

II. Overall Disease Parameters		wk-1	wk-2	wk-4	wk-8	wk-12	Time to 50% "Success"
Investigator's Global (mean) R168-120-8606	Tazarotene 0.1%	<u>1.27</u>	<u>1.17</u>	<u>1.99</u>	<u>2.29</u>	<u>2.65</u>	
	Tazarotene 0.05%	<u>1.19</u>	<u>1.45</u>	<u>1.77</u>	<u>1.99</u>	<u>2.23</u>	
	Vehicle	0.81	1.00	1.24	1.37	1.55	
Investigator's Global (mean) R168-121-8606	Tazarotene 0.1%	<u>1.77</u>	<u>2.24</u>	<u>2.86</u>	<u>3.03</u>	<u>3.23</u>	
	Tazarotene 0.05%	<u>1.95</u>	<u>2.39</u>	<u>2.53</u>	<u>2.70</u>	<u>2.90</u>	
	Vehicle	1.57	1.67	1.83	2.13	2.14	
"Treatment Success" (%pts) R168-120-8606	Tazarotene 0.1%	14	<u>29</u>	<u>36</u>	<u>51</u>	<u>65</u>	<u>wk-8</u>
	Tazarotene 0.05%	10	<u>27</u>	<u>31</u>	<u>39</u>	<u>52</u>	<u>wk-8</u>
	Vehicle	6	6	18	22	33	>wk-12
"Treatment Success" (%pts) R168-121-8606	Tazarotene 0.1%	2	<u>10</u>	<u>26</u>	<u>40</u>	<u>52</u>	<u>wk-9</u>
	Tazarotene 0.05%	4	<u>16</u>	<u>23</u>	<u>31</u>	<u>42</u>	<u>wk-9</u>
	Vehicle	2	2	6	16	33	>wk-12

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

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

These two studies gave almost identical findings. The mean global scores were higher in the second study because the grading added one level (no change and worsened split to 2 scores) to the scale so that the mean scores appeared to be approximately 1 point higher. Both tazarotene gels were better than vehicle from week-1 although it took 8-12 weeks for them to be significantly better than vehicle for erythema. There appears to be no significant differences between the two gels in efficacy parameters except for scaling at week-8 (knee/elbow; 0.1% gel superior at p=0.04; R168-121-8606), erythema at week-2 (trunk/arm/leg, 0.05% gel superior at p=0.02; R168-121-8606) and "treatment success" at week-2 (0.1% gel superior at p=0.01; R168-120-8606). These differences were not consistent, and not confirmed in a second trial.

Comment The Applicant did not perform a metaanalysis to verify their assumption that the 0.1% gel was superior to the 0.05% gel.

9.1.1.2 Active-controlled Studies

The 3 vehicle controlled-studies had very similar protocols that include a 12-week treatment and a 12-week posttreatment period. The main differences were between R168-145-8606 and the other two studies:

	<u>R168-125-8606</u>	<u>R168-126-8606</u>	<u>R168-145-8606</u>
Control	Lidex cream	Lidex cream	Dovonex ointment
Follow-up	includes week-2	includes week-2	excludes week2
Lab tests at end of posttreatment period	-	-	+
Target lesions evaluated	+	+	-
Location of Study	U.S.	U.S.	U.K. and Germany

Demographics and Baseline Disease Involvement The three studies enrolled patients with similar demographic background and baseline status, except for the fact that R168-145-8606 was a European study without Hispanics and had only one black subject. Nevertheless, the following combined data reflect very similar figures in each study.

Pt no*	Years		Percent				Involved BSA*	Years Psoriasis Duration (mean)
	Age		Sex		Race W/H/B/OR/OT*			
	Mean	Range	Males	Females				
Taz* 0.1%	46		63	37	95/1/1/2/1	8	18 (226 subjects)	
Taz 0.05%	47		59	41	94/3/1/2/0	7	19 (228 subjects)	
Lidex 0.05%	48		63	37	92/4/2/1/1	8	17 (225 subjects)	
Dovonex 0.005%	47		62	38	98/0/1/2/0	8	n/a**	
Total	47		61	39	94/2/1/2/1	7	18 (679 subjects)	

*Data given are for all enrolled patients. Patients for preferred analysis and for ITT analysis gave almost identical figures.

Taz=tazarotene, W/H/B/OR/OT=white/Hispanic/black/oriental/other. BSA=body surface area.

**Dovonex study did not collect such data.

Patient disposition Disposition of patients combined in these 3 studies is as follows for the treatment period:

	<u>Enrolled</u>	<u>Eval*</u>	<u>Completed</u>	<u>LOC</u>	<u>AE</u>	<u>Other discon</u>	<u>Disqualified</u>
Taz* 0.1%	348	314	223 (68%)	24 (7%)	70 (20%)	30(9%)	1 (0%)
Taz 0.05%	350	317	226 (76%)	32 (9%)	57 (16%)	34(10%)	1 (0%)
Lidex	225	221	202 (90%)	5 (2%)	4 (2%)	13(6%)	1 (0%)
Dovonex	122	88	92 (75%)	11 (9%)	4 (3%)	25(12%)	0 (0%)
Total	1045	940	485 (74%)	72 (7%)	135 (13%)	92(9%)	3 (0%)

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

Proportions of patients in each category in the 3 studies were similar with the following exceptions:

		<u>Completed</u>	<u>LOC</u>	<u>AE</u>	<u>Other discon</u>	<u>Comment</u>
Taz* 0.1%	R168-125-8606	79 (68%)	3 (3%)	21 (18%)	12(10%)	Lower completion rate with higher LOC rate in R168-145-8606.
	R168-126-8606	74 (67%)	1 (1%)	25 (23%)	10(9%)	
	R168-145-8606	70 (57%)	20 (16%)	24 (20%)	8(7%)	
Taz* 0.05%	R168-125-8606	89 (76%)	4 (3%)	14 (12%)	9(8%)	Lower completion rate with higher LOC rate in R168-145-8606.
	R168-126-8606	74 (67%)	1 (1%)	21 (19%)	15(14%)	
	R168-145-8606	63 (52%)	27 (22%)	22 (18%)	10(8%)	

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

For the posttreatment period, there were quite different completion rates and "need for treatment" rates as shown below:

		<u>Enrolled</u>	<u>Completed</u>	<u>Need Tx</u>	<u>AE</u>	<u>Other discon</u>	<u>Comment</u>
Taz* 0.1%	R168-125-8606	79	57 (72%)	18 (23%)	0 (0%)	4 (5%)	Lower completion & higher "need Tx" rate in R168-145-8606
	R168-126-8606	74	39 (53%)	28 (38%)	3 (3%)	4 (5%)	
	R168-145-8606	70	31 (44%)	30 (43%)	0 (0%)	9 (13%)	
Taz 0.05%	R168-125-8606	89	57 (64%)	21 (24%)	7 (8%)	4 (5%)	Lower completion & higher "need Tx" rate in R168-145-8606
	R168-126-8606	74	34 (46%)	27 (37%)	5 (7%)	8 (11%)	
	R168-145-8606	63	29 (46%)	29 (46%)	0 (0%)	5 (8%)	
Lidex	R168-125-8606	107	59 (55%)	39 (36%)	3 (3%)	5 (5%)	
	R168-126-8606	95	51 (54%)	38 (40%)	0 (0%)	6 (6%)	
Dovonex	R168-145-8606	92	31 (40%)	51 (55%)	0 (0%)	4 (4%)	

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

Primary Efficacy Variables The primary variables of these 3 studies are compared as shown below. In general, they have yielded consistent data, except for the fact that in R168-125-8606, the tazarotene gels appeared to give better "treatment successes" (global of good or better) than in the other studies.

Plaque elevation	Baseline		Reduction in Scores							
	wk-0		wk-1	wk-2	wk-4	wk-8	wk-12	wk-16	wk-20	wk-24
R168-125-8606										
T/A/L Taz 0.1%	2.4		0.7	1.0	1.1	1.4	1.4	<u>1.4</u>	1.1	1.0
Taz 0.05%	2.4		0.5*	0.9	1.1	1.3	1.3	<u>1.3</u>	0.9	0.9
Lidex	2.3		0.6	1.0	1.3	1.4	1.5	1.3	1.1	0.9
R168-126-8606										
T/A/L Taz 0.1%	2.5		0.6	1.0	1.2*	<u>1.6</u>	1.6	1.4	1.1	1.0
Taz 0.05%	2.4		0.5	0.9	1.1	<u>1.6</u>	1.2	1.2	1.1	1.0
Lidex	2.4		0.6	1.0	1.3	1.6	1.6	1.3	1.0	0.9
R168-125-8606										
K/E Taz 0.1%	2.4		0.7	1.0	1.2	1.4	1.5	<u>1.3</u>	1.1	1.0
Taz 0.05%	2.5		0.5	1.0	1.2	1.3	1.3	<u>1.2</u>	0.9	0.9
Lidex	2.5		0.7	1.1	1.3	1.4	1.4	1.0	0.9	0.8
R168-126-8606										
K/E Taz 0.1%	2.5		0.6	0.9	1.2	1.5	1.4	1.1	1.0	0.9
Taz 0.05%	2.5		0.4	0.9	1.0	1.1	1.2	1.2	1.1	1.0
Lidex	2.5		0.5	0.9	1.2	1.3	1.3	1.2	0.9	0.8
R168-145-8606 (Average Scores from 2 target lesions)										
Taz 0.1%	2.5		0.6		<u>1.2</u>	<u>1.4</u>	1.3	1.3	1.3	1.1
Taz 0.05%	2.5		0.6		<u>0.9*</u>	<u>1.0</u>	1.2	1.4	1.2	1.1
Dovonex	2.4		0.7		1.3	1.6	1.7	1.3	1.2	1.2
Scaling										
Scaling	Baseline		Reduction in Scores							
	wk-0		wk-1	wk-2	wk-4	wk-8	wk-12	wk-16	wk-20	wk-24
R168-125-8606										
T/A/L Taz 0.1%	2.4		0.7	1.0	1.0	1.3	1.3	<u>1.3</u>	1.1	<u>1.0</u>
Taz 0.05%	2.3		0.5	0.7	1.0	1.1	1.1	<u>1.1</u>	0.9	<u>0.9</u>
Lidex	2.4		0.8	1.1	1.4	1.6	1.6	1.3	1.2	1.1
R168-126-8606										
T/A/L Taz 0.1%	2.5		<u>0.6</u>	0.9	1.1	<u>1.5</u>	<u>1.6</u>	1.2	1.1	1.0
Taz 0.05%	2.4		<u>0.3</u>	0.8	0.9	<u>0.9</u>	<u>1.1</u>	1.0	1.1	1.0
Lidex	2.4		0.8	1.1	1.4	1.6	1.6	1.3	1.0	0.9
R168-125-8606										
K/E Taz 0.1%	2.5		0.6	0.9	1.0	1.3	1.3	<u>1.3</u>	1.1	1.0
Taz 0.05%	2.5		0.5	0.8	1.1	1.2	1.2	<u>1.2</u>	1.0	0.9
Lidex	2.5		0.8	1.2	1.3	1.5	1.4	1.0	0.9	0.9
R168-126-8606										
K/E Taz 0.1%	2.6		0.5	0.8	1.0	1.3	1.2	1.0	0.9	0.8
Taz 0.05%	2.7		0.4	0.7	0.9	1.0	1.1	1.2	1.1	0.9
Lidex	2.6		0.7	1.1	1.3	1.5	1.4	1.2	1.0	0.8
R168-145-8606 (Average Scores from 2 target lesions)										
Taz 0.1%	2.5		0.7		<u>1.1</u>	1.2	1.3	1.2	1.1	0.9
Taz 0.05%	2.4		0.4		<u>0.7</u>	0.8	1.0	1.2	1.1	0.9
Dovonex	2.3		1.1		1.4	1.6	1.7	1.2	1.1	1.0

*Bold italics indicate superiority of Lidex over tazarotene or Dovonex (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% doses (p<0.05).~~ T/A/L=trunk/arm/leg lesions; K/E=knee/elbow lesions; Taz=tazarotene.

Erythema	Baseline wk-0	Reduction in Scores							
		wk-1	wk-2	wk-4	wk-8	wk-12	wk-16	wk-20	wk-24
R168-125-8606									
T/A/L Taz 0.1%	2.4	<i>0.2</i>	<i>0.4</i>	<i>0.5</i>	<i>0.9</i>	<i>0.9</i>	<u>1.2</u>	<u>1.1</u>	<u>1.1</u>
Taz 0.05%	2.4	<i>0.2</i>	<i>0.3</i>	<i>0.5</i>	<i>0.8</i>	<i>0.8</i>	<u>0.9</u>	<u>0.8</u>	<u>0.7</u>
Lidex	2.4	0.6	0.9	1.2	1.4	1.4	1.1	1.0	0.8
R168-126-8606									
T/A/L Taz 0.1%	2.2	<i>0</i>	<i>0.2</i>	<i>0.4</i>	<i>0.7</i>	<i>0.9</i>	1.2	0.9	0.9
Taz 0.05%	2.3	<i>0</i>	<i>0.3</i>	<i>0.6</i>	<i>0.5</i>	<i>0.9</i>	1.0	1.2	1.0
Lidex	2.4	0.4	0.8	1.2	1.4	1.5	1.2	1.0	0.9
R168-125-8606									
K/E Taz 0.1%	2.2	<i>0.2</i>	<i>0.4</i>	<i>0.6</i>	<i>0.7</i>	<i>0.8</i>	<u>1.0</u>	<u>0.9</u>	<u>0.9</u>
Taz 0.05%	2.3	<i>0.2</i>	<i>0.4</i>	<i>0.5</i>	<i>0.8</i>	<i>0.9</i>	<u>1.0</u>	0.8	<u>0.7</u>
Lidex	2.3	0.5	0.8	1.1	1.2	1.2	0.8	0.7	0.6
R168-126-8606									
K/E Taz 0.1%	2.1	<i>0</i>	<i>0.3</i>	<i>0.5</i>	<i>0.7</i>	0.9	1.0	0.7	0.7
Taz 0.05%	2.1	<i>0.1</i>	<i>0.2</i>	<i>0.5</i>	<i>0.5</i>	<i>0.7</i>	0.8	0.8	0.6
Lidex	2.2	0.4	0.7	1.0	1.1	1.1	1.0	0.8	0.8
R168-145-8606 (Average Scores from 2 target lesions)									
Taz 0.1%	2.3	<i>0.1</i>		<i>0.4</i>	<i>0.7</i>	<i>0.8</i>	0.9	0.9	0.8
Taz 0.05%	2.2	<i>0.1</i>		<i>0.2</i>	<i>0.4</i>	<i>0.7</i>	0.8	0.8	0.5
Dovonex	2.2	0.2		0.6	0.8	1.1	1.0	0.9	0.8

Sum of Scores	Baseline wk-0	Reduction in Scores							
		wk-1	wk-2	wk-4	wk-8	wk-12	wk-16	wk-20	wk-24
R168-125-8606									
T/A/L Taz 0.1%	7.2	<i>1.6</i>	2.4	2.7	3.6	3.7	<u>3.9</u>	<u>3.4</u>	<u>3.1</u>
Taz 0.05%	7.1	<i>1.2</i>	<i>2.0</i>	<i>2.6</i>	<i>3.1</i>	<i>3.2</i>	<u>2.9</u>	<u>2.6</u>	<u>2.5</u>
Lidex	7.2	2.0	3.0	3.9	4.3	4.5	3.7	3.3	2.8
R168-126-8606									
T/A/L Taz 0.1%	7.2	<i>1.2</i>	<i>2.1</i>	<i>2.7</i>	<i>3.8</i>	<i>4.1</i>	3.8	3.2	2.9
Taz 0.05%	7.2	<i>0.8</i>	<i>2.0</i>	<i>2.6</i>	<i>2.5</i>	<i>3.2</i>	3.2	3.4	3.0
Lidex	7.2	1.8	2.8	3.9	4.5	4.7	3.8	3.1	2.7
R168-125-8606									
K/E Taz 0.1%	7.2	<i>1.5</i>	<i>2.3</i>	<i>2.9</i>	<i>3.4</i>	<i>3.6</i>	<u>3.7</u>	3.0	3.0
Taz 0.05%	7.3	<i>1.3</i>	<i>2.1</i>	<i>2.9</i>	<i>3.2</i>	<i>3.4</i>	<u>3.3</u>	2.7	2.5
Lidex	7.3	2.0	3.1	3.7	4.1	4.1	2.9	2.6	2.3
R168-126-8606									
K/E Taz 0.1%	7.1	<i>1.0</i>	<i>2.0</i>	<i>2.7</i>	<i>3.3</i>	3.5	3.1	2.6	2.5
Taz 0.05%	7.3	<i>0.9</i>	<i>1.9</i>	<i>2.3</i>	<i>2.6</i>	3.0	3.3	3.1	2.5
Lidex	7.3	1.6	2.8	3.5	3.9	3.7	3.3	2.7	2.4
R168-145-8606 (Average Scores from 2 target lesions)									
Taz 0.1%	7.3	<i>1.5</i>		<i>2.7</i>	<i>3.2</i>	<i>3.4</i>	3.3	3.3	2.9
Taz 0.05%	7.0	<i>1.1</i>		<i>1.7</i>	<i>2.2</i>	<i>2.9</i>	3.3	3.0	2.4
Dovonex	6.9	2.0		3.2	3.9	4.4	3.5	3.2	3.0

*Bold italics indicate superiority of Lidex over tazarotene or Dovonex (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% doses (p<0.05). T/A/L=trunk/arm/leg lesions; K/E=knee/elbow lesions; Taz=tazarotene.

Global of "Good or better" (% pts)	wk-1	wk-2	wk-4	wk-8	wk-12	wk-16	wk-20	wk-24
R168-125-8606 Taz 0.1%	21	40	43	59	56	59	44	<u>45</u>
Taz 0.05%	18	28	44	48	48	39	36	38
Lidex	25	47	59	66	65	46	33	30
R168-126-8606 Taz 0.1%	4	18	28	24	45	41	29	22
Taz 0.05%	4	13	18	22	38	40	35	31
Lidex	13	33	51	60	61	47	30	25
R168-145-8606 Taz 0.1%	7		26	33	41	33	26	27
Taz 0.05%	3		16	29	44	45	35	24
Dovonex	9		35	52	63	47	36	36

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

Comment

1. The primary efficacy variables are consistent with those seen in the two pivotal vehicle-controlled trials.
2. Absence of consistently superior efficacy parameters by tazarotene over fluocinolone or calcipotriol suggests lack of maintenance effect. The issue was discussed at the End-of-Phase 2 meeting and the Applicant was advised that since psoriasis was a chronic disease that could wax and wane, it would be necessary to demonstrate superiority over an active control in order to make a claim of sustained therapeutic effect.
3. The 0.1% gel has done significantly better than the 0.05% gel at various time-points for different parameters (see above Tables). However, none of these were confirmed with findings in a second study.

9.1.2 Subset Analysis

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

	Age			Sex		Race	
	<45	45-65	>65	Males	Females	whites	nonwhites
Patient nos in subsets (R168-120-8606/R168-121-8606)							
Taz 0.1%	47/41	46/42	12/21	71/69	34/35	95/92	10/12
Taz 0.05%	52/50	39/37	15/17	69/66	37/38	89/95	17/9
Vehicle	52/45	44/46	11/18	72/70	35/39	98/91	9/18
Superiority at Endpoint: week-12 (R168-120-8606/R168-121-8606)*							
Plaque Elevation Taz 0.1%	++	++	-/	++	++	++	+/-
Taz 0.05%	++	++	-/	++	++	++	-/
Scaling Taz 0.1%	++	++	-/	+/	+/	+/	-/
Taz 0.05%	+/-	+/-	-/	-/	+/	+/	-/
Erythema Taz 0.1%	+/-	+/-	-/	+/	+/	+/	+/-
Taz 0.05%	+/-	+/-	-/	-/	+/	+/	-/
"Treatment Success" Taz 0.1%	+/	+/	-/	+/	+/	+/	+/
Taz 0.05%	-/	-/	-/	-/	+/-	+/	-/

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

Comment

1. These analyses were not sufficiently powered to yield significance within the subsets. Any negative finding (e. g. in the >65 year-old group) would need to be confirmed with studies using larger samples sizes of that particular subset. A meta-analysis combining the 2 studies would be useful but this was not done.
2. The subset analyses of the two studies gave similar results. In general, they agree with analysis of the whole study population, except for the nonwhite subjects,

where there was more incongruity in findings between studies.

4. Only 3 instance of superiority of 0.1% gel over 0.05% gel were noted: scaling for males, scaling for whites and "treatment success" for nonwhites (see above).

9.2 Acne

9.2.1 Comparison between Studies

There were two Phase 3 studies for the treatment of facial acne which had almost identical protocols. The main difference between these studies are in the following:

1. Overall clinical severity and specific assessment of the severity of burning, erythema, pruritus, dryness, peeling and oiliness were eliminated from R168-221-8606.
2. Global scores in R168-221-8606 split "no change" and "worsened" into 2 scores on a 6-point scale.

Demographics and Baseline Disease Involvement The two studies enrolled patients with similar demographic background and baseline status, except for the fact that R168-221-8606 enrolled 20-26% Hispanic patients per arm, while R168-220-7997 had only 1-2% Hispanics in each treatment group. Otherwise the following combined data reflect very-similar figures in each study.

Pt no*	Years		Percent		
	Age		Sex		Race
	Mean	Range	Males	Females	W/H/B/OR/OT*
Taz* 0.1%	20		50	50	76/12/11/1/1
Taz 0.05%	22		47	53	77/11/12/0/0
Vehicle	21		50	50	77/11/11/1/0
Total	21		49	51	77/11/11/1/0

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

Patient disposition Disposition of patients was similar in the two studies and the combined data are as follows:

	Enrolled	Eval*	Completed	LOC	AE	Other discon	Disqualified
Taz* 0.1%	299	255	231 (77%)	0 (0%)	22 (7%)	42(14%)	4 (1%)
Taz 0.05%	297	253	221 (74%)	1 (0%)	22 (7%)	46(16%)	7 (2%)
Vehicle	297	265	234 (79%)	8 (3%)	4 (1%)	43(15%)	8 (3%)
Total	893	773	686 (77%)	9 (1%)	48 (5%)	131(15%)	19 (2%)

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

Primary Efficacy Variables

	Lesion counts				Reduction			
	wk-0		wk-4		wk-8		wk-12	
	220	221	220	221	220	221	220	221
Noninflammatory Lesions								
Taz* 0.1%	62	52	<u>82%</u>	19%	<u>46%</u>	36%	<u>52%</u>	<u>48%</u>
Taz 0.05%	56	52	<u>25%</u>	15%	<u>43%</u>	31%	<u>55%</u>	<u>88%</u>
Vehicle	60	50	16%	8%	31%	19%	35%	27%
Inflammatory Lesions								
Taz 0.1%	21	22	16%	17%	29%	40%	42%	47%
Taz 0.05%	20	21	22%	14%	38%	31%	39%	37%
Vehicle	23	21	17%	12%	33%	25%	30%	28%
Total Lesions								
Taz 0.1%	82	75	<u>28%</u>	19%	<u>42%</u>	38%	<u>52%</u>	45%
Taz 0.05%	75	74	25%	16%	41%	31%	<u>44%</u>	39%
Vehicle	83	71	19%	10%	32%	21%	33%	47%

Global of $\geq 50\%$ improvement	wk-4		wk-8		wk-12		
	220	221	220	221	220	221	
Taz 0.1%		28%	14%	<u>48%</u>	36%	<u>68%</u>	48%
Taz 0.05%		24%	10%	43%	27%	51%	40%
Vehicle		28%	6%	38%	20%	47%	29%

*Significant differences between tazarotene and vehicle are underlined ($p < 0.05$); ~~significant differences between the two tazarotene gels are underlined ($p < 0.05$)~~; 220=R168-220-7997, 221=R168-221-8606, Taz=tazarotene.

Comment

- The 2 studies gave similar trends in lesion reduction and global improvement. The beneficial effects of tazarotene gels appear to be less pronounced in R168-221-8606. There is no adequate explanation for this finding, although a greater number of responsive initial lesions in R168-220-8606 might have contributed to this difference.
- Both gels were successful for reducing noninflammatory and total lesion counts. The 0.1% gel was also superior to vehicle for inflammatory lesion reduction at endpoint, as well as for "treatment success". The 0.05% gel failed the criterion of global "treatment success" at endpoint as defined by the Applicant in both studies.

9.2.2 Subset Analysis

The Applicant analyzed the two vehicle-controlled trials for differences in lesion count reduction among subsets with respect to sex and race. Age was not analyzed as all of the patients were below 45. The data are summarized in the following Table:

	Sex		Race			
	Males	Females	whites	blacks	other	
Patient nos in subsets (R168-220-7997/R168-221-8606)						
Taz 0.1%	63/63	59/70	71/118	16/12	35/NA	
Taz 0.05%	61/54	63/75	83/116	15/11	26/NA	
Vehicle	76/60	53/76	84/118	16/12	29/NA	
Superiority at Endpoint: week-12 (R168-220-7997/R168-221-8606)*						
Noninflammatory Lesions	Taz 0.1%	+/+	+/+	-/-	+/na	
	Taz 0.05%	-/-	-/-	-/+	-/-	-/na
Inflammatory Lesions	Taz 0.1%	-/+	-/-	+/+	-/-	-/na
	Taz 0.05%	-/-	-/-	-/-	-/-	-/na
Total Lesions	Taz 0.1%	+/+	+/+	+/+	-/-	+/na
	Taz 0.05%	-/-	-/-	-/+	-/-	-/na

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

Comments

1. The results of subset analyses in the two studies were in general consistent with the exception of the 0.05% gel effect on noninflammatory and total lesions and the effect of 0.1% gel on inflammatory lesions.
2. As discussed in the psoriasis trials, these studies were not powered to show effects in such subsets. A meta-analysis of the combined data might be able to demonstrate significance of differences within the subsets but this was not done.
3. There were no significant effects shown in the subset analysis that had not been evident in the analysis of the entire dataset of each study.
4. Estrogen has been one of the medications used to treat acne vulgaris. These studies permitted patients to continue estrogen use if the subject had been previously using it for at least 12 weeks. This created a confounding factor, which might be examined by subset analysis. In addition, breakdown of the age groups into subsets for analysis of response (e.g., using age 25 as cutoff) might be of interest.

10. Overview of Safety

10.1 Significant/Potentially Significant Events

10.1 Deaths Two patients died of myocardial infarction (Subject [redacted] in R168-120-8606 and in R168-125-8606)

10.1.2 Other Significant/Potentially Significant Events

Psoriasis

Serious adverse events were reported in all five controlled phase 3 trials. One case was "treatment-related": moderate worsening of psoriasis requiring hospitalization in a patient treated with Lidex. "Treatment-unrelated" serious adverse events were:

Tazarotene 0.1%	Tazarotene 0.05%	Control
<p>Treatment period (N=8) myocardial infarction resulting in death [redacted] in R168-120-8606) elective surgery for kidney calculus with subsequent myocardial infarction resulting in death [redacted] in R168-125-8606) prostatic carcinoma [redacted] in R168-120-8606) chest pain [redacted] in R168-121-8606) benign abdominal neoplasm [redacted] in R168-121-8606) facial cellulitis [redacted] in R168-121-8606) depression [redacted] in R168-125-8606) dizziness, dysautonomia, hypesthesia, & hypertension [redacted] in R168-126-8606)</p>	<p>Treatment period (N=11) angina pectoris ([redacted] in R168-120-8606) cerebral vascular accident [redacted] in R168-121-8606) chest pain [redacted] in R168-125-8606) accident resulting in broken ribs [redacted] in R168-125-8606) staphylococcal infection [redacted] in R168-126-8606) edema and jaundice [redacted] in R168-126-8606) uterine disorder [redacted] in R168-126-8606) Crohn's disease [redacted] in R168-126-8606) thromboangiitis [redacted] in R168-126-8606) constipation producing obstruction in a multiple sclerosis patient [redacted] in R168-145-8606) Transient loss of vision in one eye in a patient with migraine [redacted] in R168-145-8606)</p>	<p>Treatment period (N=6) Vehicle: retinal detachment [redacted] in R168-120-8606) Lidex: colon cancer [redacted] in R168-125-8606) recurrent dizziness [redacted] in R168-126-8606) hammertoes [redacted] in R168-126-8606) skin carcinoma [redacted] in R168-126-8606) broken femur (accident) [redacted] in R168-126-8606) Dovonex: none</p>

Tazarotene 0.1%	Tazarotene 0.05%	Control
<u>Posttreatment period (n=3)</u> myocardial infarction (█████ in R168-120-8606) pneumonia (█████ in R168-120-8606) cellulitis (█████ in R168-120-8606)	<u>Posttreatment period (N=3)</u> sleep apnea (█████ in R168-125-8606) heart complaint (short circuit in defibrillator) (█████ in R168-126-8606) worsening of psoriasis (█████ in R168-145-8606)	<u>Posttreatment period (N=6)</u> <u>Vehicle:</u> bone fractures and a displaced shoulder implant (█████ in R168-120-8606) <u>Lidex:</u> asthma (█████ in R168-125-8606) worsening of psoriasis (█████ in R168-125-8606) suspected meningitis, along with pharyngitis & neck pain (█████ in R168-125-8606) angina pectoris (█████ in R168-126-8606) <u>Dovonex:</u> injuries resulting from a traffic accident (█████ in R168-145-8606)

The 12-month long-term study R168-128-8606 had 7 subjects experiencing serious adverse events: 2 cases of cholecystitis (█████, both 0.1% gel), and one of each - headache with diplopia (█████, 0.05% gel); allergy reaction to bee sting (█████, 0.1% gel); amaurosis fugax with 95% occlusion of a carotid artery (█████, 0.05% gel); cervical foraminotomy (█████, 0.1% gel) and worsening of psoriasis (erythrodermic) (█████, 0.05% gel). After completion of the study, one patient was diagnosed as having metastatic adenocarcinoma (█████, 0.1% gel).

Acne

Only two patients experienced serious adverse events during the acne trials. Both were treatment-unrelated: Patient ██████ in the tazarotene vehicle group experienced intestinal influenza requiring hospitalization. Patient ██████ also in the vehicle group, suffered a severe attack of appendicitis and underwent appendectomy.

There were 6 cases of pregnancy:

R168-120-8606:

(tazarotene 0.1%) - positive pregnancy test, discontinued study.

(tazarotene 0.1%) - discontinued in posttreatment period for "need for treatment".

(Vehicle) - discontinued in posttreatment period for personal reasons.

All 3 women gave birth to healthy babies.

R168-145-8606:

(Dovonex) - treatment discontinued; patient subsequently terminated pregnancy.

R168-120-8606:

(tazarotene 0.1%) - discontinued study. No adverse events. Gave birth to healthy baby.

(Vehicle) - positive pregnancy test at last visit; pregnancy terminated 2 months later.

10.1.3 Overdose Exposure No overdose reporting in any trials in this NDA.

10.2 Other Safety Findings

10.2.1 ADR Incidence Tables See Appendix II to IX for listing of adverse events of $\geq 1\%$ incidence and Section 8 for complete incidence of adverse events of skin and appendages of individual trials. The combined list of adverse events seen in all phase 3 trials is given in Appendix X (with R168-128-8606 cropped at 3 month cutoff point and the other psoriasis trials excluding the posttreatment periods). Appendix XI gives the terminations due to adverse events in all phase 3 trials combined. The severity of the most frequent "treatment-related" adverse events in the tazarotene-treated patients in psoriasis and in acne is shown below:

I. Psoriasis

	Tazarotene 0.1% n=568				Tazarotene 0.05% n=569			
	all	mild	moderate	severe	all	mild	moderate	severe
all	321 (57%)	68 (12%)	132 (23%)	121 (21%)	260 (46%)	69 (12%)	104 (18%)	87 (15%)
burning	127 (22%)	27 (5%)	51 (9%)	49 (9%)	102 (18%)	20 (4%)	43 (8%)	39 (7%)
erythema	106 (19%)	31 (6%)	34 (6%)	41 (7%)	86 (15%)	31 (5%)	23 (4%)	32 (6%)
itching	93 (16%)	24 (4%)	51 (9%)	18 (3%)	79 (14%)	26 (5%)	36 (6%)	17 (3%)
irritation	76 (13%)	22 (4%)	37 (7%)	17 (3%)	52 (9%)	14 (3%)	25 (4%)	13 (2%)
itching in pain	43 (8%)	8 (1%)	18 (3%)	17 (3%)	26 (5%)	9 (2%)	12 (2%)	5 (<1%)
psoriasis worsened	32 (6%)	7 (1%)	16 (3%)	9 (2%)	30 (5%)	9 (2%)	12 (2%)	9 (2%)
desquamation	29 (5%)	17 (3%)	12 (2%)	0	18 (3%)	10 (2%)	2 (<1%)	6 (1%)
itching	29 (5%)	9 (2%)	14 (3%)	6 (1%)	19 (3%)	8 (1%)	9 (2%)	2 (<1%)
itching	25 (4%)	5 (<1%)	9 (2%)	11 (2%)	17 (3%)	6 (1%)	6 (1%)	5 (<1%)
itching inflammation	11 (2%)	1 (<1%)	7 (1%)	3 (<1%)	6 (1%)	0	3 (<1%)	3 (<1%)
itching	10 (2%)	4 (<1%)	4 (<1%)	2 (<1%)	7 (1%)	6 (1%)	0	1 (<1%)
itching skin	5 (<1%)	2 (<1%)	3 (<1%)	0	8 (1%)	3 (<1%)	4 (<1%)	1 (<1%)
itching somnolence	4 (<1%)	0	3 (<1%)	1 (<1%)	0	0	0	0
itching in fissure	2 (<1%)	1 (<1%)	0	1 (<1%)	8 (1%)	2 (<1%)	4 (<1%)	2 (<1%)
itching in hemorrhage	3 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	7 (1%)	3 (<1%)	1 (<1%)	3 (<1%)
itching in discharge	2 (<1%)	0	2 (<1%)	0	4 (<1%)	3 (<1%)	0	1 (<1%)
itching in vesiculobullous	1 (<1%)	0	1 (<1%)	0	4 (<1%)	0	2 (<1%)	2 (<1%)

II. Acne

	Tazarotene 0.1% n=299				Tazarotene 0.05% n=297			
	all	mild	moderate	severe	all	mild	moderate	severe
all	139 (47%)	64 (21%)	56 (19%)	19 (6%)	123 (41%)	62 (21%)	50 (17%)	11 (4%)
desquamation	84 (28%)	42 (14%)	32 (11%)	10 (3%)	61 (21%)	38 (13%)	18 (6%)	5 (2%)
burning	74 (25%)	35 (12%)	28 (9%)	11 (4%)	57 (19%)	20 (7%)	29 (10%)	8 (3%)
itching skin	59 (20%)	35 (12%)	19 (6%)	5 (2%)	59 (20%)	36 (12%)	18 (6%)	5 (2%)
erythema	53 (18%)	28 (9%)	18 (6%)	7 (2%)	33 (11%)	20 (7%)	11 (4%)	2 (<1%)
pruritus	36 (12%)	26 (9%)	7 (2%)	3 (1%)	31 (10%)	17 (6%)	11 (4%)	3 (1%)
itching	16 (5%)	6 (2%)	6 (2%)	4 (1%)	8 (3%)	4 (1%)	3 (1%)	1 (<1%)
itching	9 (3%)	6 (2%)	2 (<1%)	1 (<1%)	10 (3%)	8 (3%)	2 (<1%)	0
itching	5 (2%)	3 (1%)	0	2 (<1%)	1 (<1%)	0	1 (<1%)	0
itching in discoloration	3 (1%)	1 (<1%)	2 (<1%)	0	0	0	0	0
itching in fissure	3 (1%)	1 (<1%)	2 (<1%)	0	1 (<1%)	1 (<1%)	0	0
itching in eczema	2 (<1%)	0	2 (<1%)	0	1 (<1%)	1 (<1%)	0	0
itching in tightness	2 (<1%)	1 (<1%)	1 (<1%)	0	3 (1%)	3 (1%)	0	0
itching	1 (<1%)	0	0	1 (<1%)	1 (<1%)	0	1 (<1%)	0
itching in swelling	1 (<1%)	0	0	1 (<1%)	1 (<1%)	1 (<1%)	0	0

Comment The difference in incidence of "severe" adverse events between the two formulations is slight.

Terminations due to "treatment-related" adverse events were primarily from local irritation symptoms. For psoriasis, burning, pruritus and psoriasis worsened were the most frequently seen events while in acne, burning, erythema and desquamation were most prevalent as factors that result in termination:

Adverse Event	Termination Rate for Psoriasis			Adverse Event	Termination Rate for Acne		
	Taz 0.1%	Taz 0.05%	Vehicle		Taz 0.1%	Taz 0.05%	Vehicle
Total Termination	18%	14%	5%	Total Termination	7%	7%	1%
Burning	5%	3%	0.5%	Burning	4%	4%	0.7%
Pruritus	4%	4%	1%	Erythema	4%	3%	0
Psoriasis worsened	4%	2%	3%	Desquamation	3%	4%	0

10.2.2 Laboratory Findings, Vital Signs, ECGs The following laboratory studies were included in all the Phase 3 clinical trials: CBC, serum chemistry and urinalysis. No consistent clinically significant abnormalities were found. In R168-128-8606, the effect of long-term use of topical tazarotene on bone and lipids was examined, but no consistent changes in serum

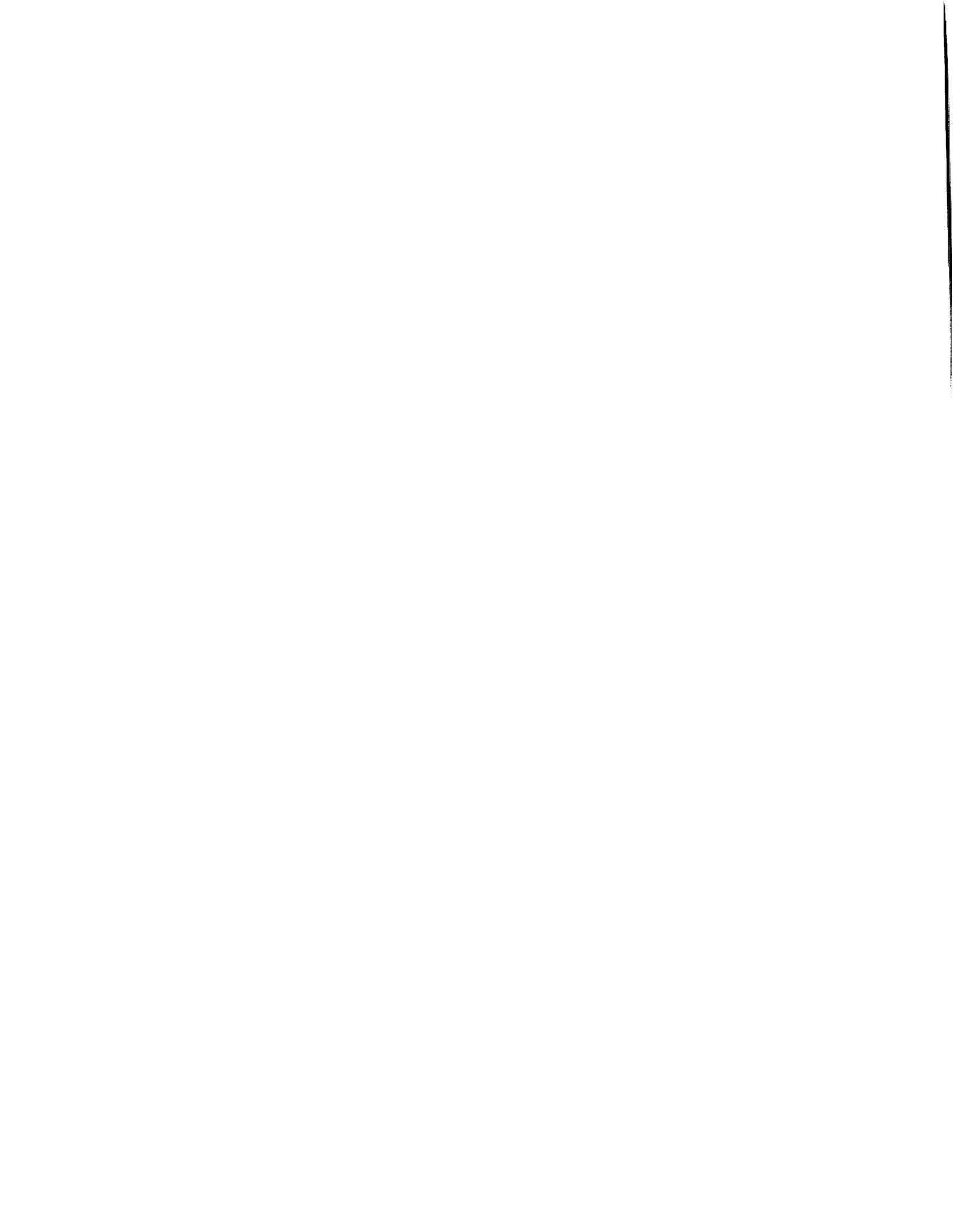
calcium, phosphate, triglyceride or cholesterol levels were observed. Vital signs and ECG were not pertinent parameters for collection in these studies. Therapeutic drug monitoring was done in selected centers in all the Phase 3 trials. The findings are discussed in the next Section. In the long-term psoriasis study (R168-128-8606), X-rays were taken for ankles, cervical and thoracic spine at baseline and at the exit visit. No consistent detectable changes in bones or ligaments were reported during the study period of up to 12 months, but the technique and interpretation of the radiologic data were not optimal.

10.2.3 Special Studies

10.2.3.1 Pharmacokinetics Studies These studies have been reviewed by the Biopharm. reviewer. The pharmacokinetics data will only be summarized here followed by a discussion of the safety findings. A listing of the studies with demographic data can be found in Appendix IA.

In summary, the clinical PK studies showed:

1. In R168-150-7997, occlusive application of 0.1% gel to normal skin for 10 hrs resulted in <6% systemic absorption. Blood concentration peaked at 10-12 hrs and urine excretion at 12 hrs. There was a gradient of tazarotene down the stratum corneum. Excretion of drug-related material was approximately equal via urine and feces (2.6% and 2.7% of the dose respectively).
2. In R168-151-7997, doubling the concentration of gel from _____ % resulted in _____% increase of systemic absorption rather than a corresponding linear increase.
3. In R168-152-8606, with daily administration of the 0.1% gel for 7 days, steady state was not reached, Mean C_{max} for AGN 190299, the active metabolite of tazarotene, increased two-fold (_____ ng/ml), while T_{max} and t_{1/2} decreased with time, suggesting chronic administration associated with increased skin permeability. Tazarotene levels were undetectable throughout.
4. In R168-154-8606, following a 10-hr nonocclusive application of ¹⁴C-tazarotene to psoriatic skin, 4.5% of the applied dose was found in the stratum corneum and 2.4% in the viable epidermis (1.4%) and dermis (1%) combined; tazarotene level down the stratum corneum was uniform. Excretion of drug-related material was approximately equal via urine and feces (0.33% and 0.44% of the dose respectively). Maximal blood concentration was found at approximately 10 hrs post-dose and urinary excretion at 11 hrs.
5. In R168-153-8606, after daily topical application of 0.1% gel for 14 doses on psoriatic skin involving 5-20% of total body surface area, the systemic bioavailability of tazarotene increased (tazarotene _____%; AGN 190299 _____%) and the mean absorption time through the skin decreased from 21 hrs after the first dose to 10 hrs after the last (4th) dose. Increased bioavailability was associated with greater decreases in plaque elevation and scaling but smaller decreases in erythema over time. The mean C_{max} of tazarotene and its chief metabolite, AGN 190299 increased about 10 fold after 8-14 daily applications (levels after Dose-1→Dose-8→Dose-14 being: 16→54→185 pg/ml for tazarotene and 1→10→12 ng/ml for AGN 190299). Steady state was reached by dose-8. By extrapolating data from the intravenous study (see below), the Applicant calculated the systemic exposure to AGN 190299 to be up to 26% of the applied dose after repeated application.
6. In R168-155-8606 intravenous administration of tazarotene was associated with (1) rapid biphasic elimination with a terminal half-life of 6 hr and (2) a terminal half-life of AGN 190299 (tazarotene's chief metabolite) comparable to that of topically applied tazarotene 0.1% gel, thus representing its elimination half-life.



The safety findings in these studies showed:

Study R168-150-7997. Percutaneous Absorption and Mass Balance of ¹⁴C-Tazarotene (AGN 190168) 0.1% Gel following Topical Administration to Healthy Subjects

In this study on percutaneous absorption and mass balance, a single dose of ¹⁴C-tazarotene 0.1% gel at 78 µCi /g was applied with occlusion for 10 hrs to 800 cm² of the trunk in 6 healthy subjects. One adverse event (diarrhea) was reported. Clinical laboratory data were not taken beyond the screening visit.

Study R168-151-7997. A Study to Determine the Plasma Concentration/Time profile following Separate Topical Administration of 2 Concentrations of Tazarotene (0.1% and 0.05%) Gels in Healthy Male Volunteers

Twenty-four subjects were enrolled in this crossover study, which involved a single application of 0.1% gel and 0.05% gel for 10 hrs to 20% of total body surface area, separated by a washout period of ≥ 14 days. Subjects were randomized as to the study period (which concentration to be applied first). Apart from one case of mild lightheadedness, adverse events were limited to local reactions:

	<u>0.05% gel</u>	<u>0.1% gel</u>
patients with adverse events	15 (63%)	17 (71%)
pruritus	12 (50%)	15 (63%)
desquamation	9 (38%)	11 (46%)
burning	1 (4%)	2 (8%)
rash	3 (12%)	2 (8%)
dry skin	0	3 (12%)
erythema	0	1 (4%)

Most of the cases of pruritus and about half of the cases of desquamation in either treatment period were reported as "severe"; so were the cases of burning and erythema in the 0.1% gel treatment period. Clinical laboratory data were not taken beyond the screening visit.

Study R168-152-8606. Pharmacokinetics of Tazarotene (AGN 190168) 0.1% Gel following Single-Dose and Multiple-Dose Topical administration to Healthy Subjects

This study involved initially a single application of tazarotene 0.1% gel 2 mg/cm² followed by a 48 hr evaluation period, and then daily application for 7 days followed by a 60 hr evaluation period after the last dose. The drug was applied for 12 hrs each time to 20% of the total body surface area (anterior surface of neck, chest, abdomen and upper thighs) in 24 healthy male subjects. Adverse events reported were: rash (21/24=88%), pruritus (20/24=83%), desquamation (12/24=50%), burning (9/24=38%), erythema (8/24=33%), dry skin (5/24=21%) and irritation (3/24=13%). In addition, there was one case each for skin pain, swelling, dizziness and headache. Clinical laboratory data were not taken beyond the screening visit.

Study R168-155-8606. Pharmacokinetics of Tazarotene (AGN 190168) administered as a Single Intravenous Infusion Dose and as a Single Topical Dose (0.1% Gel) to Healthy Subjects

This study attempted to determine the PK of iv infusion of 10-15 ml of tazarotene 0.01% solution (in 45% w/w ethanol at a dose of 1 mg/70 Kg) over 20 minutes and compare it with that of topical application of a 0.1% gel for 12 hrs. Eight male subjects were studied. No "serious" adverse events were reported. The intravenous infusion was associated with the following at the injection site: erythema (6/8), pain, edema, paresthesia and stinging (each 5/8), burning (3/8), and single reports of hematoma, vein tenderness, phlebitis, taste perversion, sweating

and vein induration. Some of the adverse events persisted for months (edema, localized numbness and venous induration). The topical application of 0.1% gel was not associated with adverse effects and there were no significant clinical laboratory findings.

Study R168-153-8606. Pharmacokinetics of Tazarotene (AGN 190168) following Single-Dose and Multiple-Dose Topical Application of 0.1% Gel or 0.05% Gel to Subjects With Stable Plaque Psoriasis

The aim of this study was to determine the PK parameters after single and multiple dose applications of two concentrations of tazarotene gel (2 mg gel/cm²) to psoriasis plaques covering 5-20% of total body surface area and to see if changes in PK parameters would correlate with changes in clinical severity. It consisted of (1) an initial application of tazarotene gel for 12 hrs followed by blood sampling over the next 60 hrs and (2) subsequent daily application at 7pm, each for 12 hrs, for 13 consecutive evenings and blood samplings at prefixed times. Due to difficulty in recruiting subjects, only the 0.1% gel was studied in 5 patients, who had psoriasis involvement covering 8%-18% of body surface area (12.7±4.5%). Adverse events reported were: rash 2, rhinitis 2, and 1 each for vasodilation, erythema, desquamation, burning, pruritus, dry skin, worsening of psoriasis, headache, epistaxis, nausea, dizziness, vaginitis and elevated triglycerides. None was considered "serious". The only significant clinical laboratory finding was triglyceride elevation in one subject, which subsided after 6 days off-treatment.

Study R168-154-8606. Percutaneous Absorption and Mass Balance of ¹⁴C-Tazarotene (AGN 190168) following a Single Topical Application of ¹⁴C-Tazarotene (AGN 190168) 0.1% Gel to Psoriatics

This study was similar to R168-150-7997 but was carried out using the 0.1% gel at 85 µCi/gm with no occlusion applied on 5% of the total body surface area involving psoriatic skin for 10 hrs, but excluding face, scalp and intertriginous regions. No adverse effects were noted apart from one case of diarrhea. Clinical laboratory data were not taken beyond the screening visit.

Study R168-712-7997. Phase I Study of Tazarotene (AGN 190168). Safety and Pharmacokinetics by Single Topical Application.

This was a single-dose study in 18 healthy Japanese subjects (6 per dosage group) for PK parameters after applications of tazarotene 0.01%, 0.05% or 0.1% gel, each at a dose of 1.6 gm/800 cm² for 12 hrs. One subject in the 0.05% gel group had erythema and itching 24 hrs after application, erythema after 48 hrs and erythema and desquamation after one week. All these symptoms were classified as "mild". CBC, serum chemistry and urinalysis did not yield abnormal findings.

Study R168-713-7997. Phase I Study of Tazarotene (AGN 190168). Safety and Pharmacokinetics by Multiple Topical Application.

This study recruited 12 healthy Japanese subjects, 6 per dosage group, for PK parameters after repeated applications of tazarotene gels as follows:

0.05% gel -- 1.6 gm/800 cm² for 24 hours, repeated 6 times (total 7 applications),

0.1% gel -- 1.6 gm/800 cm² for 24 hours, repeated 4 times (total 5 applications).

Adverse events, all considered as mild:

	<u>0.05% gel</u>	<u>0.1% gel</u>
erythema	2	0
desquamation	5	3
pruritus	1	0

No abnormalities were found with clinical laboratory tests (CBC, serum chemistry and urinalysis).

Comment No additional information on systemic or local adverse events have been obtained from these 8 studies.

10.2.3.2 Therapeutic Drug Monitoring This was performed in selected centers in the phase 2 (20 subjects) and phase 3 (678 subjects) trials. The shorter-term studies involved a total of 586 patients. For these studies, tazarotene was sporadically detected during treatment of up to 12 weeks. Ten subjects had detectable levels ranging from _____ ng/ml. The active metabolite, AGN190299, was detected in the range of _____ ng/ml: 271/474=57% of psoriasis patients and 13/92=14% of acne patients. The great majority (92%) of these positive samples had levels of AGN190299 below 1 ng/ml: 428/474=90% of psoriasis patients and 92/92 of acne patients. None of those having levels ≥ 1 ng/ml experienced systemic adverse events considered related to tazarotene, except in one case of insomnia. The positive plasma samples for AGN 190299 almost divided equally between patients treated with tazarotene 0.1% and those with the 0.05% gel.

The long term psoriasis study R168-128-8606 had 112 (0.1% gel 57, 0.05% gel 55) subjects tested for plasma levels at 0, 3, 6, 9 or 12 months. Three patients (3%) had detectable levels of tazarotene (>1 ng/ml). AGN190299 was detected in 28% of patients (31/112; 0.1% gel 18, 0.05% gel 13). Four patients (2 per group) had levels of over 1 ng/ml but none reported treatment-related systemic adverse events. However, food poisoning was reported in one and diarrhea was reported in another subject, both incidence deemed "treatment-unrelated".

Comment One possible explanation for the lower incidence of positive plasma levels with prolonged treatment is that absorption might decrease when skin inflammation has become less intense. Since short-term multiple application might actually increase systemic bioavailability, further studies would be required to clarify this discrepancy.

10.2.3.3 Dermal Safety Studies They have been listed in Appendix IB. which gives design of the studies and demographics of study populations.

1. Study R168-101-8004. 21-Day Cumulative Irritation Study of Tazarotene (AGN 190168) 0.05%, 0.01% and Vehicle Gels in Healthy Subjects

In this preliminary study done at the

the following were applied to patches and affixed (semi-occlusion) to the backs of 28 subjects: tazarotene 0.05% and 0.01% gels, vehicle, Retin-A™ 0.025%, and 0.01% gels, Retin-A™ 0.05% cream and 0.05% solution as well as sodium lauryl sulfate 0.5% in water. The patches were removed after 24 hrs and the test site evaluated on a 6-point scale. This was repeated 20 times at the same site. The mean cumulative irritation scores were as follows:

Retin A				Tazarotene			SLS
0.05% solution	0.05% cream	0.025% gel	0.01% gel	0.05% gel	0.01% gel	Vehicle	0.5% solution
16.9	10.3	7.8	7.3	15.4	8.2	2.4	4.0

Statistical analysis showed that:

1. Tazarotene 0.05% was not significantly different from Retin A 0.05% solution,

2. tazarotene 0.01% not significantly different from those for other Retin A products, &
3. tazarotene vehicle not significantly different from SLS 0.5% solution (all with p>0.05).

Comment The formulations used were different from the ones applied for marketing.

2. Study R168-101-8606. 21-Day Cumulative Irritation Study of Tazarotene (AGN 190168) 0.05%, 0.1% and Vehicle Gels in Healthy Subjects

This study was done at the

It tested older versions of tazarotene and vehicle and later formulations which the Applicant intends to market, together with other products as shown in the Table below. The procedures were the same as in Study R168-101-8004. The mean cumulative irritation scores from 29 subjects were:

Tazarotene*						Retin-A		Azelaic acid		Benzac** 5	SLS
0.1% gel		0.05% gel		vehicle gel		0.1% gel	0.05% gel	20% cream	vehicle cream	5% gel	5% solution
7997X	8606X	8607X	8225X	8608X	8006X						
38.3	37.1	34.1	33.2	2.4	2.2	34.3	26.2	20.5	2.4	29.5	2.2

The formulations 8606X for 0.1% gel and 8607X for 0.05% gel were used in seven of the eight phase 3 trials discussed in Section 8. Study R168-220-7997 used the earlier formulations 7997X, 8225X and 8006X. The vehicle gel 8608X was used in 3 out of the 4 vehicle-controlled phase 3 trials. The difference between the earlier and the later formulations was in the use of trolamine (earlier) vs tromethamine (later) as an excipient. **Benzac5 gel contained 5% benzoyl peroxide.

Comment Tazarotene 0.05% gel was as irritating as Retin A 0.1% gel. Tazarotene 0.1% gel in the current formulation was more irritating than Retin A 0.1% gel and the 0.05% gel of tazarotene (also current formulation) but these differences were not significant. P values of such differences are given below:

	Tazarotene 0.1%	Tazarotene 0.05%	Retin A 0.1%	Retin A 0.05%
Tazarotene 0.1%	--	0.1631	0.1710	<0.0001
Tazarotene 0.05%	0.1631	--	0.9684	<0.0001

3. Study R168-102-8004. Contact Sensitization, Photoallergy and Phototoxicity Potential of Tazarotene (AGN 190168) 0.05%, 0.01% and Vehicle Gels

This pilot study was also done at Fifty-five subjects were enrolled for sensitization potential but only 30 of them participated in the phototoxicity/photoallergy potential testing; number of subjects completing was 46 and 25 for these 2 portions of the study respectively. Failure to complete the study was not due to adverse events relating to the study medications.

Study medications were applied to patches to be affixed under semi-occlusion to the ventral aspects of forearms. One side was for the sensitization test and the other for photo-testing. Nine induction patches were applied, each for 24 hrs, over 3 weeks. The photo-testing sites were irradiated with 3-4 J/cm of UVA light. Sites were evaluated on a 6-point scale 48 hrs after each application. Induction was followed by a 2-week resting period. Challenge patches were applied to novel sites for 24 hrs. Photo-testing sites were again irradiated with UVA upon removal of patches. Challenge sites were read 48 and 72 hrs after patch application.

Results:

Contact sensitization: 45/46 with no reaction. One had a questionable response with both tazarotene 0.01% and 0.05% gels.

Phototoxicity: 30/30 negative.

Photoallergy: 23/25 negative. Two showed questionable responses with tazarotene 0.05% gel.

Adverse Events: One case of phlebitis and one of fainting, neither considered related to treatment.

Comment

1. This study use a formulation different from the current one applied for marketing.
2. UVA alone was used in testing.

4. Study R168-102-8606. Contact Sensitization Potential of Two Formulations of Tazarotene (AGN 190168) 0.05%, 0.01% and Vehicle Gels

This was a more definitive study on contact sensitization using 203 healthy subjects and was done. The induction and challenge procedures were the same as in R168-102-8004, except that the patches were placed on the back instead of the forearm, and evaluation after challenge was made 48 and 96 hrs after patch application. Both the earlier and the later formulations of tazarotene and vehicle (see under R168-101-8606) were studied, together with 3 other products (Azelaic acid 20% cream, Azelaic acid vehicle cream and Retin-A 0.1% cream) for comparison.

Results: Irritation was noted for the tazarotene formulations and vehicle, but no evidence of sensitization was found. Azelaic acid 20% cream and its vehicle induced skin reactions upon challenge but these were not reproducible. Adverse events leading to termination of study occurred in 5 subjects (toe fracture, cold, cold, "intestinal virus" and reaction to tape of test patch).

Comment This study used the current formulation and found lack of sensitization potential.

5. Study R168-103-8606. Phototoxicity Potential of Tazarotene (AGN 190168) 0.05%, 0.1% and Vehicle Gels in Healthy Subjects

This study conducted by tested the phototoxicity potential of the tazarotene and vehicle formulations used in most of the Phase 3 trials (8606X for 0.1% gel, 8607X for 0.05% gel and 8608X for vehicle gel). In addition, Retin-A 0.1% cream, Azelaic acid 20% cream and its vehicle were tested for comparison. The procedures for phototoxicity testing were the same as in Study R168-102-8004.

Results: Ten subjects were enrolled and all completed the study. No skin reaction or phototoxicity to the test products was noted. No adverse events were reported.

Comment 1. Current formulation was used in this study.
2. UVA alone was used in testing.

6. Study R168-104-8606. Photoallergic Potential of Tazarotene (AGN 190168) 0.05%, 0.1% and Vehicle Gels in Healthy Subjects

This study tested the same products as in R168-103-8606 for photoallergenicity potential in 28 subjects and was also carried out at. The induction and challenge procedures for photoallergenicity were the same as in R168-102-8004, except that evaluation after challenge was made 48 and 96 hrs after patch application. Twenty-two out of the 28 subjects completed the study.

Results: Tazarotene formulations produced irritation during the induction phase, of moderate to marked severity in the majority of patients. Photoallergic reactions were not found. Adverse

events possibly related to test medication occurred in 2 subjects: one with peeling and erosion of finger tip away from site of application, which led to termination of treatment, and the other developing pruritus, erythema and drying on a finger but being able to complete the study.

Comment

1. Current formulation was used in this study.
2. UVA alone was used in testing.

7. Study R168-711-7997. Phase I Study of Tazarotene (AGN 190168). Skin Irritation and Phototoxicity by Patch Test

This study was done by

The objective was to test the irritancy and phototoxicity potential of tazarotene 0.01%, 0.05% and 0.1% gel by patch testing. Six healthy males were studied and each had 50 µg of the gel applied nonocclusively and also occlusively by patch on the back over 24 hrs. The sites were evaluated upon patch removal and 24 hrs later. In addition, a duplicate set of patches on the back had the application sites irradiated (6 J/cm²) upon patch removal and then observed 30 minutes and 24 hours later for phototoxicity.

Results: No reaction was observed after 24 hrs of nonocclusive application. One subject showed erythema at the application sites upon patch removal. No evidence of phototoxicity was seen.

Comment The phototoxicity testing might be acceptable. The testing for irritancy was with a single dose method and was inadequate to elicit responses reflecting cumulative application of the drug product.

10.2.3.4 Long-term Studies There were two long-term studies: R168-128-8606, discussed in Section 8.1.6 and R168-146-8606, discussed in section 8.1.7. R168-146-8606 has not been completed. R168-128-8606 was an uncontrolled 12-month study with tazarotene 0.1% and 0.05% gels. To summarize, there was little difference in the safety profiles of the two gels in this long-term study, except in the first half-month of treatment, when there was a higher incidence of local adverse events in the 0.1% gel group. By the end of the study period, the 0.05% gel gave a higher, although not significant, rate of such adverse events than the 0.1% gel. After the first three months of treatment, there was an actual decline in incidence of local adverse events but a suggestion of increased "psoriasis worsened" and occurrence of sun-induced erythema. There were no consistent laboratory test abnormalities relating to tazarotene use during the span of this study.

10.2.4 Drug-Demographic Interactions

10.2.4.1 Psoriasis The following Table show the incidence of "treatment-related" adverse events in the 5 controlled Phase 3 trials as analyzed with demographic subsets. These only occurred in the treatment period. There were only 9 "treatment-related" adverse events in the tazarotene groups (5 for 0.1% gel and 4 for 0.05% gel) in the posttreatment period and this was not sufficient for analysis with demographic subsets.

	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>	<u>Lidex</u>	<u>Dovonex</u>
Age <45	133/260 (51%)	110/261 (42%)	20/100 (20%)	15/101 (15%)	2/52 (4%)
45-65	147/240 (61%)	104/225 (46%)	22/ 91 (24%)	10/ 85 (12%)	7/54 (13%)
>65	41/ 68 (60%)	46/ 83 (55%)	4/ 30 (13%)	2/ 39 (5%)	3/16 (19%)
Sex Females	124/202 (61%)	114/221 (52%)	16/ 75 (21%)	11/ 84 (13%)	3/46 (7%)
Males	197/366 (54%)	146/348 (42%)	30/ 46 (21%)	16/141 (11%)	9/76 (12%)
Race White	295/527 (56%)	239/523 (46%)	40/194 (21%)	23/208 (11%)	12/119 (10%)
Hispanic	11/ 21 (52%)	14/ 31 (45%)	4/ 16 (25%)	3/ 9 (33%)	0/ 0
Black	7/ 8 (88%)	3/ 4 (75%)	2/ 6 (33%)	1/ 4 (25%)	0/ 1 (0%)
Asian	6/ 10 (60%)	3/ 8 (38%)	0/ 4 (0%)	0/ 2 (0%)	0/ 2 (0%)
Other	2/ 2 (100%)	1/ 3 (33%)	0/ 1 (0%)	0/ 2 (0%)	0/ 0

Comment It appears that the incidence of "treatment-related" adverse events related to treatment was lower in younger, white or Hispanic males using the 0.05% gel, but there does not seem to be a predilection for any demographic group to develop such events.

10.2.4.2 Acne "Treatment-related" adverse event incidence by demographics was:

	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>
Age <45	139/299 (47%)	123/297 (41%)	45/295 (15%)
45-65	0/ 0	0/ 0	0/ 2 (0%)
Sex Females	73/150 (49%)	77/158 (49%)	28/148 (19%)
Males	66/149 (44%)	46/139 (33%)	17/149 (11%)
Race White	114/226 (50%)	100/229 (44%)	37/228 (16%)
Hispanic	6/ 35 (17%)	7/ 32 (22%)	3/ 33 (9%)
Black	15/ 32 (47%)	16/ 35 (46%)	4/ 33 (12%)
Asian	3/ 3 (100%)	0/ 0	1/ 3 (33%)
Other	1/ 3 (33%)	0/ 1 (0%)	0/ 0

Comment

1. Hispanics had the lowest incidence of "treatment-related" adverse events but reported more adverse events with the 0.05% gel than with the 0.1% gel. However, the sample size was not sufficiently large to draw any definitive conclusions.
2. As in the psoriasis studies, males appeared to have a lower incidence of such adverse events. The two tazarotene formulations gave about the same incidence of "treatment-related" adverse events within females, blacks or Hispanic patients.

10.2.5 Drug-Disease Interactions Patients with any skin disease that might affect evaluation were excluded from the studies. No attempt to study drug-disease interaction or analyze the effect of tazarotene on other diseases was made, apart from the studies on psoriasis and acne in this NDA.

10.2.6 Drug-Drug Interactions The clinical studies were done with patients prohibited from concurrent use of other anti-psoriatic or anti-acne drugs. No special studies or analyses were performed to evaluate systemic drug interactions or the concomitant use of other marketed drugs.

10.2.7 Withdrawal Phenomena/Abuse Potential None demonstrated.

10.2.8 Human Reproduction Data The clinical studies were done with specific emphasis on preventing pregnancies. Thus there are no data other than the 6 pregnancies reported in the

clinical trials, of which 4 resulted in birth of healthy babies and 2 were terminated.

11. Labeling Review

The draft labeling has been reviewed. Finalization will depend on the Applicant's response to deficiencies and will form an Addendum to this review.

12. Conclusions

I. Psoriasis.

a) The clinical signs of psoriasis showed variable responsiveness to daily treatment with 0.1% or 0.05% tazarotene gel, with plaque elevation and scaling scores significantly reduced sooner than erythema. At an endpoint of week-12 of tazarotene treatment, all three signs and global scores were significantly superior in tazarotene-treated patients than in vehicle-treated subjects ($p < 0.05$).

b) Follow-up of patients for an additional 12 weeks upon completion of a 12-week course of treatment showed that daily treatment with tazarotene 0.1% gel or tazarotene 0.05% gel did not consistently result in significantly superior benefit in the posttreatment period as compared to twice-a-day treatment with fluocinolone 0.05% cream or calcipotriol 0.005% ointment, neither of which have claimed maintenance of therapeutic effect upon completion of treatment.

c) Tazarotene 0.1% gel and 0.05% gel were both effective in the treatment of stable plaque psoriasis, but there were no statistically significant differences in the reduction of scores for clinical signs, overall global assessment or patients' cosmetic acceptability at endpoint (week-12 of tazarotene treatment) between these two products. There were also no consistent differences in the posttreatment period. In a long-term study where patients could be treated for up to 12 months with tazarotene gel, there were no statistically significant differences between the two gels in score reduction for the clinical signs or for global "treatment success" rates throughout the study.

d) Pharmacokinetics studies and therapeutic drug monitoring have shown that systemic exposure to tazarotene in the treatment of psoriasis is minimal. However, repeated applications of 0.1% tazarotene gel to psoriatic skin might initially increase systemic bioavailability of AGN 190299, the active metabolite of tazarotene, and the extent of exposure to AGN 190299 and distribution in the human body under such conditions remains to be clarified.

e) Topical treatment of psoriasis with tazarotene gels was associated with a high incidence of local adverse events:

i) The most common adverse events included pruritus, burning/stinging, irritation, erythema, pain, rash, dry skin and irritant contact dermatitis. In the phase 3 trials that consisted of a 12-week treatment period, the incidence of such local adverse events varied between 42-68% for the 0.1% gel and between 32-56% for the 0.05% gel. In a long-term study of up to 12 months with tazarotene treatment, the overall incidence of treatment-related adverse events were almost the same (74% for 0.1% gel vs 71% for 0.05% gel). This degree of local adverse events would appear to be higher than that seen in most psoriasis therapies, but would still be acceptable if the product is properly labeled so that adequate precautions will be taken upon clinical use.

ii) The differences in incidence or severity of adverse events among the two tazarotene gels did not seem to be clinically significant.

iii) As dermal safety tests did not reveal evidence of phototoxicity or photoallergenicity potential, the mechanism for the higher incidence of sun-induced erythema in patients treated with tazarotene for more than 3 months yet remains to be clarified.

iv) Although the accuracy of the laboratory or radiographic techniques and the

interpretation of the X-ray data cannot be ascertained, there were no consistent clinically significant laboratory or radiographic adverse events in the psoriasis trials reported.

II. Acne.

a) Tazarotene 0.1% gel was effective in reducing the total lesion count and both noninflammatory and inflammatory lesion counts at endpoint in a 12-week course of treatment for facial acne vulgaris of mild to moderate severity. In addition, "treatment success" as defined by "good or better" global scores was also superior in patients treated with tazarotene 0.1% gel as compared with those treated with vehicle. Although claimed by the Applicant, evidence that tazarotene applied daily has shown comparable efficacy as daily applied tretinoin in acne is lacking.

b) Tazarotene 0.05% gel was superior to vehicle in the reduction of total and noninflammatory but not inflammatory lesion counts at endpoint. However, it failed to show significant advantage over vehicle in "treatment success" as defined by global scores. ✓

c) Topical daily treatment of acne with tazarotene gels for 12 weeks was associated with a high incidence of local adverse events: 35-58% with 0.1% gel and 25-58% with 0.05% gel.

i) The most common adverse events included desquamation; burning/stinging, dry skin, erythema, pruritus, irritation and pain. This degree of local adverse events would appear to be higher than that seen in other acne therapies, but would still be acceptable if the product is properly labeled so that adequate precautions will be taken upon clinical use. Although the dermal safety studies were not carried out on the face, they have shown that at equivalent concentrations, tazarotene was at least as irritating as, and possibly more so than tretinoin.

ii) The differences in incidence or severity of adverse events among the two tazarotene gels did not seem to be clinically significant. ✓

III. Risk benefit analysis.

Tazarotene is a new molecular entity which has shown efficacy in the once-a-day topical treatment of stable plaque psoriasis covering less than 20% of body surface area and of mild to moderate facial acne vulgaris. Theoretically tazarotene is able to act on these disease states through multiple mechanisms; whereas in practice, it holds little advantage over existing marketed products for these indications. It poses certain local safety concerns, particularly when used to treat mild cases of these conditions but may be considered to have acceptable safety if properly labeled so that physicians may prescribe and patients may use it with due precautions.

13. Recommendations

1. It is recommended that tazarotene 0.1% gel is approvable for the daily topical treatment of stable plaque psoriasis covering not more than 20% of body surface area and in the treatment of mild to moderate facial acne vulgaris.

2. It is not recommended that tazarotene topical gels be given the claim of maintenance of therapeutic effect after cessation of treatment for psoriasis, as no consistent practical advantage over other antipsoriatic agents which lack such a claim has been observed in the posttreatment period of three active-controlled trials.

3. Since consistently significant differences have not been demonstrated between tazarotene 0.05% gel and tazarotene 0.1% gel in terms of either safety or efficacy in the ✓

treatment of psoriasis, approval of the tazarotene 0.05% drug product is not recommended for this indication. Tazarotene 0.05% gel is also not recommended for approval for the daily topical treatment of acne vulgaris, as efficacy has not been demonstrated for investigator's global treatment success in two vehicle-controlled trials for this indication.

4. It is recommended that the following Phase 4 studies be performed:

5. It is also recommended that the Applicant address the following deficiencies in this

NDA:

- a) Curriculum vitae of investigators for Study#168-120-8606 have not been provided;
- b) Name, address and qualifications of the radiologist who read the radiographs in Study 168-128-8606 have not been provided;
- c) Evidence of comparable efficacy between the topical use of tazarotene and tretinoin in the treatment of acne was claimed by the Applicant but has not been given;
- d) Documentation of an allergic component for those treatment-related allergic contact dermatitis cases in this NDA, since dermal safety studies have failed to demonstrate contact sensitization potential for tazarotene;
- e) Full study reports of R168-106-8606 and R168-146-8606 are pending.
- f) The following statistical analyses have not been presented by the Applicant. It is recommended that the Applicant present them with the proper 2-sided p values.
 - i) an analysis of efficacy data of females in the acne studies who were using estrogen vs those not using estrogen;
 - ii) separate meta-analyses of subsets for both efficacy and safety, by combining the data of the vehicle-controlled pivotal trials for each indication so that there may be adequate power to detect significant differences between some of the demographic subsets; the Applicant also has not presented data on global "treatment success" analysis for demographic subsets in acne;
 - iii) statistical significance of adverse event data in each study, including among-group comparisons of each adverse event with an incidence of >1% and termination of study due to adverse events;
 - iv) among group comparisons for efficacy data in R168-145-8606 giving significance levels between two treatment groups at a time;
 - v) comparison between treatment groups for achievement of global evaluation scores of [1] ≥75% improvement and [2] 100% improvement in each study;
 - vi) statistical significance of the dropouts among treatment groups in each study and any significance of the differences in drug exposure among these groups;
 - and vii) presence of any bias, and the significance of such bias if present, in the disproportionate sample sizes among treatment groups in the posttreatment periods of the psoriasis studies.

H. S. Ko

Hon-Sum Ko, M.D.

JMK/ky m 5/13/96

cc: Original NDA 20-600

HFD-540

HFD-340

HFD-540/CSO/Cross

HFD-540/CHEM/DeCamp

HFD-540/PHARM/Sheevers

HFD-715/BIOMETRICS/Thomson

HFD-880/BIOPHARM/Lee

HFD-540/MO/Ko

As above, except for recommendation that tazarotene 0.1% gel be approvable for the daily topical treatment of stable plaque psoriasis covering not more than 20% of body surface area. Since the 0.05% gel and 0.1% gel cannot be distinguished from each other in terms of either safety or efficacy in the treatment of psoriasis, the 0.05% gel should be approvable, not the 0.1% gel. However, I agree that the 0.1% gel is approvable in the treatment of mild to moderate facial acne vulgaris.

JW 5/17/96

Summary of Clinical Pharmacokinetics Studies

<u>Study/Design/Objective</u>	<u>Patient Numbers</u>			
	<u>Entered</u>	<u>Completed</u>	<u>M/F*</u>	<u>W/H/B/OR/OT* Age (mean)*</u>
<u>I. Healthy Volunteers in the U.S.</u>				
R168-150-7997 (single centered) Percutaneous absorption and mass balance of ¹⁴ C-tazarotene 0.1% gel following topical application	6	6		6/0/0/0/0 20-27 (22.6)
R168-151-7997 (single-centered) Plasma concentration/time-profiles upon 0.1% and 0.05% gel application to 20% of body surface area	24	24		23/0/1/0/0 18-28 (22.2)
R168-152-8606 (single-centered) Plasma concentration/time-profiles upon single- and multiple- dose 0.1% gel application to 20% of body surface area	24	24		22/0/1/1/0 20-27 (22.1)
R168-155-8606 (single centered, in U.K.) Plasma concentration/time-profiles upon iv infusion of 0.01% solution vs single application of 0.1% gel	8	8		7/1/0/0/0 21-44 (31.1)
<u>II. Healthy Volunteers in Japan</u>				
R168-712-7997 (single centered, parallel-group) Safety and PK of single application of 0.01%, 0.05% and 0.1% gel to 5% of body surface area	18	18		0/0/0/18/0 20-24 (21.5)
R168-713-7997 (single centered, parallel-group) Safety and PK of repeated applications of 0.05% and 0.1% gel to 5% of body surface area	12	12		0/0/0/12/0 20-25 (22.0)
<u>III. Psoriasis Patients</u>				
R168-153-8606 (6 centers) Plasma concentration/time-profiles upon single- and multiple-dose 0.1% and 0.05% gel application in psoriatics	5	5		5/0/0/0/0 23-47 (36.6)
R168-154-8606 (single centered) Percutaneous absorption and mass balance of ¹⁴ C-tazarotene 0.1% gel following topical application in psoriatics	6	6		6/0/0/p/q 39-60 (50.3)

*Numbers based on subjects who entered study. M/F=male/female, W/H/B/OR/OT=white/Hispanic/black/Oriental/other.

Summary of Phase I Dermal Safety Studies

<u>Study/Design/Objective</u>	<u>Patient Numbers</u>			
	<u>Entered</u>	<u>Completed</u>	<u>M/F*</u>	<u>W/H/B/OR/OT* Age(mean)*</u>
<u>I. U.S. Studies</u>				
R168-101-8004				
Irritancy potential of 0.01% and 0.05% gels	28	25		15/2/8/0/0 18-60 (43.9)
R168-101-8606				
Irritancy potential of 0.05% and 0.1% gels	30	29		29/0/0/0/0 20-64 (41.8)
R168-102-8004				
Contact sensitization, photoallergy and phototoxicity potential of 0.01% and 0.05% gels				
1. Contact sensitization	55	46		46/0/0/0/0 18-60 (44.7)
2. Photoallergy/phototoxicity	30	25		25/0/0/0/0 18-60 (44.2)
R168-102-8606				
Contact sensitization potential of 0.05% and 0.1% gels	203	181		176/3/0/2/0 18-65 (42.5)
R168-103-8606				
Phototoxicity potential of 0.05% and 0.1% gels	10	10		10/0/0/0/0 22-48 (33.8)
R168-104-8606				
Photoallergy potential of 0.05% and 0.1% gels	28	22		22/0/0/0/0 20-64 (44.0)
<u>II. Japanese Study</u>				
R168-711-7997				
Irritancy and phototoxicity potential of 0.01%, 0.05% and 0.1% gels	6	6		0/0/0/6/0 20-26 (21.8)

*Numbers based on subjects who completed study. M/F=male/female, W/H/B/OR/OT=white/Hispanic/black/Oriental/other.

Summary of Clinical Pharmacokinetics Studies

<u>Study/Design/Objective</u>	<u>Patient Numbers</u>			
	<u>Entered</u>	<u>Completed</u>	<u>M/F*</u>	<u>W/H/B/OR/OT* · Age (mean)*</u>
<u>I. Healthy Volunteers in the U.S.</u>				
R168-150-7997 (single centered) Percutaneous absorption and mass balance of ¹⁴ C-tazarotene 0.1% gel following topical application	6	6		6/0/0/0/0 20-27 (22.6)
R168-151-7997 (single-centered) Plasma concentration/time-profiles upon 0.1% and 0.05% gel application to 20% of body surface area	24	24		23/0/1/0/0 18-28 (22.2)
R168-152-8606 (single-centered) Plasma concentration/time-profiles upon single- and multiple- dose 0.1% gel application to 20% of body surface area	24	24		22/0/1/1/0 20-27 (22.1)
R168-155-8606 (single centered, in U.K.) Plasma concentration/time-profiles upon iv infusion of 0.01% solution vs single application of 0.1% gel	8	8		7/1/0/0/0 21-44 (31.1)
<u>II. Healthy Volunteers in Japan</u>				
R168-712-7997 (single centered, parallel-group) Safety and PK of single application of 0.01%, 0.05% and 0.1% gel to 5% of body surface area	18	18		0/0/0/18/0 20-24 (21.5)
R168-713-7997 (single centered, parallel-group) Safety and PK of repeated applications of 0.05% and 0.1% gel to 5% of body surface area	12	12		0/0/0/12/0 20-25 (22.0)
<u>III. Psoriasis Patients</u>				
R168-153-8606 (6 centers) Plasma concentration/time-profiles upon single- and multiple-dose 0.1% and 0.05% gel application in psoriatics	5	5		5/0/0/0/0 23-47 (36.6)
R168-154-8606 (single centered) Percutaneous absorption and mass balance of ¹⁴ C-tazarotene 0.1% gel following topical application in psoriatics	6	6		6/0/0/0/0 39-60 (50.3)

*Numbers based on subjects who entered study. M/F=male/female, W/H/B/OR/OT=white/Hispanic/black/Oriental/other.

Summary of Phase II Clinical Studies

<u>Study/Design/Objective</u>	<u>Patient Numbers</u>			
	<u>Entered</u>	<u>Completed</u>	<u>M/F*</u>	<u>W/H/B/OR/OT* Age (mean)*</u>
<u>I. Mechanism of Action Studies</u>				
R168-105-8225 (single centered) Safety and efficacy of, and effects on molecular markers by 0.05% gel applied bid for 4 weeks in <u>psoriasis</u>	10	10		8/2/0/0/0 25-78 (42.6)
R168-106-8606 (single centered) Safety and efficacy of, and effects on molecular markers by 0.1% gel applied qd for 4 weeks in <u>psoriasis</u>	20	20		15/1/3/1/0 28-83 (54.9)
<u>II. Initial Dose-Finding Studies</u>				
R168-110-8225 (3 centers) Safety and efficacy of 0.01% and 0.05% gels vs vehicle applied bid for 6 weeks in <u>psoriasis</u>	45	44		40/2/0/2/1 23-83 (49.7)
R168-210-8225 (2 centers) Safety and efficacy of 0.01% and 0.05% gels vs vehicle applied qd for 12 weeks in <u>acne</u>	92	80		91/1/0/0/0 14-44 (19.4)
<u>III. Dose-Response Studies</u>				
R168-111-7997 (6 centers) Safety and efficacy of 0.05% and 0.1% gel applied qd or bid for 8 weeks in <u>psoriasis</u>	105	76		98/4/1/1/1 25-82 (53.0)
R168-112-8606 (single centered, in U.K.) Safety and tolerability of 0.05% and 0.1% gel applied qd for 4 weeks in <u>psoriasis</u>	15	12		14/0/0/1/0 26-68 (39.9)
R168-721-7997 (5 centers in Japan) Safety, efficacy and usefulness of 0.01% and 0.05% gel applied qd for 4 weeks in <u>psoriasis</u>	24	22		0/0/0/24/0 20-69 (NA)
R168-722-8606 (25 centers in Japan) Safety, efficacy and usefulness of 0.1% and 0.05% gel applied qd for 4 weeks in <u>psoriasis</u>	99	96		0/0/0/96/0 NA

*Numbers based on subjects who entered study, except in study R168-722-8606, where data of 3 disqualified subjects were not available. M/F=male/female, NA=no data available, W/H/B/OR/OT=white/Hispanic/black/Oriental/other.

Appendix ID

Summary of Phase III Clinical Studies

<u>Study no</u>	<u>design</u>	<u>objective</u>	<u>duration of study</u>	<u>No. enrolled*</u>
R168-120-8606	multicenter, double blind, randomized, parallel-group (psoriasis)	safety/efficacy & duration of therapeutic effect vs vehicle qd	12-week treatment, post-tr: 12 weeks	<u>T.1%</u> <u>T.05%</u> <u>V</u> 108 108 108
R168-121-8606		safety/efficacy vs vehicle qd	12-week treatment	<u>T.1%</u> <u>T.05%</u> <u>V</u> 112 111 113
R168-125-8606	multicenter, investigator- masked randomized, parallel-group (psoriasis)	safety/efficacy & duration of therapeutic effect vs Lidex cream .05% bid	12-week treatment, post-tr: 12 weeks	<u>T.1%</u> <u>T.05%</u> <u>L</u> 116 117 115
R168-126-8606		safety/efficacy & duration of therapeutic effect vs Lidex cream .05% bid	12-week treatment, post-tr: 12 weeks	<u>T.1%</u> <u>T.05%</u> <u>L</u> 110 111 110
R168-145-8606		safety/efficacy & duration of therapeutic effect vs Dovonex ointment .005% bid	12-week treatment, post-tr: 12 weeks	<u>T.1%</u> <u>T.05%</u> <u>D</u> 123 122 124
R168-128-8606	multicenter, double blind, randomized, parallel-group (psoriasis)	long-term safety/efficacy of 0.1% and 0.05% tazarotene gels	up to 1 year treatment	<u>T.1%</u> <u>T.05%</u> 122 121
R168-146-8606		long-term safety/efficacy of 0.1% and 0.05% tazarotene gels	up to 24 weeks treatment	Planned 200; study incomplete
R168-220-7997	multicenter, double blind, randomized, parallel-group (acne)	safety/efficacy vs vehicle qd	12-week treatment	<u>T.1%</u> <u>T.05%</u> <u>V</u> 150 148 148
R168-221-8606		safety/efficacy vs vehicle qd	12-week treatment	<u>T.1%</u> <u>T.05%</u> <u>V</u> 149 149 149

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

Summary of Findings In Phase II Clinical Studies

<u>Study No. & Objective</u>	<u>Study Design</u>	<u>Major Findings</u>
<u>I. Mechanism of Action Studies</u>		
R168-105-8225 (single centered) Safety and efficacy of, and effects on molecular markers by 0.05% gel applied bid for 4 weeks in <u>psoriasis</u>	Bilateral comparison (0.05% gel vs vehicle) in 10 subjects	Faulty randomization; unevaluable efficacy. ↑ ICAM-1 & HLA-DR expression in epidermis, ↑ ICAM-1 expression in dermis.
R168-106-8606 (single centered) Safety and efficacy of, and effects on molecular markers by 0.1% gel applied qd for 4 weeks in <u>psoriasis</u>	Bilateral comparison (0.1% gel with vehicle) in 20 subjects	Study report not yet submitted.
<u>II. Initial Dose-Finding Studies</u>		
R168-110-8225 (3 centers) Safety and efficacy of 0.01% and 0.05% gels vs vehicle applied bid for 6 weeks in <u>psoriasis</u>	Bilateral comparison, randomized for treatment combination, in 45 subjects	0.01% gel bid as minimal effect dose. 0.05% gel bid effective in ↓ scaling and induration.
R168-210-8225 (2 centers) Safety and efficacy of 0.01% and 0.05% gels vs vehicle applied qd for 12 weeks in <u>acne</u>	Randomized, parallel-group, double-blind trial in 92 subjects	0.01% gel qd as minimal effect dose. 0.05% gel qd better than vehicle qd for ↓ of non-inflammatory lesions, but not significant (p>0.05).
<u>III. Dose-Response Studies</u>		
R168-111-7997 (6 centers) Safety and efficacy of 0.05% and 0.1% gel applied qd or bid for 8 weeks in <u>psoriasis</u>	Bilateral comparison, randomized for dose regimen in 105 subjects	0.1% gel appeared to be superior to 0.05% gel in efficacy. Bid dosing appeared to be superior to qd in efficacy. 0.1% gel more irritating than 0.05% gel.
R168-112-8606 (single centered, in U.K.) Safety and tolerability of 0.05% and 0.1% gel applied qd for 4 weeks in <u>psoriasis</u>	Randomized, parallel-group, double-blind trial in 15 subjects	"Severe" local adverse events in 38% of 0.1% gel group vs 29% of 0.05% group. Plasma levels: undetectable for tazarotene; <0.8 ng/ml for AGN 190299.
R168-721-7997 (5 centers in Japan) Safety, efficacy and usefulness of 0.01% and 0.05% gel applied qd for 4 weeks in <u>psoriasis</u>	Bilateral comparison, randomized for treatment combination (tazarotene 0.1% + vehicle) or (tazarotene 0.05% + vehicle) in 24 subjects	0.05% gel but not 0.01% gel superior to vehicle in "Global usefulness" and "global improvement".
R168-722-8606 (25 centers in Japan) Safety, efficacy and usefulness of 0.1% and 0.05% gel applied qd for 4 weeks in <u>psoriasis</u>	Bilateral comparison (0.1% vs 0.05% gel) in 99 subjects	0.1% gel better than 0.05% gel for "Superiority comparison of global usefulness" & "Superiority Comparison of global improvement".

Adverse Events (Incidence of >1% or "Treatment-Related"*) in Study R168-120-8606
(Treatment Period)

	<u>Tazarotene</u> <u>0.1%</u>	<u>Tazarotene</u> <u>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%)
Body	18 (17%)/3 (3%)	14 (13%)/0	22 (20%)/1(<1%)
headache	8 (7%)	7 (6%)	8 (7%)
cellulitis	3 (3%)/2 (2%)	0	1
back pain	2 (2%)	0	4 (4%)
"pain"	1	1	2 (2%)
"infection"	1	0	3 (3%)
accidental injury	1	0	2 (2%)
flu syndrome	0	2 (2%)	4 (4%)
abdominal pain	0	2 (2%)	0
chills	1/1	0	0
asthenia	0	0	1/1
Cardiovascular	4 (4%)/0	2 (2%)/1 (<1%)	2(2%)/0
migraine	2 (2%)	0	0
vasodilation	0	1/1	0
Digestive	8 (7%)/0	7 (7%)/0	3 (3%)/0
diarrhea	2 (2%)	3 (3%)	1
tooth disease/periodontal abscess	2 (2%)	1	2 (2%)
Endocrine/Metabolic	1 (<1%)/0	3 (3%)/1 (<1%)	4 (4%)/0
peripheral edema	1	2 (2%)/1	3 (3%)
Hematologic	1 (<1%)/0	3 (3%)/0	1 (<1%)/0
Ecchymosis/purpura	1	2 (2%)	0
Musculoskeletal	6 (6%)/0	5 (5%)/0	8 (7%)/0
bursitis	2 (2%)	0	2 (2%)
arthritis	1	3 (3%)	2 (2%)
bone fracture	0	0	2 (2%)
Neurologic	1 (<1%)/0	4 (4%)/1 (<1%)	0
tingling sensation	0	1/1	0
Respiratory	9 (8%)/0	15 (14%)/0	18 (17%)/0
"infection"	4 (4%)	9 (8%)	12 (11%)
rhinitis	4 (4%)	2 (2%)	3 (3%)
sinus infection	2 (2%)	3 (3%)	1
pharyngitis	2 (2%)	1	2 (2%)
bronchitis	0	1	2 (2%)
Special Senses	1 (<1%)/0	5 (5%)/0	5 (5%)/1 (<1%)
ear infection	1	2 (2%)	0
vision abnormality	0	0	1/1
Urogenital	3 (3%)/0	6 (6%)/0	13 (12%)/0
urinary tract infection	0	3 (3%)	7 (6%)
hematuria	0	0	2 (2%)
Dermatologic (see Section 8.1.1.4.3)			

*Incidence of "Treatment-related" adverse events is listed after a slash (/) from the total incidence. "Treatment-related" adverse events are listed irrespective of whether they are ≥1% or not.

Adverse Events (Incidence of $\geq 1\%$ or "Treatment-Related"*) in Study R168-125-8606(Treatment Period)

	<u>Tazarotene</u> <u>0.1%</u>	<u>Tazarotene</u> <u>0.05%</u>	<u>Lidex cream</u> <u>0.05%</u>
Total patients enrolled	116 (100%)	117 (100%)	115 (100%)
Patients with adverse events	97 (84%)/79 (68%)	95 (81%)/65 (56%)	65 (56%)/14 (12%)
Body	20 (17%)/3 (3%)	24 (21%)/0	23 (20%)/1(1%)
headache	6 (5%)/1	11 (9%)	7 (6%)
back pain	3 (3%)	2 (2%)	3 (3%)
asthenia	3 (3%)	2 (2%)	1
"infection"	2 (2%)/1	1	0
chills	2 (2%)	0	0
accidental injury	1	2 (2%)	2 (2%)
arm pain	1/1	2 (2%)	0
flu syndrome	0	1	8 (7%)
lab test abnormality	0	1	2 (2%)
Cardiovascular	2 (2%)/1 (<1%)	4 (3%)/1 (<1%)	0
vasodilation	1/1	1/1	0
hypertension	0	2 (2%)	0
Digestive	13 (11%)/0	7 (6%)/0	12 (10%)/0
liver function abnormality	2 (2%)	1	3 (3%)
tooth disease	2 (2%)	1	3 (3%)
nausea	2 (2%)	0	3 (3%)
vomit	2 (2%)	0	1
Endocrine/Metabolic	9 (8%)/0	11 (9%)/1 (<1%)	4 (3%)/0
hypertriglyceridemia	4 (3%)	5 (4%)	3 (3%)
hyperlipemia	3 (3%)	1	1
hypercholesterolemia	3 (3%)	1	0
hyperglycemia	1	2 (2%)	0
bilirubinemia	0	2 (2%)/1	0
SGOT increase	0	2 (2%)/1	0
Hematologic	1 (<1%)/0	2 (2%)/0	4 (4%)/0
leukocytosis	0	0	2 (2%)
Musculoskeletal	3 (3%)/0	5 (4%)/0	10 (9%)/0
myalgia	2 (2%)	1	4 (3%)
arthritis	1	1	3 (3%)
arthralgia	1	0	2 (2%)
Neurologic	7 (6%)/0	5 (4%)/0	1 (<1%)/0
nervousness	2 (2%)	0	0
dizziness	1	2 (2%)	0
Respiratory	17 (15%)/0	19 (16%)/0	18 (16%)/0
"infection"	11 (9%)	11 (9%)	7 (6%)
rhinitis	4 (3%)	6 (5%)	5 (4%)
pharyngitis	1	4 (3%)	3 (3%)
sinus infection	1	1	3 (3%)
bronchitis	0	0	2 (2%)
Special Senses	3 (3%)/0	2 (2%)/0	3 (3%)/0
Urogenital	10 (9%)/0	6 (5%)/0	9 (8%)/0
hematuria	4 (3%)	1	3 (3%)
albuminuria	2 (2%)	1	1
"urine abnormality"	2 (2%)	1	0
kidney calculus	2 (2%)	0	0
sysmenorrhea	1	2 (2%)	0
dysuria	1	0	2 (2%)
urinary tract infection	0	0	2 (2%)

Dermatologic (see Section 8.1.3.4.3)

*Incidence of "Treatment-related" adverse events is listed after a slash (/) from the total incidence. "Treatment-related" adverse events are listed irrespective of whether they are $\geq 1\%$ or not.

Adverse Events (Incidence of $\geq 1\%$ or "Treatment-Related"*) in Study R168-121-8606

	<u>Tazarotene</u> <u>0.1%</u>	<u>Tazarotene</u> <u>0.05%</u>	<u>Vehicle</u>
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%)
Body	12 (11%)/0	16 (14%)/2 (2%)	12 (11%)/1 (<1%)
headache	2 (2%)	3 (3%)	4 (4%)
flu syndrome	2 (2%)	3 (3%)	3 (3%)
accidental injury	2 (2%)	2 (2%)/1	2 (2%)
cellulitis	2 (2%)	1	0
back pain	0	3 (3%)/1	3 (3%)
fever	0	2 (2%)	0
"pain"	0	0	1/1
Cardiovascular	0	3 (3%)/0	1 (<1%)/0
vasodilation	0	2 (2%)	0
Digestive	5 (5%)/0	3 (3%)/0	5 (4%)/0
periodontal abscess	2 (2%)	1	1
liver function abnormality	1	0	2 (2%)
Endocrine/Metabolic	5 (5%)/1 (<1%)	8 (7%)/3 (3%)	9 (8%)/2 (2%)
hypertriglyceridemia	4 (4%)/1	6 (5%)/2 (2%)	2 (2%)/1
hypercholesterolemia	1	4 (4%)/1	1
peripheral edema	0	1/1	1/1
Hematologic	3 (3%)/0	3 (3%)/1 (<1%)	6 (5%)/0
eosinophilia	3 (3%)	3 (3%)	3 (3%)
lymphadenopathy	0	1/1	1
Musculoskeletal	0	3 (3%)/1 (<1%)	4 (4%)/0
arthritis	0	2 (2%)	2 (2%)
bone pain	0	1/1	0
Neurologic	0	5 (5%)/0	2 (2%)/0
insomnia	0	1	2 (2%)
Respiratory	17 (15%)/0	14 (13%)/0	13 (12%)/0
"infection"	10 (9%)	5 (5%)	9 (8%)
pharyngitis	2 (2%)	3 (3%)	2 (2%)
rhinitis	1	2 (2%)	1
Special Senses	1 (<1%)/0	3 (3%)/0	2 (2%)/0
Urogenital	4 (4%)/0	7 (6%)/0	4 (4%)/0
urinary tract infection	0	2 (2%)	1
hematuria	1	2 (2%)	2 (2%)
Dermatologic (see Section 8.1.2.4.3)			

*Incidence of "Treatment-related" adverse events is listed after a slash (/) from the total incidence. "Treatment-related" adverse events are listed irrespective of whether they are $\geq 1\%$ or not.

**Adverse Events (Incidence of $\geq 1\%$ or "Treatment-Related"*) in Study R168-126-8606
(Treatment Period)**

	<u>Tazarotene</u> <u>0.1%</u>	<u>Tazarotene</u> <u>0.05%</u>	<u>Lidex cream</u> <u>0.05%</u>
Total patients enrolled	110 (100%)	111 (100%)	110 (100%)
Patients with adverse events	97 (84%)/79 (68%)	95 (81%)/65 (56%)	65 (56%)/14 (12%)
Body –	14 (13%)/2 (2%)	14 (13%)/0	16 (15%)/0
headache	5 (5%)	5 (5%)	5 (5%)
flu syndrome	2 (2%)	5 (5%)	5 (5%)
accidental injury	2 (2%)	1	0
"pain"	2 (2%)	0	2 (2%)
chills	2 (2%)/2 (2%)	0	0
back pain	1	2 (2%)	2 (2%)
Cardiovascular	3 (3%)/0	2 (2%)/1 (<1%)	4 (4%)/0
hypertension	3 (3%)	0	2 (2%)
vasodilation	0	1/1	1
Digestive	5 (5%)/0	6 (5%)/0	10 (9%)/0
tooth disease	2 (2%)	1	4 (4%)
Endocrine/Metabolic	4 (4%)/0	4 (4%)/1 (<1%)	1 (<1%)/0
hypertriglyceridemia	0	2 (2%)/1	0
Musculoskeletal	2 (2%)/0	4 (4%)/0	6 (6%)/0
myalgia	1	2 (2%)	2 (2%)
arthritis	0	1	2 (2%)
Neurologic	4 (4%)/0	3 (3%)/0	6 (6%)/0
dizziness	3 (3%)	0	2 (2%)
insomnia	1	0	2 (2%)
Respiratory	18 (16%)/0	19 (17%)/0	23 (21%)/0
"infection"	11 (10%)	11 (10%)	15 (14%)
rhinitis	4 (4%)	2 (2%)	6 (5%)
pharyngitis	2 (2%)	1	1
sinus infection/sinusitis	2 (2%)	4 (4%)	7 (6%)
cough increase	1	1	4 (4%)
bronchitis	0	2 (2%)	0
lung disease	0	2(2%)	0
Special Senses	3 (3%)/0	5 (5%)/0	2 (2%)/0
ear infection	1	3 (3%)	0
Urogenital	5 (5%)/0	3 (3%)/0	4 (4%)/0
urinary tract infection	2 (2%)	0	2 (2%)
Dermatologic (see Section 8.1.4.4.3)			

*Incidence of "Treatment-related" adverse events is listed after a slash (/) from the total incidence. "Treatment-related" adverse events are listed irrespective of whether they are $\geq 1\%$ or not.

**Adverse Events (Incidence of $\geq 1\%$ or "Treatment-Related"*) in Study R168-145-8606
(Treatment Period)**

	<u>Tazarotene</u> <u>0.1%*</u>	<u>Tazarotene</u> <u>0.05%</u>	<u>Donovex</u> <u>0.005%*</u>
Total patients enrolled	122 (100%)	122 (100%)	122 (100%)
Patients with adverse events	69 (57%)/57 (47%)	64 (53%)/49 (40%)	30 (25%)/12 (10%)
Body	10 (8%)/0	2 (2%)/0	5 (4%)/0
flu syndrome	6 (5%)	0	2 (2%)
Cardiovascular	0	1 (<1%)/0	0
Digestive	1 (1%)/1 (<1%)	4 (3%)/1 (<1%)	1 (<1%)/0
cheilitis	1/1	1/1	0
oral dryness	0	1/1	0
Hematologic	1 (<1%)/1 (<1%)	0	0
ecchymosis	1/1	0	0
Endocrine/Metabolic	1 (<1%)/0	1 (<1%)/0	2 (2%)/1 (<1%)
peripheral edema	1	0	1/1
Musculoskeletal	2 (2%)/0	1 (<1%)/0	2 (2%)/0
Neurologic	4 (3%)/4 (3%)	1 (<1%)/0	1 (<1%)/0
insomnia	4 (3%)/4 (3%)	0	0
neurosis	1/1	0	0
Respiratory	10 (8%)/1 (<1%)	9 (7%)/0	8 (7%)/0
pharyngitis	5 (4%)	3 (2%)	6 (5%)
"infection"	3 (2%)	3 (2%)	0
epistaxis	1/1	0	0
Special Senses	0	1 (<1%)/0	1 (<1%)/0
Urogenital	1 (<1%)/0	2 (2%)/1 (<1%)	0
dysuria	0	1/1	0
Dermatologic (see Section 8.1.5.4.3)			

*Incidence of "Treatment-related" adverse events is listed after a slash (/) from the total incidence. "Treatment-related" adverse events are listed irrespective of whether they are $\geq 1\%$ or not. This analysis excluded one patient in tazarotene 0.1% group and two patients in Dovonex 0.005% group who did not take study medication.

Adverse Events (Incidence of $\geq 1\%$ or "Treatment-Related"*) in Study R168-128-8606

	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>
Total patients enrolled	122 (100%)	121 (100%)
Patients with adverse events	106 (87%)/91 (75%)	101 (84%)/86 (71%)
Body	41 (34%)/6 (5%)	36 (30%)/5 (4%)
headache	12 (10%)/2 (2%)	11 (9%)
flu syndrome	7 (6%)	7 (6%)
accidental injury	6 (5%)	9 (7%)
"pain"	6 (5%)/1	5 (4%)/2 (2%)
back pain	5 (4%)	5 (4%)
cyst	4 (3%)	0
"infection"	3 (2%)	2 (2%)
neck pain	3 (2%)	0
chills	2 (2%)/1	0
knee pain	1	6 (5%)/1
arm pain	1/1	2 (2%)
fever	0	3 (2%)/1
cellulitis	1/1	1/1
scalp pain	0	1/1
Cardiovascular	5 (4%)/1 (<1%)	8 (7%)/2 (2%)
hypertension	2	2 (2%)
vasodilation	1/1	2 (2%)/2 (2%)
Digestive	12 (10%)/0	15 (12%)/0
dyspepsia	4 (3%)	4 (3%)
diarrhea	2 (2%)	3 (2%)
cholecystitis	2 (2%)	0
colitis	2 (2%)	0
gastroenteritis	0	2 (2%)
nausea	0	2 (2%)
Hematologic	2 (2%)/0	1 (<1%)/0
Metabolic	5 (4%)/0	9 (7%)/0
peripheral edema	3 (2%)	3 (2%)
hypertriglyceridemia	2 (2%)	0
diabetes mellitus	2 (2%)	2 (2%)
hyperglycemia	2 (2%)	2 (2%)
Musculoskeletal	13 (11%)/2 (2%)	15 (12%)/0
arthralgia	6 (5%)/2 (2%)	5 (4%)
myalgia	4 (3%)	4 (3%)
arthritis	2 (2%)	3 (2%)
bone fracture	2 (2%)	2 (2%)
bursitis	2 (2%)	0
Neurologic	4 (3%)/1 (<1%)	5 (4%)/2 (2%)
anxiety	0	2 (2%)
hypertonia	1/1	1
paresthesia	0	1/1
sleep disorder	0	1/1
Respiratory	24 (20%)/0	21 (17%)/0
infection	12 (10%)	12 (10%)
bronchitis	4 (3%)	3 (2%)
rhinitis	2 (2%)	5 (4%)
asthma	2 (2%)	1
dyspnea	2 (2%)	1
pneumonia	2 (2%)	0
cough increase	1	2 (2%)
pharyngitis	1	2 (2%)
Special Senses	6 (5%)/0	5 (4%)/1 (<1%)
ear infection	2 (2%)	0
eye pruritus	0	1/1
Urogenital	6 (5%)/0	5 (4%)/2 (2%)
hematuria	3 (2%)	2 (2%)/1
urinary infection	2 (2%)	1
vaginitis	1	1/1

Dermatologic Adverse Events (see Section 8.1.6.4.3)

*Incidence of "Treatment-related" adverse events is listed after a slash (/) from the total incidence. "Treatment-related" adverse events are listed irrespective of whether they are $\geq 1\%$ or not.

Adverse Events (Incidence of $\geq 1\%$ or "Treatment-Related"*) in Study R168-220-8606

	<u>Tazarotene</u> <u>0.1%</u>	<u>Tazarotene</u> <u>0.05%</u>	<u>Vehicle</u>
Total patients enrolled	150 (100%)	148 (100%)	148 (100%)
Patients with adverse events	71 (53%)/53 (35%)	54 (37%)/37 (25%)	36 (24%)/11 (7%)
Body	8 (5%)/0	7 (5%)/1 (<1%)	11 (7%)/0
accidental injury	3 (2%)	2 (1%)	1
headache	3 (2%)	0	7 (5%)
flu syndrome	1	2 (1%)	3 (2%)
"infection"	0	1/1	0
Digestive	5 (3%)/2 (1%)	1 (<1%)/1 (<1%)	1 (<1%)/0
cheilitis	2 (1%)/2 (1%)	1/1	0
Hematologic	1 (<1%)/0	1 (<1%)/0	0
Endocrine/Metabolic	1 (<1%)/0	0	0
Musculoskeletal	0	2 (1%)/0	1 (<1%)/0
Neurologic	3 (2%)/1 (<1%)	0	0
paresthesia	2 (1%)/1	0	0
Respiratory	11 (7%)/0	15 (10%)/0	14 (10%)/0
"infection"	6 (4%)	8 (5%)	4 (3%)
pharyngitis	2 (1%)	4 (3%)	2 (1%)
bronchitis	1	2 (1%)	2 (1%)
rhinitis	1	1	5 (3%)
Special Senses	3 (2%)/0	2 (1%)/0	0
ear infection	3 (2%)	2 (1%)	0
Urogenital	2 (1%)/0	4 (3%)/0	2 (1%)/0
urinary tract infection	0	2 (1%)	1
menstrual disorder	0	2 (1%)	0

Dermatologic (see Section 8.2.1.4.3)

*Incidence of "Treatment-related" adverse events is listed after a slash (/) from the total incidence. "Treatment-related" adverse events are listed irrespective of whether they are $\geq 1\%$ or not.

Adverse Events (Incidence of $\geq 1\%$ or "Treatment-Related"*) in Study R168-221-8606

	<u>Tazarotene</u> <u>0.1%</u>	<u>Tazarotene</u> <u>0.05%</u>	<u>Vehicle</u>
Total patients enrolled	149 (100%)	149 (100%)	149 (100%)
Patients with adverse events	106 (71%)/86 (58%)	107 (72%)/86 (58%)	76 (51%)/34 (23%)
Body	22 (15%)/1 (<1%)	24 (16%)/0	13 (9%)/0
headache	13 (9%)	14 (9%)	6 (4%)
flu syndrome	4 (3%)	6 (4%)	3 (2%)
back pain	1	3 (2%)	0
photosensitivity	1/1	0	0
Cardiovascular	1 (<1%)/0	0	2 (1%)/0
vasodilation	1	0	0
syncope	0	0	2 (1%)
Digestive	2 (1%)/0	2 (1%)/0	2 (1%)/0
Hematologic	0	1 (<1%)/0	0
Endocrine/Metabolic	0	1 (<1%)/0	2 (1%)/0
Musculoskeletal	2 (1%)/0	3 (2%)/0	6 (4%)/0
myalgia	2 (1%)	3 (2%)	2 (1%)
Neurologic	1 (<1%)/0	0	3 (2%)/1 (<1%)
anxiety	0	0	2 (1%)
tingling	0	0	1/1
Respiratory	27 (18%)/0	23 (15%)/0	36 (24%)/0
"infection"	13 (9%)	13 (9%)	19 (13%)
pharyngitis	6 (4%)	2 (1%)	7 (5%)
rhinitis	6 (4%)	1	9 (6%)
sinusitis	1	6 (4%)	3 (2%)
bronchitis	1	0	4 (3%)
cough increase	0	1	4 (3%)
Special Senses	3 (2%)/0	1 (<1%)/0	4 (3%)/0
otitis media	0	0	3 (2%)
Urogenital	2 (1%)/0	4 (3%)/0	3 (2%)/0
dysmenorrhea	2 (1%)	0	1
urinary tract infection	0	1	2 (1%)
Dermatologic (see Section 8.2.2.4.3)			

*Incidence of "Treatment-related" adverse events is listed after a slash (/) from the total incidence. "Treatment-related" adverse events are listed irrespective of whether they are $\geq 1\%$ or not.

Adverse Events in Phase 3 Clinical Trials of Tazarotene 0.1% and 0.05% Gels in Psoriasis and Acne (including Studies 120, 121, 125, 126, 128, 145, 220 and 221)

	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.05%</u>	<u>Vehicle</u>	<u>Lidex 0.05%</u>	<u>Dovonex 0.005%</u>
Total Patients	989 (100%)	987 (100%)	518 (100%)	225 (100%)	122 (100%)
With Adverse Events	674 (68%)/545(55%)*	641 (65%)/456(46%)	235 (45%)/91(18%)	119 (53%)/27(12%)	30 (25%)/12(10%)
System/Event					
<u>BODY</u>	<u>130 (13%)/15 (2%)</u>	<u>125 (13%)/4</u>	<u>58 (11%)/2</u>	<u>39 (17%)/1</u>	<u>5 (4%)/0</u>
headache	44 (4%)/3	47 (5%)	25 (5%)	12 (5%)	0
flu syndrome	21 (2%)	24 (2%)	13 (3%)	10 (4%)	2 (2%)
accidental injury	13 (1%)	12 (1%)/1	6 (1%)	2	0
back pain	9	12 (1%)/1	7 (1%)	5 (2%)	0
arm pain	3/2	4	0	1	0
knee pain	3	5	3	0	0
chest pain	2	2	0	2	0
abdominal pain	2	4	0	1	1
neck pain	1	2	1	1	0
rigid neck	0	1	0	0	0
face pain	0	0	0	1	0
scalp pain	0	1/1	0	0	0
"pain"	8/1	5	3/1	3 (1%)	1
chills	8/4	0	0	0	0
infection	7/1	6/1	4	1	0
"inflammation"	3	1	2	0	0
cellulitis	6/3	1	1	0	0
abscess	1	0	0	0	0
monilia	2	1	0	0	0
dermatitis	3	4	1/1	1	0
ulcer	2	6	0	1	0
cyst	3	2	1	0	0
"Lab test abnormality"	1	1	0	2/1	1
allergic reaction	1	0	0	0	0
injection site reaction	1	0	0	0	0
malaise	1	0	0	0	0
neoplasm	1	0	0	0	0
"photosensitivity"	1/1	0	0	0	0
hemia	0	1	0	1	0
granuloma	0	1	0	0	0
<u>CARDIOVASCULAR</u>	<u>12 (1%)/3</u>	<u>15 (2%)/4</u>	<u>5 (1%)/0</u>	<u>4 (2%)/0</u>	<u>0</u>
hypertension	4	2	0	2	0
vasodilatation	3/3	6/4	1	1	0
myocardial infarction	2	0	0	0	0
migraine	3	1	0	0	0
palpitations	1	1	1	0	0
angina pectoris	0	2	0	0	0
syncope	0	1	2	1	0
arterial thrombosis	0	1	0	0	0
arrhythmia	0	0	1	0	0
carotid occlusion	0	1	0	0	0
<u>DIGESTIVE</u>	<u>47 (5%)/3</u>	<u>34 (3%)/2</u>	<u>11 (2%)/0</u>	<u>22 (10%)/0</u>	<u>1/0</u>
"tooth disease"	6	4	2	7 (3%)	1
periodontal abscess	3	2	1	1	0
oral ulcer	2	0	1	0	0
oral dryness	1	1/1	0	0	0
thirst	1	0	0	0	0
gastroesophageal reflux	3/3	2/2	0	0	0
pharyngeal stenoses	1	0	0	0	0
esophageal ulcer	0	1	0	0	0

anorexia	0	1	0	0	0
nausea/vomit	5	5	1	4 (2%)	0
headache	4	6	3	2	0
colibacillary enteritis	3	1	1	1	0
dyspepsia	8	4	1	0	0
gastritis	2	1	0	0	0
duodenal ulcer	0	1	0	0	0
enteritis	0	1	1	0	0
ileitis	0	1	0	0	0
colitis	3	0	0	1	0
rectal disease	1	2	0	1	0
constipation	0	2	1	1	0
GI carcinoma	0	0	0	1	0
liver function abnormality	4	3	2	4 (2%)	0
jaundice	0	1	0	0	0
cholecystitis	3	0	0	0	0
ENDOCRINE	1/0	2/0	3/0	0	0
diabetes mellitus	1	1	1	0	0
hypothyroidism	0	1	0	0	0
"cyst"	0	0	1	0	0
hyperthyroidism	0	0	1	0	0
HEMATOLOGIC	9/1	11 (1%)/1	7 (1%)/0	4 (2%)/0	0/0
eosinophilia	3	2	3	0	0
leukocytosis	0	0	0	2	0
leukopenia	0	0	1	0	0
white cell abnormality	0	1	1	0	0
petechia	1	0	0	0	0
ecchymosis	3/1	3	0	1	0
purpura	0	1	0	0	0
thrombocytopenia	0	0	1	0	0
anemia	1	0	1	0	0
hemoglobin abnormality	0	0	0	1	0
thyroid adenopathy	1	4/1	1	0	0
METABOLIC	20 (2%)/1	26 (3%)/6	12 (2%)/2	5 (2%)/0	2 (2%)/1
hypertriglyceridemia	8/1	13 (1%)/3	3/1	3 (1%)	1
hypercholesterolemia	5	5/1	2	0	0
hyperlipemia	3	1	0	1	0
hyperglycemia	2	3	0	0	0
hyperuricemia	2	0	0	0	0
gout	0	1	1	0	0
amyloidosis	0	1	0	0	0
anemia of B12 deficiency	0	0	1	0	0
creatinine increase	0	1	0	0	0
hyperkalemia	0	0	1	0	0
albuminuria	0	0	1	0	0
globulin increase	1	0	0	0	0
SGOT increase	1	2/1	1	1	0
SGPT increase	1	2	1	1	0
bilirubinemia	0	2/1	0	0	0
peripheral edema	4	3/2	4/1	0	1/1
edema	1	1	0	0	0
MUSCULOSKELETAL	21 (2%)/1	30 (3%)/1	19 (4%)/0	16 (7%)/0	2 (2%)/0
myalgia	7	8	3	6 (3%)	0
"joint disease"	3	1	0	1	0
arthritis	3	8	5	5 (2%)	0
arthralgia	2/1	5	1	2	1
bursitis	4	0	3	0	0
tenosynovitis	0	2	1	1	0
general spasm	1	1	1	0	0
osteoporosis	0	1	0	0	0
osteoporosis	1	0	0	0	0

bone fracture	1	2	4	1	1
bone pain	0	2/1	0	0	0
"eye disease"	0	0	1	0	0
OROLOGIC	22 (2%)/6	21 (2%)/2	5 (1%)/1	7 (3%)/0	1/0
insomnia	6/4	1	2	2	0
somnolence	1	0	0	0	0
dizziness	4	4	0	2	0
anxiety	2	4	2	1	1
depression	2	3	0	0	0
nervousness	2	1	0	0	0
emotional lability	1	1	0	0	0
neurosis	1/1	0	0	0	0
hypertonia	2/1	1	0	1	0
dysautonomia	1	0	0	0	0
paresthesia	3/1	1/1	1/1	0	0
hyperkinesia	1	0	0	0	0
cerebrovascular accident	0	1	0	0	0
dementia	0	1	0	0	0
paralysis	0	1	0	0	0
facial paralysis	1	1	0	0	0
seizure	0	1	0	0	0
sleep disorder	0	1/1	0	0	0
"thinking abnormality"	0	1	0	0	0
"coordination abnormality"	0	0	0	1	0
vertigo	0	0	0	1	0
RESPIRATORY	117 (12%)/1	124 (13%)/0	81 (16%)/0	41 (18%)/0	8 (7%)/0
"infection"	63 (6%)	65 (7%)	44 (9%)	22 (10%)	0
pharyngitis	20 (2%)	19 (2%)	13 (3%)	4 (2%)	6 (5%)
rhinitis	20 (2%)	18 (2%)	18 (4%)	11 (5%)	0
sinus infection	6	10 (1%)	3	7 (3%)	0
otitis	3	7	4	4 (2%)	1
sputum increase	3	6	6 (1%)	4 (2%)	0
asthma	4	3	1	0	0
bronchitis	4	8	9 (2%)	2	0
epistaxis	2/1	0	0	0	0
pneumonia	2	0	0	0	0
dyspnea	2	0	0	0	0
"lung disease"	0	3	0	0	0
laryngitis	0	1	1	0	0
abscess	0	1	0	0	0
lung fibrosis	0	1	0	0	0
sputum increase	0	0	0	1	0
bronchiectasis	0	0	0	0	1
DERMATOLOGIC	575 (58%)/537 (54%)	506 (51%)/452 (46%)	107 (21%)/89 (17%)	44 (20%)/26 (12%)	14 (12%)/11 (9%)
burning/stinging	234 (24%)/227 (23%)	169 (19%)/181 (18%)	21 (4%)/21 (4%)	17 (8%)/16 (7%)	1
pruritus	215 (22%)/198 (20%)	173 (18%)/161 (16%)	48 (10%)/45 (9%)	8 (4%)/6 (3%)	7 (6%)/7 (6%)
erythema	183 (19%)/171 (17%)	137 (14%)/133 (14%)	4/4	2/1	4 (3%)/4 (3%)
desquamation	128 (13%)/124 (13%)	85 (9%)/84 (9%)	6 (1%)/6 (1%)	0	1/1
irritation	116 (12%)/113 (11%)	82 (8%)/80 (8%)	6 (1%)/5 (1%)	1/1	1
Contact dermatitis, irritant	41 (4%)/37 (4%)	31 (3%)/26 (3%)	3/2	2/1	0
contact dermatitis, allergic	6/3	0	0	0	0
"skin reaction"	4/4	1/1	0	0	0
dry skin	69 (7%)/67 (7%)	81 (8%)/74 (8%)	18 (4%)/17 (3%)	0	0
skin pain	74 (8%)/64 (7%)	39 (4%)/36 (4%)	7 (1%)/7 (1%)	1	1/1
rash	38 (4%)/37 (4%)	32 (3%)/25 (3%)	7 (1%)/3	2	1
rash, vesiculobullous	4/1	7/5	1/1	0	0
rash, maculopapular	2/2	5/2	0	0	0
urticaria	4	2	0	1/1	0
"skin inflammation"	11 (1%)/11 (1%)	9/7	5/4	0	2/2
"conjunctivitis"	2/2	4/1	1	0	0
asthma	0	5/1	0	0	0