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APPLICATION NUMBER: NDA 20-600

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 20-600

1. General Information

NDA #20-600

Original

Submission date: June 16, 1995

Received date: June 19, 1995

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Drug name: tazarotene

Generic name: tazarotene

Proposed trade name: Zorac™

Chemical name : Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate

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

Pharmacologic Category: Retinoid

Proposed Indication(s): 1. for the topical treatment of plaque psoriasis
and 2. for the topical treatment of acne vulgaris

Dosage Form(s) and Route(s) of Administration: topical gel

NDA Drug Classification: 1 S

Related NDAs: none. Studies in NDA 20-600 were conducted under IND of
Allergan Herbert, Skin Care Division of Allergan, Inc.

Related Reviews: Statistical Review dated: pending
Biopharm Review dated: pending

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3. Material Reviewed

This review was based on vols 1.1, 1.2 (Overall Summary), 1.73 through 1.154 (Clinical Data) and vols 1.193-220 (Case Report Forms) from the original NDA 20-600 submission and vol 2.1, 2.16 through 2.26 from the 120-day safety update. In addition, the Applicant submitted, upon request, the required CRFs of the long-term clinical study reported in the safety update and selected CRFs of patients who discontinued in Phase 3 clinical trials from the original submission. This review was also assisted by data submission in ACCESS 2.0 upon request

4. Chemistry/Manufacturing Controls

The formulations of Tazarotene Gels are as follows:

Ingredients	Tazarotene .1% gel	Tazarotene .05% gel
✓Tazarotene		
✓Benzyl alcohol		
✓Ascorbic acid		
✓Butylated hydroxyanisole		
✓Butylated hydroxytoluene		
✓Edetate disodium		
✓Polyethylene glycol 400		
✓Hexylene glycol		
✓Carbomer 934P		
✓Tromethamine		
✓Poloxamer 407		
✓Polysorbate 40		
✓Purified water		
Total		

Tazarotene exhibits strong UV-VIS absorption in acidic solution. A series of superimposed spectra measured at various pH values indicates that there are 3 isosbestic points at approximately _____ nm.

5. Animal Pharmacology/Toxicology

The Applicant has submitted numerous preclinical studies including *in vitro* activity; topical, oral and parenteral administration in different species (rat, guinea pigs, rabbit, miniswine, dog and monkey) for toxicity and special studies on reproductive toxicity (Segment I to III); as well as studies on mutagenicity, carcinogenicity and photocarcinogenicity. See review by pharmacologist/toxicologist for details.

6. Clinical Background

6.1 Relevant human experience

Tazarotene is a novel retinoid developed by the Applicant. There is no previous human experience with this molecular entity other than data presented in this NDA.

6.2 Important information from related INDs and NDAs

Studies in NDA 20-600 were conducted under IND

6.3 Foreign Experience None other than in the clinical trials to be discussed.

6.4 Human pharmacology, pharmacokinetics and pharmacodynamics

Tazarotene is rapidly metabolized into its active acidic metabolite, AGN190299, upon administration. Plasma levels of tazarotene after topical application is usually undetectable while AGN 190299 is detectable in a proportion of patients, but its level appeared to be independent of disease state and extent of application. The pharmacokinetics studies are listed in Appendix IA (See Biopharm review for details of these studies). A brief account will be given in Section 10 of this review. In addition, the Applicant performed therapeutic drug monitoring in the trials to be presented. There is no information on human pharmacology or pharmacodynamics other than in the studies to be discussed below.

6.5 Other relevant background information

This current NDA stems from studies conducted under IND _____ which was originally submitted on 1-9-90. An end-of phase 2 meeting, between the Agency and the Applicant on 12-10-92, addressed several issues on further development of tazarotene including: (1) development of 2 concentrations, 0.1% and 0.05% gel, (2) "maintenance of a therapeutic effect" claim, (3) efficacy variables for psoriasis, and (4) determination of treatment success or failure.

On 10-24-94, a Pre-NDA meeting was held and the following clinical issues were discussed: (1) "treatment success", (2) usefulness of the 0.05% gel and (3) interim analysis of the long-term clinical study which was being performed.

6.6 Directions for Use See individual studies and proposed labeling

6.7 Description of Clinical Data Sources

See Appendix IA through Appendix ID for a listing of the clinical studies. The Phase 1 dermal safety studies will be discussed in Section 10. The Phase 2 studies are summarized in this section, as they form the basis of the Phase 3 clinical trials, which will be discussed in Section 8.

7. Summary of Phase II Clinical Studies

7.1 Mechanism of Action Studies

7.1.1 Study R168-105-8225. Safety and Efficacy of Tazarotene (AGN 190168) 0.05% Gel vs Vehicle Gel in Psoriasis and Effect on Molecular Markers in Treated Plaques

This study was performed under Dr. Madeleine Duvic at the University of Texas Dermatology Clinical Research Center (6655 Travis, Houston, TX 77030) and was planned as a randomized block trial with 10 patients having tazarotene 0.05% gel to be applied to a plaque on one side of the body and vehicle to another on the opposite side twice daily for 4 weeks.

Results: Due to a labeling error, 9 out of 10 patients received the same medication to both sides. This was therefore an unevaluable study from the standpoint of efficacy. However, the scores for efficacy variables (plaque elevation, scaling and erythema) did decrease with tazarotene 0.05% gel treatment (significant vs baseline and vehicle) and continued to show decrease from baseline (not statistically significant vs vehicle) 2 weeks after the end of a 2-week treatment course. Molecular markers of epidermal differentiation (keratinocyte transglutaminase, filaggrin, keratin-16, involucrin, and EGF receptor) tended to normalize but changes from baseline were not statistically significant. Markers for inflammation (ICAM-1 and HLA-DR) showed significant decrease in expression in epidermis, and ICAM-1 expression also decreased in the dermis (published in *J Amer Acad Dermatol* 30: 581, 1994). Adverse events were only reported in 4 cases: isomorphic reaction, severe burning, urinary tract infection and respiratory infection, although irritation of surrounding skin was seen at mild to moderate severity in most subjects.

Comment Acceptable safety but unevaluable efficacy of the 0.05% gel.

7.1.2 Study R168-106-8606. Safety and Efficacy of Tazarotene (AGN 190168) 0.1% Gel vs Vehicle Gel in Stable Plaque Psoriasis and Effect on Molecular Markers in Treated Plaques

Although this study has been completed, its study report has not been submitted. This was a one-month study of daily dosing with tazarotene 0.1% or vehicle gel and was a bilateral comparison where each patient applied the 0.1% gel to one side and vehicle gel to the other. Efficacy and molecular marker data were not submitted. Out of 20 patients studied, 8 reported adverse events: "irritation" 2 (both cases were Koebnerization of psoriasis), burning 3, pruritus 3 and lack of efficacy 3. In-addition, there was one case of arthritis believed to be psoriatic in nature.

Comment Full study report and raw data are required.

7.2 Initial Dose-Finding Studies

7.2.1 Indication: Psoriasis

7.2.1.1 Study R168-110-8225. Safety and Efficacy of Tazarotene (AGN 190168) in the Treatment of Psoriasis: Tazarotene 0.05% and 0.01% Gels vs Vehicle Gel

This was a pilot study comparing two concentrations of tazarotene gel (0.01% and 0.05%) with vehicle used twice a day in 45 psoriasis patients. The investigators were:

Peter M. Elias, M.D.	Gerald G. Kreuger, M.D	Nicholas Lowe, M.D
San Francisco, CA 94121	Salt Lake City, UT 84132	Santa Monica, CA 90404

Each subject was given two preparations, each preparation to be applied to one psoriasis lesion (2.5 cm in diameter) twice a day for 6 weeks. The treated lesions on both sides were evaluated on days-3, 7, 14, 21, 28 and 42. The combinations were: Tazarotene 0.1% gel plus tazarotene 0.05% gel, Tazarotene 0.1% gel plus vehicle gel, and Tazarotene 0.05% gel plus vehicle gel.

Results:

- Forty-four subjects completed the study (see Table 7b for demographics). One patient discontinued treatment because of generalized pruritus.
- Efficacy

Variable	Treatment-Days showing Significant Differences (p<0.05) between Treated Lesions		
	Tazarotene 0.05% better than vehicle	Tazarotene 0.01% better than vehicle	Tazarotene 0.05% better than Tazarotene 0.01%
"global" response of treated site	7-42	42	7-42
Percent change in scores of			
overall clinical severity	7-42	42	21 and 28
induration	7-42	42	7, 14, 21 and 42
scaling	7-42	7	7-28
erythema	none	none	none
∑induration, scaling & erythema	7-42	42	7-42

- Safety Twelve patients reported adverse events possibly related to treatment:

<u>Tazarotene 0.05%</u>	<u>Tazarotene 0.01%</u>	<u>Vehicle</u>	<u>Tazarotene 0.05% plus 0.01%</u>
erythema 8*	burning 1	hyper-	generalized pruritus 1
pruritus 2*		pigmentation 1	
irritation 1*			
atrophy 1			
sensitive to touch 1			

*one case of "severe" adverse event was reported for each of these in the 0.05% gel-treated group.

No clinically significant laboratory abnormalities were reported (CBC, serum chemistry and urinalysis).

Comment

1. As in other studies involving bilateral comparisons of topical medications, interpretations in this study were dependent on the lack of significant systemic absorption and distribution to the contralateral treatment site. Since the lesions to be treated were <2.5cm in diameter and other studies have shown low systemic exposure to topically applied tazarotene, such assumptions might be reasonable. Findings were also dependent on correct applications of the study medications.

2. Tazarotene 0.05% bid appeared effective in the reduction of scores for scaling and induration in psoriasis lesions in a 6-week treatment course. The effect of the 0.01% gel was minimal. Safety seemed acceptable for both.

7.2.2 Indication: Acne

7.2.2.1 Study R168-210-8225. Safety and Efficacy of Tazarotene (AGN 190168) in the Treatment of Acne: Tazarotene 0.05% and 0.01% Gels vs Vehicle Gel

This was a double-blind, parallel-group, randomized pilot study comparing the safety and efficacy of tazarotene gels 0.01% and 0.05% with vehicle in the once-a-day treatment of acne vulgaris. Subjects were treated for 12 weeks with evaluation visits at weeks-2, 4, 8 and 12 at 2 centers:

James J. Leyden, M.D.
Broomall, PA 19008

Bruce H. Miller, M.D.
Portland, OR 97223

Comment It is noted that the Final Report stated that the formulations used were 8225X for the 0.05% gel, 8195X for the 0.01% gel and 8006X for the vehicle gel. However, Dr. Miller's protocol number was R168-210-8004, suggesting that he might have been using an earlier preparation for the 0.05% gel (8004X). However, all these preparations were of the "old" formulation, which used trolamine for the final neutralization step instead of tromethamine, as in the current formulation.

Results:

- Ninety-two evaluable patients were enrolled and 80 completed the study (for demographics, see Table 7b).
- Efficacy This is summarized in the following Table:

Endpoint Percent Reduction in	0.05% gel	0.01% gel	Vehicle
total inflammatory lesions	53	54	57
total noninflammatory lesions	40	34	29
total lesions	44	43	39

"Treatment success rates" (defined as 50% or better improvement vs baseline) were identical among the 3 groups. None of the data shown above for the tazarotene gels showed statistically significant differences vs vehicle (p>0.05). Patients' cosmetic assessment (5-point scale consisting of "highly favorable", "favorable", "neutral",

"slightly unfavorable", and "highly unfavorable") were favorable or better in 80% of the tazarotene treatment groups and 70% of the vehicle group.

3. Safety Adverse events reported as treatment-related:

	<u>0.05% gel (n=31)</u>	<u>0.01% gel (n=29)</u>	<u>Vehicle (n=32)</u>
Irritation	3	0	1
burning	2	0	1
erythema	2	0	0
peeling	2	0	0
pruritus	2	1	0
edema	1	0	0

None of the adverse events were classified as severe. CBC, serum chemistry and urinalysis showed no clinically significant abnormalities.

Comment This study showed some promise of tazarotene in the once-a-day treatment of noninflammatory lesions of acne but was insufficiently powered to give statistical significance. The 0.5% gel was only slightly better than the 0.01% gel but gave higher incidence of adverse events. A higher concentration of gel (>0.05%) might do better if the safety profile remained acceptable.

7.3 Dose-Response Studies in Psoriasis

7.3.1 Study R168-111-7997. Comparison of Tazarotene (AGN 190168) 0.1% and 0.05% Gels Applied Once Daily and Twice Daily in the Treatment of Psoriasis: A Pilot Study

This was a multicenter, investigator-masked, randomized, balanced, incomplete-block trial designed as a dose-finding study with the objective of comparing the efficacy and safety of two concentrations (0.1% and 0.05%) of tazarotene gel applied at two frequencies (qd and bid) for 8 weeks in psoriasis. Subjects were randomized to 2 out of 6 possible combinations of 4 regimens for bilateral treatment of psoriatic plaques and evaluated at weeks-0, 1, 2, 4 and 8 of treatment and weeks-10, 12 and 16

posttreatment. The investigators were:

Peter M. Elias, M.D. San Francisco, CA 94121	Gerald G. Kreuger, M.D. Salt Lake City, UT 84132	Nicholas Lowe, M.D. Santa Monica, CA 90404
Gerald S. Lazarus, M.D. Philadelphia, PA 19104	Lynn A. Drake, M.D. Scott B. Phillips, M.D. Joseph A. Muccini, Jr., M.D. Boston, MA 02114	Gerald D. Weinstein, M.D. Irvine, CA 92717

Results:

1. Demographics of the 108 patients have been shown in Table 7b. Seventy-six of the subjects completed the study (152 evaluable plaques). Four patients were terminated on the basis of adverse events relating to local irritation; one had a body flare of psoriasis and another "allergic" contact dermatitis which occurred within 5 days after start of therapy with tazarotene gel. The others were discontinued because of lack of efficacy, protocol violation or failure to return.

2. Efficacy All the regimens were able to give significant reduction in scores of the efficacy variables at endpoints for the treatment and posttreatment periods (week-8 and week-16 respectively). Comparison between regimens can be summarized in the following Table:

Tazarotene Regimen	Weeks with Significant Differences (p<0.05) between Treatment Regimens					
	Induration	Scaling	Erythema	Score Totals	Global	Overall Scores
<u>0.05% qd better than*</u>						
0.05% qd	1 to 8	1 to 8	4	1 to 8	1, 2, 4	1 to 8
0.1% qd	2, 4	2, 4		1 to 4	1, 2	4
<u>0.1% qd better than</u>						
0.05% qd	8, 10	10	10, 12	8, 10	10	8, 10
<u>0.1% bid better than</u>						
0.05% qd	1 to 12	1 to 10	4, 10, 12	1 to 10	1,2,4,10	4 to 10
0.05% bid	4, 10					
0.1% qd	1, 2	2, 4		2, 4	2	2, 4

*Better than=statistically significant at p<0.05.

In addition, both formulations given bid and 0.1% gel qd were significantly better than 0.05% gel qd in reduction of pruritus scores at week 10.

In the posttreatment period, induration, scaling, erythema and sum of scores were significantly reduced from baseline (p<0.05) at all visits for each regimen. Global improvement was maintained (mean scores at week 16 ranging from 2.2 for 0.05% qd to 2.7 for 0.05% bid; not significant between treatment regimens, with p>0.05). The number of plaques listed as cleared either increased or stayed the same for all regimens. However, no regimen held a comparative advantage over another beyond the 12th week (see above Table).

3. Safety Discontinuations due to adverse events have been mentioned above. Each treatment regimen was associated with two reports of "severe" burning, stinging or irritation. The following treatment-related adverse events were noted among the 216 treated plaques (54 per regimen):

	0.05% gel qd	0.05% gel bid	0.1% gel qd	0.1% gel bid
burning/stinging	3	9	16	9
pruritus	4	3	5	6
erythema	3	2	4	5
irritation	1	1	1	3
contact dermatitis	2	2	0	1
other*	0	2	2	0

*other= skin pain and vasodilation, each 1 case in 0.05% bid group and dry skin and vesiculobullous rash, each 1 case in the 0.1% qd group.

No clinically significant laboratory abnormalities were reported (CBC, serum chemistry and urinalysis).

Comment

1. This is another bilateral comparison study subject to the same assumptions discussed under study R168-110-8225 (Section 7.2.1.1).
2. Tazarotene regimens used in this study appeared to be associated with beneficial effect maintained in the posttreatment period. However, since it was an uncontrolled study, a lasting effect could not be clearly attributed to tazarotene treatment.
3. For efficacy, tazarotene qd regimens were not better than bid regimens at any point in treatment.
4. The 0.1% gel qd regimen was better than 0.05% gel qd later in the course of treatment for induration, total scores and overall clinical severity scores, and continued to be better in the posttreatment period.
5. The 0.1% gel bid regimen was better than 0.05% gel bid only for induration at weeks-4 and -10; however, it was superior to 0.1% gel qd for several

variables earlier in the treatment course.

6. The 0.05% gel given qd was least irritating, followed by 0.05% gel bid. The 0.1% gel given qd was not less irritating than when given bid.

7.3.2 Study R168-112-8606. A One-Month Comparison of the Safety and Tolerability of Tazarotene (AGN 190168) 0.1% and 0.05% Gels Once Daily in Volunteers with Mild to Moderate Plaque Psoriasis.

This was a single-center, double-blind, randomized, parallel-group phase 2 study in the United Kingdom comparing qd use of 0.1% and 0.05% tazarotene gels. Patients were treated for 4 weeks and assessed at weeks-0, 2, 4 and 6. The investigator was Professor R. Marks at the University of Wales College of Medicine, Health Park, Cardiff CF4 4XN, U.K.

Results:

1. Fifteen patients (0.1% gel: 8 and 0.05% gel: 7) were enrolled and 12 completed the study (see Table 7b for demographics). Two were terminated because of adverse events (one in each treatment group because of severe "skin inflammation").
2. Efficacy Efficacy was not among the primary aims of the study and there was no vehicle or active control treatment group. Nevertheless, there was improvement in the scores for erythema, scaling and plaque elevation vs baseline. The changes were not significant as the sample size was small.
3. Safety and tolerability During the 4-week treatment period, reports of "severe" pruritus, inflammation, burning, stinging and peeling were reported in both treatment groups (3/8 with 0.1% gel and 2/7 with 0.05% gel). However, none was classified as "serious". Plasma levels of tazarotene were below detection while levels of its metabolite, AGN 190299, were never higher than 0.8 ng/ml. No apparent relationship between dose and plasma level was seen. Washout periods of 14-28 days appeared adequate to achieve nondetectable plasma levels of AGN 190299. There were no clinically significant laboratory abnormalities.

Comment

1. Plasma levels of tazarotene and AGN 190299 appeared acceptable during the 4-week treatment with 0.1% or 0.05% gel at once-a-day dosage.
2. In this study, "severe" local adverse events occurred with both gels, slightly more with the 0.1% gel (3/8=38% vs 2/7=29% with 0.05% gel). Larger studies would be needed to corroborate its findings in safety or efficacy.

7.3.3 Study R168-721-7997. Early Phase II Clinical Study on Tazarotene (AGN 190168). Efficacy, Safety and Usefulness against Psoriasis.

This study was a multicenter, open trial in Japan under the chief investigatorship of Yasumasa Ishibashi, M.D. in the Faculty of Medicine, University of Tokyo. Psoriasis patients were given one of the two following combinations and were to apply once a day tazarotene gel to one test lesion (each <900 cm²) and vehicle to another for 4 weeks: (tazarotene 0.01% gel + vehicle gel) or (tazarotene 0.05% gel + vehicle gel).

Results:

1. Twenty-four patients enrolled. Two dropped out for non-adverse event reasons. There were 10 patients in the (0.01% gel + vehicle) group and 12 in the (0.05% gel + vehicle) group. Demographics parameters were comparable between the two groups.

2. Efficacy

a) Symptoms and signs were not individually assessed.

b) The primary evaluation of efficacy was with investigator's "global" by a 6-point scale; a global improvement rate was defined as the proportion of patients achieving improvement better than "slightly improved".

Time-point	Global Improvement Rate					
	0.01% gel + vehicle group			0.05% gel + vehicle group		
	Tazarotene	Vehicle	p	Tazarotene	vehicle	p
Week-1	0/8	0/8	1.00	4/10=40%	0/10	0.31
week-2	3/10=30%	1/10=10%	0.63	6/13=46%	2/13=15%	<0.01
week-3	6/8=75%	4/8=50%	0.75	6/7=85%	3/7=43%	0.06
week-4	6/10=60%	5/10=50%	1.00	8/12=75%	4/12=33%	0.03

c) The parameter "global usefulness" (defined as 1=markedly useful, 2=useful, 3=slightly useful, 4=useless and 5=unfavorable) at exit visit showed no significant difference between tazarotene and vehicle in either treatment group ($p > 0.05$).

d) Superiority comparison between the two treated lesions in each patient for "global improvement rate" and for "global usefulness" was also made on a 5-point scale from tazarotene "distinctly superior" to vehicle to "distinctly inferior" to vehicle:

- i) for "global improvement rate", the 0.01% gel did not result in significantly more "superiors" than vehicle ($p > 0.05$), while the 0.05% gel gave a significantly higher rate than vehicle over week-2 to week-4 (p between 0.03 and 0.008);
- ii) for "global usefulness", which was only evaluated at the exit visit, the 0.05% gel showed significant superiority in "usefulness" over vehicle ($p < 0.03$).

3. **Safety** Adverse events were reported in 5 subjects –one case of dryness of lip believed to be treatment-unrelated (0.01% gel + vehicle) group (10%) and one case each of pruritus, irritation, petechial eruption and one with erythema plus irritation around application site in the (0.05% gel + vehicle) group (33%). No laboratory test abnormalities were reported.

Comment This study employed such small sample size, unconventional efficacy parameters and a bilateral comparison design, making it difficult to evaluate. However, there was a suggestion of superiority of the 0.05% gel given qd vs vehicle qd in psoriasis.

7.3.4 Study R168-722-8606. Late Phase II Clinical Study on Tazarotene (AGN 190168) against Psoriasis. Double-masked controlled Study for dose Response of Tazarotene.

This study was completed after the original NDA filing and was not reported in the 120-day safety update. The Applicant responded to request for information and submitted the final report on January 9, 1996. It was a multicenter, double-masked bilateral comparison study in Japan with the 61 investigators in 25 institutions, conducted under the chief investigatorship of Dr. Yasumasa Ishibashi, Director of Tokyo Teishin Hospital.

The objective was to compare the two formulations of tazarotene: 0.1% and 0.05% gel in the treatment of psoriasis. The subjects were to apply tazarotene 0.1% gel to a lesion on one side and 0.05% gel to another lesion on the contralateral side for up to 8 weeks; each lesion was not to exceed 400 cm² in size. Clearing would result in

cessation of treatment. The efficacy parameters were the same as in Study R168-721-8606 (see above). In addition, clinical signs (induration, scaling and erythema) were evaluated on a scale of 0-4 (0=none, 1=slight, 2=mild, 3=moderate and 4=severe).

Results:

1. Ninety-nine patients were enrolled and 3 were disqualified; 62 completed the study. Of the 34 discontinuations, 4 were due to "side effects" (symptoms of local irritation).

2. Efficacy evaluation

a) Comparison of symptom scores at endpoint (week-8) between the two gels showed no statistically significant difference. For scaling alone and at weeks-4 and -6, 0.1% gel was superior to 0.05% gel.

b) "Global improvement rates" were not significantly different ($p > 0.05$) between the 2 treatment groups. However, "superiority comparison of global improvement rate" showed the 0.1% gel better at all visits:

Visit	N	0.1% >> 0.05%	0.1% > 0.05%	0.1% = 0.05%	0.1% < 0.05%	0.1% << 0.05%	p
wk-2	92	3	29	46	14	0	<0.01
wk-4	79	4	29	35	11	0	<0.01
wk-6	67	3	29	27	6	2	<0.01
wk-8	62	3	23	27	7	2	0.01

c) "Global usefulness" also was not significantly different ($p > 0.05$) when the two treatment groups were compared. However, "superiority comparison of global usefulness" showed 0.1% gel to be "superior" ($p < 0.01$).

3. Safety There were no significant abnormalities in clinical laboratory tests. Adverse event profiles of the two formulations were similar:

Adverse event	Tazarotene 0.05% gel	Tazarotene 0.05% gel
skin irritation	11	10
local pain	2	2
erythema	1	2
flare	1	1
flush	2	3
desquamation	2	2
edema	1	1
pruritus	4	5
dry mouth	1	0
oral irritation	1	0

Comment Similar to R168-721-7997, this study used unconventional efficacy parameters. The "global improvement rate" and "global usefulness" in general were not significantly different among the two treatments; however, "superiority comparisons" of the two treated lesions of the same patients did show significantly better effect by the 0.1% gel. The report concluded that the 0.1% gel represented the "optimum dose" in psoriasis. This is problematic. The more conventional parameters (scores for clinical signs including induration, erythema and scaling and investigator's global) in this study have not shown significant differences among the 2 formulations in terms of efficacy at endpoint or safety. In addition, interpretation of data is subject to the assumptions made in topical treatment studies involving bilateral comparisons.

7.4 Overall Conclusions from Phase II Studies

The major findings of Phase 2 studies have been summarized (see Appendix IE). Only limited conclusions can be drawn from the Phase 2 studies because of several

problems associated with these trials:

1. Psoriasis studies.

- a) Six out of 7 studies were bilateral comparisons.
- b) The only study not involving bilateral comparison (U.K. trial) had only 15 patients (8 using 0.1% gel and 7 0.05% gel).
- c) Two of these studies used unconventional parameters for efficacy.
- d) The two studies on mechanism of action were either unevaluable due to experimental error or inadequate in terms of data presented.
- e) Only 2 of the 7 studies involved treatment for more than 4 weeks.

2. Acne study.

- a) The only Phase 2 acne study was not sufficiently powered.
- b) The 0.1% gel had not been compared with other concentrations in dose-response studies.

Despite these shortcomings the following conclusions appear reasonable:

a) The 0.01% gel given bid was a minimal effect dose for efficacy and safety in psoriasis (R168-110-8225) or acne (R168-210-8225).

b) In psoriasis, the 0.05% gel given bid was superior to vehicle in efficacy parameters but was associated with a significant degree of local adverse events (R168-110-8225). When given qd, there was a suggestion of superiority over vehicle and the adverse event profile seemed acceptable (R168-721-7997). The 0.05% gel given qd also showed some promise in the reduction of noninflammatory lesions in acne (R168-210-8225).

c) In psoriasis, the 0.1% gel was not adequately studied against vehicle in phase 2 studies but primarily compared with the 0.05% gel. When given qd, it appeared to be better than the 0.05% gel in efficacy after 8 weeks of treatment. However, there was a greater incidence of local irritation. A bid regimen of the 0.1% gel offered only slightly more benefit during the initial weeks of treatment without substantial change in the safety profile (R168-111-7997).

d) The 0.1% or 0.05% gels given qd for up to 4 weeks in psoriasis were associated with undetectable plasma levels of tazarotene, while its primary metabolite, AGN190299, remained below 0.8 ng/ml (R168-112-8606); thus, systemic exposure was quite limited.

e) In psoriasis, follow-up of patients to week-16 after an 8-week course of 0.1% or 0.05% gel suggested possible beneficial effect of tazarotene in the posttreatment period (R168-111-7997). However, as psoriasis is a chronic disease which waxes and wanes, it would be necessary to have proper control in order to confirm a sustained effect.

8. Phase III Clinical Studies

8.1 Indication #1. Treatment of psoriasis.

8.1.1 Trial #1. Study#R168-120-8606: Safety, Efficacy and Duration of Therapeutic Effect of Once-Daily Tazarotene (AGN 190168) 0.1% Gel or 0.05% Gel versus Vehicle Gel in Stable Plaque Psoriasis.

8.1.1.1 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 vehicle gel in the treatment of stable plaque psoriasis.

The rationale of this study was based on tazarotene's ability to modulate the three pathogenetic factors in psoriasis: 1) keratinocyte hyperproliferation, 2) abnormal keratinocyte differentiation and 3) infiltration of inflammatory components into skin. Tazarotene blocks induction of epidermal ornithine decarboxylase (ODC) activity, which is associated with cell proliferation and hyperplasia and it inhibits cornified envelope formation and build-up, which are elements of the psoriatic scale. In addition, tazarotene has been shown to modulate the expression of some markers associated with inflammation, such as ICAM-1 and HLA-DR.

8.1.1.2 Design

This study was a 24-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 for 12 weeks in patients having plaque psoriasis, with a 12-week posttreatment follow-up (see Table below).

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

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

**Pregnancy tests done if applicable.

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

8.1.1.3 Protocol

8.1.1.3.1 Population/Procedures

Patient Selection Either sex, 12 years or older, with stable plaque psoriasis involving <20% of total body surface area and 2 target lesions of similar severity (minimum size=2 cm in diameter and score for baseline plaque elevation ≥ 2 [0-4 scale in $\frac{1}{2}$ point increments: 0=none, 1=mild, 2=moderate, 3=severe and 4=very severe]) on (1) elbow or knee and (2) trunk or limbs. A normal menstrual cycle prior to entry and negative urine pregnancy test at time of entry were mandatory for females of child-bearing potential. The following were exclusion criteria:

1. known sensitivity to any of the components of the study medication

2. history of other skin conditions that would interfere with evaluation of test medication
3. spontaneously improving or rapidly deteriorating plaque lesions or pustular/exfoliative psoriasis
4. concomitant use of tar shampoos, topical or systemic therapies that might alter the course of psoriasis
5. uncontrolled systemic disease
6. females who were pregnant or nursing, or planning a pregnancy during the study, or thought they might be pregnant at the start of the study (females of child-bearing potential were required to use reliable forms of contraception throughout the study, e.g., abstinence, oral contraceptives for at least 12 consecutive weeks prior to study entry, or spermicide and condoms)
7. washout periods: topical drugs that might alter the course of psoriasis- 2 weeks, oral retinoids- 8 weeks, non-retinoid systemic drugs that might alter the course of psoriasis- 4 weeks, PUVA- 4 weeks, UVB- 2 weeks
8. concurrent participation in another drug research study or within 30 days prior to enrollment.

Concomitant Medications

1. Any other medication that might alter the course of psoriasis was disallowed.
2. Medications necessary for the subject's welfare and not affecting the course of psoriasis would be allowed.
3. Use of proscribed drug in emergency would be done with the safety of the subject as the prime consideration. the Sponsor and Investigator would decide if the subject should continue to be in the study.

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. Subjects applied their treatment daily (every evening) to all psoriatic plaques for 12 weeks, or less if a global response of "completely cleared" was achieved. Subjects were to bathe/shower in the morning and refrain from using tar shampoos but non-medicated shampoos were allowed as often as needed. Emollient (Eucerin Lotion® or Moisturel Lotion®) was allowed as needed, but only on non-target lesions and at least one hour after application of study medication. Emollient was not allowed on the evening prior to a visit and until the visit was completed. Visits were scheduled as shown in the Section on Design (8.1.1.2).

The following parameters were to be evaluated:

A) Efficacy

1. plaque elevation of each target lesion.
2. scaling of each target lesion.
3. erythema of each target lesion.
4. overall clinical severity grade of all treated lesions.

These four parameters were scored as follows with ½-point increments: 0=none, 1=mild, 2=moderate, 3=severe and 4=very severe.

5. sum of plaque elevation, scaling and erythema=sum of scores for 1, 2 and 3.
6. target lesion response to treatment at postbaseline visit (for a target lesion).
7. global response to treatment at postbaseline visit (for all treated lesions).

These two postbaseline parameters were scored as follows: 5=complete (100%) clearance; 4=excellent=75-99% improvement; 3=good=50-74% improvement; 2=fair=25-49% improvement; 1=poor=1-24% improvement and 0=lesion unchanged or worsened.

8. treatment success (a) for target lesion and (b) overall: defined as scores of 3, 4 or 5 for target lesion response or for global response respectively.
9. time to initial treatment success: visit at which treatment success was first noted

(global or for target lesion).

B) Pharmacokinetics

At 3 sites (Lowe, Shmunis and Tschien), 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 8.1.1.2).

D) Others Parameters assessed or recorded by the subjects were:

1. pruritus and
2. pain.

Both pruritus and pain were scored by the subjects with ½-point increments as follows: 0=none, 1=mild, 2=moderate, 3=severe and 4=very severe.

3. cosmetic acceptability: assessed at the end of study with a 0-4 scale: 0=highly unfavorable, 1=slightly unfavorable, 2=neutral, 3=favorable and 4=highly favorable.
4. comparison with previous treatments: assessed at the end of study – comparison between tazarotene with the subject's most recent prior treatment as follows: never had previous treatment, cannot decide, much worse, worse, same, superior or far superior. These grades had no numeric representation.
5. emollient use: frequency as in diaries and amount by weight of emollient bottles.

8.1.1.3.2 Subject Dispositions and Endpoints

There were 5 categories for patient disposition:

1. **Completed**-(a) for treatment period: completed the 12-week treatment phase, (b) for posttreatment period: completed all posttreatment follow-up visits. Patients with a global response of 5 during treatment phase went directly into posttreatment phase - considered as having completed treatment phase.
2. **Terminated**- exit from study due to lack of efficacy or adverse event.
3. **Disqualified**- not meeting enrollment criteria &/or baseline laboratory test abnormality.
4. **Discontinued**- missed visits, noncompliance, concomitant therapy, unacceptable lab results, pregnancy test positivity, etc.
5. **Needed treatment**- exit from posttreatment phase due to psoriasis treatment; subjects were also discontinued from study if "overall clinical severity score" was ≥ 2 .

Endpoints for **treatment phase** were one of the following: (1) week-12 visit, (2) a global response of "complete clearing" resulting in discontinuation of treatment or (3) time of exit from study due to lack of efficacy or adverse event; and for **posttreatment phase** (1) week-24 visit or (2) exit from study due to need for treatment or "overall clinical severity score" ≥ 2 .

The **Primary Efficacy Variables** were not defined in the original clinical protocol, which merely stated that the "main efficacy variables for psoriasis are erythema, plaque elevation and scaling" (vol 1.87 p 288) but in the Final Report (vol 1.87 p 027), they were given as:

1. plaque elevation of target lesion,
2. scaling of target lesion,
3. erythema of target lesion,
4. sum of plaque elevation, scaling and erythema scores,
5. target lesion response to treatment,
6. global response to treatment and

6. global response to treatment and
 7. time to initial treatment success for both target lesions and all treated lesions.
- However, this Report also stated under "Criteria for Effectiveness" that "as planned in the protocol, the main efficacy variables were changes from baseline in plaque elevation (the variable upon which power calculations were based), scaling and erythema; target lesion response to treatment; and global response to treatment."

Comment

1. There are too many primary variables.
2. The Applicant has been inconsistent in defining the primary variables for efficacy. The original protocol did not specify changes from baseline as criteria for effectiveness, although it has been acceptable to compare these changes as efficacy parameters.
3. For the purpose of this review, the primary variables will be the changes in scores for erythema, induration and scaling of the target lesions and the global response to treatment.
4. The parameter "treatment success" allows for any lesion or anyone having $\geq 50\%$ improvement over baseline in the target lesion response or global evaluation respectively. The Applicant established this criterion on advice by its consulting physicians. Clinically, it seems more appropriate to regard success as improvement of at least 75% over baseline. For this reason, a 75% cutoff is also used in a post-hoc analysis in this review.

8.1.1.3.3 Statistical Considerations

Comparisons between treatment groups for demographic and background data were done using ANOVA and the Mantel-Haenszel test. Comparisons for efficacy data (plaque erythema, elevation, scaling, sum of scores, overall severity and globals) were done using extended Mantel-Haenszel test for ordinal data. Time to initial treatment success was tested by stratified log-rank test and Kaplan-Meier method. Two-tailed tests were used and statistical significance was defined by $p \leq 0.05$. The analyses to be performed were defined on the basis of patient inclusion as follows:

Analysis type	Patient Criteria*						
	≥ 1 dose	≥ 1 FU visit	Eval	Noneval	Cleared	Term	D/C
Safety	+	±	±	±	±	±	±
Efficacy							
1. Preferred	+	+	+	-	±	±	-
2. Last observation carried forward (LOCF)	+	+	+	-	±	±	±
3. Intent-to-treat (ITT)	+	+	+	+	±	±	±

*FU visit=follow-up visit, Eval=evaluable efficacy data, Noneval=nonevaluable efficacy data, Cleared=patient discontinuing treatment because of "global"="cleared", Term=terminated from study due to lack of efficacy or adverse events, D/C=discontinued from study for reasons other than termination due to lack of efficacy or adverse events.

Comment The term "last observation carried forward" analysis is misleading. All 3 types of efficacy analyses used the last observation carried forward method. The only difference lies in the degree of data or patient inclusion shown in the above Table.

8.1.1.4 Results

8.1.1.4.1 Patient Disposition, Comparability

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

<u>Investigator</u>	<u>Center no.</u>	<u>Total</u>	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>
Krueger	0088	36	12	12	12
Weinstein	0188	42	14	14	14
Lowe	0228	36	12	12	12
Tschen	1104	36	12	12	12
Jorizzo	1275	30	10	10	10
Jagothy	1557	36	12	12	12
Shmunes	1558	36	12	12	12
Duvic	1882	30	10	10	10
Friedman	2108	<u>42</u>	<u>14</u>	<u>14</u>	<u>14</u>
		324	108	108	108

- Comment**
1. Curriculum vitae of the investigators are missing.
 2. Drug-investigator interaction in this study was minimal.

Completion Status:

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

*Numbers in parentheses indicate unevaluable patient numbers

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

Six patients were "unevaluable":

Tazarotene 0.1% gel - entry criteria violation (previous treatment washout period) 1, concomitant therapy 1 and no evaluable postbaseline visit 1.

Tazarotene 0.05% gel - no postbaseline visit 2.

Vehicle - concomitant therapy 1.

Only one patient had complete clearing () on vehicle, cleared at week-4).
Most patients were exposed to the study drug for between 8-12 weeks:

	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>
Enrolled	108	108	108
Exposed for ≥8weeks	94	89	95
Completed treatment	81	80	81
Exposed for ≥12 weeks	70	63	67
Exposed for ≥14 weeks	4	2	0

Comparability of Treatment Groups

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

Comment

1. The small number of unevaluable patients had minimal impact on data analyses and all 3 analyses (preferred, LOCF and ITT) gave virtually the same results. Only data from the preferred analysis will be presented here.
2. The three arms of this study were comparable.

8.1.1.4.2 Efficacy Parameters

8.1.1.4.2.1 Main Variables at Endpoint

Endpoint 1. Treatment period. At week-12:

A. Target Lesions

Table 8.1.1.4.2.1a Target Lesion Responses at Treatment Period Endpoint

	<u>Trunk/Arm/Leg</u>			<u>Knee/Elbow</u>		
	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>
Plaque Elevation						
Baseline (mean±SD)	2.46±0.51	2.49±0.48	2.44±0.49	2.56±0.59	2.55±0.53	2.57±0.54
Endpoint (mean)	1.07	1.08	1.67	1.09	1.20	1.86
Reduction (mean±SD)	<u>1.39±0.90*</u>	<u>1.41±0.90</u>	0.77±0.90	<u>1.47±0.95</u>	<u>1.35±0.96</u>	0.71±0.99
Scaling						
Baseline (mean±SD)	2.36±0.56	2.35±0.69	2.39±0.65	2.47±0.73	2.47±0.74	2.52±0.63
Endpoint (mean)	1.11	1.22	1.71	1.22	1.36	1.90
Reduction (mean±SD)	<u>1.25±0.93</u>	<u>1.13±0.92</u>	0.68±0.99	<u>1.25±0.94</u>	<u>1.11±1.08</u>	0.62±0.91
Erythema						
Baseline (mean±SD)	2.44±0.63**	2.37±0.68	2.28±0.66	2.26±0.65	2.22±0.67	2.17±0.68
Endpoint (mean)	1.43	1.41	1.69	1.30	1.35	1.67
Reduction (mean±SD)	<u>1.01±0.91</u>	<u>0.96±0.99</u>	0.59±0.79	<u>0.96±0.90</u>	<u>0.87±0.98</u>	0.50±0.87
Total Sign scores						
Baseline (mean±SD)	7.26±1.30	7.21±1.43	7.12±1.35	7.29±1.53	7.25±1.49	7.26±1.39
Endpoint (mean)	3.61	3.70	5.07	3.61	3.92	5.44
Reduction (mean±SD)	<u>3.65±2.44</u>	<u>3.51±2.45</u>	2.05±2.39	<u>3.68±2.38</u>	<u>3.33±2.60</u>	1.82±2.40
Mean Treatment Response Score						
Response Score	<u>2.86±1.45*</u>	<u>2.62±1.54</u>	1.75±1.52	<u>2.73±1.40</u>	<u>2.49±1.61</u>	1.65±1.55
"Treatment Success" (% pts)						
	<u>70</u>	<u>59</u>	35	<u>60</u>	<u>60</u>	35
Time to initial "Treatment Success" in 50% of pts						
	<u>week-5.4</u>	<u>week-6.5</u>	week-11.7	<u>Week-5.4</u>	<u>Week-8.0</u>	week-12.0

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

**Baseline for erythema of trunk/arm/leg lesions for 0.1% gel group significantly different vs vehicle (p<0.03).

Figures highlighted show significant differences among 0.1% gel and 0.05% gel treatment groups (p<0.02)

B. Overall Evaluation

Table 8.1.1.4.2.1b Overall Responses at Treatment Period Endpoint

		<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>
Overall Clinical Severity	Baseline (mean±SD)	2.49±0.46	2.45±0.49	2.46±0.45
	Reduction (mean)	<u>1.21*</u>	<u>1.13</u>	0.66
Investigator's Global Score (mean)		<u>2.65</u>	<u>2.23</u>	1.55
Overall "Treatment Success" (% of patients)		<u>65</u>	<u>52</u>	33
Time to initial "Treatment Success" in 50% of pts		<u>week 6-8</u>	<u>week 9</u>	>week-12

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

†Figures highlighted show significant difference among 0.1% gel and 0.05% gel treatment groups (p<0.02)

Endpoint 2. Posttreatment Period.

At week-24:

A. Target Lesions

Table 8.1.1.4.2.1c Target Lesion Responses at Posttreatment Period Endpoint

	<u>Trunk/Arm/Leg</u>			<u>Knee/Elbow</u>		
	<u>Tazarotene</u>	<u>Tazarotene</u>	<u>Vehicle</u>	<u>Tazarotene</u>	<u>Tazarotene</u>	<u>Vehicle</u>
	<u>0.1%</u>	<u>0.05%</u>		<u>0.1%</u>	<u>0.05%</u>	
Plaque Elevation						
Baseline (mean±SD)	2.44±0.54	2.48±0.49	2.45±0.48	2.58±0.60	2.57±0.55	2.50±0.52
Endpoint (mean)	1.34	1.24	1.56	1.57	1.46	1.76
Change (mean±SD)	1.10±1.06	<u>1.24±1.06*</u>	0.89±0.85	1.01±0.87	<u>1.11±1.01</u>	0.74±0.90
Scaling						
Baseline (mean±SD)	2.35±0.63	2.32±0.73	2.39±0.68	2.43±0.71	2.43±0.78	2.44±0.64
Endpoint (mean)	1.37	1.43	1.57	1.58	1.62	1.76
Change (mean±SD)	0.98±1.15	0.89±1.11	0.82±1.06	0.85±1.00	0.81±1.09	0.68±0.95
Erythema						
Baseline (mean±SD)	2.39±0.63**	2.38±0.69	2.23±0.68	2.24±0.67	2.18±0.70	2.11±0.70
Endpoint (mean)	1.48	1.33	1.57	1.47	1.44	1.52
Change (mean±SD)	0.91±1.01	<u>1.05±1.08</u>	0.66±0.85	0.77±0.94	0.74±1.16	0.59±0.87
Total Sign scores						
Baseline (mean±SD)	7.18±1.35	7.18±1.48	7.07±1.38	7.24±1.57	7.18±1.59	7.06±1.38
Endpoint (mean)	4.19	4.00	4.70	4.61	4.52	5.05
Change (mean±SD)	2.99±2.94	3.18±2.91	2.37±2.37	2.63±2.40	2.66±2.89	2.01±2.34
Mean Tx Response						
Score	2.10±1.16	<u>2.45±1.94*</u>	1.79±1.50	1.93±1.57	2.16±1.77	1.61±1.59
"Treatment Success" (% pts)	41	<u>52</u>	33	40	43	33

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

**Baseline for erythema of trunk/arm/leg lesions for 0.1% gel group significantly different vs vehicle (p<0.04).

B. Overall Evaluation

Table 8.1.1.4.2.1d Overall Responses at Posttreatment Period Endpoint

		<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>
Overall Clinical Severity	Baseline (mean±SD)	2.44±0.45	2.44±0.52	2.42±0.46
	Reduction (mean)	0.93	0.97	0.73
Investigator's Global Score (mean)		1.58	1.88	1.42
Overall "Treatment Success" (% of patients)		28	40	25

*Figures would have been underlined if significantly different from those of vehicle (p<0.05).

8.1.1.4.2.2 Other efficacy parameters

A. Patient evaluation at the end of treatment

	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>
Cosmetic Acceptability (% pts)			
Highly favorable	26	26	18
Favorable	45	45	41
Neutral	15	15	26
Slightly unfavorable	3	9	5
Unfavorable	12	6	11
Comparison to Past Therapy (% pts)			
- Far Superior	21	16	-11
Superior	29	29	15
Same	17	19	18
Worse	18	20	35
Much Worse	9	7	5
Can't Decide	1	7	12
No Past Therapy	4	1	5

B. Subjective Symptoms and Emollient Use

The subjective scores (for pain and pruritus) were not significantly different ($p > 0.05$) among the three treatment groups at baseline or at endpoint. Emollient use was needed in $>97\%$ of patients in all 3 groups, and the frequency of usage and total quantities used during the study were similar among the groups ($p > 0.05$).

8.1.1.4.2.3 Onset of action and duration of effect of Tazarotene

A. Onset of Action

Table 8.1.1.4.2.3a Drug Effect on Target Lesions before Endpoint in Treatment Period

	<u>Trunk/Arm/Leg</u>				<u>Knee/Elbow</u>			
	<u>wk-1</u>	<u>wk-2</u>	<u>wk-4</u>	<u>wk-8</u>	<u>wk-1</u>	<u>wk-2</u>	<u>wk-4</u>	<u>wk-8</u>
I. Mean Score Reduction								
Plaque Elevation								
Tazarotene 0.1%	<u>0.63*</u>	<u>0.99</u>	<u>1.13</u>	<u>1.24</u>	<u>0.59</u>	<u>0.92</u>	<u>1.10</u>	<u>1.29</u>
Tazarotene 0.05%	<u>0.71</u>	<u>0.81</u>	<u>1.08</u>	<u>1.38</u>	<u>0.60</u>	<u>0.88</u>	<u>1.03</u>	<u>1.28</u>
Vehicle	0.28	0.41	0.70	0.69	0.31	0.39	0.60	0.70
Scaling								
Tazarotene 0.1%	<u>0.52</u>	<u>0.72</u>	<u>0.93</u>	<u>1.00</u>	<u>0.36</u>	<u>0.60</u>	<u>0.81</u>	<u>1.01</u>
Tazarotene 0.05%	<u>0.48</u>	<u>0.67</u>	<u>0.90</u>	<u>1.12</u>	<u>0.37</u>	<u>0.62</u>	<u>0.77</u>	<u>0.98</u>
Vehicle	0.30	0.42	0.54	0.67	0.30	0.35	0.42	0.67
Erythema								
Tazarotene 0.1%	0.16	0.49	0.65	<u>0.90</u>	0.15	0.41	<u>0.65</u>	<u>0.83</u>
Tazarotene 0.05%	0.25	0.36	0.57	0.82	0.16	0.29	0.51	0.75
Vehicle	0.19	0.32	0.46	0.57	0.25	0.31	0.42	0.56
Total Scores								
Tazarotene 0.1%	<u>1.30</u>	<u>2.20</u>	<u>2.71</u>	<u>3.14</u>	1.10	<u>1.93</u>	<u>2.56</u>	<u>3.12</u>
Tazarotene 0.05%	<u>1.45</u>	<u>1.83</u>	<u>2.55</u>	<u>3.31</u>	1.14	<u>1.79</u>	<u>2.31</u>	<u>3.01</u>
Vehicle	0.76	1.14	1.70	1.93	0.86	1.04	1.44	1.93
II. Target Lesion "Treatment Success" (% pts)								
Tazarotene 0.1%	16	<u>33</u>	<u>89</u>	<u>51</u>	16	<u>31</u>	<u>36</u>	<u>53</u>
Tazarotene 0.05%	16	<u>24</u>	<u>28</u>	<u>50</u>	14	<u>19</u>	<u>32</u>	<u>44</u>
Vehicle	8	12	17	23	9	14	17	23

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

Figures highlighted show significant difference among 0.1% and 0.05% of treatment groups ($p < 0.02$).

Table 8.1.1.4.2.3b Overall Disease Variables before Endpoint in Treatment Period

		<u>wk-1</u>	<u>wk-2</u>	<u>wk-4</u>	<u>wk-8</u>
Investigator's Global (mean)	Tazarotene 0.1%	<u>1.27</u>	<u>1.17</u>	<u>1.99</u>	<u>2.29</u>
	Tazarotene 0.05%	<u>1.19</u>	<u>1.45</u>	<u>1.77</u>	<u>1.99</u>
	Vehicle	0.81	1.00	1.24	1.37
"Treatment Success" (%pts)	Tazarotene 0.1%	14	<u>29</u>	<u>36</u>	<u>51</u>
	Tazarotene 0.05%	10	<u>29</u>	<u>31</u>	<u>39</u>
	Vehicle	6	6	18	22

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

Figures highlighted show significant difference among 0.1% and 0.05% treatment groups (p<0.02)

B. Duration of Effect in the Posttreatment Period

Table 8.1.1.4.2.3c Target Lesion Condition in Posttreatment Period

	<u>Trunk/Arm/Leg</u>			<u>Knee/Elbow</u>		
	<u>week-16</u>	<u>week-20</u>	<u>week-24</u>	<u>week-16</u>	<u>week-20</u>	<u>week-24</u>
I. Mean Score Reduction						
Plaque Elevation						
Tazarotene 0.1%	1.21	1.17	1.10	<u>1.19*</u>	<u>1.12</u>	1.01
Tazarotene 0.05%	<u>1.39</u>	<u>1.32</u>	<u>1.24</u>	<u>1.31</u>	<u>1.19</u>	<u>1.11</u>
Vehicle	0.99	0.92	0.89	0.82	0.80	0.74
Scaling						
Tazarotene 0.1%	1.05	0.96	0.98	0.89	0.83	0.85
Tazarotene 0.05%	1.08	1.01	0.89	<u>1.09</u>	<u>0.95</u>	0.81
Vehicle	0.96	0.92	0.82	0.75	0.67	0.68
Erythema						
Tazarotene 0.1%	0.99	0.95	0.91	<u>0.94</u>	0.87	0.77
Tazarotene 0.05%	<u>1.13</u>	<u>1.02</u>	<u>1.05</u>	0.88	0.79	0.74
Vehicle	0.81	0.72	0.66	0.66	0.64	0.59
Total Scores						
Tazarotene 0.1%	3.24	3.08	2.99	<u>3.01</u>	<u>2.82</u>	2.63
Tazarotene 0.05%	<u>3.61</u>	<u>3.35</u>	3.18	<u>3.28</u>	<u>2.93</u>	2.66
Vehicle	2.75	2.55	2.37	2.22	2.11	2.01
II. Target Lesion "Treatment Success" (% pts)						
Tazarotene 0.1%	53%	46%	41%	44%	41%	40%
Tazarotene 0.05%	61%	54%	<u>52%</u>	<u>58%</u>	45%	43%
Vehicle	45%	39%	33%	39%	34%	33%

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

Table 8.1.1.4.2.3d Overall Disease Variables before Endpoint in Posttreatment Period

		<u>week-12</u>	<u>week-16</u>	<u>week-20</u>	<u>week-24</u>
Investigator's Global (mean)	Tazarotene 0.1%	<u>2.83</u>	<u>2.15</u>	1.86	1.58
	Tazarotene 0.05%	<u>2.41</u>	<u>2.28</u>	1.91	1.88
	Vehicle	1.74	1.71	1.48	1.42
"Treatment Success" (% pts)	Tazarotene 0.1%	<u>70</u>	47	36	28
	Tazarotene 0.05%	<u>56</u>	<u>56</u>	43	40
	Vehicle	38	36	27	25

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

Figures highlighted show significant difference among 0.1% and 0.05% treatment groups (p<0.02)

Table 8.1.1.4.2.3e Exit due to "Need for Treatment"

<u>Timepoint</u>	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>
wk-12	1	1	4
wk-16	28	25	39
<u>wk-20</u>	<u>10</u>	<u>9</u>	<u>6</u>
Total	39 (49%)	35 (44%)	49 (60%)

Comment

1. The Applicant used a response (target lesion or overall) of "good or better", i.e. >50% improvement over baseline, as treatment success. This criterion is problematic. More stringent criteria might shed more light on the real efficacy of tazarotene. The data have been reexamined by looking at the rates of "excellent or better", i.e. >75% improvement and "cleared", i.e. 100% improvement (see below).

It does seem that the tazarotene gels did better than the vehicle in terms of "excellent or better" response in overall or target lesion responses. This was not the case for clearing. In addition, the 0.05% gel did better than the 0.1% gel in the posttreatment period with these criteria.

Target Lesion "Treatment Success" as Defined by "Excellent or Better" or "Cleared"

<u>I. Treatment Period</u>	<u>Trunk/Arm/Leg</u>					<u>Knee/Elbow</u>				
	<u>wk-1</u>	<u>wk-2</u>	<u>wk-4</u>	<u>wk-8</u>	<u>wk-12</u>	<u>wk-1</u>	<u>wk-2</u>	<u>wk-4</u>	<u>wk-8</u>	<u>wk-12</u>
"Excellent or better" (% pts)										
Tazarotene 0.1%	1	15	21	30	43	0	15	14	24	41
Tazarotene 0.05%	6	12	17	26	39	4	12	15	20	35
Vehicle	2	3	6	10	17	1	2	5	9	15
"cleared" (% pts)										
Tazarotene 0.1%	0	0	4	2	5	0	0	1	1	2
Tazarotene 0.05%	0	0	1	1	6	0	0	1	2	5
Vehicle	0	0	3	2	4	0	0	2	3	2

<u>II. Posttreatment Period</u>	<u>Trunk/Arm/Leg</u>				<u>Knee/Elbow</u>			
	<u>wk-12</u>	<u>wk-16</u>	<u>wk-20</u>	<u>wk-24</u>	<u>wk-12</u>	<u>wk-16</u>	<u>wk-20</u>	<u>wk-24</u>
"Excellent or better" (% pts)								
Tazarotene 0.1%	46	35	31	27	44	28	28	23
Tazarotene 0.05%	40	41	40	40	39	35	32	36
Vehicle	20	19	21	19	19	36	16	15
"cleared" (% pts)								
Tazarotene 0.1%	6	6	7	8	3	3	3	3
Tazarotene 0.05%	6	13	17	19	5	4	6	7
Vehicle	5	6	3	3	4	6	4	4

Global "Treatment Success" as Defined by "Excellent or Better" or "Cleared"

<u>I. Treatment Period</u>		<u>wk-1</u>	<u>wk-2</u>	<u>wk-4</u>	<u>wk-8</u>	<u>wk-12</u>
"Excellent or better" (% pts) (>75% improvement)	Tazarotene 0.1%	0	11	15	23	38
	Tazarotene 0.05%	2	11	13	18	28
	Vehicle	1	1	2	4	12
"cleared" (% pts) (100% improvement)	Tazarotene 0.1%	0	0	0	0	0
	Tazarotene 0.05%	0	0	0	0	2
	Vehicle	0	0	1	1	1

<u>II. Posttreatment Period</u>		<u>wk-12</u>	<u>wk-16</u>	<u>wk-20</u>	<u>wk-24</u>
"Excellent or better" (% pts) (>75% improvement)	Tazarotene 0.1%	41	22	14	11
	Tazarotene 0.05%	30	28	23	27
	Vehicle	14	13	10	12
"cleared" (% pts) (100% improvement)	Tazarotene 0.1%	0	3	0	0
	Tazarotene 0.05%	2	0	0	1
	Vehicle	2	1	1	0

2. Caution should be exercised in interpreting the results of "need for treatment" in the posttreatment period. As the number of subjects entering this period were about equal and yet "treatment success" on entry were unequal, the dropout rate due to "need for treatment" would not be an accurate measure of the duration of therapeutic effect. Moreover, psoriasis is a disease which may wax and wane.

3. Tazarotene 0.05% appeared to significantly confer benefit upon plaque elevation in the 12-week posttreatment period. It had a lasting effect on erythema of the trunk/arm/leg target sites and a shorter effect for scaling of knee/elbow sites. Tazarotene 0.1% also had a sustained therapeutic effect on plaque elevation and erythema of the knee/elbow sites but this did not persist throughout the 24 weeks. For conclusions regarding the effect of tazarotene on primary efficacy variables in psoriasis, see Section 8.1.1.5.

8.1.1.4.3 Safety Comparison

8.1.1.4.3.1 Adverse Events See Appendix II. Adverse events of skin and appendages are listed in the following Table. All adverse events will be considered in assessing safety. However, for local adverse events, most of them were in fact "treatment-related".

	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>
Total patients enrolled	108 (100%)	108 (100%)	108 (100%)
Patients with adverse events	70 (65%)/45 (42%)*	70 (65%)/35 (32%)	63 (58%)/19 (18%)
Dermatologic adverse events	53 (49%)/44 (41%)	41 (38%)/34 (32%)	25 (23%)/18 (17%)
pruritus	28 (26%)/25 (23%)	20 (19%)/18 (17%)	10 (9%)/9 (8%)
burning/stinging	23 (21%)/20 (19%)	18 (17%)/16 (15%)	7 (6%)/7 (6%)
irritation	10 (9%)/10 (9%)	3 (3%)/3 (3%)	0
psoriasis worsened	10 (9%)/4 (4%)	5 (5%)/1	4 (4%)
erythema	9 (8%)/9 (8%)	7 (6%)/7 (6%)	1/1
skin pain	6 (6%)/5 (5%)	4 (4%)/4 (4%)	2 (2%)/2 (2%)
rash/vesiculobullous rash	5 (5%)/3 (3%)	3 (3%)/2 (2%)	2 (2%)/1
contact dermatitis, irritant	2 (2%)/2 (2%)	1	1
desquamation	2 (2%)/2 (2%)	1/1	0
skin fissure	2 (2%)	2 (2%)/1	1
skin laceration/excoriation	2 (2%)	0	1
skin hemorrhage	1/1	2 (2%)/2 (2%)	0
skin discharge	1/1	0	0
nail disorder	1/1	0	0
dry skin	1	0	0
skin focal edema	0	1/1	0
hyperkeratosis	0	1	0
rosacea	0	1	0
"dermatitis"	0	0	1
folliculitis	0	0	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:

<u>Treatment period</u>	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>
Total patients terminated for AE	13 (12%)	11 (10%)	3 (3%)
pruritus	7 (6%)	4 (4%)	1
burning/stinging	4 (4%)	4 (4%)	1
erythema	3 (3%)	2 (2%)	1
psoriasis worsened	3 (3%)	0	0
irritation	2 (2%)	0	0
skin pain	1	0	0
rash	1	1	0

Myocardial infarct/death	1	0	0
Ca prostate	1	0	0
skin fissure	0	1	0
skin focal edema	0	1	0
arthralgia/diarrhea/hemorrhoids	0	1	0
headache/vision abnorm/periph edema	0	1	0
"dermatitis" & skin infection	0	0	1

In the **posttreatment period**, one patient in the 0.1% gel group was terminated due to myocardial infarction.

Pregnancy occurred in 3 women (vehicle 1, Tazarotene 0.1% 2) - all resulted in birth of healthy babies and none experienced drug-related adverse events.

8.1.1.4.3.2 Laboratory Studies

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

8.1.1.5 Conclusions

Both tazarotene 0.1% and 0.05% gels appear to be safe and effective in the treatment of stable plaque psoriasis as shown in this study (see following Table). Differences among the two gels are slight in terms of safety and efficacy. The commonest adverse events were pruritus, burning/stinging, irritation, erythema and psoriasis worsened.

Table 8.1.1.5 Summary of Findings in R168-120-8606

	SUPERIORITY OF		
	Taz* 0.1% vs vehicle	Taz* 0.05% vs vehicle	Taz 0.1% vs Taz 0.05%
1° Variables at Treatment Endpoint			
↓ plaque elevation	<0.001/<0.001	<0.001/0.001	-/-
↓ scaling	0.001/<0.001	0.004/0.001	-/-
↓ erythema	<0.001/<0.001	0.027/0.007	-/-
↓ sum of scores	<0.001/<0.001	<0.001/0.001	-/-
Global (treatment success)	<0.001	0.008	-
Onset of Action*			
week-1	PST/P. -	PST/P. -	-/- -
week-2	PST/PST. G	PST/PST. G	-/- G
week-4	PST/PSET. G	PST/PST. G	-/- -
week-8	PSET/PSET. G	PST/PST. G	-/- -
Duration of Effect*			
week-16	-/PET. -	PET/PST. -	-/- -
week-20	-/PT. -	PET/PST. -	-/- -
week-24	-/- -	PE/P. -	-/- -
Safety			
All/ "treatment-related" AE* rates (%)	65/42 vs 58/18	65/32 vs 58/18	65/42 vs 65/32

*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 lesions before 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.

8.1.2 Trial #2. Study#R168-121-8606: Safety and Efficacy of Once-Daily Tazarotene (AGN 190168) 0.1% Gel or 0.05% Gel versus Vehicle Gel in Stable Plaque Psoriasis.

8.1.2.1 Objective/Rationale

The objective was to evaluate the safety and efficacy of once-daily tazarotene 0.1% and 0.05% gels versus vehicle gel in the treatment of stable plaque psoriasis.

8.1.2.2 Design Similar to that of R168-120-8606, except that there was no posttreatment period.

8.1.2.3 Protocol Similar to that of R168-120-8606, with the following exceptions: (a) Since there was no posttreatment period, emollient was not dispensed at the week-12 visit, (b) posttreatment evaluations were not performed and (3) Investigator's global was a 6-point scale, having "lesion unchanged" and "lesion worsened" separated out (these two giving the same score in R168-120-8606).

8.1.2.4 Results

8.1.2.4.1 Patient Disposition, Comparability

Three hundred and thirty-six patients were enrolled into the study among 10 Investigators. The Investigators and enrollment are as follows:

<u>Investigator</u>	<u>Center no.</u>	<u>Total</u>	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>
DeVillez	2165	36	12	12	12
Drake	0581	36	12	12	12
Fiedler	2167	48	16	16	16
Funicella	2234	19	7	6	6
Hanifin	1185	36	12	12	12
Hickman	0674	27	9	9	9
Horwitz	0093	44	14	14	16
Koo	1603	36	12	12	12
Milbauer	2183	36	12	12	12
Smith	1145	<u>18</u>	<u>6</u>	<u>6</u>	<u>6</u>
		336	112	111	113

Comment

1. The Applicant combined the data of Drs. Funicella and Smith for analysis because of the small sample sizes of these centers (≤ 7 per arm) and because of their proximity. However, Dr. Hickman's center with 9 per arm was treated as a separate entity. The original protocol planned to have 324 subjects at 9 centers, i.e. 12/arm/site.

2. The following drug-investigator interactions were noted:

a) Trunk/arm/leg lesions: scaling (wk-1 & -2), erythema (wk-12), sum of scores (wk-1);

b) Knee/elbow lesions: erythema (wk-8 & -12); and

c) Global scores and "treatment success rate" (wk-1 & -8).

These interactions were sporadic and not consistent. Their existence did not materially affect the outcome of the overall analysis.

Completion Status

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

*Numbers in parentheses indicate unevaluable patient numbers.

***"Other" refers to discontinuation besides disqualification or termination (AE or lack of efficacy) in treatment period.

There were a total of 19 unevaluable patients :

Tazarotene 0.1% gel - 8: Entry violation 2 (baseline laboratory test abnormality 1, inadequate washout of previous therapy 1), no evaluable postbaseline visit 6;

Tazarotene 0.05% gel - 7: No evaluable postbaseline visit 5 (two of the 5 were terminated for adverse events), noncompliance 2; and

Vehicle - 4: Entry violation 2 (baseline laboratory test abnormality 2) and no postbaseline visit 2.

Only one patient achieved a global of "cleared" and only at endpoint; thus, no subject had treatment discontinuation due to complete clearing. Most were exposed to drug for 8-12 weeks:

	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>
Enrolled	112	111	113
Exposed for ≥8 wks	79	88	97
Completed study	69	86	88
Exposed for ≥12 wks	62	66	73
Exposed for ≥14 wks	0	0	1

Comments

1. See Section 8.1.1.4.3 for termination due to adverse events. Twice as many exited the study due to adverse events in the 0.1% gel group vs the 0.05% gel or vehicle group. There were also more discontinued for "other" reasons in the 0.1% gel group (see comment #2). This resulted in a lower rate of study completion among the 0.1% gel-treated subjects (69/112=62% vs 86/111=77% for 0.05% gel and 88/113=78% for vehicle).

2. The patients discontinued for "other" reasons were dropouts who missed visits, did not return, did not comply, etc. but this might have been due to adverse events which were not considered by the investigator to be the primary cause of discontinuation. It is noted that local adverse events were reported in these patients in all 3 groups (0.1% gel 4/16=25%, 0.05% gel 1/7=14% and vehicle gel 2/10=20%). Thus, it would be important to examine the intent-to-treat analysis in this study.

3. Patient numbers for efficacy analysis are as follows:

	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>
Enrolled	112	111	113
Completed study	69	86	88
Preferred analysis	104	104	109
LOCF analysis	104	104	109
ITT analysis	108	109	111

The ITT analysis included all available data, both evaluable and nonevaluable. It excluded 2-4 patients who lacked follow-up data per arm. Nevertheless, outcome of ITT analysis yielded the same result as the preferred analysis in terms of statistical significance. This was also true for the LOCF analysis. The preferred analysis will be used in this review for analysis of efficacy.

Comparability of Treatment Groups

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

Comment The 3 arms were comparable at baseline. ITT subjects showed almost the same demographics and baseline data.

8.1.2.4.2 Efficacy Parameters

8.1.2.4.2.1 Main Variables at Endpoint (week-12)

A. Target Lesions

Table 8.1.2.4.2.1a Target Lesion Responses at Treatment Period Endpoint

	Trunk/Arm/Leg			Knee/Elbow		
	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Scale Elevation						
Baseline (mean±SD)	2.60±0.62	2.56±0.65	2.59±0.56	2.63±0.59	2.59±0.61	2.59±0.62
Endpoint (mean)	1.19	1.27	1.88	1.35	1.47	1.97
Change (mean±SD)	<u>1.41±1.04*</u>	<u>1.29±0.95</u>	0.71±0.96	<u>1.28±0.86</u>	<u>1.12±0.91</u>	0.62±0.89
Scaling						
Baseline (mean±SD)	2.61±0.80	2.52±0.77	2.62±0.69	2.73±0.75	2.62±0.78	2.68±0.68
Endpoint (mean)	1.31	1.41	1.96	1.50	1.70	2.10
Change (mean±SD)	<u>1.30±1.04</u>	<u>1.11±1.14</u>	0.66±1.05	<u>1.23±1.06</u>	<u>0.92±1.04</u>	0.58±1.01
Erythema						
Baseline (mean±SD)	2.79±0.67	2.66±0.67	2.71±0.66	2.50±0.66	2.52±0.63	2.51±0.69
Endpoint (mean)	1.71	1.83	2.17	1.68	1.71	2.01
Change (mean±SD)	<u>1.08±1.07</u>	<u>0.83±0.99</u>	0.54±0.92	<u>0.82±1.02</u>	<u>0.81±0.83</u>	0.50±0.80
Total Sign scores						
Baseline (mean±SD)	8.00±1.65	7.74±1.76	7.92±1.67	7.86±1.59	7.73±1.65	7.78±1.71
Endpoint (mean)	4.20	4.51	6.00	4.53	4.88	6.09
Change (mean±SD)	<u>3.80±2.67</u>	<u>3.23±2.62</u>	1.92±2.71	<u>3.33±2.53</u>	<u>2.85±2.36</u>	1.69±2.42
Mean Tx Response Score	<u>3.58±1.47*</u>	<u>3.13±1.69</u>	2.30±1.57	<u>3.32±1.51</u>	<u>3.06±1.59</u>	2.16±1.45
"Treatment Success" (% pts)	<u>55</u>	<u>47</u>	27	<u>49</u>	<u>43</u>	23
Time to initial "Treatment Success" in 50% of pts	<u>week-8</u>	<u>week-6</u>	>week-12	<u>week-6.6</u>	<u>week-8</u>	>week-12

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

B. Overall Evaluation

Table 8.1.2.4.2.1b Overall Responses at Treatment Period Endpoint

		<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>
All Clinical Severity	Baseline (mean±SD)	2.72±0.50	2.63±0.56	2.68±0.52
	Reduction (mean)	<u>1.17*</u>	<u>1.02</u>	0.58
Investigator's Global Score (mean)		<u>3.23</u>	<u>2.90</u>	2.14
Overall "Treatment Success" (% of patients)		<u>52</u>	<u>42</u>	23
Time to initial "Treatment Success" in 50% of pts		<u>week-9</u>	<u>week-9</u>	>week-12

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

8.1.2.4.2.2 Other efficacy parameters

A. Patient evaluation at the end of treatment

	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>
Cosmetic Acceptability (% pts)			
Highly favorable	17	13	13
Favorable	35	38	28
Neutral	21	23	28
Slightly unfavorable	13	17	15
Unfavorable	15	10	16
Comparison to Past Therapy (% pts)			
Far Superior	13	9	1
Superior	26	21	14
Same	10	24	21
Worse	21	21	23
Much Worse	17	14	27
Can't Decide	13	6	12
No Past Therapy	1	6	2

B. Subjective Symptoms and Emollient Use

Pruritus scores were comparable at baseline but significantly worse in the 0.1% gel group at endpoint:

	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>
Baseline (mean±SD)	1.65±1.23	1.63±1.23	1.84±1.17
Endpoint (mean)	1.29	1.03	0.93
Change (mean±SD)	<u>0.36±1.76 (p<0.05)</u>	0.60±1.48	0.91±1.29

The subjective scores for pain were not significantly different among the three treatment groups at baseline or at endpoint. **Emollient use** was needed in over 96% of patients in all three groups, and the frequency of usage as well as total quantities used during the course of the study were similar among the groups.

8.1.2.4.2.3 Onset of action

Table 8.1.2.4.2.3a Drug Effect on Target Lesions before Endpoint in Treatment Period

	<u>Trunk/Arm/Leg</u>				<u>Knee/Elbow</u>			
	<u>wk-1</u>	<u>wk-2</u>	<u>wk-4</u>	<u>wk-8</u>	<u>wk-1</u>	<u>wk-2</u>	<u>wk-4</u>	<u>wk-8</u>
Mean Scores for Reduction of								
Plaque Elevation								
Tazarotene 0.1%	<u>0.63*</u>	<u>0.93</u>	<u>1.11</u>	<u>1.26</u>	<u>0.44</u>	<u>0.78</u>	<u>1.00</u>	<u>1.19</u>
Tazarotene 0.05%	<u>0.56</u>	<u>0.93</u>	<u>1.08</u>	<u>1.15</u>	<u>0.50</u>	<u>0.67</u>	<u>0.89</u>	<u>1.01</u>
Vehicle	0.26	0.36	0.44	0.61	0.26	0.26	0.37	0.56
Scaling								
Tazarotene 0.1%	<u>0.45</u>	<u>0.77</u>	<u>0.96</u>	<u>1.08</u>	0.25	<u>0.60</u>	<u>0.84</u>	<u>1.05*</u>
Tazarotene 0.05%	<u>0.46</u>	<u>0.75</u>	<u>0.86</u>	<u>0.89</u>	0.30	<u>0.49</u>	<u>0.64</u>	<u>0.72</u>
Vehicle	0.22	0.36	0.44	0.62	0.18	0.24	0.45	0.56
Erythema								
Tazarotene 0.1%	0.07	<u>0.37</u>	<u>0.49</u>	<u>0.85</u>	0	0.21	0.45	0.71
Tazarotene 0.05%	0.19	<u>0.37</u>	0.42	0.60	0.09	0.28	<u>0.48</u>	<u>0.71</u>
Vehicle	0.10	0.27	0.29	0.47	0.09	0.24	0.28	0.47
Total Scores								
Tazarotene 0.1%	<u>1.15</u>	<u>1.88</u>	<u>2.57</u>	<u>3.18</u>	0.68	<u>1.58</u>	<u>2.28</u>	<u>2.98</u>
Tazarotene 0.05%	<u>1.21</u>	<u>2.04</u>	<u>2.35</u>	<u>2.63</u>	<u>0.89</u>	<u>1.45</u>	<u>2.02</u>	<u>2.46</u>
Vehicle	0.59	0.99	1.17	1.71	0.53	0.74	1.09	1.60
II. Target Lesion "Treatment Success" (% pts)								
Tazarotene 0.1%	<u>10</u>	<u>15</u>	<u>40</u>	<u>50</u>	<u>8</u>	<u>17</u>	<u>31</u>	<u>44</u>
Tazarotene 0.05%	<u>11</u>	<u>23</u>	<u>28</u>	<u>37</u>	<u>6</u>	<u>16</u>	<u>28</u>	<u>40</u>
Vehicle	2	6	7	20	2	4	12	15

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

†Figures highlighted show significant difference among 0.1% gel and 0.05% gel treatment groups (p<0.05).

Table 8.1.2.4.2.3b Overall Disease Variables before Endpoint in Treatment Period

		<u>wk-1</u>	<u>wk-2</u>	<u>wk-4</u>	<u>wk-8</u>
Investigator's Global (mean)	Tazarotene 0.1%	<u>1.77</u>	<u>2.24</u>	<u>2.86</u>	<u>3.03</u>
	Tazarotene 0.05%	<u>1.95</u>	<u>2.39</u>	<u>2.53</u>	<u>2.70</u>
	Vehicle	1.57	1.67	1.83	2.13
"Treatment Success" (%pts)	Tazarotene 0.1%	2	<u>10</u>	<u>26</u>	<u>40</u>
	Tazarotene 0.05%	4	<u>16</u>	<u>23</u>	<u>31</u>
	Vehicle	2	2	6	16

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

Comment The data was reexamined by looking at the rates of "excellent or better", i.e. >75% improvement and "cleared", i.e. 100% improvement (see Table below). It does seem that the tazarotene gels did better than the vehicle in terms of "excellent or better" response in overall or target lesion responses. This was not seen for clearing, since almost no subjects cleared before week-12 (except for trunk/arm/leg lesions, where 1 patient per arm cleared at week-8). The 0.1% gel did better numerically than the 0.05% gel for "excellent or better" scores in most instances, but such differences were not significant.

Target Lesion "Treatment Success" as Defined by "Excellent or Better" or "Cleared"

I. Treatment Period	<u>Trunk/Arm/Leg</u>					<u>Knee/Elbow</u>				
	<u>wk-1</u>	<u>wk-2</u>	<u>wk-4</u>	<u>wk-8</u>	<u>wk-12</u>	<u>wk-1</u>	<u>wk-2</u>	<u>wk-4</u>	<u>wk-8</u>	<u>wk-12</u>
"Excellent or better" (% pts)										
Tazarotene 0.1%	2	2	13	26	32	0	2	11	19	26
Tazarotene 0.05%	1	6	9	15	27	0	3	11	16	27
Vehicle	0	1	5	9	9	0	0	2	4	7
"cleared" (% pts)										
Tazarotene 0.1%	0	0	0	1	6	0	0	0	0	3
Tazarotene 0.05%	0	0	0	1	4	0	0	0	0	1
Vehicle	0	0	0	1	2	0	0	0	0	0

Global "Treatment Success" as Defined by "Excellent or Better" or "Cleared"

I. Treatment Period		wk-1	wk-2	wk-4	wk-8	wk-12
"Excellent or better" (% pts) (>75% improvement)	Tazarotene 0.1%	0	0	8	16	25
	Tazarotene 0.05%	0	3	8	10	18
	Vehicle	0	0	3	9	10
"cleared" (% pts) (100% improvement)	Tazarotene 0.1%	0	0	0	0	0
	Tazarotene 0.05%	0	0	0	0	1
	Vehicle	0	0	0	0	0

8.1.2.4.3 Safety Comparison

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

	Tazarotene 0.1%	Tazarotene 0.05%	Vehicle
Total patients enrolled	112 (100%)	111 (100%)	113 (100%)
Patients with adverse events	83 (74%)/73 (65%)	81 (73%)/51 (46%)	60 (53%)/27 (24%)
Dermatologic adverse events	77 (69%)/72 (64%)	60 (54%)/49 (44%)	35 (31%)/26 (23%)
pruritus	32 (29%)/30 (27%)	25 (23%)/17 (15%)	16 (14%)/15 (13%)
erythema	23 (21%)/22 (20%)	18 (16%)/18 (16%)	3 (3%)/3 (3%)
psoriasis worsened	18 (16%)/14 (13%)	12 (11%)/8 (7%)	16 (14%)/9 (8%)
burning/stinging	17 (15%)/17 (15%)	14 (13%)/13 (12%)	5 (4%)/5 (4%)
irritation	16 (14%)/16 (14%)	10 (9%)/10 (9%)	2 (2%)/1
skin pain	15 (13%)/12 (11%)	10 (9%)/8 (7%)	5 (4%)/5 (4%)
rash/maculopapular rash	10 (9%)/10 (9%)	8 (7%)/4 (4%)	2 (2%)/1
desquamation	7 (6%)/7 (6%)	3 (3%)/2 (2%)	0
contact dermatitis, irritant "dermatitis"	6 (5%)/6 (5%)	3 (3%)/3 (3%)	1/1
dry skin	6 (5%)/6 (5%)	2 (2%)/2 (2%)	5 (4%)/4 (4%)
skin excoriation/erosion	2 (2%)/2 (2%)	4 (4%)/2 (2%)	3 (3%)/3 (3%)
skin hemorrhage	2 (2%)/2 (2%)	0	2 (2%)/2 (2%)
acne	2 (2%)/1	0	1/1
skin hypertrophy	2 (2%)	0	0
skin fissure	1/1	2 (2%)	2 (2%)/1
nail disorder	1	1	1
urticaria	1	1	0
skin discoloration	1/1	0	0
sun-induced erythema	1/1	0	0
sweat	1/1	0	0
skin discharge	0	3 (3%)/3 (3%)	2 (2%)/2 (2%)
herpes simplex	0	1	1
skin atrophy	0	1/1	0
furunculosis	0	1	0
infestation	0	1	0
skin tightness	0	1/1	0
nail pain	0	0	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	21 (19%)	10 (9%)	9 (8%)
psoriasis worsened	7 (6%)	1	6 (5%)
burning/stinging	4 (4%)	2 (2%)	0
pruritus	4 (4%)	2 (2%)	2 (2%)
skin pain	2 (2%)	1	0
hypertriglyceridemia*	2 (2%)	1	0

contact dermatitis, irritant	2 (2%)	0	1
erythema	1	2 (2%)	0
irritation	1	0	0
rash	1	0	0
respiratory infection	1	0	1
intraabdominal neoplasm	1	0	0
acne	1	0	0
SGPT increase*	1	0	0
"skin inflammation"	0	1	0
hypercholesterolemia	0	1	0
bone pain/lymphadenopathy	0	1	0
headache/knee pain	0	0	1

*Patient (Tazarotene 0.1% gel, 43 WM) had SGPT and triglyceride increase but also had high alcohol intake.

The study medication was stopped at day 42:	Baseline	week-4	week-6	week-7
SGPT (U/ml)	88	284	137	75
Triglycerides (mg/dl)	296	315	265	322

Pregnancy did not occur in any women enrolled in this study.

8.1.2.4.3.2 Laboratory Studies

A. CBC, chemistry and urinalysis - no consistent, significant abnormalities. However, there were 4 cases of hypertriglyceridemia, which occurred at the same site and were attributed by the investigator to be "treatment-related". However, one of them (vehicle) had been disqualified because of this abnormality at baseline. Precise relationship to treatment is unclear in the remaining 3 cases.

B. Therapeutic drug monitoring -see Section 10.

8.1.2.5 Conclusions

Both tazarotene 0.1% and 0.05% gels appear to be safe and effective in the treatment of stable plaque psoriasis as shown in the following Table. Differences among the two gels are slight in terms of safety and efficacy. The commonest adverse events were pruritus, burning/stinging, irritation, erythema and psoriasis worsened.

Table 8.1.2.5 Summary of Findings in R168-121-8606

	SUPERIORITY OF		
	<u>Taz* 0.1% vs vehicle</u>	<u>Taz* 0.05% vs vehicle</u>	<u>Taz 0.1% vs Taz 0.05%</u>
1° Variables at Treatment Endpoint			
↓ plaque elevation	<0.001/<0.001	<0.001/0.001	-/-
↓ scaling	<0.001/<0.001	0.011/0.028	-/-
↓ erythema	0.001/ 0.042	0.029/0.012	-/-
↓ sum of scores	<0.001/<0.001	<0.001/0.004	-/-
Global (treatment success)	<0.001	0.003	-
Onset of Action*			
week-1	PST/P. -	PST/PT. -	-/- -
week-2	PST/PST. G	PST/PST. G	<u>E/-</u> -
week-4	PSET/PST. G	PST/PSET. G	-/- -
week-8	PSET/PST. G	PST/PSET. G	-/S. -
Safety			
All/ "treatment-related" AE* rates (%)	74/65 vs 53/24	73/46 vs 53/24	74/65 vs 73/46

*=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" are for variables with an among group comparison showing p<0.05.

Parameters are given for Trunk/arm /leg lesions before 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.

Significant inferiority is represented by highlighting in shaded areas.

8.1.3 Trial #3. Study#R168-125-8606: 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.

8.1.3.1 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 Lidex (fluocinolone) 0.05% cream in the treatment of stable plaque psoriasis.

The rationale of this study was based on the observation in Study R168-120-8086 that subjects treated with tazarotene appeared to have better scores of some clinical variables when compared to the vehicle group in the posttreatment period (see Section 8.1.1.4.2). In an End-of-Phase 2 Meeting the Applicant and the Agency came to the understanding that to make the claim of maintenance of therapeutic effect, the Applicant would need to have 2 comparative studies where tazarotene demonstrated a continued effect not seen with an active corticosteroid control. Therefore the Applicant designed studies comparing the therapeutic effect of tazarotene in the posttreatment period with that of a corticosteroid, fluocinolone.

Comment Corticosteroids may exhibit tachyphylaxis and possible rebound phenomenon when withdrawn, resulting in flares of psoriasis. Therefore, it might not be the most useful comparison comparison by using fluocinolone as an active control.

8.1.3.2 Design Multicenter (9 centers), investigator-masked, randomized, parallel-group clinical trial, with posttreatment follow-up (see Table below).

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

Pregnancy tests done if applicable.

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

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

8.1.3.3 Protocol The design of this trial was similar to that of R168-120-8606, with the following exceptions:

1. Vehicle was replaced by Lidex 0.05% cream to be applied twice daily.

Comment There are problems in design:

1. The study could have used a double dummy method to mask the dosing differences.
2. Steroid effect with rapid onset of antiinflammatory action could have resulted in unintentional unblinding.
2. Under exclusion criteria, patients requiring excessive or prolonged sun exposure were added.
3. Patients were to complete quality of life questionnaires at the week-0, week-12 and week-24 visits. The Dermatology Life Quality Index and the Psoriasis Disability Index would be derived from the questionnaires (for details, see references cited below).

Comment These indices depend on subjective responses and their validity in the evaluation of anti-psoriatic therapies remains to be substantiated.

4. There were 6 levels for target lesion treatment response and investigator global (See Section 8.1.2.2 as in R168-121-8606).

5. In the posttreatment period, an additional analysis was made for the "time to initial overall lesional severity of ≥ 2 ", based on those who had a score of less than 2 at the final treatment period visit.

6. Instead of plaque elevation, sample size selection and power calculation were based on (a) Overall lesional severity, (b) Global "treatment success" and (c) Disqualification due to overall lesional severity ≥ 2 in the posttreatment period.

7. Intent-to-treat analysis and last-observation-carried-forward analysis were not done, as the applicant contended that this was not a primary vehicle-controlled study for efficacy.

Comment The logic of this explanation is unclear. This review will be based on the preferred analysis. Definition of this analysis is as in R168-120-8606.

8.1.3.4 Results

8.1.3.4.1 Patient Disposition, Comparability

Three hundred and forty-eight patients were enrolled into the study among 10 Investigators. The Investigators and enrollment are as follows:

<u>Investigator</u>	<u>Center no.</u>	<u>Total</u>	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Lidex cream 0.05%</u>
Ast	2187	36	12	12	12
Callen	1487	33	11	11	11
Cullen	0273	32	11	11	10
Hogan	2170	36	12	12	12
Hong	2168	34	11	12	11
Lebwohl	2172	42	14	14	14
Lowe	0228	36	12	12	12
Phillips	2171	36	12	12	12
Rosen	2169	32	10	11	11
Wolf	2235	<u>31</u>	<u>11</u>	<u>10</u>	<u>10</u>
		348	116	117	115

Comment The following drug-by-investigator interactions were found. However, these interactions were sporadic and did not materially alter the outcome of or conclusions derived from the data.

Knee/elbow lesions: scaling at wk-8, -12, 20 & 24;

sum of scores for erythema, scaling and plaque elevation at wk-2;

Trunk/limbs lesions: erythema at wk-24 and

sum of scores for erythema, scaling and plaque elevation at wk-24.

Completion Status:

	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Lidex</u>
<u>Treatment period</u>			
Enrolled	116 (4)*	117 (2)	115 (2)
Completed study	79	89	107-(1)
Not completed	37	28	-8
- lack of efficacy	3	4	- 0
adverse event	21 (1)	14	2
not meeting entry criteria	1 (1)	1 (1)	0
"other"***	12 (2)	9 (1)	6 (1)
<u>Posttreatment period</u>			
Started	79/45*	89/42	107 (1)/70 (1)
Completed follow-up	57/35	57/31	59/42
Not completed	22/10	32/11	48/28
need for treatment	18/8	21/7	39/23
adverse event	0	7/1	- 3/1
not meeting entry criteria	0	0	1 (1)/1 (1)
"other"	4/2	4/3	5/3

*Numbers in parentheses indicate unevaluable patient numbers.

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

*Figures in posttreatment period are given as: total patient number/number of patients who had "Treatment Success" at entry of the posttreatment period.

Patient was inadvertently not disqualified due to baseline laboratory test results (hypercholesterolemia) and was classified as terminated due to adverse event.

The unevaluable patients were:

Treatment period

(Tazarotene 0.1%). Terminated for skin irritation (used medication for only 3 days).

(Tazarotene 0.1%). Entry criteria violation (abnormal lab results).

(Tazarotene 0.05%). Entry criteria violation (abnormal lab results).

(Tazarotene 0.1%). Prohibited concomitant medication after visit-1.

(Tazarotene 0.1%). No evaluable postbaseline visit.

(Tazarotene 0.05%). Discontinued at week-2 for missed visits.

(Lidex 0.05%). No evaluable postbaseline visit.

(Lidex 0.05%). Patient completed treatment period but discovered to have been using prohibited drug during that period.

Posttreatment period

(Lidex 0.05%). Prohibited concomitant medication ("investigational drug") discovered.

Eleven patients achieved complete clearing (global) at the end of the treatment period. Only one patient (Lidex) "cleared" at week-4. At the week-8 visit, 7 patients were classified as "cleared" (0.1% gel 2, Lidex 5) and would have discontinued treatment on this basis.

Duration of drug exposure was:

	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Lidex</u>
Enrolled	113	115	114
Exposed for ≥8weeks	83	99	111
Completed treatment	79	89	107
Exposed for ≥12 weeks	70	80	94
Exposed for ≥14 weeks	1	5	6

Comments

1. The small number of unevaluables (2-4 per arm) would not be expected to affect the analyses substantially.
2. The posttreatment period started with an imbalance of patient numbers (Lidex group having 28 more than 0.1% gel group and 19 more than 0.05% gel group). For comparison of maintenance of therapeutic effect, it would be desirable to compare subjects having similar baseline disease condition. However, there were also more "treatment success" patients in the Lidex group from the start (0.01% gel 45/79=57%, 0.05% gel 42/89=47% and Lidex 70/107=71%) [see "Completion Status" Table shown above].
3. Although more subjects exited the study in the Lidex group due to "need for treatment" in the posttreatment period, this group started with a greater number (see above). Moreover, the proportion of subjects who had "treatment success" in the beginning but needed treatment during this period was only slightly higher in the Lidex group (0.01% gel 8/45=18%, 0.05% gel 7/42=17% and Lidex 23/70=21%).
4. The protocol required discontinuation of treatment with a global of "cleared". It is likely that this was violated, since there were more patients "cleared" (5) than discontinued from Lidex (114-111=3) at the week-8 visit.

Comparability of Treatment Groups

Total patient no	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Lidex cream 0.05%</u>
Age (Yrs)	44±14	47±15	46±16
Sex			
M	66	59	70
F	46	56	43
Race			
White	103	107	103
Hispanic	2	4	5
Black	3	2	2
Oriental	2	1	1
"other"	2	1	2
% Body area with psoriasis	9±6	8±5	8±6
Duration of psoriasis (Yrs)	14±9	18±13	16±12

Comment The 3 arms were comparable at baseline.

8.1.3.4.2 Efficacy Parameters

Since this is a comparative study with the main aim of showing maintenance of therapeutic effect in the posttreatment period for tazarotene, the emphasis is on the efficacy variables in that period, although significant differences in the treatment period will also be noted.

8.1.3.4.2.1 Main Variables

Table 8.1.3.4.2.1 Primary Efficacy Variables in R168-125-8606

Clinical Signs	Baseline		Mean Reduction in Scores							
	wk-0	wk-1	wk-2	wk-4	wk-8	wk-12	wk-16	wk-20	wk-24	
Plaque elevation										
T/A/L** Taz 0.1%	2.4	0.7	1.0	1.1	1.4	1.4	1.3	1.1	1.0	
Taz 0.05%	2.4	0.5*	0.9	1.1	1.3	1.3	1.3	0.9	0.9	
Lidex	2.3	0.6	1.0	1.3	1.4	1.5	1.3	1.1	0.9	
K/E Taz 0.1%	2.4	0.7	1.0	1.2	1.4	1.5	1.3	1.1	1.0	
Taz 0.05%	2.5	0.5	1.0	1.2	1.3	1.3	1.2	0.9	0.9	
Lidex	2.5	0.7	1.1	1.3	1.4	1.4	1.0	0.9	0.8	
Scaling										
T/A/L Taz 0.1%	2.4	0.7	1.0	1.0	1.3	1.3	1.3	1.1	1.1	
Taz 0.05%	2.3	0.5	0.7	1.0	1.1	1.1	1.1	0.9	0.9	
Lidex	2.4	0.8	1.1	1.4	1.6	1.6	1.3	1.2	1.1	
K/E Taz 0.1%	2.5	0.6	0.9	1.0	1.3	1.3	1.3	1.1	1.0	
Taz 0.05%	2.5	0.5	0.8	1.1	1.2	1.2	1.2	1.0	0.9	
Lidex	2.5	0.8	1.2	1.3	1.5	1.4	1.0	0.9	0.9	
Erythema										
T/A/L Taz 0.1%	2.4	0.2	0.4	0.5	0.9	0.9	1.2	1.1	1.1	
Taz 0.05%	2.4	0.2	0.3	0.5	0.8	0.8	0.9	0.8	0.7	
Lidex	2.4	0.6	0.9	1.2	1.4	1.4	1.1	1.0	0.8	
K/E Taz 0.1%	2.2	0.2	0.4	0.6	0.7	0.8	1.0	0.9	0.9	
Taz 0.05%	2.3	0.2	0.4	0.5	0.8	0.9	1.0	0.8	0.7	
Lidex	2.3	0.5	0.8	1.1	1.2	1.2	0.8	0.7	0.6	
Sum of Scores										
T/A/L Taz 0.1%	7.2	1.6	2.4	2.7	3.6	3.7	3.9	3.2	3.1	
Taz 0.05%	7.1	1.2	2.0	2.6	3.1	3.2	2.9	2.6	2.5	
Lidex	7.2	2.0	3.0	3.9	4.3	4.5	3.7	3.3	2.8	
K/E Taz 0.1%	7.2	1.5	2.3	2.9	3.4	3.6	3.7	3.0	3.0	
Taz 0.05%	7.3	1.3	2.1	2.9	3.2	3.4	3.3	2.7	2.5	
Lidex	7.3	2.0	3.1	3.7	4.1	4.1	2.9	2.6	2.3	
Overall Evaluations			wk-1	wk-2	wk-4	wk-8	wk-12	wk-16	wk-20	wk-24
I. Global "Treatment Success" (% pts)										
Taz 0.1%			21	40	43	59	56	59	44	45
Taz 0.05%			18	28	44	48	48	39	36	38
Lidex			25	47	59	66	65	46	33	30
II. Overall Global (mean)										
Taz 0.1%			2.4	3.0	3.3	3.6	3.5	3.5	3.2	3.1
Taz 0.05%			2.1	2.7	3.2	3.4	3.3	2.9	2.7	2.8
Lidex			2.7	3.3	3.6	3.8	3.8	2.9	2.6	2.5

*Bold italics indicate superiority of Lidex over tazarotene (p<0.05). Underlined figures show superiority of tazarotene over Lidex (p<0.05). ~~Highlighted figures indicate a difference between 0.1% and 0.05% (p<0.05).~~

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

8.1.3.4.2.2 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 8.1.3.4.2.2 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%	34.0	Only values for end of treatment and posttreatment periods were given				2.5				4.4
	Taz 0.05%	30.7					0.2				2.3
	Lidex	29.6					5.4				2.8
DQLS											
	Taz 0.1%	29.0	Only values for end of treatment and posttreatment periods were given				3.8				<u>11.2</u>
	Taz 0.05%	24.0					-0.3				<u>2.9</u>
	Lidex	23.8					8.3				3.1
Overall Clinical Severity											
	Taz 0.1%	2.5	0.4	<u>0.7</u>	0.8	1.1	1.1	<u>0.9</u>	<u>0.8</u>	<u>0.9</u>	
	Taz 0.05%	2.5	0.3	<u>0.5</u>	0.8	0.9	0.9	<u>0.9</u>	<u>0.7</u>	<u>0.7</u>	
	Lidex	2.5	0.6	0.9	1.2	1.3	1.2	0.9	0.8	0.7	
Percent Body Surface Area involved											
	Taz 0.1%	8.8	0.1	0.3	0.6	<u>1.5</u>	1.7	<u>2.7</u>	2.8	2.6	
	Taz 0.05%	7.6	0.2	0.4	0.1	<u>0.2</u>	0.2	<u>0.5</u>	0.6	0.7	
	Lidex	8.3	0.2	0.9	1.9	2.9	3.0	-1.6	1.4	1.0	
Pain											
	Taz 0.1%	0.7	0.1	0.1	0.2	<u>0.4</u>	<u>0.4</u>	<u>0.6</u>	<u>0.6</u>	<u>0.6</u>	
	Taz 0.05%	0.5	0	0.1	0.1	<u>0</u>	<u>0.2</u>	<u>0.3</u>	<u>0.2</u>	<u>0.3</u>	
	Lidex	0.6	0.4	0.5	0.5	0.5	0.4	0.1	0	0	
Pruritus											
	Taz 0.1%	1.6	0.1	0.2	0.2	0.4	0.5	0.9	1.0	<u>1.0</u>	
	Taz 0.05%	1.7	0.3	0.4	0.3	0.4	0.6	0.7	0.6	<u>0.6</u>	
	Lidex	1.6	0.7	1.0	1.1	1.0	0.9	0.7	0.5	0.5	

Italics indicate superiority of Lidex over tazarotene (p<0.05). Underlined figures show superiority of tazarotene over Lidex (p<0.05). ~~Underlined figures indicate a difference between 0.1% and 0.05% oels (p<0.05).~~
 z=tazarotene.

8.1.3.4.2.3 Duration of Therapeutic Effect in Posttreatment Period

The changes in efficacy variables have been shown in 8.1.3.4.2.1 and 8.1.3.4.2.2. 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=48	N=45	N=44	N=44	N=49	N=41	N=41	N=43	N=73	N=69	N=67	N=68
% "success"	100	78	66	59	100	68	61	60	100	74	60	53
Knee/elbow	N=51	N=48	N=46	N=47	N=47	N=40	N=40	N=42	N=71	N=66	N=63	N=65
% "success"	100	77	59	64	100	70	60	55	100	68	56	54
Overall	N=45	N=42	N=41	N=41	N=42	N=37	N=37	N=38	N=69	N=66	N=64	N=65
% "success"	100	76	61	59	100	68	59	58	100	62	45	40

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

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

	Tazarotene 0.1%			Tazarotene 0.05%			Lidex 0.05%		
	Failure*	Censored	Total	Failure	Censored	Total	Failure	Censored	Total
week-12	0	0	50	0	0	46	0	0	74
week-16	7 (14%)	4	39	9 (20%)	4	33	22 (30%)	4	48
week-20	2 (4%)	3	34	4 (9%)	2	27	12 (16%)	0	36
week-24	0	34	0	3 (7%)	24	0	5 (7%)	31	0
Total	9 (18%)	41		16 (35%)	30		39 (53%)	35	

Time to initial overall clinical severity ≥2	>week-24*	>week-12	week-12

*Failure defined as overall clinical severity reaching 2 or over in posttreatment period. *significantly longer than Lidex group.

There was a statistically significant lower rate of failure in the 0.1% gel group when compared with Lidex group.

Comment As the patient numbers were disproportionate at the beginning of the posttreatment period, caution must be exercised in interpreting the maintenance effect. It is unclear whether factors other than therapeutic effect might have introduced bias affecting patient participation in the posttreatment period that could have changed the comparability of this subset of the treatment groups. Analyses of subsets not previously randomized are fraught with dangers in interpretation. For instance, since Lidex was superior in the treatment period, the "treatment success" subjects in the Lidex group might have included patients who would have been resistant to tazarotene treatment and not expected to have therapeutic effect maintained for any substantial length of time posttreatment.

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

	Tazarotene 0.1%	Tazarotene 0.1%	Lidex
Total participating	79	89	107
Exit at wk-12	4 (5%)	2 (2%)	8 (7%)
at wk-16	9 (11%)	14 (16%)	23 (21%)
at wk-20	5 (6%)	5 (6%)	8 (7%)
Total	18 (22%)	21 (24%)	39 (35%)

Comment

1. The "need for treatment" rates among the 3 groups were similar at different visit points except for the greater rate of the Lidex group (21%) vs the 0.1% gel group (11%) at wk-16.

2. It would be expected that in a study of the posttreatment period, since the entire treatment group of patients contained both subjects having overall clinical severity of <2 and those ≥2, there would be a greater proportion exiting the study in the entire group than the subset beginning with clinical severity <2, especially early in the posttreatment period. However, the opposite was the case in most instances. This suggests that overall clinical severity of 2 might not necessarily have been a fair measure for maintenance of therapeutic effect.

	Tazarotene 0.1%	Tazarotene 0.05%	Lidex
Entire Posttreatment Period			
"need for treatment" in whole group	18/79=22%	21/89=24%	39/107= 35%
OCS* reaching 2 in OCS<2 subset	9/50=18%	16/46=35%	39/74= 53%
Week-12 to week-16			
"need for treatment" in whole group	13/79=16%	16/89=18%	31/107= 29%
OCS* reaching 2 in OCS<2 subset	9/50=18%	13/46=28%	34/107= 46%

*OCS=overall clinical severity. "Need for treatment" as defined in R168-120-8606 (See Section 8.1.1.3.2).