	0	0	1	0
skin erosion	0	1	0	0	0
folliculitis	0	1	0	0	0
SPECIAL SENSES	**0**	**3 (<1%)**	**0**	**0**	**0**
"vision abnormality"	0	2	0	0	0
amaurosis fugax	0	1	0	0	0
GENITAL	**1 (<1%)**	**0**	**0**	**0**	**0**
e carcinoma	1	0	0	0	0

*Percentages of individual adverse events are only given for those occurring with a rate of 1% or more.

subject to the same pitfalls as discussed in Studies R168-125-8606 and R168-126-8606. Statistical significance for "exit due to need for treatment" has not been analyzed by the Applicant.

8.1.5.4.3 Safety Comparison

8.1.5.4.3.1 Adverse Events See Appendix VI. Adverse events of skin and appendages are listed in the following Table:

	Tazarotene 0.1%	Tazarotene 0.05%	Dovonex 0.005%
Total patients enrolled	122 (100%)	122 (100%)	122 (100%)
Patients with adverse events	69 (57%)/57 (47%)	64 (53%)/49 (40%)	30 (25%)/12 (10%)
Dermatologic adverse events	53 (43%)/53 (43%)	55 (45%)/49 (40%)	14 (12%)/11 (9%)
burning/stinging	17 (14%)/17 (14%)	14 (11%)/13 (11%)	1
erythema	16 (13%)/15 (12%)	13 (11%)/13 (11%)	4 (3%)/4 (3%)
irritation	15 (12%)/15 (12%)	13 (11%)/13 (11%)	1
pruritus	13 (11%)/13 (11%)	18 (15%)/17 (14%)	7 (6%)/7 (6%)
skin pain	12 (10%)/11 (9%)	5 (4%)/5 (4%)	1 /1
skin inflammation/"eczema"	4 (3%)/4 (3%)	5 (4%)/4 (3%)	2 (2%)/2 (2%)
rash/maculopapular/vesiculobullous rash	3(2%)/3(2%)	5 (4%)/4 (3%)	1
desquamation	3 (2%)/1	2 (2%)/2 (2%)	1 /1
skin focal edema	2 (2%)/2 (2%)	0	0
contact dermatitis, irritant	2 (2%)/1	0	0
psoriasis worsened	1 /1	4 (3%)/2 (2%)	0
sweat	1 /1	0	0
skin discharge	0	1 /1	1 /1
acne	0	1 /1	0
skin erosion	0	1 /1	0
skin fissure	0	1 /1	0
infection	0	1	0
herpes zoster	0	0	1

Incidence of "Treatment-related" adverse events is listed after a slash (/) from the total incidence.

Termination of study due to adverse events was as follows:

Treatment period	Tazarotene 0.1%	Tazarotene 0.05%	Dovonex
Total patients terminated for AE	24 (20%)	22 (18%)	5 (4%)
burning/stinging	11 (9%)	5 (4%)	1
irritation	7 (6%)	7 (6%)	0
erythema	5 (4%)	0	1
skin pain	5 (4%)	3 (2%)	0
pruritus	3 (2%)	6 (5%)	2 (2%)
rash	2 (2%)	3 (2%)	0
skin inflammation	2 (2%)	3 (2%)	2 (2%)
skin swelling	2 (2%)	0	0
insomnia	2 (2%)	0	0
desquamation	1	0	0
neurosis	1	0	0
skin fissure	0	2 (2%)	0
psoriasis worsened	0	2 (2%)	0
visual loss	0	1	0
depression	0	0	1

Posttreatment period - There were no terminations due to adverse events.

One woman given Dovonex became pregnant during the course of study. She was discontinued from study and had her pregnancy terminated. No deaths were reported in this study.

8.1.5.4.3.2 Laboratory Studies

A. CBC, chemistry and urinalysis - no consistent, significant abnormalities.

B. Therapeutic drug monitoring -see Section 10.

8.1.5.5 Conclusions

Tazarotene gels qd were not better than Dovonex 0.005% ointment bid during the treatment period for stable plaque psoriasis, and in the posttreatment period, tazarotene gels were no better than Dovonex ointment (see Table below). Tazarotene 0.1% gel was better than the 0.05% gel in some efficacy variables during treatment period (see Table below). Their safety profiles were similar. The commonest adverse events were pruritus, burning/stinging, irritation, erythema and psoriasis worsened. However, this study is plagued by postrandomization exclusions and problem in design (not double dummy masking). Conclusions derived from this study must be viewed with caution.

Table 8.1.5.5 Summary of Findings in R168-145-8606

	SUPERIORITY OF		
	Taz* 0.1% vs Dovonex	Taz* 0.05% vs Dovonex	Taz 0.1% vs Taz 0.05%
1° Variables in Treatment Period			
week-1	[redacted]	[redacted]	T. -
week-4	[redacted]	[redacted]	PT. -
week-8	[redacted]	[redacted]	PT. -
week-12 (Endpoint)	[redacted]	[redacted]	-. -
Duration of Effect*			
week-16	-/-. -	-/-. -	-/-. -
week-20	-/-. -	-/-. -	-/-. -
week-24	-/-. -	-/-. -	-/-. -
Safety			
All/ "treatment-related" AE* rates (%)	57/47 vs 25/10	53/40 vs 25/10	57/47 vs 53/40

*Taz=tazarotene, AE=adverse event, P=↓ plaque elevation, S=↓ scaling, E=↓ erythema, T=↓ total of scores, G=global treatment success, -=not significant (p>0.05).
Letters given under are for variables with an among group comparison showing p<0.05.
Global "treatment success" is given after the target lesion parameters after a period (.) when applicable.
Significant inferiority is represented by highlighting in shaded areas.

8.1.6 Trial #6. Study#R168-128-8606: Safety and Efficacy of Once-Daily Tazarotene (AGN 190168) 0.1% Gel and 0.05% Gel in the Long-Term (up to one year) Treatment of Stable Plaque Psoriasis.

8.1.6.1 Objective/Rationale

The objective was to evaluate the safety and efficacy of once-daily tazarotene 0.1% and 0.05% gels in the treatment of stable plaque psoriasis for up to a one year period.

The rationale of this study was based on tazarotene's efficacy in previous clinical trials. Since psoriasis is a chronic disease, it would be necessary to find out the long-term safety and efficacy of tazarotene when used in this condition.

Comment Although this study purported to studying safety and efficacy, it was uncontrolled and was basically a safety study for long-term use. However, some information might be obtained on the differences, if any, between the two tazarotene

gels.

8.1.6.2 Design

This study was a 12-month randomized, multicenter (12 centers), double-blind, parallel-group uncontrolled trial (see Table below).

Visit	Weeks/ month	History, Baseline Exam & Consent	Radiographs (at 9 centers)	Lab Screen	Pregnancy Test	Evaluate Sites	Tubes of Study Med to dispense
1	0	x	x	x	x	x	3
2	week-2				x	x	3
3	month-1				x	x	5
4	month-2				x	x	5
5	month-3			x	x	x	5
6	month-4				x	x	5
7	month-5				x	x	5
8	month-6			x	x	x	5
9	month-7				x	x	5
10	month-8				x	x	5
11	month-9			x	x	x	5
12	month-10				x	x	5
13	month-11				x	x	5
14	month-12		xx	x	x	x	

Pregnancy tests done if applicable.
Lab screen: CBC, chemistry panel and urinalysis, with additional blood for drug level and metabolites at 2 sites; if week-12 result outside normal range or unacceptable to investigator (CBC, chemistry or urinalysis), the test was repeated until normal or explained.
Radiographs: X-rays included cervical and thoracic spine and ankle, all from a right lateral view; xx=repeat radiograph in patients who completed at least 3 months of treatment.

8.1.6.3 Protocol

8.1.6.3.1 Population/Procedures

Patient Selection

The following selection criteria were used for this study:-

a) Inclusion:

Except for removing the requirement for target lesions in the subjects, the criteria were identical to those in R168-120-8606 (Section 8.1.1.3).

b) Exclusion:

Identical to those in R168-120-8606 (Section 8.1.1.3).

Concomitant Medications Identical to those in R168-120-8606 (Section 8.1.1.3).

Application of Study Medication, Visits and Evaluations

Each subject was assigned to tazarotene 0.1% or 0.05% with equal randomization to each treatment group in each center. Subjects applied their treatment daily (every evening) to all psoriatic plaques for up to 12 months. Subjects were to bathe/shower in the morning and refrain from using tar shampoos but non-medicated shampoos were allowed as often as needed. Emollient (Eucerin Lotion® or others) was allowed as needed, but only 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 shown in the Section on Design (8.1.6.2). Should a patient's overall lesional severity score become 0, treatment was to be stopped. Treatment would be resumed when this score reached 1 or higher AND if body area involved was 1% or more.

The following parameters were to be evaluated:

A) Efficacy Same as those in R168-120-8606 (Section 8.1.1.3), **EXCEPT THAT** scores for the clinical signs were for the overall condition rather than for target lesions.

B) Pharmacokinetics

At 2 sites (Bushong and Erianne), blood was taken at baseline and months-3, 6, 9 and 12 for plasma levels of (a) tazarotene and (b) its primary metabolite (AGN 190299). This was subsequently extended to all patients in the study.

C) Safety Same as those in R168-120-8606 (Section 8.1.1.3), but the laboratory specimen samples were to be taken at month-0, 3, 6, 9 and 12. In addition, X-rays of cervical and thoracic spine and right ankle were included at baseline and the final visit (in patients who completed at least 3 months of the study). The following variables were compared between baseline and final visit by a radiologist who was blinded for the dates of the X-rays:

1. spine - osteophyte formation, ossification of anterior longitudinal ligament and other ligaments, fractures and osteoporosis;
2. ankle - ligamentous ossification and fractures.

8.1.6.3.2 Subject Dispositions and Endpoints

Categories for patient disposition were the same as those in R168-120-8606 (Section 8.1.1.3), except that there was no "needed treatment" category, as this protocol does not contain a comparable "posttreatment phase" .

Endpoint of this study was visit-14, at the end of the 12-month study period. The endpoint parameters were the same as those in R168-120-8606 (Section 8.1.1.3), except that there was no requirement for target lesion selection.

8.1.6.3.3 Statistical Considerations

Similar to those in R168-120-8606 (Section 8.1.1.3). The Applicant does not consider this a pivotal study and analyses by demographics was not performed (p. 2.18-039). Because of the variable treatment periods, the by-time analysis of efficacy data was done by last observation carried forward or using subgroups having similar lengths of treatment. For safety data, analysis was done on subgroups based on length of treatment. Sites with <10 patients per arm were pooled based on geographic location (east coast, west coast, etc).

8.1.6.4 Results

8.1.6.4.1 Patient Disposition, Comparability

Two hundred and forty-three patients were enrolled into the study among 12 sites. The Investigators and enrollment are as follows:

Investigator	Center no.	Total	Tazarotene 0.1%	Tazarotene 0.05%
Berberian	2136	20	10	10
Bushong	2132	20	10	10
Dickens	2139	13	7	6
Eaglstein	0527	18	9	9

Erianne	2135	32	16	16
Goffe	2141	20	10	10
Gross	2133	20	10	10
Kraus	2138	20	10	10
Menter	2137	20	10	10
Olsen	2140	20	10	10
Powers	2182	20	10	10
Prystowsky	2134	20	10	10
		243	122	121

Comment The patients in Dr. Dickens and Dr. Eaglstein's sites were combined as one center due to the small numbers.

Completion Status:

	Tazarotene 0.1%	Tazarotene 0.05%
Enrolled	122 (9)*	121 (7)
Completed study	53	48
Not completed	69	73
lack of efficacy	14	20
adverse event	30 [redacted]	29 (2)
not meeting entry criteria	4 (4)	3 (3)
"other"**	21 (4)	21 (2)

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

Patient [redacted] was listed as an adverse event discontinuation; in fact it was a baseline lab result violation.

Unevaluability:

Apart from the 7 patients excluded on the basis of not meeting entry criteria (laboratory test abnormalities or concurrent medication), the other 9 under adverse events or "other" were excluded due to lack of evaluable postbaseline visit information. It is noted that 40 subjects took prohibited concomitant medications (mostly corticosteroids). Because of the length of the study, it was decided to leave them in ITT analysis, but exclude the visits falling within washout period for the prohibited medication (see exclusion criteria).

Comment

1. Only 16 of the patients were disqualified in the preferred analysis for efficacy and 10 of them already were excluded on the basis of entry violation or adverse events. Thus, the preferred analysis dataset would have included at least 40-(16-10)=34 subjects given prohibited medication.
2. With a high dropout rate (~60% in each group) in this study, caution must be exercised in interpreting efficacy data. Nevertheless, the different categories for discontinuation appear to be balanced.
3. This review is based on the preferred analysis.

Drug exposure The mean length of time patients were in the study (not drug exposure) was 32.4 weeks and 30.7 weeks for the tazarotene 0.1% and 0.05% groups respectively.

	Months of Exposure													
	≤½	½-1	>1-2	>2-3	>3-4	>4-5	>5-6	>6-7	>7-8	>8-9	>9-10	>10-11	>11-12	>12
Tazarotene 0.1%														
Pt. Nos.	4	18	6	6	7	3	8	8	1	7	3	1	42	6
	<-------28%------->				<-------72%------->									
								<-------57%------->						
													<---40%--->	
Tazarotene 0.05%														
Nos.	6	10	15	13	5	7	4	5	3	1	2	3	38	7
	<-------37%------->				<-------63%------->									
								<-------50%------->						
													<---38%--->	

Comparability of Treatment Groups

Total patient no		Tazarotene 0.1% 113	Tazarotene 0.05% 114
Age (Yrs)		49±13	48±15
Sex	M	68	73
	F	45	41
Race	White	105	103
	Hispanic	6	6
	Black	1	4
	Oriental	0	0
	"other"	1	1
% Body area with psoriasis		6±5	6±5
Duration of psoriasis (Yrs)		17±12	19±15

Comment The 2 arms were comparable at baseline.

8.1.6.4.2 Efficacy Parameters

This was an uncontrolled safety study with no target lesion selection. Thus, the efficacy scores for plaque elevation, scaling and erythema represented general impressions of the investigator and did not refer to any specific lesion.

Table 8.1.6.4.2a Changes in Clinical Parameters in R168-128-8606

		Mean Reduction in Scores					
	Baseline	month-½	month-1	month-3	month-6	month-9	month-12
Plaque elevation							
Taz* 0.1%	2.5	0.5	1.0	1.3	1.4	1.3	1.3
Taz 0.05%	2.6	0.5	0.8	1.2	1.2	1.2	1.1
Scaling							
Taz 0.1%	2.5	0.4	0.8	1.0	1.2	1.1	1.1
Taz 0.05%	2.4	0.4	0.6	0.9	1.0	1.0	0.9
Erythema							
Taz 0.1%	2.2	-0.1	0.2	0.5	0.8	0.6	0.8
Taz 0.05%	2.3	0.1	0.2	0.5	0.7	0.6	0.6
Total Scores							
Taz 0.1%	7.3	0.8	1.9	2.7	3.4	3.1	3.2
Taz 0.05%	7.3	0.9	1.6	2.6	3.0	2.7	2.6
Overall Clinical Severity							
Taz 0.1%	2.5	0.3	0.6	0.9	1.1	1.0	1.0
Taz 0.05%	2.5	0.3	0.5	0.8	0.9	0.8	0.8
Percent Body Area involved by Psoriasis							
Taz 0.1%	5.9	-0.2	0.1	0.1	0.9	1.2	1.2
Taz 0.05%	6.3	-0.1	-0.1	0.3	0.6	0.2	0.2

*Taz=tazarotene

Table 8.1.6.4.2b Global Evaluation in R168-128-8606

	Mean Scores					
	month-½	month-1	month-3	month-6	month-9	month-12
Mean Global Score						
Taz** 0.1%	1.0	[redacted]*	1.9	2.4	2.4	2.4
Taz 0.05%	0.9	[redacted]	1.8	2.1	2.0	1.9
Global Response						
Taz 0.1%						
good or better	7%	22%	41%	55%	49%	43%
excellent or better	0	5%	16%	31%	32%	35%
cleared	0	0	0	0	5%	2%
Taz 0.05%						
good or better	6%	13%	33%	43%	45%	42%
excellent or better	1%	3%	10%	23%	24%	22%
cleared	0	1	1	1	1%	1%

[redacted]

*Taz=tazarotene

Median time to Initial "treatment success" was week-21 for tazarotene 0.1% and week-20 for tazarotene 0.05% (p>0.05). There were no significant differences in reduction of the subjective symptoms of pain and pruritus or in the use of emollients among the two treatment groups (from 89-97% of patients in either arm used emollients during the study).

Comment

1. Only the mean global scores at the month-1 visit showed a significant difference between the 2 gels.
2. The beneficial effects of the tazarotene gels appear to plateau between month 3 and month 6 and remain at that level on chronic usage. Since 43-50% of patients have dropped out by 6 months for various reasons, it is not clear whether the remaining subjects might have represented a different subset.

8.1.6.4.3 Safety Comparison

8.1.6.4.3.1 Adverse Events

A. Adverse Event Profile See Appendix VII. Adverse events of skin and appendages are listed in the following Table:

	Tazarotene 0.1%	Tazarotene 0.05%
Total patients enrolled	122 (100%)	121 (100%)
Patients with adverse events	106 (87%)/91 (75%)	101 (84%)/86 (71%)
Dermatologic	101 (83%)/90 (74%)	93 (77%)/85 (70%)
pruritus	48 (39%)/44 (36%)	39 (32%)/38 (31%)
irritation	37 (30%)/25 (20%)	24 (20%)/24 (20%)
burning/stinging	32 (26%)/31 (25%)	29 (24%)/25 (21%)
erythema	32 (26%)/29 (24%)	23 (19%)/21 (17%)
psoriasis worsened	22 (18%)/9 (7%)	22 (18%)/12 (10%)
skin pain	22 (18%)/21 (17%)	12 (10%)/11 (9%)
rash/papules/vesiculobullous rash	16 (13%)/11 (9%)	11 (9%)/9 (7%)
desquamation	12 (10%)/12 (10%)	5 (4%)/5 (4%)
contact dermatitis, irritant	13 (11%)/13 (11%)	11 (9%)/10 (8%)
skin laceration/excoriation/erosion	6 (5%)/3 (2%)	5 (4%)/5 (4%)
contact dermatitis, allergic	6 (5%)/3 (2%)	0
"dermatitis"/skin inflammation/eczema	5 (4%)/3 (2%)	10 (8%)/5 (4%)
dry skin	4 (3%)/3 (2%)	13 (11%)/8 (7%)
skin focal edema	4 (3%)/4 (3%)	8 (7%)/8 (7%)

skin fissure	4 (3%)/4 (3%)	1/1
sun-induced erythema	3 (2%)/2 (2%)	3 (2%)/2 (2%)
skin hemorrhage	3 (2%)/3 (2%)	1/1
urticaria	3 (2%)	0
acne	2 (2%)	1
alopecia	2 (2%)	0
skin monilia	2 (2%)	0
skin neoplasm	2 (2%)	0
"skin disorder"	1/1	1/1
skin discharge	1/1	0
furunculosis	1/1	1
sweat	1/1	0
folliculitis	1	1/1
herpes simplex	1	1
nail disorder	1	1
seborrhea	1	1
chemical burns	1	0
skin discoloration	1	0
scar	1	0
"infection"	0	2 (2%)/1
fungal dermatitis	0	1
skin tightness	0	1

*Incidence of "Treatment-related" adverse events is listed after a slash (/) from the total incidence.

Termination of study due to adverse events was as follows:

	Tazarotene 0.1%	Tazarotene 0.05%
Total patients terminated for AE	30 (25%)	29 (24%)
psoriasis worsened	9 (7%)	9 (7%)
pruritus	7 (6%)	8 (7%)
burning/stinging	5 (4%)	6 (5%)
irritation	5 (4%)	5 (4%)
skin pain	3 (2%)	3 (2%)
skin swelling	3 (2%)	1
erythema	2 (2%)	4 (3%)
rash	2 (2%)	4 (3%)
contact dermatitis, irritant	1	0

In addition, there was one case of each in the 0.1% gel group with discontinuation due to: alopecia, skin excoriation, urticaria and "allergic contact dermatitis", and one case each in the 0.05% group for: skin erosion, dermatitis, folliculitis, arthritis, and carotid artery occlusion with amaurosis fugax.

No pregnancies or deaths were reported during the course of the study. Survival analysis showed the time to discontinuation due to adverse events in 25% of patients was ≤30 weeks for the 0.1% gel group and ≤31 weeks for the 0.05% gel group. This difference is not statistically significant.

Comment There were six cases of "allergic contact dermatitis" reported as adverse event. As the dermal safety studies showed a lack of sensitization potential, the presence of 6 cases in a 243-patient study is of interest. Three of them were deemed not related to treatment: Rhus dermatitis contact dermatitis "due to Eucerin" . None of the remaining cases truly had an allergic component proven for allergic contact dermatitis.

B. Adverse Event Incidence with Time

1. Analysis of Local Adverse Events at Different Visits

	Incidence of Adverse Event					
	month-½	month-1	month-3	month-6	month-9	month-12
All "Treatment -Related" Adverse Events						
Taz* 0.1%	60/111=54%	43/111=39%	34/96=35%	33/92=36%	29/77=38%	26/78=33%
Taz 0.05%	35/108=32%	39/111=35%	32/95=34%	33/84=39%	34/73=47%	31/76=41%
Pruritus						
Taz 0.1%	21/111=19%	18/107=17%	13/88=15%	11/78=14%	12/61=20%	11/63=17%
Taz 0.05%	10/106=9%	11/108=10%	8/81=10%	10/66=15%	9/54=17%	7/55=13%
Burning						
Taz 0.1%	19/111=17%	6/106=6%	17/84=8%	5/74=7%	5/57=9%	6/58=10%
Taz 0.05%	12/106=11%	5/108=5%	5/80=6%	6/65=9%	6/53=11%	5/54=9%
Erythema						
Taz 0.1%	22/111=20%	8/107=7%	6/83=7%	5/73=7%	6/53=11%	6/58=10%
Taz 0.05%	6/106=6%	12/109=11%	5/82=6%	7/65=11%	7/57=13%	5/54=9%
Irritation						
Taz 0.1%	10/112=9%	12/108=11%	8/84=10%	6/74=8%	6/53=11%	5/58=9%
Taz 0.05%	10/107=9%	11/109=10%	6/81=7%	5/65=8%	6/57=11%	7/54=13%

*Taz=tazarotene, highlighted boxes indicate a significant difference between 0.1% and 0.05% gels ($p<0.05$)

Comment The incidence of these local irritation adverse events appeared to be consistent throughout the study except for the fact that for the 0.1% gel, pruritus, burning, erythema and total patient numbers having such events were higher in the first half month of the study. The following are possible explanations: (1) patients got used to the study drug and subjectively became more accommodative; (2) those having more severe symptoms dropped out of the study [unlikely, see Drug Exposure Table in 8.1.6.4.1] and (3) chronic administration changed bioavailability to the epidermis and possibly modulated the inflammatory components, on which tazarotene was supposed to have an effect.

2. Adverse Event Analysis using a Cutoff at the End of Third Month

	Changes seen in the Period 3-12 months vs First 3 Months	
	Tazarotene 0.1%	Tazarotene 0.05%
Rate for All Adverse Events	Decreased (82%→71%)	Increased (75%→77%)
Rate for "Treatment -related" Adverse Events	Decreased (70%→45%)	Decreased (60%→50%)
Non-Dermatologic Events		
Notable Changes in Incidence		
Respiratory System	Rate ↑ (8%→21%)	Rate ↑ (8%→20%)
Respiratory infections	Rate ↑ (4%→8%)	Rate ↑ (4%→11%)
Musculoskeletal System		
Arthralgia	Rate ↑ (0.8%→6%)	Rate ↑ (2.5%→4%)
Myalgia	Rate ↑ (0.8%→4%)	Rate ↓ (0.8%→0)
Metabolic/endocrine	Rate ↑ (0→6%) peripheral edema & hypertriglyceridemia	Rate ↑ (0→11%) Diabetes mellitus/hyperglycemia, gout & SGPT↑
Dermatologic Adverse Events		
Notable Changes in Incidence (All/Treatment-related)		
Total	74%→57%/69%→44%	65%→56%/ 60%→46%
pruritus	31%→19%/29%→17%	24%→18%/ 23%→17%
erythema	24%→11%/21%→11%	18%→6%/ 17%→5%
burning/stinging	23%→12%/22%→12%	20%→13%/ 17%→11%
irritation	18%→11%/17%→9%	17%→5%/ 17%→5%
pain	14%→7%/13%→7%	8%→3%/ 7%→3%
psoriasis worsened	(↑) 10%→13%/5%→7% (↑)	(↑) 8%→17%/ 6%→6%
irritant contact dermatitis	9%→4%/9%→4%	7%→3%/ 7%→3%
desquamation	9%→2%/9%→2%	4%→0/ 4%→0
sun-induced erythema	(↑) 0→4%/0%→2% (↑)	(↑) 0.8%→2.5%/ 0.8%→1.3% (↑)

Comment

1. In general, after the first 3 months, there was decrease in the incidence of local adverse events of an irritative nature. Some possibilities have been discussed in the Comments of the last Section. It may also be due to the fact that the denominator for adverse event incidence was not adjusted for dropouts in the later months of the study (enrolled: 122 and 121, end of 3 months: 85 and 79, and end of 12 months: 54 and 53 for the 0.1% and 0.05% gels respectively).
2. There was a small increase in "psoriasis worsened". Sun-induced erythema which was rarely seen before the end of the first 3 months, more likely appeared after those initial months. Since in 7 Phase 3 studies (5 psoriasis trials and 2 acne trials) involving up to 12 weeks of drug treatment in each of them, the combined incidence of sun-induced erythema or related events, irrespective of relationship to treatment, was <0.5% for each formulation (1/867 for tazarotene 0.1% gel and 4/866 for tazarotene 0.05% gel), the increased incidence in this study between 3-12 months was especially intriguing. The long-term effects of clinical use involving photo-exposure remains to be clarified.

8.1.6.4.3.2 Laboratory Studies

A. CBC, chemistry and urinalysis - no consistent, significant abnormalities. An analysis was made on the changes in triglyceride and cholesterol levels on fasting patients. No significant changes over a 12-month period was found.

B. Therapeutic drug monitoring -see Section 10.

C. Radiographic findings in 86 subjects. The length of time between baseline and follow-up X-rays were:

	Mean	Median	Range
Tazarotene 0.1% (weeks)	46	52	
Tazarotene 0.05% (weeks)	45	52	

Table 8.1.6.4.3.2 Radiologic Fiindings in R168-128-8606

	Changes seen in the Period 3-12 months vs First 3 Months			
	Tazarotene 0.1%(n=45)		Tazarotene 0.05% (n=41)	
	BL>FU*	BL<FU	BL>FU	BL<FU
Ankles				
Ligamentous ossification	1/44=2%	2/44=5%	1/41=2%	2/41=5%
Fractures	1/44=2%	1/44=2%	0	0
Cervical Spine				
Osteophyte formation	1/44=2%	1/44=2%	1/38=3%	0
Ossification of Ant. Ligament	0	1/44=2%	0	0
Other ligamentous ossification	0	0	0	0
Fracture(s)	0	0	0	0
Osteoporosis	0	0	0	0
Thoracic Spine				
Osteophyte formation	1/45=2%	0	1/41=2%	2/41=5%
Ossification of Ant. Ligament	0	0	0	0
Other ligamentous ossification	0	0	0	0
Fracture(s)	0	0	0	0
Osteoporosis	0	0	0	0

*BL>FU=more in quantity or intensity at baseline than at follow-up, BL<FU=less in quantity or intensity at baseline than at follow-up.

Comment There was no mention of the radiologist or his qualifications. There were many unevaluable X-rays due to poor technique. There were also differences in rotation in taking the X-rays which made them difficult to interpret. The findings suggest that there were no significant changes over an average follow-up period of 11 months.

8.1.6.5 Conclusions

1. General

This study for long-term safety for one year had patients exposed to drug for an average of 31-32 weeks. As with other long-term studies, there was a significant dropout rate and only 38-40% remained in the study for the final 2 months. In addition, a substantial proportion (40 subjects) used concomitant corticosteroid treatment (with data collected during corticosteroid exposure and washout periods excluded for analysis).

2. Efficacy

As this was an uncontrolled study, efficacy parameters could only be compared to baseline or between the two tazarotene treatments. As well, the data on the efficacy parameters were for the overall impression by the investigator because there were no specific target lesions. The findings were consistent with the vehicle-controlled pivotal trials that demonstrated effectiveness in improving psoriasis from baseline status. In addition, they showed that after 3 months of treatment, the beneficial effect plateaued out and the median time to initial "treatment success" was 20-21 weeks. There was little difference between the two gels in efficacy, apart from the fact that the 0.1% gel was significantly better in the first half-month for global scores ($p=0.04$).

3. Safety

There was also little difference in the safety profiles of the two gels in this long-term study, except in the first half-month of treatment, when there was a higher incidence of local adverse events in the 0.1% gel group. By the end of the study period, the 0.05% gel gave a higher, although not significant, rate of such adverse events than the 0.1% gel. After the first three months of treatment, there was an actual decline in incidence of local adverse events but a suggestion of increased "psoriasis worsened" and occurrence of sun-induced erythema. There were no consistent laboratory test abnormalities relating to tazarotene use during the span of this study. The radiographic studies in this trial have been inconclusive but suggest no significant effect of topical tazarotene on bones.

8.1.7 Trial #7. Study# R168-146-8606. A multi-center, Parallel-group, Double Blind Study to Evaluate the Safety and Efficacy of Tazarotene 0.05% and 0.1% Gels in the Long-term (up to 24 weeks) Treatment of Plaque Psoriasis.

This is a phase 3 study being conducted in Europe and not yet completed. The clinical protocol has not been presented in the NDA and is not found in the IND. Patients were to be treated with tazarotene gel for up to 6 months with flexibility in dosing frequency (qd, qod or q3d). Upon request, the applicant submitted adverse event data, which was lacking in the 120-day safety update. As of 12/31/95, the study had not been unblinded and had enrolled 129 out of a total of 200 planned subjects. Twenty-one terminated study on the basis of adverse events and 5 due to lack of efficacy. There were no other dropouts. Adverse events were: psoriasis worsened 21, erythema 3, dry skin 1, retroauricular ear pain 1, burning 11,"discomfort" 3, skin fissure 1, middle ear infection 1, pruritus 10, soreness 2, stiffness 1,flu 1, irritation 7, friable skin 2, infected finger 1, pollinosis 1, "inflammation" 6, focal edema 1 and sciatica 1 .The following "severe" adverse events were reported: burning 3, "inflammation" 2, erythema 1, discomfort 1 and skin fissures 1.

Comment Inadequate information for comments.

8.2 Indication #2. Treatment of acne vulgaris.

8.2.1 Trial #1. 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

8.2.1.1 Objective/Rationale

The objective was to evaluate the safety and efficacy of once-daily tazarotene 0.1% and 0.05% gels vs vehicle gel in the treatment of acne vulgaris.

The rationale of this study is based on tazarotene's ability to inhibit corneocyte accumulation in rhino mouse skin *in vivo* and cross-linked envelope formation in cultured human keratinocytes *in vitro.* The Applicant believes the primary mechanisms of action by tazarotene in acne are: normalization of keratinization and decrease in the coherence of follicular keratinocytes. Both contribute to a comedolytic effect and prevent new microcomedone formation. An earlier preliminary study R168-210-8225 established that tazarotene 0.01% gel had a minimal effect while the 0.05% gel offered substantial benefit as compared to baseline (see Section 7.2.2.1). Therefore, a larger trial comparing the two concentrations: 0.1% and 0.05% vs vehicle was planned.

8.2.1.2 Design

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 (see Table below):

	Initial visit (week-0)	week-4	week-8	week-12
Consent	x			
Qualification/history	x			
Urine pregnancy test	x	x	x	x
Laboratory screen*	x		x	x
Drug dispensing	x	x	x	
Drug collection		x	x	x
Global (investigator's)		x	x	x
Lesion counts	x	x	x	x
Overall clinical severity grade	x	x	x	x
Signs and symptoms	x	x	x	x
Patient's cosmetic acceptability				x
Final Evaluation Exit Form				x

*Laboratory screen included CBC, serum chemistry and urinalysis, and in 2 centers (Drs. Miller and Tschen) also pharmacokinetics analysis of plasma concentrations of tazarotene and its metabolite, AGN 190299.

8.2.1.3 Protocol

8.2.1.3.1 Population/Procedures

Patient Selection

This study enrolled males and females, 14 years or older, having stable, mild to moderate acne vulgaris, with 10 to 60 facial inflammatory lesions (sum of papules and pustules), 25 to 200 facial non-inflammatory lesions (sum of open and closed comedones) and ≤6 facial nodular cystic lesions (≥5 mm diameter) but negative urine pregnancy tests (in women of child-bearing potential). It excluded anyone with the following: known hypersensitivity to any of the components of the study medications, concomitant antibiotics or anti-acne medication, topical antibiotics or other anti-acne therapy within 14 days prior to study entry, systemic

antibiotics within 4 weeks prior to study entry, previous treatment with systemic retinoids (e.g., Accutane®, Roche Dermatologics), presence of acne known to be resistant to oral antibiotics, presence of any skin condition that would interfere with evaluation of acne and participation in another drug research study concurrent with this study or within 30 days prior to enrollment in this study. Females who were pregnant, nursing or planning a pregnancy or who thought they might be pregnant (throughout the course of the study, females of childbearing potential must use reliable forms of contraception) were excluded. Entry was not allowed for those having estrogen treatment for 12 weeks or less immediately preceding study entry (patients treated with estrogens for more than 12 consecutive weeks immediately prior to study entry were not excluded unless the patient expected to discontinue estrogen use during study).

Comment Estrogens have been used to treat acne. The inclusion of patients using estrogens introduced a confounding factor which requires subset analysis or a covariate analysis of the data.

Concomitant Medications

Any other medication that might alter the course of acne including topical or systemic antibiotics or other anti-acne drugs was disallowed. Medications necessary for the subject's welfare and not affecting the course of acne would be allowed.

Application of Study Medication, Visits and Evaluations

Each subject was assigned to tazarotene 0.1%, 0.05% or vehicle with equal randomization to each treatment group in each center. Visits were scheduled as shown in the Section on Design (8.2.1.2). Subjects applied their treatment daily for 12 weeks according to the following instructions: Wash face with the supplied nonmedicated cleansing bar (Dove) or other nonmedicated cleanser before application. Apply a thin film of the study drug in the evening, at least 30 minutes after face washing. Intolerable irritation might result in reduction of dose from qd to qod for one week, and if this was still intolerable upon resumption of qd regimen, the investigator could maintain the subject on qod regimen for the rest of the study. Nonmedicated shampoos or cosmetics were allowed if used consistently. Cosmetics was to be avoided on visit days. Avoidance: other lotions, creams, powders or solutions, and sunscreens on treated areas as well as excessive or prolonged periods of sun exposure.

Comment

1. Changes in dosing regimen might confound analysis of data.
2. It would be of interest to look for occurrences of photosensitivity. The gels were to be used without concomitant sunscreens on a sun-exposed part of the body.
3. The inclusion criteria and instruction for use in the study involved only facial acne. The claim to be made by the Applicant should be as such.

The following parameters were evaluated:

A) Efficacy

Primary efficacy parameters were -

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.*
"Treatment success" was defined as a global response of good, excellent or cleared.

Comment As discussed in the psoriasis trials, "treatment success" as defined is too broad in scope and it would be preferable to narrow it to those with improvement far exceeding 50% (see Comments in Section 8.1.1.3.2). For this review, the primary variables for efficacy will be lesion counts and the distribution of global scores, and effectiveness is judged by superiority over vehicle in these variables.

Secondary efficacy parameters were -

3. Overall clinical severity grade *none, mild, moderate or severe*;
4. Signs and symptoms *none, mild, moderate or severe for the following:*
peeling, dryness, burning, erythema, pruritus, oiliness and others;
5. Cosmetic acceptability *rated by patients at their last visit,*
i) overall impression of cosmetic characteristics of medication as highly favorable, favorable, neutral, slightly unfavorable or highly unfavorable,
ii) texture, ease of application, appearance and odor of medication.

B) Pharmacokinetics

At 2 sites (Miller and Tschen), blood was taken at weeks-0, 4, 8 and 12 for plasma levels of (a) tazarotene and (b) its primary metabolite (AGN 190299).

C) Safety

1. adverse event profile and 2. laboratory tests (see Table under 8.2.1.2).

8.2.1.3.2 Subject Dispositions and Endpoints

The 4 categories for patient disposition are the same as those for the treatment period in psoriasis studies (completed, terminated due to lack of efficacy or adverse events, disqualified, and discontinued due to protocol violation). Endpoint was the week-12 visit.

The **Primary Efficacy Variables** were not defined in the original clinical protocol, which merely stated that the "main efficacy variables are the percent changes in the numbers of lesions from baseline, the overall clinical evaluation, and the investigator's global evaluation of response to treatment measured on an ordinal scale" (vol 1.139 p 128) but in the Final Report (vol 1.139 p 024), they were given under "Criteria for Effectiveness" as:
1. percent change from baseline in lesion counts and 2. global evaluation of response.

Comment

1. The use of percent change in lesional counts is valid if the treatment groups start with similar counts at baseline. Although reduction in lesion counts has been traditionally used as a criteria for effectiveness, it would appear that clinically the absolute counts are more relevant. Since the Applicant has not used absolute counts as a parameter, the global assessment of clearing is an important criterion for success. The definition of "treatment success" as presented in this NDA (improvement of ≥50%) is inadequate.
2. The Applicant dropped the overall clinical severity grade as a primary parameter, since all but 11 patients (tazarotene 0.1% gel 3, 0.05% gel 2 and Vehicle 6) entered the study with mild or moderate acne. Thus, the reduction in grade might not be sufficient to achieve success when compared with vehicle. Although this deviation is acceptable, it would place limitation in the claim to be made on the acne indication to mild and moderate cases.

8.2.1.3.3 Statistical Considerations

Lesional counts were analyzed by 2-way ANOVA (including effects of drug, investigator and drug-by-investigator interaction). Other statistical procedures were the same as in the psoriasis studies. Power calculation was based on total lesional count.

8.2.1.4 Results

8.2.1.4.1 Patient Disposition, Comparability

Four hundred and forty-six patients were enrolled into the study among 9 Investigators. The Investigators and enrollment are as follows:

Investigator	Center no.	Total	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Chalker	1206	48	16	16	16
Griffith	1567	26	10	8	8
Herbert	1593	48	16	16	16
Hickman	0674	54	18	18	18
Maloney	1566	54	18	18	18
Miller	1421	54	18	18	18
Shalita	0626	48	16	16	16
Tschen	1104	60	20	20	20
Zaias	0598	54	18	18	18
		446	150	148	148

Comment

1. Due to the small number of patients at Dr. Griffith's site, data from Drs. Griffith and Herbert were combined due to proximity of their sites (Dallas and Houston, TX).
2. A significant drug-by investigator interaction at baseline was noted for total inflammaotry lesions and appeared to be caused by two sites (Drs. Hickman and Shalita). These 2 groups were omitted from an additional subgroup analysis of total inflammaotry lesions.

Completion Status

	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.

Comment

1. More patients in the tazarotene groups terminated due to adverse events.
2. Definitions for the types of analyses were the same as in the psoriasis trials (see Section 8.1.1.3.3). There were 13-19% of patients per treatment group excluded from the preferred analysis. The small differences in ITT analysis and preferred analysis patient numbers (between 4-9) did not impact on the outcome of data analysis. This review will be based on the preferred analysis.

Unevaluability was based on the following reasons:

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
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.

Drug-Exposure of enrolled subjects:

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Enrolled	150	148	148
Exposed for ≥8weeks	120	115	121
Completed treatment	111	103	119
Exposed for ≥12 weeks	104	100	112
Exposed for ≥16 weeks	1	0	0

Comments Two-thirds to three-quarters of subjects were exposed for ≥12 weeks.

Comparability of Treatment Groups

		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
Baseline "Overall Clinical Severity"		1.52±0.53	1.48±0.56	1.61±0.59

Comment The 3 arms were comparable according to baseline demographics (data shown above being from preferred analysis dataset; ITT data similar).

8.2.1.4.2 Efficacy Parameters

A. Endpoint Primary variables

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Non inflammatory Lesions			
Baseline (mean±SD)	62±40	56±33	60±38
Endpoint (mean)	28	31	39
Percent reduction	55±34	46±36	*35±37*
Inflammatory Lesions			
Baseline (mean±SD)	21±11	20±10	23±13
Endpoint (mean)	12	12	16
Percent reduction	*42±41*	*39±38*	*30±47*
Total Lesions			
Baseline (mean±SD)	82±44	75±38	83±44
Endpoint (mean)	39	42	55
Percent reduction	52±32	44±33	*33±34*
Global Scores at Endpoint			
cleared	1 (1%)	0	0
excellent	39 (37%)	26 (26%)	23 (20%)
good	31 (30%)	25 (25%)	24 (21%)
fair	11 (10%)	22 (22%)	25 (21%)
poor	12 (11%)	19 (19%)	23 (20%)
unchanged or worse	11 (10%)	8 (8%)	22 (19%)
"Treatment Success rate" (good or better)	68%	51%	*40%*
Global Score Endpoint (mean±SD)	2.74±1.37	2.42±1.28	2.03±1.40

*Significant differences between tazarotene and vehicle are underlined ($p<0.05$); significant differences between the two tazarotene gels are highlighted ($p<0.05$)

B. Effect during Study Period

	wk-0	wk-4 reduction	wk-4 count	wk-8 reduction	wk-8 count	wk-12 reduction	wk-12 count
Noninflammatory Lesions							
Taz 0.1%	62	32%	42	46%	33	55%	28
Taz 0.05%	56	25%	42	43%	32	45%	31
Vehicle	60	16%	50	31%	41	35%	39
Inflammatory Lesions							
Taz 0.1%	21	16%	18	29%	15	42%	12
Taz 0.05%	20	22%	16	38%	12	39%	12
Vehicle	23	17%	19	33%	15	30%	16
Total Lesions							
Taz 0.1%	82	28%	59	42%	48	52%	39
Taz 0.05%	75	25%	56	41%	44	44%	42
Vehicle	83	19%	67	32%	56	33%	56
Overall Clinical Severity Scores							
Taz 0.1%	1.5	0.1		0.3		0.3	
Taz 0.05%	1.5	0.1		0.2		0.3	
Vehicle	1.6	0.2		0.3		0.3	
Mean Global Scores							
Taz 0.1%		1.84±1.14		2.33±1.30		2.74±1.37	
Taz 0.05%		1.63±1.14		2.20±1.19		2.42±1.28	
Vehicle		1.48±1.21		1.91±1.22		2.09±1.40	
Global "Treatment success" (Scores of "≥50% improvement")							
Taz 0.1%		28%		48%		68%	
Taz 0.05%		24%		43%		51%	
Vehicle		28%		38%		47%	

*Significant differences between tazarotene and vehicle are underlined ($p<0.05$); significant differences between the two tazarotene gels are highlighted ($p<0.05$).

Comment

1. Treatment success as defined by the Applicant was too broad and an analysis was therefore made comparing the treatment groups using >75% or 100% improvement as cutoff:

	wk-4	wk-8	wk-12
≥75% improvement			
Taz 0.1%	8%	24%	38%
Taz 0.05%	4%	14%	26%
Vehicle	7%	10%	20%
100% improvement			
Taz 0.1%	0	0	1%
Taz 0.05%	0	0	0
Vehicle	0	0	0

2. Tazarotene was effective primarily against the noninflammatory lesions as predicted by its mechanism of action. The 0.1% gel also was better than vehicle at endpoint (week-12) for reduction of inflammatory lesions (p=0.003), although the actual inflammatory lesion count was the same as in the 0.05% group. The global and reduction of total lesion counts were also better in the tazarotene groups. Inflammatory lesion counts did not increase in the 0.05% gel group, although the reduction was not statistically different from that given by vehicle (p>0.05).

3. In view of the substantial reduction of total lesion counts by vehicle (33%, vs 44% by the 0.05% gel and 52% by the 0.1% gel), the clinical significance of these statistically significant differences is less clear. It would be more helpful if the medication also provided a better response for the inflammatory lesions. As the study showed, the tazarotene gels beat vehicle by a reduction of only 4 inflammatory lesion counts at endpoint (12 vs 16; reduced by 8-9 counts by tazarotene and 7 counts by vehicle).

C. Patients' Cosmetic Acceptability

There was little difference in patient acceptability among the 3 arms when assessed with the following criteria:

	% Patients Reporting Neutral or Better Scores		
	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Texture	78	72	74
Ease of Application	100	99	100
Appearance	82	89	80
Odor	92	89	86
Overall Impression	90	85	84

8.2.1.4.3 Safety Comparison

8.2.1.4.3.1 Adverse Events See Appendix VIII. Adverse events of skin and appendages are listed in the following Table:

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Total patients enrolled	150 (100%)	148 (100%)	148 (100%)
Patients with adverse events	71 (47%)/53 (35%)	54 (37%)/37 (25%)	36 (24%)/11 (7%)
Dermatologic adverse events	52 (43%)/52 (35%)	39 (26%)/37 (25%)	12 (8%)/11 (7%)
burning/stinging	32 (21%)/32 (21%)	19 (13%)/19 (13%)	2 (1%)/2 (1%)
desquamation	28 (19%)/28 (19%)	18 (12%)/18 (12%)	2 (1%)/2 (1%)
dry skin	23 (15%)/23 (15%)	20 (14%)/20 (14%)	5 (3%)/5 (3%)
erythema	22 (15%)/21 (14%)	8 (5%)/8 (5%)	0
pruritus	18 (12%)/18 (12%)	13 (9%)/13 (9%)	(3%)/5 (3%)
irritation	9 (6%)/9 (6%)	5 (3%)/5 (3%)	2 (1%)/2 (1%)

skin pain	4 (3%)/4 (3%)	0	0
skin focal edema	2 (1%)/1	0	0
contact dermatitis, irritant	1 /1	0	0
rash/vesiculobullous rash	1 /1	1	2 (1%)/2 (1%)
skin tightness	1 /1	1 /1	0
seborrhea	1	1 /1	0
herpes simplex	1	0	0
sun-induced erythema	0	2 (2%)	0
acne worsened	0	1	2 (1%)/1

Incidence of "Treatment-related" adverse events is listed after a slash (/) from the total incidence.

Termination of study due to adverse events was as follows:

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Total patients terminated for AE	13 (9%)	12 (8%)	3 (2%)
burning/stinging	9 (6%)	7 (5%)	2 (1%)
erythema	7 (5%)	5 (3%)	0
desquamation	7 (5%)	7 (5%)	0
pruritus	4 (3%)	4 (3%)	1
dry skin	4 (3%)	5 (3%)	0
irritation	3 (2%)	2 (1%)	0
contact dermatitis, irritant	1	0	0
cheilitis	1	0	0
edema	1	0	0
paresthesia	1	0	0
tightness	0	1	0
secondary infection	0	1	0
rash	0	0	2 (1%)

One case of pregnancy occurred during the course of the study in the vehicle group. She was discontinued from study and subsequently gave birth to a healthy baby. No deaths were reported. Relation between drug exposure and termination due to adverse events is as follows:

	Tazarotene 0.1%		Tazarotene 0.05%		Vehicle	
	InStudy	Terminated for AE	InStudy	Terminated for AE	InStudy	Terminated forAE
Enrolled	150		148		148	
Exposed for						
≥4weeks	130	8 (5%)	126	5 (3%)	132	2(1%)
≥8weeks	120	4 (3%)	115	4 (3%)	121	0
≥12 weeks	104	3 (2%)	100	3 (2%)	112	0
Total		13 (9%)		12 (8%)		2(1%)

Comment Most adverse events occurred in the early part of the study and were of irritation in nature.

8.2.1.4.3.2 Laboratory Studies

A. CBC, chemistry and urinalysis - no consistent, significant abnormalities.

B. Therapeutic drug monitoring -see Section 10.

8.2.1.5 Conclusions

Tazarotene 0.1% and 0.05% gels given daily were both effective in reducing lesion counts in acne, and the 0.1% gel was better than vehicle in global "treatment success" as defined by ≥50% improvement as well as in reducing inflammatory lesions (see Table below). The commonest adverse events associated with their use were pruritus, burning/stinging, irritation, erythema, dry skin and desquamation.

	SUPERIORITY OF		
	Taz* 0.1% vs vehicle	Taz* 0.05% vs vehicle	Taz 0.1% vs Taz 0.05%
1° Variables at Treatment Endpoint			
↓ Noninflammatory lesions	<0.001	<0.001	0.035
↓ Inflammatory lesions	0.009	-	-
↓ Total lesions	<0.001	0.002	-
Global (treatment success)	<0.001	-	-
Onset of Action*			
week-4	NTG	NT	-
week-8	NITG	NT	-
Safety			
All "treatment-related" AE* rates (%)	47/35 vs 24/7	37/25 vs 24/7	47/35 vs 37/25

*Taz=tazarotene, AE=adverse event, N=↓noninflammatory lesion count, I=↓inflammatory lesion count, T=↓total lesion count, G=global "treatment success", -=Not significant (p>0.05).
Letters given under "Onset of Action" are for variables with an among group comparison showing p<0.05.

8.2.2 Trial #2. 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

8.2.2.1 Objective/Rationale Same as that of R168-220-7997.

8.2.2.2 Design Same as that of R168-220-7997.

8.2.2.3 Protocol The Protocol was almost identical to that of R168-220-7997 EXCEPT:

Table 8.2.2.3 Differences between the Protocols of R168-220-8606 and R168-221-8606

	R168-220-7997	R168-221-8606
Soap	Dove	Neutrogena; also nonmedicated cleansers
Normal menstrual cycle before entry	not required	required
Additional exclusion criteria*	-	+
Global	5 grades	6 grades (split "no change" and "worsened")
Overall clinical severity/some symptoms*	+	eliminated from assessment
Formulation	"old formulation"	"current formulation"

*Additional exclusion criteria: uncontrolled systemic disease, inability to avoid sun-exposure and history of other skin conditions that might interfere with evaluation; some symptoms=burning, erythema, pruritus, dryness, peeling and oiliness.

8.2.2.4 Results

8.2.2.4.1 Patient Disposition, Comparability

Four hundred and forty-seven patients were enrolled into the study among 9 Investigators. The Investigators and enrollment are as follows:

Investigator	Center no.	Total	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Berger	1962	55	18	19	18
Breneman	1565	54	18	18	18
Jones	1967	48	16	16	16
Lesher	1562	48	16	16	16
Leyden	0084	48	16	16	16
Luckey	1900	48	16	16	16

Strauss	0376	48	16	16	16
Swinyer	1964	48	16	16	16
Thiboutot	2148	50	17	16	17
		447	149	149	149

Comment No significant drug-investigator interactions were noted.

Completion Status:

	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.

Comment

1. More patients in the tazarotene groups terminated due to adverse events.
2. There were 9-13% of patients per treatment group excluded from preferred analysis. The small differences in ITT analysis and preferred analysis patient numbers (between 2-5, see below) did not impact on the outcome of data analysis.
3. This review is based on the preferred analysis.

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.

Drug Exposure of enrolled subjects:

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Enrolled	149	149	149
Exposed for ≥8weeks	124	122	129
Completed treatment	120	118	115
Exposed for ≥12 weeks	105	92	95

Comments Sixty-four to 70% of subjects were exposed for ≥12 weeks.

Comparability of Treatment Groups

		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

Comment The 3 arms were comparable according to baseline demographics (data shown above from preferred analysis; ITT data similar).

8.2.2.4.2 Efficacy Parameters

A. Endpoint Primary variables

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Non inflammatory Lesions			
Baseline (mean±SD)	52±30	52±30	50±25
Endpoint (mean)	30	32	37
Percent reduction	*48±33*	*38±31*	*27±35*
Inflammatory Lesions			
Baseline (mean±SD)	22±12	21±12	21±11
Endpoint (mean)	12	13	15
Percent reduction	*47±28*	*37±44*	*28±51*
Total Lesions			
Baseline (mean±SD)	75±36	74±38	71±31
Endpoint (mean)	41	45	52
Percent reduction	*45±26*	*39±27*	*27±34*
Global Scores at Endpoint			
cleared	0	0	0
excellent	21 (18%)	13 (11%)	11 (10%)
good	35 (30%)	33 (29%)	21 (19%)
fair	31 (26%)	29 (25%)	24 (22%)
poor	18 (15%)	20 (17%)	22 (20%)
unchanged	8 (7%)	13 (11%)	20 (18%)
worse	4 (3%)	7 (6%)	12 (11%)
"Treatment Success rate" (good or better)	*48%*	*40%*	*29%*
Global Score			
Endpoint (mean±SD)	3.26±1.30	2.96±1.69	2.50 ±1.51

*Significant differences between tazarotene and vehicle are underlined ($p<0.05$); significant differences between the two tazarotene gels are highlighted ($p<0.05$)

B. Effect during Study Period

	wk-0	wk-4 reduction	wk-4 count	wk-8 reduction	wk-8 count	wk-12 reduction	wk-12 count
Noninflammatory Lesions							
Taz 0.1%	52	19%	42	36%	33	48%	30
Taz 0.05%	52	15%	44	31%	36	38%	31
Vehicle	50	8%	46	19%	41	27%	39
Inflammatory Lesions							
Taz 0.1%	22	17%	18	40%	13	47%	12
Taz 0.05%	21	14%	18	31%	14	37%	13
Vehicle	21	12%	18	25%	16	28%	15
Total Lesions							
Taz 0.1%	75	19%	61	38%	46	45%	41
Taz 0.05%	74	16%	62	31%	51	39%	45
Vehicle	71	10%	64	21%	56	27%	52
Mean Global Scores							
Taz 0.1%		2.05±1.15		2.90±1.20		3.26±1.30	
Taz 0.05%		1.83±1.15		2.60±1.35		2.93±1.39	
Vehicle		1.72±1.11		2.25±1.28		2.50±1.51	
Global "Treatment success" (Scores of "≥50% improvement")							
Taz 0.1%		14%		36%		48%	
Taz 0.05%		10%		27%		40%	
Vehicle		6%		20%		29%	

*Significant differences between tazarotene and vehicle are underlined ($p<0.05$); significant differences between the two tazarotene gels are highlighted ($p=0.05$).

Comment

1. Treatment success as defined by the Applicant was too broad and an analysis was therefore made comparing the treatment groups using >75% or 100% improvement as cutoff:

	wk-4	wk-8	wk-12
75% improvement or better			
Taz 0.1%	1%	6%	18%
Taz 0.05%	0	7%	11%
Vehicle	2%	1%	10%
100% improvement	No subject cleared 100% during this study.		

2. The findings in this trial confirm the conclusions drawn from R168-220-7997:
a) Tazarotene was effective primarily against the noninflammatory lesions.
b) The 0.1% gel was statistically significantly better than vehicle at endpoint (week-12) for reduction of inflammatory lesions ($p=0.003$) but the actual inflammatory lesion counts were similar among the 3 groups.
c) The global and reduction of total lesion counts were also better in the tazarotene groups.
d) Inflammatory lesion counts did not increase in the 0.05% gel group, although the reduction was not statistically different from that given by vehicle.
3. In view of the substantial reduction of total lesion counts by vehicle (vehicle=27% vs tazarotene 0.05% gel=39% and tazarotene 0.1% gel=45%), the clinical significance of these statistically significant differences is less clear. It would be preferable if the medication also provided a better response for the inflammatory lesions. Both gels beat vehicle by a reduction of only 2-3 inflammatory lesion counts at endpoint (12-13 vs 15; reduced by 7-10 counts by tazarotene and 6 counts by vehicle from baseline).

C. Patients' Cosmetic Acceptability

There was little difference in patient acceptability among the 3 arms when assessed with the following criteria:

	% Patients Reporting Neutral or Better Scores		
	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Texture	73	68	79
Ease of Application	98	99	99
Appearance	83	83	78
Odor	91	93	87
Overall Impression	91	82	88

8.2.2.4.3 Safety Comparison

8.2.2.4.3.1 Adverse Events See Appendix IX. Adverse events of skin and appendages are listed in the following Table:

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Total patients enrolled	149 (100%)	149 (100%)	149 (100%)
Patients with adverse events	106 (71%)/86 (58%)	107 (72%)/86 (58%)	76 (51%)/34 (23%)
Dermatologic adverse events	91 (61%)/86 (58%)	90 (60%)/86 (58%)	35 (24%)/34 (23%)
desquamation	56 (38%)/56 (38%)	43 (29%)/43 (29%)	4 (3%)/4 (3%)
burning/stinging	52 (35%)/51 (34%)	48 (32%)/48 (32%)	7 (5%)/7 (5%)
dry skin	36 (24%)/36 (24%)	40 (27%)/39 (26%)	10 (7%)/9 (6%)
erythema	33 (22%)/32 (21%)	25 (17%)/25 (17%)	0
pruritus	19 (13%)/18 (12%)	18 (12%)/18 (12%)	17 (11%)/16 (11%)
irritation	7 (5%)/7 (5%)	3 (2%)/3 (2%)	2 (1%)/2 (1%)
skin fissure	3 (2%)/3 (2%)	1 /1	0
skin discoloration	3 (2%)/3 (2%)	0	0
skin tightness	1 /1	2 (1%)/2 (1%)	0
skin pain	1 /1	1 /1	0
sweat	1 /1	0	0
contact dermatitis, irritant	1	2 (1%) /1	1 /1
skin laceration/excoriation	1	2 (1%)/1	0
skin focal edema	1	1 /1	0
seborrhea	1	0	1 /1
acne worsened	0	3 (2%)/2 (1%)	3 (2%)/2 (1%)
rash/vesiculobullous rash	0	2 (1%)	2 (1%)
herpes simplex	0	1	0
urticaria	0	1	0

Incidence of "Treatment-related" adverse events is listed after a slash (/) from the total incidence.

Termination of study due to adverse events was as follows:

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Total patients terminated for AE	9 (6%)	10 (7%)	2 (1%)
erythema	5 (3%)	4 (3%)	0
burning/stinging	4 (3%)	5 (3%)	0
dry skin	2 (1%)	1	0
pruritus	1	1	0
irritation	1	1	0
desquamation	1	4 (3%)	0
contact dermatitis, irritant	1	1	0
photosensitivity	1	0	0
skin swelling	1	0	0

skin tightness	1	0	0
skin fissure	1	0	0
skin laceration	1	0	0
skin vasodilation	1	0	0
headache	1	0	0
acne worsened	0	2 (1%)	2 (1%)
secondary infection	0	2 (1%)	0
rash	0	1	0
skin pain	0	1	0

One patient who became pregnant during the course of the study in the vehicle group was discontinued from study. She subsequently had her pregnancy terminated. No deaths were reported. Relation between drug exposure and termination due to adverse events is as follows:

	Tazarotene 0.1%		Tazarotene 0.05%		Vehicle	
	InStudy	Terminated for AE	InStudy	Terminated for AE	InStudy	Terminated forAE
Enrolled	149		149		149	
Exposed for						
≥4weeks	135	5 (3%)	130	6 (4%)	140	1(0.7%)
≥8weeks	124	4 (3%)	122	3 (2%)	129	1(0.7%)
≥12 weeks	105	0	92	1 (1%)	95	0
	Total	9 (6%)		10 (7%)		2(1.4%)

Comment Most adverse events occurred in the early part of the study and were of irritation in nature.

8.2.2.4.3.2 Laboratory Studies

A. CBC, chemistry and urinalysis - no consistent, significant abnormalities.

B. Therapeutic drug monitoring -see Section 10.

8.2.2.5 Conclusions

Tazarotene 0.1% and 0.05% gels given daily were both effective in reducing lesion counts in acne, and the 0.1% gel was better than vehicle in global "treatment success" as defined by ≥50% improvement as well as in reducing inflammatory lesions (see Table below). The commonest adverse events associated with their use were pruritus, burning/stinging, irritation, erythema, dry skin and desquamation.

	SUPERIORITY OF		
	Taz* 0.1% vs vehicle	Taz* 0.05% vs vehicle	Taz 0.1% vs Taz 0.05%
			1°
Variables at Treatment Endpoint			
↓ Noninflammatory lesions	<0.001	0.032	0.002
↓ Inflammatory lesions	0.003	-	-
↓ Total lesions	<0.001	0.017	0.005
Global (treatment success)	<0.001	0.008	0.005
Onset of Action*			
week-4	NT	-	N
week-8	NTG	NTG	-
Safety			
All "treatment-related" AE* rates (%)	71/58 vs 51/23	72/58 vs 51/23	71/58 vs 72/58

*Taz=tazarotene, AE=adverse event, N=↓noninflammatory lesion count, I=↓inflammatory lesion count, T=↓total lesion count, G=global "treatment success", -=not significant (p>0.05).

Letters given under "Onset of Action" are for variables with an among group comparison showing p<0.05.

9. Overview of Efficacy

9.1 Psoriasis

9.1.1 Comparison between Studies

There were seven Phase 3 studies, of which one (R168-146-8606) is ongoing and one (R168-128-8606) was a 2-arm (both tazarotene) uncontrolled trial, with the primary objective of studying long-term safety. The remaining 5 studies consisted of 2 vehicle-controlled and 3 active controlled studies. See Appendix ID for comparison of these 7 studies for their objective, design and patient enrollment.

The Applicant would like to have both formulations of tazarotene gel approved for the treatment of plaque psoriasis. This was to be supported by the two vehicle-controlled trials (R168-120-8606 and R168-121-8606). In addition, the Applicant wished to make the claim that the therapeutic effect of tazarotene is maintained in a 12-week posttreatment period. The 3 comparative studies with active controls were designed to address this (R168-125-8606, R168-126-8606 and R168-145-8606).

9.1.1.1 Vehicle-controlled Studies

The 2 vehicle controlled-studies had one major difference between them: which was the posttreatment period, present only in R168-120-8606. Comparison of efficacy data in these studies will be confined to the 12-week treatment period.

Demographics and Baseline Disease Involvement The two studies enrolled patients with similar demographic background and baseline status. The following combined data reflect very similar figures in each study.

		Years		Percent				Years
		Age		Sex		Race	Involved	Psoriasis
	Pt no*	Mean	Range	Males	Females	W/H/B/OR/OT*	BSA*	Duration (mean)
Taz* 0.1%		49		67	33	90/8/1/1/0	8	17
Taz 0.05%		47		64	36	88/10/1/1/1	8	18
Vehicle		48		66	34	88/7/3/2/1	7	20
Total		48		66	34	89/8/2/1/1	8	18

*Data given are for all enrolled patients. Patients for preferred analysis and for ITT analysis gave almost identical figures. Taz=tazarotene, W/H/B/OR/OT=white/Hispanic/black/oriental/other. BSA=body surface area.

Patient disposition Disposition of patients combined in these 2 studies is as follows for the treatment period (no posttreatment period in R169-121-8606 for comparison):

	Enrolled	Eval*	Completed	LOC	AE	Other discon	Disqualified
Taz* 0.1%	220	209	150 (68%)	8 (4%)	34 (16%)	25(11%)	3 (1%)
Taz 0.05%	219	210	166 (76%)	13 (6%)	21 (10%)	19(9%)	0 (0%)
Vehicle	221	216	169 (77%)	10 (5%)	12 (5%)	28(13%)	2 (1%)
Total	660	635	485 (74%)	31 (5%)	67 (10%)	72(11%)	5 (1%)

*Eval=evaluable subjects, LOC=termination due to lack of efficacy, AE=termination due to adverse events, other discon=discontinuation for other reasons (missed visits, protocol violations, personal, etc, disqualified=not meeting entry criteria.

Proportions of patients in each category in the 2 studies were similar with the following exceptions:

		Completed	AE	Other discon	Comment
Taz* 0.1%	R168-120-8606	81 (75%)	13 (12%)	9(8%)	Lower completion rate in R168-121-8606: ↑AE & other discon.
	R168-121-8606	69 (62%)	21 (19%)	16(14%)	
Taz* 0.05%	R168-120-8606	80 (74%)	11 (10%)	12(11%)	Fewer other discon patients in R168-121-8606.
	R168-121-8606	86 (78%)	10 (9%)	7(6%)	
Vehicle	R168-120-8606	81 (75%)	3 (3%)	18(17%)	More AE & fewer other discon in R168-121-8606
	R168-121-8606	68 (78%)	9 (8%)	10(9%)	

It is noted that the termination rate for adverse events was higher for the 0.1% gel in the second study so that there was a 10% difference between the two gels in that study, in contrast to the very close similarity in R168-120-8606.

Primary Efficacy Variables

		Reduction in Scores Trunk/Arm/Leg						Reduction in Scores Knee/Elbow				
I. Mean Scores for	BL	wk-1	wk-2	wk-4	wk-8	wk-12	BL	wk-1	wk-2	wk-4	wk-8	wk-12
Plaque Elevation												
R168-120-8606												
Tazarotene 0.1%	2.5	0.63*	0.99	1.13	1.24	1.39	2.6	0.59	0.92	1.10	1.29	1.47
Tazarotene 0.05%	2.5	0.71	0.81	1.08	1.38	1.41	2.6	0.60	0.88	1.03	1.28	1.35
Vehicle	2.4	0.28	0.41	0.70	0.69	0.77	2.6	0.31	0.39	0.60	0.70	0.71
R168-121-8606												
Tazarotene 0.1%	2.6	0.63*	0.93	1.11	1.26	1.41	2.6	0.44	0.78	1.00	1.19	1.28
Tazarotene 0.05%	2.6	0.56	0.93	1.08	1.15	1.29	2.6	0.50	0.67	0.89	1.01	1.12
Vehicle	2.6	0.26	0.36	0.44	0.61	0.71	2.6	0.26	0.26	0.37	0.56	0.62
Scaling												
R168-120-8606												
Tazarotene 0.1%	2.4	0.52	0.72	0.93	1.00	1.25	2.5	0.36	0.60	0.81	1.01	1.25
[illegible]rotene 0.05%	2.3	0.48	0.67	0.90	1.12	1.13	2.5	0.37	0.62	0.77	0.98	1.11
[illegible]le	2.4	0.30	0.42	0.54	0.67	0.68	2.5	0.30	0.35	0.42	0.67	0.62
[illegible]8-121-8606												
Tazarotene 0.1%	2.6	0.45	0.77	0.96	1.08	1.30	2.7	0.25	0.60	0.84	[illegible]	1.23
Tazarotene 0.05%	2.5	0.46	0.75	0.86	0.89	1.11	2.6	0.30	0.49	0.64	[illegible]	0.92
Vehicle	2.6	0.22	0.36	0.44	0.62	0.66	2.7	0.18	0.24	0.45	0.56	0.58
Erythema												
R168-120-8606												
Tazarotene 0.1%	2.4	0.16	0.49	0.65	0.90	1.01	2.3	0.15	0.41	0.65	0.83	0.96
Tazarotene 0.05%	2.4	0.25	0.36	0.57	0.82	0.96	2.2	0.16	0.29	0.51	0.75	0.87
Vehicle	2.3	0.19	0.32	0.46	0.57	0.59	2.2	0.25	0.31	0.42	0.56	0.50
R168-121-8606												
Tazarotene 0.1%	2.8	0.07	[illegible]	0.49	0.85	1.08	2.5	0	0.21	0.45	0.71	0.82
Tazarotene 0.05%	2.7	0.19	[illegible]	0.42	0.60	0.83	2.5	0.09	0.28	0.48	0.71	0.81
Vehicle	2.7	0.10	0.27	0.29	0.47	0.54	2.5	0.09	0.24	0.28	0.47	0.50
Total Scores												
R168-120-8606												
Tazarotene 0.1%	7.3	1.30	2.20	2.71	3.14	3.65	7.3	1.10	1.93	2.56	3.12	3.68
Tazarotene 0.05%	7.2	1.45	1.83	2.55	3.31	3.51	7.3	1.14	1.79	2.31	3.01	3.33
Vehicle	7.1	0.76	1.14	1.70	1.93	2.05	7.3	0.86	1.04	1.44	1.93	1.82
R168-121-8606												
Tazarotene 0.1%	8.0	1.15	1.88	2.57	3.18	3.80	7.9	0.68	1.58	2.28	2.98	3.33
Tazarotene 0.05%	7.7	1.21	2.04	2.35	2.63	3.23	7.7	0.89	1.45	2.02	2.46	2.85
Vehicle	7.9	0.59	0.99	1.17	1.71	1.92	7.8	0.53	0.74	1.09	1.60	1.69

*Figures underlined are significantly different from those of vehicle ($p<0.05$).

[illegible]Figures highlighted show significant difference among 0.1% gel and 0.05% gel treatment groups ($p\leq 0.02$)