

skin fissure	10 (1%)/8	13 (1%)/10 (1%)	3/1	0	0
skin laceration	5	3	1	1	0
skin ulceration	7/5	9/9	2/2	0	0
"skin disorder"	8/5	1	0	1	0
skin local edema	3/2	0	0	0	0
skin discoloration	10 (1%)/8	10 (1%)/10 (1%)	0	1	0
skin hemorrhage	5/4	0	0	0	0
skin tightness	5/5	7/7	1/1	0	0
skin discharge	2/2	6/5	0	0	0
skin hypertrophy	3/3	4/4	2/2	0	1/1
skin atrophy	2	0	0	0	0
hyperkeratosis	0	1/1	0	2/2	0
sun-induced erythema	0	1	0	0	0
photodermatitis	1/1	5/2	0	0	0
furunculosis	0	1	0	0	0
infestation	2/1	3	0	1	0
infection	1	1	0	1	0
folliculitis	0	4/1	0	1	0
nail disorder	1	1/1	1/1	0	0
nail pain	3/1	1	1	0	0
skin neoplasm/carcinoma	0	0	1/1	0	0
rosacea	0	0	0	2/2	0
alopecia	1	1	0	0	0
seborrhea	2	0	0	1/1	0
psoriasis	2	2/1	1/1	0	0
acne	1	0	0	0	0
psoriasis worsened	4/1	3/1	0	1	0
acne worsened	69 (7%)/38 (4%)	66 (7%)/37 (4%)	20 (4%)/9 (2%)	15 (7%)/4 (2%)	0
herpes simplex	0	4/2	5 (1%)/3	0	0
zoster	3	2	1	0	0
skin	0	0	0	0	1
papules	1	0	0	0	0
chemical burns	1/1	1	0	0	0
SPECIAL SENSES	17 (2%)/0	21 (2%)/1	11 (2%)/1	5 (2%)/0	1/0
Ear infection	1	8	1	1	0
Eye infection	2	2	0	0	1
ear pain	1	2	1	1	0
conjunctivitis	1	0	0	0	0
lacrimation	1	0	0	0	0
retinitis	1	0	0	0	0
eye edema	1	0	0	0	0
eye pruritus	0	1/1	0	0	0
tinnitus	1	0	0	0	0
burning eye	0	2	0	0	0
otitis media	0	1	4	1	0
otitis externa	0	1	1	0	0
"vision abnormality"	0	1	1/1	0	0
amaurosis fugax	0	1	0	0	0
hyperemia	0	1	0	0	0
uveitis	0	1	0	0	0
"vestibule disease"	0	1	0	0	0
"vision abnormality" (NOS)	0	1	0	0	0
cataract	0	0	1	0	0
eye trauma	0	0	1	0	0
retinal detachment	0	0	1	0	0
taste perversion	0	0	1	0	0
cyst of eyelid	0	0	0	2	0
UROGENITAL	30 (3%)/0	36 (4%)/2	22 (4%)/0	13 (6%)/0	0
uria	5	6	5 (1%)	3 (1%)	0
hemorrhage	5	2	1	0	0
"urine abnormality"	4	4	0	1	0
cystitis	3	2	1	1	0

kidney calculus	3	0	2	0	0
urinary tract infection	2	9	11 (2%)	4 (2%)	0
hematuria	2	3	1	1	0
pyuria	1	0	0	0	0
dysuria	2	2/1	0	2	0
"prostate disease"	1	1	1	0	0
menorrhagia	1	1	0	0	0
metrorrhagia	1	0	0	0	0
vaginitis	2	2/1	0	0	0
pyuria	1	0	1	0	0
salpingitis	1	0	1	0	0
prostate carcinoma	1	0	0	0	0
"testis disease"	1	0	0	0	0
monilia vaginitis	0	3	0	0	0
"menstual disease"	0	2	0	0	0
"uterine disease"	0	2	0	0	0
menopause	0	0	1	0	0
urine casts	0	0	1	0	0
"cervix disease"	0	0	0	2	0
"ovary disease"	0	0	0	1	0
breast pain	0	0	0	1	0

*Incidence of "Treatment-related" adverse events is listed after a slash (/) from the total incidence. Percentages of individual adverse events are only given for those occurring with a rate of 1% or more.

Terminations due to 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%)
Terminated with Adverse Events	156 (16%)	129 (13%)	16 (3%)	4 (2%)	4 (3%)
System/Event					
BODY	<u>4 (<1%)</u>	<u>4 (<1%)</u>	<u>2 (<1%)</u>	<u>0</u>	<u>0</u>
infection	1	2	1	0	0
headache	1	1	1	0	0
chills	1	0	0	0	0
neoplasm	1	0	0	0	0
"photosensitivity"	1	0	0	0	0
chest pain	0	1	0	0	0
knee pain	0	0	1	0	0
CARDIOVASCULAR	<u>3 (<1%)</u>	<u>1 (<1%)</u>	<u>0</u>	<u>0</u>	<u>0</u>
myocardial infarction	2	0	0	0	0
vasodilatation	1	0	0	0	0
carotid artery occlusion	0	1	0	0	0
DIGESTIVE	<u>2 (<1%)</u>	<u>3 (<1%)</u>	<u>0</u>	<u>1 (<1%)</u>	<u>0</u>
cheilitis	1	0	0	0	0
liver function abnormality	1	0	0	0	0
diarrhea	0	1	0	0	0
ileitis	0	1	0	0	0
jaundice	0	1	0	0	0
disease	0	1	0	0	0
cinoma	0	0	0	1	0
HEMATOLOGIC	<u>0</u>	<u>1 (<1%)</u>	<u>0</u>	<u>0</u>	<u>0</u>
lymphadenopathy	0	1	0	0	0
METABOLIC	<u>4 (<1%)</u>	<u>3 (<1%)</u>	<u>0</u>	<u>0</u>	<u>0</u>
hypertriglyceridemia	2	1	0	0	0
edema	1	2	0	0	0
hypercholesterolemia	1	1	0	0	0
SGPT increase	1	2	0	0	0
MUSCULOSKELETAL	<u>0</u>	<u>3 (<1%)</u>	<u>0</u>	<u>1 (<1%)</u>	<u>0</u>
arthritis	0	1	0	0	0
arthralgia	0	1	0	0	0
bone pain	0	1	0	0	0
traumatic bone fracture	0	0	0	1	0
NEUROLOGIC	<u>4 (<1%)</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>
insomnia	1	0	0	0	0
nevousness	1	0	0	0	0
neurosis	1	0	0	0	0
paresthesia	1	0	0	0	0
RESPIRATORY	<u>2 (<1%)</u>	<u>3 (<1%)</u>	<u>1 (<1%)</u>	<u>0</u>	<u>0</u>
pharyngitis	1	0	1	0	0
pneumonia	1	0	0	0	0
"infection"	0	2	0	0	0
"lung disease"	0	1	0	0	0
DERMATOLOGIC	<u>115 (13%)</u>	<u>90 (10%)</u>	<u>14 (3%)</u>	<u>2 (<1%)</u>	<u>4 (3%)</u>
Burning/stinging	47 (5%)*	36 (4%)	3	0	1
erythema	33 (3%)	19 (2%)	1	0	1
pruritus	35 (4%)	34 (3%)	4	0	2
ion	26 (3%)	19 (2%)	0	0	0
sis worsened	29 (3%)	19 (2%)	6 (1%)	1	0
skin pain	19 (2%)	11 (1%)	0	0	0

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

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

DEC 19 1996

**Medical Officer's Review of NDA 20-600
Amendments**

**NDA #20-600
AZ & BZ**

Submission dates: 6/27/96 and 7/30/96
Received date: 7/3/96 and 8/4/96
Review completed: 10/10/96
Review revised: 10/30/96, 11/25/96
& 12/10/96

Drug name: tazarotene

Generic name: tazarotene

Proposed trade name: Tazorac™

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

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

Pharmacologic Category: Retinoid

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

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

NDA Drug Classification: 1 S

Related NDAs: none. Studies in NDA 20-600 were conducted under IND

Related Reviews: **Statistical Review dated:** 11/14/96
Biopharm Review dated: 10/31/96

Material Reviewed

This review is based on the clinical sections from the Applicant's responses dated 6/27/96 and 7/30/96. These are responses to the nonapprovable letter of 6/6/96 and an accompanying FAX relating deficiencies that were not the basis of the nonapprovability. As the responses were according to items in these 2 documents. This review will be presented in a likewise manner.

Table of Contents

General	1
Table of Contents	2
1 Responses to Nonapprovable letter of 6/6/96	3
1.1 Clinical Issue. Differences in Formulations in Pivotal Trials	3
1.2 Safety Update	3
1.2.1 Retabulation of ALL Safety Data	3
1.2.2 Information on All Studies Worldwide and Uses of the Drug	5
1.2.3 New Dropouts	5
1.2.4 Case Report Forms for Deaths and Discontinuations due to Adverse Events	5
1.2.5 Details of Significant Changes or Findings	5
1.2.6 Worldwide Experience	5
2 Responses to Issues in the FAX of 6/6/96	5
2.1 Curriculum Vitae of Investigators for Study R168-120-8606	5
2.2 Name, Address and Qualifications of Radiologist for Study R168-128-8606	6
2.3 Justification to Support Claim of Comparable Efficacy between the Topical Use of Tazarotene and Tretinoin in Acne	6
2.4 Allergic Component for Treatment-Related Allergic Contact Dermatitis Cases	6
2.5 Full Study Reports of R168-106-8606 and R168-146-8606	6
2.5.1 R168-106-8606	6
2.5.2 R168-146-8606	9
2.6 Requested Statistical Analyses	9
2.6.1 Analysis of Efficacy Data of Women in the Acne Studies Who Were Using Estrogen vs Those Not Using Estrogen	9
2.6.2 Demographic Subset Analyses in Pivotal Clinical Trials	10
2.6.3 Statistical Significance of Adverse Event Data in Each Study	20
2.6.4 Between Group Comparisons for Efficacy Data in R168-145-8606	23
2.6.5 Comparisons between Treatment Groups for Achievement of Global Evaluation Scores of [1] $\geq 75\%$ Improvement and [2] 100% Improvement in Each Study	24
2.6.6 Statistical Significance of Dropouts among Treatment Groups in Each Study and Significance of the Differences in Drug Exposure among These Groups	27
2.6.7 Bias arising from the Disproportionate Sample Sizes among Treatment Groups in the Posttreatment Periods of Psoriasis Studies	27
2.7. Justification to Support the Claim that the 0.1% and 0.05% Concentrations of Tazarotene Gel Are Distinguishable from Each Other by Efficacy and/or Safety	28
3 Conclusions	32
4 Labeling Review	34
5 Risk Benefit Analysis	45
6 Recommendations	45

1. Responses to Nonapprovable Letter of 6/6/96

1.1 Clinical Issue Differences in the Formulations Used in the Pivotal Trials

Table 1.1A Formulations used in Pivotal Trials of NDA 20-600

Trial Numbers	Psoriasis Trials		Acne Trials	
	R168-120-8606	R168-121-8606	R168-220-8606	R168-221-8606
0.05% Gel	8607X	8607X-A	8225X	8607-XA
0.10% Gel	8606X	8606X	7997X	8606X

Table 1.1B Compositions of Formulations used in Pivotal Trials of NDA 20-600

Formulation Number	Formulation Percentage				
	7977X	8225X	8606X	8607X	8607X-A
Tazarotene					
Benzyl alcohol					
Ascorbic Acid					
Butylated Hydroxyanisole					
Butylated Hydroxytoluene					
Disodium Edetate					
PEG 400					
Hexylene Glycol					
Poloxamer 407					
Polysorbate 40					
Carbomer 934P					
Tromethamine					
Purified water					

Comment The difference between the older formulations (7997X and 8225X) and the more current ones (8606X, 8607X and 8607X-A) has been noted previously. Tromethamine instead of is now to be used for neutralization. The only new information is that formulations 8225X and 8607X actually contain 0.0525% rather than 0.05% of tazarotene. The Applicant explained that an overage of 5% was used for the manufacture of the 0.05% gel before. This is unnecessary due to the stability of the preparation. The later and intended marketing formulations have therefore not included the 5% overage. This difference (0.0525% vs 0.05%) is unlikely to be clinically detectable or significant.

1.2 Safety Update

1.2.1 Retabulation of all Safety Data, including Results of Trials ongoing at the Time of NDA Submission

At the time of submission of the original NDA, data from the following 5 studies were not available. Three of these studies have been submitted subsequently in the safety update amendment of 10/30/95.

<u>Study#, Location and Nature of Study</u>	<u>Patient number</u>	<u>Status of Study Report</u>
R168-153-8606 (U.S.) Plasma concentration/time-profiles upon single- and multiple-dose 0.1% and 0.05% gel application in psoriatics	5	Submitted 10/30/95
R168-155-8606 (U.S.) Plasma concentration/time-profiles upon iv infusion of 0.01% solution vs single application of 0.1% gel	8	Submitted 10/30/95
R168-128-8606 (U.S.) One-year study of safety/efficacy of 0.1% and 0.05% gels given daily in the treatment of plaque psoriasis.	243	Submitted 10/30/95
R168-106-8606 (U.S.) Eight week study with bilateral comparison of 0.1% gel vs vehicle applied qd.	20	Submitted 7/30/96
R168-722-8606 (Japan) Eight week study with bilateral comparison of 0.1% gel vs 0.05% gel applied qd.	96	Submitted 1/9/96 & resubmitted 6/27/96

Comments

1. Study R168-146-8606, a phase 3 trial being conducted in the U.K., has not been included in this safety update. Although it has not been unblinded, available safety data should be submitted.
2. Study R168-722-8606 has previously been submitted and reviewed. This was a bilateral comparison study (of tazarotene 0.1% and 0.05% gels) where patients applied one treatment to a psoriasis plaque on each side. This report mentioned that 19/96 subjects had topical side effects, while systemic side effects were noted in one patient (oral dryness and stomatitis). The only additional information provided on this study was addition of a Table of ALL adverse events shown as follows (Safety Update Table 2c from 6/27/96 submission, p. 1-050):

	<u>Tazarotene 0.1% gel</u>	<u>Tazarotene 0.05% gel</u>
<u>Total patient numbers enrolled</u>	<u>96*</u>	<u>96*</u>
<u>Number of patients with AE</u>	<u>40</u>	<u>36</u>
Digestive		
oral dryness	1	1
stomatitis	1	1
Skin (total)	40	36
skin irritation	23	22
desquamation	11	10
erythema	9	8
pruritus	9	8
psoriasis worsened	9	8
vasodilation	7	6
local pain	2	2
atrophy	1	1
focal edema	1	1
papules	1	1
vesiculobullous rash	1	1

*Same patients using either gel: this was a bilateral comparison study where patients apply one treatment to a psoriasis plaque on each side.

This Table does not agree with that in the study report (Table 8 of study report, p. 4-069 of 6/27/96 submission) as shown below:

<u>Adverse Event</u>	<u>Tazarotene 0.1% gel</u>	<u>Tazarotene 0.05% gel</u>
Topical		
skin irritation	10	11
local pain	2	2
erythema	2	1
flare	1	1
flush	3	2
desquamation	2	2
edema	1	1
pruritus	5	4
Systemic		
dry mouth	1	1
oral irritation	1	1

Since most of the events listed here are local adverse events, it remains unexplained why there is a substantial difference between the current safety update data and those from previously submitted material, especially since the original data were identical to that given in the study report submitted on 6/27/96, showing that 19 subjects had topical adverse events.

3. The retabulation of data from material which have been submitted and reviewed before (R168-128-8606) does not add any further insight into the safety of tazarotene. Data from the other studies were not included in the retabulation. They either involved small numbers of subjects or were not reliable (R168-722-8606, see above comment, #2 and original review) and did not add substantially to the established database.

1.2.2 Information on all studies worldwide and uses of the drug including:

A. Those involving indications not being sought in the present submission.

B. Other dosage forms, and other dose levels, etc.

All additional studies have been listed under Section 1.2.1. There have been no studies other than those for psoriasis and acne. No other dosage forms or dose levels have been used apart from those presented in this NDA or its amendments.

1.2.3 New Dropouts None

1.2.4 Case Report Forms for Deaths and Discontinuations due to Adverse Events.

Case report forms for the following studies were provided: R168-128-8606, R168-112-8606 and R168-722-8606. No new information has been gained from these case report forms.

1.2.5 Details of Significant Changes or Findings, if Any None

1.2.6 Worldwide Experience Drug not being marketed

2. Responses to Issues in the FAX of 6/6/96

2.1 Curriculum Vitae of investigators for Study R168-120-8606.

The Applicant has provided the curriculum vitae and Form 1572s of the Investigators in Study R168-120-8606. These had been inadvertently omitted in the original submission.

Comment Review of the curriculum vitae showed that the Investigators were qualified to conduct the study.

2.2. Name, Address and Qualifications of the Radiologist Who read the Radiographs in Study R168-128-8606.

The curriculum vitae of Dr. Jack Philip Lawson, Attending Radiologist, Yale-New Haven Hospital has been provided.

Comment Dr. Lawson is qualified to interpret the skeletal X-rays in Study R168-128-8606.

2.3. Justification to Support Claim of Comparable Efficacy between the Topical Use of Tazarotene and Tretinoin in the Treatment of Acne.

In the original submission of NDA 20-600 (Vol 1.2, p. 2-033), the Applicant stated:

"Tazarotene Gel applied topically once daily has demonstrated efficacy in acne comparable to tretinoin applied once daily."

The Applicant now states that such studies have not been performed and they are not making any "claim" in the label on comparable efficacy.

Comment This correction is noted.

2.4. Identification of the Allergic Component for the Treatment-Related Allergic Contact Dermatitis Cases cited in this NDA, despite Failure to Demonstrate Contact Sensitization Potential in Dermal Safety Studies.

Three cases of treatment-related "allergic" contact dermatitis were listed in R168-128-8606. The Applicant is unable to document an allergic component and has conceded that the reactions represent local irritation produced by tazarotene gel.

Comment The Applicant still classifies them as allergic contact dermatitis in their data analysis. This needs to be corrected.

2.5. Full Study Reports of R168-106-8606 and R168-146-8606.

Final study report of R168-106-8606 was provided. That of R168-146-8606 was not submitted, as the Applicant states that it is still ongoing.

2.5.1 Study R168-106-8606. "Safety and Efficacy of AGN 190168 0.1% Gel versus Vehicle Gel in Stable Plaque Psoriasis and Effect on Molecular Markers in Treated Plaques."

Objective/Rationale: To evaluate the safety and efficacy of tazarotene 0.1% gel vs vehicle applied once a day in the treatment of stable plaque psoriasis and the effect on molecular markers in treated plaques.

Design: Phase 2, single-center, investigator-blind, randomized-block study (paired comparison) of qd tazarotene 0.1% gel vs vehicle to designated bilateral target psoriasis plaques over 8 weeks. One side received tazarotene and the other vehicle. There were 4

visits: day-3, -14, -28 and -56.

Protocol: Patient selection included both sexes aged 18 or older with 3 or more psoriatic plaques, two of which were bilateral on trunk, legs or arms (and negative urine pregnancy test in women of child-bearing potential). Exclusions were: sensitivity to ingredients of test drugs, conditions or use of medications that might affect evaluation, uncontrolled systemic disease, pregnancy/lactation or lack of contraception in women of child-bearing potential and pustular/exfoliative psoriasis.

The following were evaluated:

Efficacy - plaque elevation, scaling, erythema, sum of scores and overall lesional severity (these 5 parameters scored on a 5-point scale of none to very severe), global evaluation (6-point scale from worsened/unchanged to completely cleared) and bilateral comparison (right plaque better, left plaque better or the same); derived variables: "treatment success" (global of good or better) and time to initial "treatment success".

Molecular markers - gene expression in epidermis and dermis for MRP8, SKALP and TIG1 (6-point scale from no signal to very strong) from biopsies of uninvolved skin, one psoriasis plaque at baseline, and each target lesion at day-3 and -14, using *in situ* hybridization with sense and antisense RNAs labeled with 11-UTP digoxigenin.

Clinical laboratory tests - hematology, chemistry and urinalysis.

Investigator: Madeleine Duvic, M.D.
Houston, TX 77030

Results:

Patient Disposition

Enrolled: 20 (12 males, 8 females, aged 28-83, race - white 15, black 1, Hispanic 3 and Oriental 1).

Completed: 15 (5 discontinued: 2 for noncompliance, 1 for prohibited therapy and 2 needed treatment for psoriasis).

Efficacy Parameters

Table 2.5.1.A Baseline and Score Reductions in Target Plaques

	Tazarotene				Vehicle			
	BL*	day-14	day-28	day-56	BL	day-14	day-28	day-56
plaque elevation	2.18**	<u>-0.83*</u> p<0.01	<u>-1.15</u> p<0.01	<u>-1.62</u> p<0.01	2.13	0.03	-0.21	-0.68
scaling,	2.70	<u>-0.68</u> p=0.01	<u>-1.21</u> p=0.01	-1.62	2.70	-0.05	-0.41	-1.18
erythema,	2.63	-0.20	-0.44	-0.97	2.65	-0.13	-0.21	-0.65
sum of scores	7.50	<u>-1.70</u> p<0.01	<u>-2.79</u> p<0.01	<u>-4.21</u> p=0.02	7.48	-0.15	-0.82	-2.50
overall lesional severity	2.60	<u>-0.53</u> p<0.01	<u>-1.00</u> p<0.01	<u>-1.50</u> p<0.01	2.58	-0.08	-0.24	-0.76

*BL=baseline, scores underlined indicate statistically significant difference vs vehicle (p<0.05).

**scored as 0=none, 1=mild, 2=moderate, 3=severe and 4=very severe.

Table 2.5.1.B "Global" Evaluation of Target Plaques and "Treatment Success"

	Tazarotene			Vehicle		
	day-14	day-28	day-56	day-14	day-28	day-56
mean scores	<u>4.65</u> ** <small>p<0.01</small>	<u>3.88</u> <small>p<0.01</small>	<u>3.06</u> <small>p=0.01</small>	5.55	5.24	4.18
patients with score of 1*	0	0	4	0	0	0
of 2	0	3	2	0	0	2
of 3	2	2	4	0	1	2
of 4	6	6	3	1	2	5
of 5	9	6	4	7	6	7
of 6	3	0	0	12	8	1
"treatment success"	10%	29%	<u>59%</u> <small>p=0.03</small>	0	6%	24%

*scored as 1=completely cleared, 2=excellent, 3=good, 4=fair, 5=poor and 6=unchanged/worse.

**underlined data indicate statistically significant difference vs vehicle (p<0.05).

Time to initial "treatment success" in 50% subjects=45.4d vs >56d (p<0.001).

Table 2.5.1.C Bilateral Comparison

	Tazarotene Side better	Vehicle Side better	Same on Both Sides	p
day-3	2 (10%)	2 (10%)	16 (80%)	>0.999
day-14	14 (74%)	2 (11%)	3 (80%)	0.004
day-28	14 (100%)	0	0	<0.001
day-56	13 (76%)	2 (12%)	2 (12%)	0.007

Evaluation of pain and pruritus by patient did not show significant difference between the two target plaques during any time in the study (p>0.05). Evaluation of scaling, erythema and pruritus in the skin surrounding the treated lesions showed greater incidence of these signs and symptom for the tazarotene-treated plaques at day-14, -28 and -56, while the incidence of pain around tazarotene-treated lesions was greater at day-14 (statistical comparisons not made).

Molecular Markers

Table 2.5.1.D Molecular Marker Scores* in Target Plaques

Treatment:	MRP8		SKALP		TIG1	
	Tazarotene	Vehicle	Tazarotene	Vehicle	Tazarotene	Vehicle
day-3						
epidermis	3.79**	3.42	2.43	4.10	5.30	4.73
dermis	0.68	0.53	2.85	2.15	4.80	4.88
day-14						
epidermis	4.28	4.97	3.41	2.69	6.09	5.69
dermis	0.97	0.83	3.38	2.47	5.74	5.53

*Scored as 0=no signal, 1+=low signal, 2=signal present, 3=moderately strong signal, 4=strong signal and 5=very strong signal.

**None of the intergroup comparisons for actual scores given in this Table were statistically significant (p>0.05). Intragroup comparisons for change from baseline (not shown) showed one significant change: epidermis SKALP at day-3 in vehicle group (p<0.003).

Safety Findings

Adverse events occurred in 5/20 patients: arthritis 1, skin burning 3, pruritus 3 and psoriasis worsened 2. There were no discontinuations due to adverse events. Clinical laboratory tests showed no significant abnormalities.

Comments and Conclusions:

1. Primary and secondary efficacy variables were not defined. However, at the end of the 56-day treatment period, reduction in plaque elevation, sum of clinical scores, overall lesional severity, mean global, "treatment success" and time to initial "treatment success" in the tazarotene-treated plaques showed superiority over those in vehicle-treated lesions.
2. Expression of the molecular markers MRP8, SKALP and TIG1 did not show significant differences between the tazarotene- and the vehicle-treated plaques. The Applicant tried to reanalyze these data by using the following subsets: tazarotene-responders and -nonresponders and vehicle-responders and -nonresponders (defined using several different criteria [analyses not reviewed]). These post-hoc analyses were not in the original protocol, used very small patient numbers in the subgroups and were clearly of an exploratory nature. The Applicant has also conceded that the *in situ* hybridization procedure had too much variability to be useful in studies of this nature. In addition, the Investigator violated the protocol and consent form by taking an additional biopsy from uninvolved skin at baseline. A DSI audit may be required.
3. There were no safety issues arising from this study that have not been addressed in the phase 3 trials.
4. In conclusion, this study was unwarranted. The objective to evaluate safety/efficacy was not expected to reveal anything new additional to the phase 3 trials, which involved much larger sample sizes and more prolonged tazarotene use and follow-up. The molecular marker study used a procedure which would not enable the achievement of the study objective. Protocol violation exposed patients to risks of an additional biopsy.

2.5.2 Study R168-146-8606. No report presented.

2.6. Requested Statistical Analyses

2.6.1 Analysis of Efficacy Data of Women in Acne Studies who were using Estrogen vs Those not using Estrogen.

The following analysis has been provided:

Table 2.6.1.A Incidence of Estrogen Users and Nonusers

	USERS			NONUSERS		
	Taz 0.1%	Taz 0.05%	Veh	Taz 0.1%	Taz 0.05%	Veh
R168-220	7/59 (12%)	7/63 (11%)	7/53 (13%)	52/59 (88%)	56/63 (89%)	46/53 (87%)
R168-221	9/70 (13%)	14/75 (19%)	12/76 (16%)	61/70 (87%)	61/75 (81%)	64/76 (84%)
COMBINED	16/129 (12%)	21/138 (15%)	19/129 (15%)	16/129 (88%)	117/138 (85%)	110/129 (85%)

Table 2.6.1.Bi Lesion Counts of Estrogen Users and Nonusers from Pooled Studies R168-220 & R168-221

	USERS			NONUSERS		
	Taz 0.1% (n=16)	Taz 0.05% (N=21)	Veh (N=19)	Taz 0.1% (n=113)	Taz 0.05% (N=117)	Veh (N=110)
Total Lesion Counts						
wk-0	69	64	76	71	65	67
wk-4	49 (29)* p=0.04	44 (31) p=0.03	67 (12)	54 (74)	50 (22)	54 (20)
wk-8	45 (35)	33 (49) p<0.01	56 (26)	40 (44) p<0.01	40 (38)	47 (30)
wk-12	43 (37)	34 (47)	44 (42)	34 (52) p<0.01	36 (44) p=0.02	45 (33)
Inflammatory Lesion Counts						
wk-0	17	18	17	19	17	19
wk-4	12 (27)	12 (33)	14 (21)	15 (22)	14 (20)	15 (18)
wk-8	9 (48) p=0.04	8 (53) p=0.01	12 (28)	12 (40)	11 (36)	13 (33)
wk-12	11 (36)	9 (50) p=0.05	8 (51)	10 (50) p=0.03	10 (42)	12 (35)
Noninflammatory Lesion Counts						
wk-0	52	46	59	52	48	48
wk-4	38 (28) p=0.04	33 (28)	54 (7)	39 (24)	37 (23)	39 (19)
wk-8	37 (28)	25 (46) p=0.02	44 (25)	28 (45) p<0.01	29 (39) p=0.04	34 (29)
wk-12	33 (36)	26 (44)	36 (39)	25 (52) p<0.01	26 (45) p=0.02	32 (32)

*Percent reduction is given in parentheses. Superiority over vehicle (p<0.05) is shown underlined. Highlighted data show significant difference between the 0.1% and 0.05% gels (p<0.05).

Table 2.6.1.Bii "Treatment Success" in Estrogen Users and Nonusers from Pooled Studies R168-220 & R168-221

	USERS			NONUSERS		
	Taz 0.1%	Taz 0.05%	Veh	Taz 0.1%	Taz 0.05%	Veh
wk-4	4/16 (25%)	6/21 (29%)	3/18 (17%)	22/106 (21%)	20/111 (18%)	18/108 (17%)
wk-8	5/13 (38%)	9/21 (60%)	5/17 (29%)	46/97 (47%)* p=0.04	38/96 (40%)	32/99 (32%)
wk-12	7/14 (50%)	15/21 (67%)	7/12 (58%)	63/97 (65%) p<0.01	49/96 (51%)	37/95 (39%)

*Superiority over vehicle (p<0.05) is shown underlined.

Comments

1. The number of subjects using estrogen is small. No firm conclusions can be drawn from the data, especially when there is substantial vehicle effect among the estrogen users.
2. It might appear difficult to explain that only 12%-15% of the females were using estrogen. In these two studies, practically all the participating females were in child-bearing age (14-45 years of age). The Applicant should provide documentation of adequate birth control measures by giving listings of exact birth control methods in the females in these two studies. It may be noted that one patient in R168-220-8606 and two patients in R168-221-8606 became pregnant during the course of the studies. Two of these pregnancies were terminated and one gave birth to a healthy baby.

2.6.2 Demographic Subset Analyses in Pivotal Clinical Trials

For the pivotal clinical trials, Applicant was requested to perform the following analyses, which were lacking in the original NDA submission: global "treatment success" analysis for

demographic subsets in acne and meta-analyses of subsets for efficacy and safety for both indications.

The analyses submitted were done using the two vehicle-controlled phase 3 psoriasis trials: R168-120-8606 and R168-121-8606, and the two vehicle-controlled phase 3 acne trials: R168-220-8606 and R168-221-8606.

2.6.2.1 Global "Treatment Success" Analysis for Demographic Subsets in Acne.

Analysis by age is not presented here. The Applicant analyzed by one "subset" (<45 age group) which included practically all subjects.

Table 2.6.2.1A "Treatment Success" Subset Analysis of Individual and of Pooled Acne Studies: SEX

	MALES									FEMALES								
	Taz 0.1%			Taz 0.05%			Veh			Taz 0.1%			Taz 0.05%			Veh		
	220	221	comb	220	221	comb	220	221	comb	220	221	comb	220	221	comb	220	221	comb
wk-4	28*	15	19	17	11	14	15	7	11	31	13	21	32	10	20	32	5	17
wk-8	43	31	<u>37</u>	31	20	26	23	17	20	54	40	46	58	32	42	45	22	32
			p<0.01															
wk-12	<u>56</u>	47	<u>51</u>	36	38	<u>37</u>	32	24	29	<u>80</u>	48	<u>63</u>	70	42	53	52	33	41
	p<0.01		p<0.01			p<0.04				p<0.01		p<0.01						

*Figures given are percentages of "treatment success" defined as a global score of "good" or better. Superiority over vehicle (p<0.05) is shown underlined. Highlighted data show significant difference between the 0.1% and 0.05% gels (p<0.05)

Table 2.6.2.1B "Treatment Success" Subset Analysis of Individual and of Pooled Acne Studies: RACE*

	WHITES									HISPANICS								
	Taz 0.1%			Taz 0.05%			Veh			Taz 0.1%			Taz 0.05%			Veh		
	220	221	comb	220	221	comb	220	221	comb	220	221	comb	220	221	comb	220	221	comb
wk-4	32**	14	21	28	11	18	23	6	13	16	0	16	16	0	15	17	0	16
wk-8	43	<u>37</u>	<u>39</u>	44	26	33	34	20	26	55	0	53	39	50	40	26	0	23
		p=0.01	p=0.01															
wk-12	<u>69</u>	<u>49</u>	<u>56</u>	49	41	<u>44</u>	43	29	35	61	100	62	57	100	60	33	50	34
	p<0.01	p<0.01	p<0.01	p=0.03		p=0.03												

*Data on Blacks and "Other" not presented as the number of subjects were small and no statistically significant differences in between-group comparisons were observed (p>0.05 for all comparisons).

**Figures given are percentages of "treatment success" defined as a global score of "good" or better. Superiority over vehicle (p<0.05) is shown underlined. Highlighted data show significant difference between the 0.1% and 0.05% gels (p<0.05)

Comments

1. Results obtained by combining the two acne trials have in general corresponded to the data from individual studies.
2. These data do not support superiority of the 0.05% gel over placebo in any subset, even with pooled data.
3. Sample sizes of nonwhite ethnic subsets may be inadequate to demonstrate significance.

2.6.2.2 Meta-analyses of Demographic Subsets for Efficacy and Safety

2.6.2.2.1 Efficacy

2.6.2.2.1.1 Psoriasis

Subset Analyses of Pooled Studies R168-120 and R168-121 are shown in the following Tables:

Table 2.6.2.2.1.1Ai Plaque Elevation (Baseline Score and Reduction from Baseline) of Trunk/Arm/Leg Target Lesions

	AGE											
	<45			45-65			>65					
	Taz 0.1% (n=88)	Taz 0.05% (N=102)	Veh (N=97)	Taz 0.1% (n=88)	Taz 0.05% (N=76)	Veh (N=90)	Taz 0.1% (n=33)	Taz 0.05% (N=32)	Veh (N=29)			
wk-0	2.5	2.6	2.4	2.5	2.5	2.5	2.5	2.4	2.7			
wk-1	0.5 p<0.02	0.6 p<0.01	0.4	0.8 p<0.01	0.7 p<0.01	0.2	0.4	0.6	0.3			
wk-2	0.9 p<0.01	0.9 p<0.01	0.4	1.1 p<0.01	0.9 p<0.01	0.4	0.8 p=0.01	0.8 p=0.01	0.4			
wk-4	1.2 p<0.01	1.0 p<0.01	0.4	1.2 p<0.01	1.1 p<0.01	0.5	0.7 p=0.04	1.1 p=0.02	0.7			
wk-8	1.3 p<0.01	1.3 p<0.01	0.6	1.3 p<0.01	1.4 p<0.01	0.6	0.9	1.0	0.9			
wk-12	1.5 p<0.01	1.4 p<0.01	0.7	1.5 p<0.01	1.5 p<0.01	0.6	1.0	1.1	1.1			
	SEX						RACE**					
	MALES			FEMALES			WHITES			HISPANICS		
	Taz 0.1% (n=140)	Taz 0.05% (N=135)	Veh (N=142)	Taz 0.1% (n=69)	Taz 0.05% (N=75)	Veh (N=74)	Taz 0.1% (n=187)	Taz 0.05% (N=184)	Veh (N=189)	Taz 0.1% (n=17)	Taz 0.05% (N=21)	Veh (N=16)
wk-0	2.5	2.6	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.7	2.7	2.9
wk-1	0.6 p<0.01	0.6 p<0.01	0.2	0.7 p<0.01	0.7 p<0.01	0.4	0.7 p<0.01	0.6 p<0.01	0.3	0.7	0.9	0.4
wk-2	0.9 p<0.01	0.8 p<0.01	0.4	1.0 p<0.01	1.0 p<0.01	0.4	1.0 p<0.01	0.9 p<0.01	0.4	1.1 p=0.01	1.0 p=0.04	0.4
wk-4	1.1 p<0.01	1.0 p<0.01	0.6	1.2 p<0.01	1.2 p<0.01	0.5	1.1 p<0.01	1.1 p<0.01	0.6	1.3	1.2	0.6
wk-8	1.2 p<0.01	1.2 p<0.01	0.7	1.4 p<0.01	1.4 p<0.01	0.6	1.2 p<0.01	1.3 p<0.01	0.7	1.4	1.3	0.8
wk-12	1.4 p<0.01	1.3 p<0.01	0.8	1.5 p<0.01	1.5 p<0.01	0.7	1.4 p<0.01	1.4 p<0.01	0.8	1.8	1.5	1.0

Percent reduction is given in parentheses. Superiority over vehicle (p<0.05) is shown underlined. Highlighted data show significant difference between the 1% and 0.05% gels (p<0.05).

**Blacks and "others" not presented here as the numbers of subjects in each treatment group were small (<6) and no inter-group comparison data showed statistical significance.

Table 2.6.2.2.1.1Aii Plaque Elevation (Baseline Score and Reduction from Baseline) of Knee/Elbow Target Lesions

	AGE								
	<45			45-65			>65		
	Taz 0.1% (n=88)	Taz 0.05% (N=102)	Veh (N=97)	Taz 0.1% (n=88)	Taz 0.05% (N=76)	Veh (N=90)	Taz 0.1% (n=33)	Taz 0.05% (N=32)	Veh (N=29)
wk-0	2.6	2.6	2.5	2.6	2.6	2.7	2.6	2.5	2.6
wk-1	0.4	0.5 p<0.01	0.3	0.6 p<0.01	0.5 p<0.01	0.2	0.4	0.7	0.3
wk-2	0.8 p<0.01	0.8 p<0.01	0.4	0.9 p<0.01	0.7 p<0.01	0.3	0.8 p=0.01	0.9 p=0.03	0.4
wk-4	1.1 p<0.01	1.0 p<0.01	0.5	1.1 p<0.01	0.9 p<0.01	0.5	0.9 p=0.01	0.9 p=0.02	0.5
wk-8	1.3 p<0.01	1.2 p<0.01	0.6	1.2 p<0.01	1.2 p<0.01	0.6	1.1	0.9	0.9
wk-12	1.5 p<0.01	1.3 p<0.01	0.6	1.4 p<0.01	1.4 p<0.01	0.6	1.2	0.9	0.9

	SEX						RACE**					
	MALES			FEMALES			WHITES			HISPANICS		
	Taz 0.1% (n=140)	Taz 0.05% (N=135)	Veh (N=142)	Taz 0.1% (n=69)	Taz 0.05% (N=75)	Veh (N=74)	Taz 0.1% (n=187)	Taz 0.05% (N=184)	Veh (N=189)	Taz 0.1% (n=17)	Taz 0.05% (N=21)	Veh (N=16)
wk-0	2.6	2.6	2.6	2.5	2.5	2.6	2.6	2.6	2.6	2.6	2.6	2.8
wk-1	<u>0.5</u> p<0.01	<u>0.5</u> p<0.01	0.3	<u>0.6</u> p<0.01	<u>0.6</u> p<0.01	0.3	<u>0.5</u> p<0.01	<u>0.5</u> p<0.01	0.3	<u>0.4</u>	0.7	0.3
wk-2	<u>0.8</u> p<0.01	<u>0.7</u> p<0.01	0.4	<u>0.9</u> p<0.01	<u>0.8</u> p<0.01	0.3	<u>0.9</u> p<0.01	<u>0.8</u> p<0.01	0.3	0.8	0.9	0.5
wk-4	<u>1.1</u> p<0.01	<u>0.9</u> p<0.01	0.5	<u>1.1</u> p<0.01	<u>1.1</u> p<0.01	0.4	<u>1.1</u> p<0.01	<u>1.0</u> p<0.01	0.5	<u>1.0</u> p=0.04	<u>1.2</u> p=0.03	0.5
wk-8	<u>1.2</u> p<0.01	<u>1.1</u> p<0.01	0.7	<u>1.3</u> p<0.01	<u>1.3</u> p<0.01	0.5	<u>1.3</u> p<0.01	<u>1.2</u> p<0.01	0.7	<u>1.0</u> p=0.03	<u>1.2</u> p=0.02	0.5
wk-12	<u>1.3</u> p<0.01	<u>1.2</u> p<0.01	0.7	<u>1.5</u> p<0.01	<u>1.3</u> p<0.01	0.6	<u>1.4</u> p<0.01	<u>1.2</u> p<0.01	0.7	1.5	1.3	0.7

*Percent reduction is given in parentheses. Superiority over vehicle (p<0.05) is shown underlined. Highlighted data show significant difference between the 0.1% and 0.05% gels (p<0.05).

**Blacks and "others" not presented here as the numbers of subjects in each treatment group were small (<6) and no inter-group comparison data showed statistical significance.

Table 2.6.2.2.1.1Bi Scaling (Baseline Score and Reduction from Baseline) of Trunk/Arm/Leg Target Lesions

	AGE								
	<45			45-65			>65		
	Taz 0.1% (n=88)	Taz 0.05% (N=102)	Veh (N=97)	Taz 0.1% (n=88)	Taz 0.05% (N=76)	Veh (N=90)	Taz 0.1% (n=33)	Taz 0.05% (N=32)	Veh (N=29)
wk-0	2.5	2.5	2.5	2.5	2.4	2.5	2.6	2.4	2.7
wk-1	0.4	0.5	0.4	<u>0.6</u> p<0.01	<u>0.5</u> p<0.01	0.1	0.3	0.5	0.3
wk-2	<u>0.7</u> p=0.02	<u>0.7</u> p<0.01	0.5	<u>0.8</u> p=0.01	<u>0.6</u> p=0.01	0.3	0.7	0.8	0.4
wk-4	<u>1.0</u> p<0.01	<u>0.9</u> p<0.01	0.5	<u>1.0</u> p<0.01	<u>0.8</u> p<0.01	0.4	0.8	1.0	0.5
wk-8	<u>1.1</u> p<0.01	<u>1.1</u> p<0.01	0.6	<u>1.1</u> p=0.01	<u>1.0</u> p=0.01	0.6	0.8	0.9	0.9
wk-12	<u>1.3</u> p<0.01	<u>1.2</u> p<0.01	0.6	<u>1.4</u> p<0.01	<u>1.1</u> p<0.01	0.6	1.0	0.9	1.0

	SEX						RACE**					
	MALES			FEMALES			WHITES			HISPANICS		
	Taz 0.1% (n=140)	Taz 0.05% (N=135)	Veh (N=142)	Taz 0.1% (n=69)	Taz 0.05% (N=75)	Veh (N=74)	Taz 0.1% (n=187)	Taz 0.05% (N=184)	Veh (N=189)	Taz 0.1% (n=17)	Taz 0.05% (N=21)	Veh (N=16)
wk-0	2.5	2.5	2.5	2.4	<u>2.3</u> p<0.01	2.5	2.5	2.4	2.5	2.4	2.6	2.6
wk-1	<u>0.5</u> p<0.01	<u>0.5</u> p<0.01	0.2	0.4	0.4	0.3	<u>0.5</u> p<0.01	<u>0.4</u> p<0.01	0.2	0.4	0.8	0.4
wk-2	<u>0.7</u> p<0.01	<u>0.7</u> p<0.01	0.4	<u>0.8</u> p<0.01	<u>0.8</u> p<0.01	0.4	<u>0.8</u> p<0.01	<u>0.7</u> p<0.01	0.4	0.9	1.0	0.6
wk-4	<u>1.0</u> p<0.01	<u>0.8</u> p<0.01	0.5	<u>0.9</u> p<0.01	<u>1.0</u> p<0.01	0.5	<u>1.0</u> p<0.01	<u>0.9</u> p<0.01	0.5	0.9	1.4	0.5
wk-8	<u>1.0</u> p<0.01	<u>0.9</u> p<0.01	0.6	<u>1.1</u> p=0.02	<u>1.1</u> p<0.01	0.6	<u>1.1</u> p<0.01	<u>1.0</u> p<0.01	0.7	1.0	1.4	0.6
wk-12	<u>1.3</u> p<0.01	<u>1.1</u> p<0.01	0.7	<u>1.3</u> p<0.01	<u>1.2</u> p<0.01	0.7	<u>1.3</u> p<0.01	<u>1.1</u> p<0.01	0.7	<u>1.6</u> p=0.05	<u>1.6</u> p=0.01	0.8

*Percent reduction is given in parentheses. Superiority over vehicle (p<0.05) is shown underlined. Highlighted data show significant difference between the 0.1% and 0.05% gels (p<0.05).

**Blacks and "others" not presented here as the numbers of subjects in each treatment group were small (<6) and no inter-group comparison data showed statistical significance.

Table 2.6.2.2.1.1Bii Scaling (Baseline Score and Reduction from Baseline) of Knee/Elbow Target Lesions

	AGE											
	<45			45-65			>65					
	Taz 0.1% (n=88)	Taz 0.05% (N=102)	Veh (N=97)	Taz 0.1% (n=88)	Taz 0.05% (N=76)	Veh (N=90)	Taz 0.1% (n=33)	Taz 0.05% (N=32)	Veh (N=29)			
wk-0	2.6	2.6	2.6	2.6	2.6	2.6	2.5	2.4	2.8			
wk-1	0.3	0.4	0.3	<u>0.4</u> p=0.01	0.3	0.2	(0.1)***	0.3	0.1			
wk-2	<u>0.7</u> p=0.02	<u>0.7</u> p=0.02	0.4	<u>0.6</u> p<0.01	<u>0.5</u> p=0.04	0.2	0.4	0.5	0.2			
wk-4	<u>1.0</u> p<0.01	<u>0.8</u> p<0.01	0.4	<u>0.7</u> p<0.01	<u>0.6</u> p=0.04	0.4	0.6	0.6	0.7			
wk-8	<u>1.2</u> p<0.01	<u>1.0</u> p<0.01	0.7	<u>1.0</u> p<0.01	0.8	0.5	0.7	0.6	1.0			
wk-12	<u>1.4</u> p<0.01	<u>1.1</u> p<0.01	0.6	<u>1.3</u> p<0.01	<u>1.0</u> p<0.01	0.5	0.8	0.6	0.7			
	SEX						RACE**					
	MALES			FEMALES			WHITES			HISPANICS		
	Taz 0.1% (n=140)	Taz 0.05% (N=135)	Veh (N=142)	Taz 0.1% (n=69)	Taz 0.05% (N=75)	Veh (N=74)	Taz 0.1% (n=187)	Taz 0.05% (N=184)	Veh (N=189)	Taz 0.1% (n=17)	Taz 0.05% (N=21)	Veh (N=16)
wk-0	2.7	2.7	2.6	<u>2.4</u> p=0.04	<u>2.3</u> p<0.01	2.6	2.6	2.5	2.6	2.5	2.7	2.7
wk-1	0.3	0.3	0.2	0.3	0.4	0.2	0.3	0.3	0.2	0.3	0.6	0.4
wk-2	<u>0.6</u> p<0.01	<u>0.5</u> p<0.01	0.3	<u>0.6</u> p=0.03	<u>0.6</u> p=0.02	0.3	<u>0.6</u> p<0.01	<u>0.5</u> p<0.01	0.3	0.5	0.9	0.3
wk-4	<u>0.8</u> p<0.01	0.6	0.5	<u>0.8</u> p<0.01	<u>0.8</u> p<0.01	0.4	<u>0.9</u> p<0.01	<u>0.7</u> p<0.01	0.4	0.6	1.2	0.4
wk-8	<u>1.0</u> p<0.01	0.8	0.6	<u>1.0</u> p=0.03	<u>1.0</u> p=0.02	0.7	<u>1.1</u> p<0.01	<u>0.9</u> p=0.03	0.7	0.8	1.1	0.3
wk-12	<u>1.2</u> p<0.01	<u>1.0</u> p<0.01	0.6	<u>1.3</u> p<0.01	<u>1.1</u> p<0.01	0.6	<u>1.3</u> p<0.01	<u>1.0</u> p=0.04	0.6	1.3	1.3	0.6

*Percent reduction is given in parentheses. Superiority over vehicle (p<0.05) is shown underlined. Highlighted data show significant difference between the 0.1% and 0.05% gels (p<0.05).

**Blacks and "others" not presented here as the numbers of subjects in each treatment group were small (<6) and no inter-group comparison data showed statistical significance.

***Datum in parenthesis indicate increase instead of reduction in score.

Table 2.6.2.2.1.1Ci Erythema (Baseline Score and Reduction from Baseline) of Trunk/Arm/Leg Target Lesions

	AGE											
	<45			45-65			>65					
	Taz 0.1% (n=88)	Taz 0.05% (N=102)	Veh (N=97)	Taz 0.1% (n=88)	Taz 0.05% (N=76)	Veh (N=90)	Taz 0.1% (n=33)	Taz 0.05% (N=32)	Veh (N=29)			
wk-0	2.6	2.6	2.4	2.6	2.5	2.5	2.8	2.5	2.7			
wk-1	0.1	0.2	0.2	0.2	0.3	0.1	0.1	0.2	0.2			
wk-2	0.3	0.4	0.3	0.3	0.4	0.3	0.3	0.4	0.4			
wk-4	0.6	0.5	0.4	0.6	0.4	0.3	0.6	0.6	0.4			
wk-8	<u>1.0</u> p<0.01	0.8	0.6	<u>0.9</u> p=0.02	<u>0.7</u> p=0.04	0.4	0.6	0.5	0.7			
wk-12	<u>1.1</u> p<0.01	<u>1.0</u> p<0.01	0.5	<u>1.1</u> p<0.01	<u>0.8</u> p<0.04	0.5	0.7	0.8	0.8			
	SEX						RACE**					
	MALES			FEMALES			WHITES			HISPANICS		
	Taz 0.1% (n=140)	Taz 0.05% (N=135)	Veh (N=142)	Taz 0.1% (n=69)	Taz 0.05% (N=75)	Veh (N=74)	Taz 0.1% (n=187)	Taz 0.05% (N=184)	Veh (N=189)	Taz 0.1% (n=17)	Taz 0.05% (N=21)	Veh (N=16)
wk-0	<u>2.7</u> p<0.01	2.6	2.5	2.5	2.4	2.6	2.6	2.5	2.5	2.7	2.7	2.8
wk-1	0.1	0.2	0.1	0.2	0.3	0.3	0.1	0.2	0.2	0.2	0.3	0.1
wk-2	0.2	0.3	0.2	0.6	0.5	0.5	0.3	0.4	0.3	0.4	0.2	0.1
wk-4	0.5	0.4	0.3	0.7	0.7	0.5	0.6	0.5	0.4	0.7	0.6	0.1
wk-8	<u>0.8</u> p=0.01	0.6	0.4	<u>1.1</u> p=0.01	0.9	0.7	<u>0.9</u> p<0.01	<u>0.7</u> p=0.04	0.5	1.0	0.7	0.5
wk-12	<u>1.0</u> p<0.01	0.8	0.6	<u>1.2</u> p<0.01	<u>1.1</u> p<0.01	0.5	<u>1.0</u> p<0.01	<u>0.9</u> p<0.01	0.6	<u>1.3</u> p<0.01	0.9	0.5

*Percent reduction is given in parentheses. Superiority over vehicle (p<0.05) is shown underlined. Highlighted data show significant difference between the 0.1% and 0.05% gels (p<0.05). **Blacks and "others" not presented here as the numbers of subjects in each treatment group were small (<6) and no inter-group comparison data showed statistical significance.

Table 2.6.2.2.1.1Cii Erythema (Baseline Score and Reduction from Baseline) of Knee/Elbow Target Lesions

	AGE								
	<45			45-65			>65		
	Taz 0.1% (n=88)	Taz 0.05% (N=102)	Veh (N=97)	Taz 0.1% (n=88)	Taz 0.05% (N=76)	Veh (N=90)	Taz 0.1% (n=33)	Taz 0.05% (N=32)	Veh (N=29)
wk-0	2.4	2.4	2.3	2.3	2.3	2.3	2.5	2.4	2.5
wk-1	0.1	0.1	0.2	0.1	0.1	0.1	0	0.2	0.2
wk-2	0.4	0.2	0.3	0.3	0.3	0.2	0.2	0.4	0.4
wk-4	0.6	0.6	0.5	0.5	0.4	0.2	0.5	0.5	0.4
wk-8	<u>1.0</u> p<0.01	0.9	0.7	<u>0.7</u> p<0.01	<u>0.6</u> p<0.01	0.3	0.5	0.4	0.7
wk-12	<u>1.1</u> p<0.01	<u>1.0</u> p<0.01	0.6	<u>0.8</u> p<0.03	<u>0.8</u> p<0.01	0.4	0.5	0.5	0.6

	SEX						RACE**					
	MALES			FEMALES			WHITES			HISPANICS		
	Taz 0.1% (n=140)	Taz 0.05% (N=135)	Veh (N=142)	Taz 0.1% (n=69)	Taz 0.05% (N=75)	Veh (N=74)	Taz 0.1% (n=187)	Taz 0.05% (N=184)	Veh (N=189)	Taz 0.1% (n=17)	Taz 0.05% (N=21)	Veh (N=16)
wk-0	2.5	2.5	2.3	2.2	2.2	2.4	2.4	2.4	2.3	2.5	2.6	2.6
wk-1	0	0.1	0.1	0.2	0.1	0.3	0.1	0.1	0.2	0.3	0.2	0.3
wk-2	0.2	0.3	0.2	0.5	0.3	0.4	0.3	0.3	0.3	0.6	0.3	0.2
wk-4	0.5	0.4	0.3	0.7	<u>0.7</u> p<0.01	0.4	<u>0.5</u> p<0.02	<u>0.5</u> p<0.02	0.4	0.6	0.6	0.2
wk-8	<u>0.7</u> p<0.01	0.6	0.5	0.9	0.9	0.6	<u>0.8</u> p<0.01	<u>0.8</u> p<0.01	0.5	0.7	0.7	0.5
wk-12	<u>0.8</u> p<0.01	<u>0.7</u> p<0.02	0.5	<u>1.0</u> p<0.01	<u>1.0</u> p<0.01	0.5	<u>0.9</u> p<0.01	<u>0.9</u> p<0.01	0.5	1.2	0.9	0.4

*Percent reduction is given in parentheses. Superiority over vehicle (p<0.05) is shown underlined. Highlighted data show significant difference between the 0.1% and 0.05% gels (p<0.05). Bold italicized datum indicates vehicle significantly superior (p<0.05).

**Blacks and "others" not presented here as the numbers of subjects in each treatment group were small (<6) and no inter-group comparison data showed statistical significance.

Table 2.6.2.2.1.1D "Treatment Success" Subset Analysis of Pooled studies (R168-120 and R168-121)

AGE	<45									45-65								
	Taz 0.1%			Taz 0.05%			Veh			Taz 0.1%			Taz 0.05%			Veh		
	TAL	KE	ALL	TAL	KE	ALL	TAL	KE	ALL	TAL	KE	ALL	TAL	KE	ALL	TAL	KE	ALL
wk-1	11*	9	8	15	9	8	8	8	7	17	14	9	15	11	8	4	5	2
wk-2	24	27	19	24	17	18	11	11	7	24	22	19	23	16	16	8	7	2
wk-4	42	41	38	32	32	34	13	17	16	40	30	30	21	24	18	10	13	8
wk-8	55	57	55	44	46	41	23	23	23	54	44	42	43	39	29	21	15	15
wk-12	68	60	67	53	53	53	32	34	33	64	54	61	56	52	40	28	24	23

	>65								
	Taz 0.1%			Taz 0.05%			Veh		
	TAL	KE	ALL	TAL	KE	ALL	TAL	KE	ALL
wk-1	6	10	3	6	6	0	0	0	0
wk-2	25	22	<u>23</u> p<0.01	23	19	13	4	7	0
wk-4	32	26	20	32	<u>39</u> p<0.03	26	12	12	12
wk-8	33	41	33	40	37	31	19	22	22
wk-12	50	46	33	43	39	41	36	28	28

SEX	MALES									FEMALES								
	Taz 0.1%			Taz 0.05%			Veh			Taz 0.1%			Taz 0.05%			Veh		
	TAL	KE	ALL	TAL	KE	ALL	TAL	KE	ALL	TAL	KE	ALL	TAL	KE	ALL	TAL	KE	ALL
wk-1	<u>11*</u> p=0.01	7	<u>6</u> p=0.04	<u>13</u> p<0.01	10	<u>7</u> p<0.01	2	4	1	17	21	11	16	10	7	10	9	10
wk-2	<u>18</u> p<0.01	18	<u>17</u> p<0.01	<u>19</u> p<0.01	16	<u>13</u> p=0.02	7	9	4	<u>37</u> p<0.01	<u>37</u> p<0.01	<u>26</u> p<0.01	<u>31</u> p<0.01	20	<u>22</u> p=0.01	12	9	3
wk-4	<u>39</u> p<0.01	<u>32</u> p<0.01	<u>30</u> p<0.01	<u>21</u> p=0.02	24	20	10	15	11	<u>41</u> p<0.01	<u>37</u> p<0.01	<u>34</u> p<0.01	<u>39</u> p<0.01	<u>40</u> p<0.01	<u>38</u> p<0.01	15	13	13
wk-8*	<u>45</u> p<0.01	<u>45</u> p<0.01	<u>40</u> p<0.01	<u>33</u> p=0.01	<u>35</u> p=0.02	29	19	20	18	<u>62</u> p<0.01	<u>57</u> p<0.01	<u>59</u> p<0.01	<u>59</u> p<0.01	<u>54</u> p<0.01	<u>45</u> p=0.01	27	17	22
wk-12	<u>59</u> p<0.01	<u>51</u> p<0.01	<u>54</u> p<0.01	<u>45</u> p=0.04	43	40	32	30	28	<u>72</u> p<0.01	<u>63</u> p<0.01	<u>69</u> p<0.01	<u>65</u> p<0.01	<u>64</u> p<0.01	<u>58</u> p<0.01	28	26	28

RACE	WHITES									HISPANICS								
	Taz 0.1%			Taz 0.05%			Veh			Taz 0.1%			Taz 0.05%			Veh		
	TAL	KE	ALL	TAL	KE	ALL	TAL	KE	ALL	TAL	KE	ALL	TAL	KE	ALL	TAL	KE	ALL
wk-1	<u>13*</u> p=0.03	12	7	<u>13</u> p=0.02	9	7	6	6	5	12	12	12	19	14	10	0	0	0
wk-2	<u>24</u> p<0.01	<u>24</u> p<0.01	<u>19</u> p<0.01	<u>22</u> p<0.01	17	<u>17</u> p<0.01	10	10	4	25	<u>31</u> p=0.04	25	<u>35</u> p=0.01	20	15	0	0	0
wk-4	<u>39</u> p<0.01	<u>34</u> p<0.01	<u>32</u> p<0.01	<u>27</u> p<0.01	<u>28</u> p<0.01	<u>26</u> p<0.01	13	15	13	<u>47</u> p<0.01	33	27	<u>47</u> p<0.01	47	<u>41</u> p<0.01	0	7	0
wk-8	<u>50</u> p<0.01	<u>49</u> p<0.01	<u>47</u> p<0.01	<u>44</u> p<0.01	<u>41</u> p<0.01	<u>34</u> p=0.03	22	22	21	58	<u>42</u> p=0.04	45	50	<u>56</u> p<0.01	50	17	0	17
wk-12	<u>63</u> p<0.01	<u>54</u> p<0.01	<u>59</u> p<0.01	<u>52</u> p<0.01	<u>50</u> p<0.01	<u>47</u> p<0.01	33	31	30	<u>70</u> p=0.03	<u>70</u> p=0.03	70	<u>63</u> p=0.05	<u>63</u> p=0.05	56	18	18	18

Figures given are percentages of "treatment success" defined as a global score of "good" or better. Superiority over vehicle (p<0.05) is shown underlined. Highlighted data show significant difference between the 0.1% and 0.05% gels (p<0.05)

2.6.2.2.1.2 Acne

Subset Analyses of Pooled Studies R168-220 and R168-221 are shown in the following Tables, except for "treatment success" data, which have been shown above (see 2.6.2.1).

Table 2.6.2.2.1.2A Total Lesion Counts

	AGE			SEX								
	<45			MALES			FEMALES			FEMALES		
	Taz 0.1% (n=255)	Taz 0.05% (N=253)	Veh (N=264)	Taz 0.1% (n=126)	Taz 0.05% (N=115)	Veh (N=136)	Taz 0.1% (n=129)	Taz 0.05% (N=138)	Veh (N=129)	Taz 0.1% (n=129)	Taz 0.05% (N=138)	Veh (N=129)
wk-0	78	74	77	86	86	85	71	65	68			
wk-4	<u>60 (23)*</u> (p<0.01)	59 (20)	66 (14)	<u>67 (22)</u> (p<0.01)	72 (16)	76 (10)	53 (25)	49 (24)	55 (19)			
wk-8	<u>47 (40)</u> (p<0.01)	<u>48 (36)</u> (p<0.01)	57 (26)	<u>55 (36)</u> (p<0.01)	58 (32)	65 (24)	<u>40 (43)</u> (p<0.01)	<u>39 (40)</u> (p<0.01)	48 (29)			
wk-12	<u>40 (48)</u> (p<0.01)	<u>44 (41)</u> (p<0.01)	53 (30)	<u>46 (46)</u> (p<0.01)	<u>54 (37)</u> (p=0.03)	62 (27)	<u>35 (50)</u> (p<0.01)	<u>36 (45)</u> (p=0.01)	45 (34)			

	RACE											
	WHITES			BLACKS			HISPANICS			OTHER		
	Taz 0.1% (n=189)	Taz 0.05% (N=199)	Veh (N=202)	Taz 0.1% (n=28)	Taz 0.05% (N=26)	Veh (N=28)	Taz 0.1% (n=33)	Taz 0.05% (N=27)	Veh (N=32)	Taz 0.1% (n=5)	Taz 0.05% (N=1)	Veh (N=3)
wk-0	77	74	75	86	72	85	80	77	84	86	98	71
wk-4	<u>59 (24)*</u> (p<0.01)	<u>59 (20)</u> (p=0.02)	66 (12)	66 (24)	59 (18)	65 (24)	65 (19)	60 (23)	66 (21)	49 (44)	81 (17)	67 (6)
wk-8	<u>48 (38)</u> (p<0.01)	<u>48 (35)</u> (p<0.01)	57 (26)	49 (43)	49 (32)	57 (33)	44 (46)	45 (42)	66 (22)	44 (49)	34 (65)	63 (11)
wk-12	<u>40 (47)</u> (p<0.01)	<u>44 (41)</u> (p=0.01)	53 (29)	46 (47)	54 (25)	59 (30)	38 (52)	36 (53)	52 (38)	28 (68)	33 (66)	74 (4)

Percent reduction is given in parentheses. Superiority over vehicle (p<0.05) is shown underlined. Highlighted data show significant difference between the 0.1% and 0.05% gels (p<0.05). Only the <45 age group was analyzed, as all but 2 subjects were >45 years of age.

Table 2.6.2.2.1.2B Inflammatory Lesion Counts

	AGE			SEX								
	<45			MALES			FEMALES					
	Taz 0.1% (n=255)	Taz 0.05% (N=253)	Veh (N=264)	Taz 0.1% (n=126)	Taz 0.05% (N=115)	Veh (N=136)	Taz 0.1% (n=129)	Taz 0.05% (N=138)	Veh (N=129)			
wk-0	22	21	22	24	24	26	19	17	19			
wk-4	18 (17)*	17 (18)	19 (14)	22 (10)	21 (13)	23 (10)	15 (23)	14 (22)	15 (18)			
wk-8	14 (35)	14 (34)	16 (29)	17 (29)	17 (30)	19 (26)	11 (41)	11 (39)	13 (32)			
wk-12	12 (45) (p<0.01)	13 (38) (p=0.05)	16 (29)	14 (41) (p<0.01)	16 (33)	20 (22)	10 (48)	10 (43)	12 (36)			

	RACE											
	WHITES			BLACKS			HISPANICS			OTHER		
	Taz 0.1% (n=189)	Taz 0.05% (N=199)	Veh (N=202)	Taz 0.1% (n=28)	Taz 0.05% (N=26)	Veh (N=28)	Taz 0.1% (n=33)	Taz 0.05% (N=27)	Veh (N=32)	Taz 0.1% (n=5)	Taz 0.05% (N=1)	Veh (N=3)
wk-0	22	21	22	18	15	20	25	24	27	18	30	18
wk-4	18 (18)*	17 (16)	19 (11)	15 (19)	10 (33)	13 (37)	23 (5)	20 (16)	22 (16)	13 (28)	24 (20)	18 (+1)
wk-8	14 (34)	14 (34)	16 (28)	9 (48)	10 (33)	11 (43)	18 (28)	14 (40)	21 (23)	11 (35)	17 (43)	20 (+8)
wk-12	12 (46) (p<0.01)	13 (38) (p=0.03)	17 (26)	9 (48)	11 (25)	10 (48)	15 (38)	13 (46)	19 (31)	11 (38)	5 (83)	21 (+12)

*Percent reduction is given in parentheses. Superiority over vehicle (p<0.05) is shown underlined. Highlighted data show significant difference between the 0.1% and 0.05% gels (p<0.05). Only the <45 age group was analyzed, as all but 2 subjects were >45 years of age.

Table 2.6.2.2.1.2C Noninflammatory Lesion Counts

	AGE			SEX								
	<45			MALES			FEMALES					
	Taz 0.1% (n=255)	Taz 0.05% (N=253)	Veh (N=264)	Taz 0.1% (n=126)	Taz 0.05% (N=115)	Veh (N=136)	Taz 0.1% (n=129)	Taz 0.05% (N=138)	Veh (N=129)			
wk-0	57	54	55	62	62	60	52	47	49			
wk-4	43 (25)* (p<0.01)	43 (20) (p=0.03) (p=0.05)	48 (12)	46 (25) (p<0.01)	52 (16) (p=0.03)	55 (7)	39 (25)	36 (23)	41 (17)			
wk-8	34 (41) (p<0.01)	34 (36) (p<0.01)	41 (25)	38 (38) (p<0.01)	42 (32)	46 (22)	30 (43) (p<0.01)	29 (40) (p<0.01)	35 (28)			
wk-12	29 (49) (p<0.01)	32 (41) (p<0.01) (p=0.03)	38 (31)	33 (47) (p<0.01)	39 (37) (p=0.01)	42 (29)	26 (50) (p<0.01)	26 (45) (p=0.02)	33 (33)			

	RACE											
	WHITES			BLACKS			HISPANICS			OTHER		
	Taz 0.1% (n=189)	Taz 0.05% (N=199)	Veh (N=202)	Taz 0.1% (n=28)	Taz 0.05% (N=26)	Veh (N=28)	Taz 0.1% (n=33)	Taz 0.05% (N=27)	Veh (N=32)	Taz 0.1% (n=5)	Taz 0.05% (N=1)	Veh (N=3)
wk-0	55	54	53	68	57	65	55	54	57	69	68	52
wk-4	41 (25)* (p<0.01)	43 (20) (p=0.02)	48 (10)	51 (24)	49 (13)	52 (19)	42 (24)	40 (25)	45 (21)	37 (46)	57 (16)	49 (7)
wk-8	34 (38) (p<0.01)	35 (35) (p<0.01)	39 (25)	41 (40)	38 (33)	46 (30)	27 (52)	31 (42)	46 (19)	34 (51)	17 (75)	44 (17)
wk-12	29 (47) (p<0.01)	32 (41) (p=0.01) (p=0.03)	36 (31)	37 (46)	42 (25)	49 (25)	24 (57)	24 (56)	35 (39)	17 (75)	28 (59)	54 (3)

*Percent reduction is given in parentheses. Superiority over vehicle (p<0.05) is shown underlined. Highlighted data show significant difference between the 0.1% and 0.05% gels (p<0.05). Only the <45 age group was analyzed, as all but 2 subjects were >45 years of age.

Comment for Section 2.6.2.2.1

Efficacy Data from subset analyses are consistent with information previously gained. Due to smaller sample sizes, it is difficult to demonstrate significance with the data in female or nonwhite subjects.

2.6.2.2.2 Safety
2.6.2.2.2.1 Subset Analysis of Adverse Events of >1% in Incidence & showing Significant Differences in Incidences between Treatment Groups

2.6.2.2.2.1.1 Psoriasis

Table 2.6.2.2.1.1A Adverse Event Analysis in Psoriasis Trials by AGE

	<45				45-65			>65		
	0.1%*	0.05%	Veh	0.1%vs <u>0.05%</u>	0.1%	0.05%	Veh	0.1%	0.05%	Veh
Total pt no	95	106	100		92	80	91	33	33	30
Pts with AE	63 (66)	66 (62)	52 (52)		64 (70)	60 (75)	55 (60)	26 (79)	25 (76)	16 (53)
Body										
Flu Syndrome					0 0.014	2 (3)	6 (7)			
Skin	55 (58) <0.001*	43 (41)	28 (28)	<u>0.017**</u>	51 (55) 0.001	40 (50) 0.008	27 (30)	24 (73) <0.001	18 (55) 0.003	5 (17)
Pruritus	26 (27) 0.006	16 (15)	11 (11)	<u>0.038</u>				11 (33) <0.001	7 (21) 0.011	0
Burning	23 (24) 0.001	13 (12)	7 (7)	<u>0.042</u>	13 (14) 0.016	8 (10)	3 (3)	2 (6)	7 (21) 0.011	0
Erythema	16 (17) <0.001	13 (12) 0.006	2 (2)		14 (15) 0.001	9 (11) 0.006	1 (1)			
Psoriasis worse	13 (14)	5 (5)	9 (9)	<u>0.045</u>				8 (24) 0.028	4 (12)	1 (3)
Skin pain	10 (11) 0.045	9 (9)	3 (3)							
Irritation	10 (11) 0.004	5 (5)	1 (1)		12 (13) 0.002	6 (8)	1 (1)			
Urogenital										
					3 (3) 0.028	7 (9)	11 (12)			
					0 0.029	2 (3)	5 (6)			

*0.1% and 0.05% represent tazarotene 0.1% and 0.05% gels respectively. Percent incidences given in parentheses, with actual patient numbers preceding them.

*p-values for significant differences in incidence rates between vehicle and tazarotene gels are highlighted (p<0.05).

**p-values for significant differences in incidence rates between tazarotene gels are shown double-underlined (p<0.05).

Table 2.6.2.2.2.1.1B Adverse Event Analysis in Psoriasis Trials by SEX

	Males				Females					
	0.1%*	0.05%	Veh	0.1% vs <u>0.05%</u>	0.1%	0.05%	Veh			
Total pt no	148	141	146		72	78	75			
Pts with AE	97 (66) 0.018	94 (67) 0.012	75 (51)		56 (78)	57 (73)	48 (64)			
Skin	81 (55) <0.001*	57 (40) 0.008	37 (25)	<u>0.018</u>	49 (68) <0.001*	44 (56) 0.002	23 (31)			
Pruritus	34 (23) 0.013	27 (19)	17 (12)		26 (36) 0.001	18 (23)	9 (12)			
Burning	23 (16) 0.003	15 (11)	7 (5)		15 (21) 0.002	13 (17) 0.015	3 (4)			
Erythema	21 (14) <0.001*	14 (10) 0.005	3 (2)		11 (15) 0.002	11 (14) 0.005	1 (1)			
Irritation	14 (10) 0.001	8 (6) 0.018	1 (1)		12 (17) 0.001	5 (6)	1 (1)			
Rash	8 (5) 0.007	4 (3)	0							
Desquamation	7 (5) 0.015	4 (3)	0							
Skin Pain					12 (17) 0.001	9 (12) 0.018	1 (1)			
Urogenital										
					3 (4) 0.027	9 (12)	12 (16)			
UTI					0 0.014	5 (6)	7 (9)			

*0.1% and 0.05% represent tazarotene 0.1% and 0.05% gels respectively. Percent incidences given in parentheses, with actual patient numbers preceding them.

*Significant differences in incidence rates between vehicle and tazarotene gels are highlighted (p<0.05).

**Significant differences in incidence rates between tazarotene gels are shown double-underlined (p<0.05).

Table 2.6.2.2.1.1C Adverse Event Analysis in Psoriasis Trials by RACE

	Whites			0.1%vs 0.05%	Blacks			Other*		
	0.1%*	0.05%	Veh		0.1%	0.05%	Veh	0.1%	0.05%	Veh
Total pt no	198	193	194		3	2	6	2	3	5
Pts with AE	137 (69) 0.005	138 (72) 0.001	107 (55)		3 (100)	2 (100)	3 (50)	2 (100)	3 (100)	5 (100)
Body										
Flu Syndrome	1 (0.5) 0.036	5 (3)	7 (4)							
Nervous	1 (0.5)	8 (4)	2 (1)							
Skin				0.019						
Pruritus	116 (59) <0.001	92 (48) <0.001	49 (25)	0.034	3 (100) 0.048	1 (50)	1 (17)			
Burning	51 (26) <0.001	40 (21) 0.013	22 (11)							
Erythema	34 (17) <0.001	26 (14) 0.003	9 (5)							
Irritation	30 (15) <0.001	23 (12) <0.001	4 (2)							
Irritant contact dermatitis	24 (12) <0.001	13 (7) 0.003	2 (1)							
Desquamation	8 (4) 0.037	4 (2)	1 (1)					2 (100) 0.048	0	0
Urogenital										
UTI	6 (3) 0.028	12 (6)	16 (8)							
	0	5 (3)	8 (4)	0.029						

*0.1% and 0.05% represent tazarotene 0.1% and 0.05% gels respectively. Percent incidences given in parentheses, with actual patient numbers preceding them.

*Significant differences in incidence rates between vehicle and tazarotene gels are highlighted (p<0.05).

**Significant differences in incidence rates between tazarotene gels are shown double-underlined (p<0.05).

***Other=other than white, black or Hispanic; there were no significant inter-group comparisons among Hispanic patients.

2.6.2.2.2.1.2 Acne

Age Only one "subset" by age was analyzed. As there were no patients over 45, all patients were included in this "subset".

Comment The Applicant could have analyzed age subsets within those <45 of age.

Table 2.6.2.2.2.1.2A Adverse Event Analysis in Acne Trials by SEX

	Males			0.1%vs 0.05%	Females		
	0.1%*	0.05%	Veh		0.1%	0.05%	Veh
Total pt no	149	139	149		150	158	148
Pts with AE	90 (60) <0.001	67 (48) 0.008	49 (33)	0.044	87 (58) 0.011	94 (60) 0.004	63 (43)
Respiratory							
Rhinitis					2 (1)	0 0.012	6 (4)
Skin							
Desquamation	69 (46) <0.001	50 (36) <0.001	17 (11)		74 (49) <0.001	79 (50) <0.001	30 (20)
Burning	41 (28) <0.001	22 (16) <0.001	2 (1)	0.022	43 (29) <0.001	39 (25) <0.001	4 (3)
Erythema	33 (22) <0.001	19 (14) <0.001	2 (1)		42 (28) <0.001	38 (24) <0.001	6 (4)
Dry skin	27 (18) <0.001	8 (6) 0.003	0	0.002	28 (19) <0.001	25 (16) <0.001	0
Pruritus	26 (17) <0.001	26 (19) <0.001	6 (4)		33 (22) <0.001	34 (22) <0.001	9 (6)
					24 (16) 0.030	21 (13)	11 (7)

*0.1% and 0.05% represent tazarotene 0.1% and 0.05% gels respectively. Percent incidences given in parentheses, with actual patient numbers preceding them.

*p-values for significant differences in incidence rates between vehicle and tazarotene gels are highlighted (p<0.05).

**p-values for significant differences in incidence rates between tazarotene gels are shown double-underlined (p<0.05).

Table 2.6.2.2.1.2B Adverse Event Analysis in Acne Trials by RACE*

	Whites			<u>0.1%vs 0.05%</u>	Blacks		
	0.1%**	0.05%	Veh		0.1%	0.05%	Veh
Total pt no	226	229	228		32	35	33
Pts with AE	143 (63) <u><0.001</u>	133 (58) <u><0.001</u>	93 (41)		18 (56)	19 (54)	11 (33)
Respiratory							
Rhinitis	6 (3)	2 (1) 0.012	11 (5)				
Skin	117 (52) <u><0.001</u>	104 (45) <u><0.001</u>	38 (17)		16 (50) 0.001	18 (51) 0.001	4 (12)
Desquamation	68 (30) <u><0.001</u>	50 (22) <u><0.001</u>	4 (2)		10 (31) <u><0.001</u>	7 (20) 0.011	0
Burning	62 (27) <u><0.001</u>	48 (21) <u><0.001</u>	7 (3)				
Dry skin	50 (22) <u><0.001</u>	53 (23) <u><0.001</u>	11 (5)				
Erythema	47 (21) <u><0.001</u>	29 (13) <u><0.001</u>	0		5 (16) 0.024	2 (6)	0
Irritation	14 (6) 0.002	7 (3)	2 (1)	<u>0.024</u>			
Skin stinging	8 (4) 0.020	9 (4) 0.020	1 (0.4)				
Irritation	5 (2) 0.030	1 (0.4)	0				

*Only data of whites and blacks are shown, as there were no significant inter-group comparisons among Hispanic or "other" patients.

**0.1% and 0.05% represent tazarotene 0.1% and 0.05% gels respectively. Percent incidences given in parentheses, with actual patient numbers preceding them.

*p-values for significant differences in incidence rates between vehicle and tazarotene gels are highlighted (p<0.05).

**p-values for significant differences in incidence rates between tazarotene gels are shown double-underlined (p<0.05).

Comments for Section 2.6.2.2.1

1. Most of the adverse events showing significant differences between tazarotene and vehicle are related to local irritation.
2. Significant differences between the 0.1% and the 0.05% gels in adverse event incidence were seen in males, whites and the <45 age group for either indication. The lack of statistical significance in the other subsets might be due to the smaller sample sizes. It is noted, however, within each subset, tazarotene 0.1% gel usually was associated with more and a greater variety of adverse events showing significant difference in incidence vs vehicle than tazarotene 0.05% gel.
3. In psoriasis trials, the 45-65 and <45 age groups were comparable in size and yet statistical significance was still not reached in the 45-65 group.

2.6.2.2.2 Subset Analysis for Laboratory Findings.

Changes in laboratory values for the various demographic subsets showed no consistent clinically significant drug-related effects in either indication.

2.6.3 Statistical Significance of Adverse Event Data in Clinical Studies and Termination of Study due to Adverse Events.

2.6.3.1 Adverse Event Comparisons between Tazarotene Gels and Controls

Comparisons between tazarotene and controls are presented here. Comparisons between tazarotene 0.1% and 0.05% gels are discussed in Section 2.7.

Table 2.6.3.1 Significant Differences in Adverse Event Incidence between Vehicle or Active Control vs 0.1% or 0.05% Tazarotene Gels in Phase 3 Clinical Trials of Tazarotene

	<u>Tazarotene 0.1% vs Control</u>			<u>Tazarotene 0.05% vs Control</u>		
	<u>Taz</u>	<u>Control</u>	<u>P</u>	<u>Taz</u>	<u>Control</u>	<u>P</u>
<u>R168-120 (Vehicle as Control)</u>						
<u>Treatment Period</u>						
Body infection	1/108	3/108	0.037			
Respiratory infection	4/108	12/108	0.037			
Dermatologic (total)	53/108	25/108	<0.001	41/108	25/108	0.026
pruritus	28/108	10/108	0.002			
burning	21/108	6/108	<0.003	17/108	6/108	0.026
irritation	10/108	0/108	<0.002			
erythema	9/108	1/108	<0.019			
Urogenital (total)	3/108	13/108	<0.017			
urinary tract infection	0/108	7/108	<0.014			
<u>R168-121 (Vehicle as Control)</u>						
Total patients with AE	83/112	60/113	0.001	81/111	60/113	0.002
Dermatologic (total)	77/112	35/113	<0.001	60/111	35/113	0.001
pruritus	32/112	16/113	0.009			
erythema	23/112	3/113	<0.001	18/111	3/113	<0.001
burning	17/112	4/113	0.003			
irritation	16/112	2/113	<0.001	10/111	2/113	0.018
skin pain	15/112	5/113	0.020			
rash	9/112	2/113	0.034			
desquamation	7/112	0/113	0.007			
<u>R168-125 (Lidex as Control)</u>						
<u>Treatment Period</u>						
Total patients with AE	97/116	65/115	<0.001	95/117	65/115	<0.001
Body Flu syndrome	0/116	8/115	0.003	1/117	8/115	0.018
Musculoskeletal (total)	3/116	10/115	0.050			
Dermatologic (total)	90/116	25/115	<0.001	80/117	25/115	0.001
pruritus	40/116	4/115	<0.001	24/117	4/115	0.001
erythema	35/116	1/115	<0.001	26/117	1/115	0.001
burning	27/116	8/115	0.001	25/117	8/115	0.002
desquamation	13/116	0/115	<0.001	7/117	0/115	0.014
irritant contact dermatitis	11/116	2/115	0.019	11/117	2/115	0.019
skin pain	11/116	1/115	0.005			
irritation	10/116	1/115	0.010			
<u>Posttreatment Period</u>						
Dermatologic (total)	4/79	21/107	0.004	6/89	21/107	0.012
psoriasis worsened	2/79	14/107	0.015	4/89	14/107	0.047
<u>R168-126 (Lidex as Control)</u>						
<u>Treatment Period</u>						
Total patients with AE	78/110	54/110	0.001	79/111	54/110	0.001
Dermatologic (total)	69/110	19/110	<0.001	63/111	19/110	<0.001
burning	28/110	5/110	<0.001	24/111	5/110	<0.001
pruritus	27/110	4/110	<0.001	26/111	4/110	<0.001
irritation	27/110	0/110	<0.001	21/111	0/110	<0.001
erythema	16/110	1/110	<0.001	18/111	1/110	<0.001
psoriasis worsened				17/111	5/110	0.012
rash	10/110	0/110	0.002	9/111	0/110	0.003
desquamation	8/110	0/110	0.007	6/111	0/110	0.029

	<u>Tazarotene 0.1% vs Control</u>			<u>Tazarotene 0.05% vs Control</u>		
	<u>Taz</u>	<u>Control</u>	<u>P</u>	<u>Taz</u>	<u>Control</u>	<u>P</u>
R168-126 (Lidex as Control)						
<u>Treatment Period (cont'd)</u>						
skin pain	8/110	0/110	0.007	6/111	0/110	0.029
irritant contact dermatitis	7/110	0/110	0.014			
R168-145 (Dovonex as Control)						
<u>Treatment Period</u>						
Total patients with AE	69/122	30/122	<0.001	64/122	30/122	<0.001
Dermatologic (total)	53/122	14/122	<0.001	55/122	14/122	<0.001
erythema	16/122	4/122	0.009	13/122	4/122	0.041
burning	15/122	1/122	<0.001	13/122	1/122	0.001
irritation	15/122	1/122	<0.001	13/122	1/122	0.001
pruritus				18/122	7/122	0.033
skin pain	12/122	1/122	0.003			
R168-220 (Vehicle as Control)						
Total patients with AE	71/150	36/148	<0.001	54/148	36/148	0.031
Body headache				0/148	7/148	0.015
Dermatologic (total)	52/150	12/148	<0.001	39/148	12/148	<0.001
burning	30/150	2/148	<0.001	18/148	2/148	<0.001
desquamation	28/150	2/148	<0.001	18/148	2/148	<0.001
dry skin	23/150	5/148	0.001	10/148	5/148	0.003
erythema	22/150	0/148	<0.001	8/148	0/148	0.007
pruritus	18/150	5/148	0.008			
R168-221 (Vehicle as Control)						
Total patients with AE	106/149	76/149	0.001	107/149	76/149	<0.001
Respiratory rhinitis				1/149	9/149	0.019
Dermatologic (total)	91/149	35/149	<0.001	90/149	35/149	<0.001
desquamation	56/149	4/149	<0.001	43/149	4/149	<0.001
burning	45/149	6/149	<0.001	39/149	6/149	<0.001
dry skin	36/149	10/149	<0.001	40/149	10/149	<0.001
erythema	33/149	0/149	<0.001	25/149	0/149	<0.001
stinging				9/149	1/149	<0.001

Comment The significant differences in incidence are mostly related to local irritation effect of tazarotene.

2.6.3.2 Terminations due to Adverse Events

2.6.3.2.1 Psoriasis Trials

Table 2.6.3.2.1 Termination due to Adverse Events in Psoriasis Trials*

<u>Study</u>	<u>Tazarotene 0.1%</u>		<u>Tazarotene 0.05%</u>		<u>Vehicle</u>
	<u>Rate</u>	<u>p (vs vehicle)</u>	<u>Rate</u>	<u>p (vs vehicle)</u>	
R168-120	13/108 (12%)	0.017	11/108 (10%)	0.050	3/108 (3%)
R168-121	21/112 (19%)	0.019	10/111 (9%)	N/S	9/113 (8%)
R168-125	21/116 (18%)	<0.001	14/117 (12%)	0.003	2/115 (2%)
R168-126	25/110 (23%)	<0.001	21/111 (19%)	<0.001	2/110 (2%)
R168-145	24/123 (20%)	0.001	22/122 (18%)	0.001	5/124 (4%)
R168-128	30/122 (25%)	N/A	29/121 (24%)	N/A	(No vehicle)

*Treatment period only

2.6.3.2.2 Acne Trials

Table 2.6.3.2.2 Termination due to Adverse Events in Acne Trials*

Study	Tazarotene 0.1%		Tazarotene 0.05%		Vehicle
	Rate	p (vs vehicle)	Rate	p (vs vehicle)	
R168-220	13/150 (9%)	0.006	12/148 (8%)	0.011	2/148 (1%)
R168-221	9/149 (6%)	N/S	10/149 (7%)	0.035	2/149 (1%)

2.6.4 Between group comparisons for efficacy data in R168-145-8606

In the original submission, between group comparisons for efficacy data in this active-controlled study (with Dovonex 0.005% ointment) were not adequately presented. The Applicant was requested to submit this analysis.

Table 2.6.4 Efficacy Variables in R168-145-8606

I. Clinical Signs	Baseline	Reduction in Scores						
	wk-0	wk-1	wk-4	wk-8	wk-12	wk-16	wk-20	wk-24
Plaque elevation								
Taz** 0.1%	2.5***	0.6	1.2	1.4	1.3	1.3	1.3	1.1
Taz 0.05%	2.5	0.6	0.9*	1.0	1.2	1.4	1.2	1.1
Dovonex	2.4	0.7	1.3	1.6	1.7	1.3	1.2	1.2
Scaling								
Taz 0.1%	2.5***	0.7	1.1	1.2	1.3	1.2	1.1	0.9
Taz 0.05%	2.4	0.4	0.7	0.8	1.0	1.2	1.1	0.9
Dovonex	2.3	1.1	1.4	1.6	1.7	1.2	1.1	1.0
Erythema								
Taz 0.1%	2.3	0.1	0.4	0.7	0.8	0.9	0.9	0.8
Taz 0.05%	2.2	0.1	0.2	0.4	0.7	0.8	0.8	0.5
Dovonex	2.2	0.2	0.6	0.8	1.1	1.0	0.9	0.8
Sum of scores								
Taz 0.1%	7.3***	1.5	2.7	3.2	3.4	3.3	3.3	2.9
Taz 0.05%	7.0	1.1	1.7	2.2	2.9	3.3	3.0	2.4
Dovonex	6.9	2.0	3.2	3.9	4.4	3.5	3.2	3.0
II. Overall Assessments								
Wk-0		wk-1	wk-4	wk-8	wk-12	wk-16	wk-20	wk-24
Overall Clinical Severity Scores								
Baseline		Reduction in Scores						
Taz* 0.1%	2.4	0.3	0.6	0.8	0.8	0.9	0.9	0.6
Taz 0.05%	2.3	0.2	0.3	0.5	0.6	0.8	0.7	0.5
Dovonex	2.2	0.4	0.7	0.9	1.1	0.8	0.7	0.7
Global "Treatment Success" (% pts)								
Taz 0.1%		7	26	33	41	33	26	27
Taz 0.05%		3	16	29	44	45	35	24
Dovonex		9	35	52	63	47	36	3

was for evaluation of success using stricter criteria.

2.6.5.1 Psoriasis

In three psoriasis trials (R168-120-8606, R168-121-8606 and R168-145-8606), there were no significant differences over control (vehicle or active) shown by tazarotene 0.1% or tazarotene 0.05% gels when analyzed in terms of a global of "cleared". Data other than these 3 analyses are shown below:

R168-120 Globals of "Excellent" or Better

Drug*	Trunk/Arm/Leg					Knee/Elbow					Global for All Lesions				
	wk-1	wk-2	wk-4	wk-8	wk-12	wk-1	wk-2	wk-4	wk-8	wk-12	wk-1	wk-2	wk-4	wk-8	wk-12
Taz 0.1%	1	<u>15</u> p<0.01	<u>21</u> p<0.01	<u>30</u> p<0.01	<u>43</u> p<0.01	0	<u>15</u> p<0.01	<u>14</u> p=0.02	<u>24</u> p<0.01	<u>41</u> p<0.01	0	<u>11</u> p<0.01	<u>15</u> p<0.01	<u>23</u> p<0.01	<u>38</u> p<0.01
Taz 0.05%	6	<u>12</u> p=0.02	<u>17</u> p<0.01	<u>26</u> p<0.01	<u>39</u> p<0.01	4	<u>12</u> p<0.01	<u>15</u> p<0.01	<u>20</u> p=0.03	<u>35</u> p<0.01	2	<u>9</u> p=0.01	<u>13</u> p<0.01	<u>18</u> p<0.01	<u>28</u> p<0.01
Vehicle	2	3	6	10	17	1	2	5	9	15	1	1	2	4	12

*Taz refers to tazarotene. Significant differences between tazarotene and vehicle data are underlined (p<0.05 for between group comparisons only significant when overall among group p-values were 0.05 or less). Data shown are percentages of patients.

R168-121 Globals of "Excellent" or Better

Drug*	Trunk/Arm/Leg					Knee/Elbow					Global for All Lesions				
	wk-1	wk-2	wk-4	wk-8	wk-12	wk-1	wk-2	wk-4	wk-8	wk-12	wk-1	wk-2	wk-4	wk-8	wk-12
Taz 0.1%	2	2	13	<u>26</u> p<0.01	<u>32</u> p<0.01	0	2	<u>11</u> p<0.01	<u>19</u> p<0.01	<u>26</u> p<0.01	0	0	8	16	25
Taz 0.05%	1	6	9	15	<u>27</u> p<0.01	0	3	<u>11</u> p<0.01	<u>16</u> p<0.01	<u>27</u> p<0.01	0	3	8	10	18
Vehicle	0	1	5	9	9	0	0	2	4	7	0	0	3	9	10

*Taz refers to tazarotene. Significant differences between tazarotene and vehicle data are underlined (p<0.05 for between group comparisons only significant when overall among group p-values were 0.05 or less). Data shown are percentages of patients.

R168-125 Globals of "Excellent" or Better

Drug*	Trunk/Arm/Leg					Knee/Elbow					Global for All Lesions				
	wk-1	wk-2	wk-4	wk-8	wk-12	wk-1	wk-2	wk-4	wk-8	wk-12	wk-1	wk-2	wk-4	wk-8	wk-12
Taz 0.1%	8	<u>15</u> p<0.01	<u>24</u> p=0.03	41	40	9	17	28	40	43	7	<u>12</u> p=0.03	21	35	31
Taz 0.05%	3	<u>13</u> p<0.01	<u>22</u> p<0.01	30	<u>29</u> p<0.01	5	<u>11</u> p<0.01	21	27	32	3	<u>9</u> p<0.01	17	<u>22</u> p<0.01	28
Lidex	9	28	38	46	50	9	22	32	39	44	9	21	28	38	42

Globals of "Cleared"

Drug*	Trunk/Arm/Leg					Knee/Elbow					Global for All Lesions				
	wk-1	wk-2	wk-4	wk-8	wk-12	wk-1	wk-2	wk-4	wk-8	wk-12	wk-1	wk-2	wk-4	wk-8	wk-12
Taz 0.1%	0	1	2	10	<u>11</u> p=0.03	0	0	1	5	8	0	0	0	2	3
Taz 0.05%	0	0	0	4	<u>8</u> p<0.01	0	0	2	2	7	0	0	0	0	1
Lidex	1	3	5	12	24	0	2	5	8	4	0	0	1	5	7

*Taz refers to Tazarotene. Significant differences between tazarotene and Lidex ointment data are underlined (p<0.05 for between group comparisons only significant when overall among group p-values were 0.05 or less). Data shown are percentages of patients.

126 Globals of "Excellent" or Better

Drug*	Trunk/Arm/Leg					Knee/Elbow					Global for All Lesions				
	wk-1	wk-2	wk-4	wk-8	wk-12	wk-1	wk-2	wk-4	wk-8	wk-12	wk-1	wk-2	wk-4	wk-8	wk-12
Taz 0.1%	2	<u>7</u>	<u>17</u>	<u>23</u>	<u>36</u>	1	<u>2</u>	<u>10</u>	<u>18</u>	25	1	1	<u>7</u>	<u>15</u>	26
		p<0.01	p<0.01	p<0.01	p<0.01		p<0.01	p<0.01	p<0.01				p<0.01	p<0.01	
Taz 0.05%	2	<u>5</u>	<u>11</u>	<u>16</u>	<u>21</u>	2	<u>3</u>	<u>7</u>	<u>14</u>	<u>19</u>	1	2	<u>5</u>	<u>9</u>	14
		p<0.01	p<0.01	p<0.01	p<0.01		p<0.01	p<0.01	p<0.01	p<0.05			p<0.01	p<0.01	
Lidex	7	49	36	50	55	4	14	24	34	33	2	5	18	30	29

Globals of "Cleared"

Drug*	Trunk/Arm/Leg					Knee/Elbow					Global for All Lesions				
	wk-1	wk-2	wk-4	wk-8	wk-12	wk-1	wk-2	wk-4	wk-8	wk-12	wk-1	wk-2	wk-4	wk-8	wk-12
Taz 0.1%	0	2	<u>1</u>	<u>3</u>	8	0	0	1	<u>0</u>	3	0	0	0	0	2
			p<0.01	p<0.02					p<0.02						
Taz 0.05%	0	1	2	<u>3</u>	<u>3</u>	0	0	0	<u>0</u>	<u>0</u>	0	0	0	0	0
				p<0.01	p<0.01				p<0.02	p<0.04					
Lidex	0	2	10	14	18	0	1	5	7	7	0	0	1	3	2

*Taz refers to Tazarotene. Significant differences between tazarotene and Lidex ointment data are underlined (p<0.05 for between group comparisons only significant when overall among group p-values were 0.05 or less). Data shown are percentages of patients.

R168-145 Globals of "Excellent" or Better

Drug*	Lesion A				Lesion B				Global for All Lesions			
	wk-1	wk-4	wk-8	wk-12	wk-1	wk-4	wk-8	wk-12	wk-1	wk-4	wk-8	wk-12
Taz 0.1%	1	7	<u>12</u>	<u>26</u>	1	9	<u>15</u>	<u>31</u>	0	4	<u>13</u>	<u>26</u>
			p<0.01	p<0.01			p<0.01	p<0.02			p<0.01	p<0.02
Taz 0.05%	0	5	<u>22</u>	<u>30</u>	0	8	<u>22</u>	<u>26</u>	0	6	22	<u>26</u>
			p<0.04	p<0.01			p<0.01	p<0.01				p<0.02
Dovonex	0	11	40	54	0	13	44	52	0	9	33	47

*Taz refers to Tazarotene. Significant differences between tazarotene and Dovonex data are underlined (p<0.05 for between group comparisons only significant when overall among group p-values were 0.05 or less). Data shown are percentages of patients.

128 Globals of "Excellent" or Better

Drug*	Mth-0.5	Mth-1	Mth-2	Mth-3	Mth-4	Mth-5	Mth-6	Mth-7	Mth-8	Mth-9	Mth-10	Mth-11	Mth-12
Taz 0.1%	0	5	11	16	25	25	31	32	31	37	31	32	36
Taz 0.05%	1	4	6	11	21	25	24	23	24	25	28	26	23

Globals of "Cleared"

Drug*	Mth-0.5	Mth-1	Mth-2	Mth-3	Mth-4	Mth-5	Mth-6	Mth-7	Mth-8	Mth-9	Mth-10	Mth-11	Mth-12
Taz 0.1%	0	0	0	0	0	0	0	4	3	5	3	2	2
Taz 0.05%	0	1	1	1	1	1	1	1	2	1	1	3	1

*Taz refers to Tazarotene. No significant differences between the two gels in terms of either cutoff. Data shown are percentages of patients.

2.6.5.2 Acne

R168-220 and R168-221 Globals of "Excellent" or Better

Drug*	R168-220			R168-221		
	wk-4	wk-8	wk-12	wk-4	wk-8	wk-12
Taz 0.1%	8	<u>24</u>	<u>38</u>	1	<u>6</u>	18
		p<0.01	p<0.01		p<0.01	
Taz 0.05%	4	14	26	0	<u>7</u>	11
		p<0.05	p<0.02		p<0.02	
Vehicle	7	10	20	2	1	10

*Taz refers to Tazarotene. Significant differences between tazarotene and vehicle data are underlined (p<0.05 for between group comparisons only significant when overall among group p-values were 0.05 or less). Significant differences between tazarotene gels are highlighted. Data shown are percentages of patients.

Globals of "Cleared"

Only one subject in tazarotene 0.1% group in R168-220 achieved "cleared" at any timepoint. No valid comparisons were made.

ent As expected, stricter criteria for success resulted in lower success rates but the data corresponded in general to those using $\geq 50\%$ improvement as cutoff. However, these stricter criteria also resulted in no significant differences between the two tazarotene concentrations in achieving success except in one acne trial.

2.6.6 Dropouts and of Differences in Drug Exposure among Treatment Groups.

Table 2.6.6A Study Completion and Mean Duration of Drug Exposure in Tazarotene Trials

	Patients Completing Treatment			Patients Dropping out of Treatment		
	Taz 0.1%	Taz 0.05%	Veh/Active	Taz 0.1%	Taz 0.05%	Veh/Active
R168-120	n=81; 12 wks	n=80; 12 wks	n=81; 12 wks	n=27; 6 wks	n=28; 6 wks	n=27; 7 wks
R168-121	<u>n=69</u> ; 12 wks (p=0.009)	n=86; 12 wks	n=88; 12 wks	n=43; <u>4 wks</u> (p=0.040)	n=25; <u>3 wks</u> (p=0.015)	n=25; 6 wks
R168-125	<u>n=79</u> ; 12 wks (p<0.001)	<u>n=89</u> ; 12 wks (p<0.001)	n=107; 12 wks	n=37; 4 wks	n=28; 6 wks	n=8; 8 wks
R168-126	<u>n=74</u> ; 12 wks (p=0.001)	<u>n=74</u> ; 12 wks (p<0.001)	n=95; 12 wks	n=36; <u>4 wks</u> (p=0.026)	n=37; 6 wks	n=15; 7 wks
R168-145	<u>n=70</u> ; 12 wks (p=0.004)	<u>n=63</u> ; 12 wks (p<0.001)	n=92; 12 wks	n=52; 7 wks	n=59; 7 wks	n=30; 8 wks
R168-220	n=111; 12 wks	<u>n=103</u> ; 12 wks (p=0.044)	n=119; 12 wks	n=39; 4 wks	n=45; 4 wks	n=29; 3 wks
R168-221	n=120; 12 wks	n=118; 12 wks	n=115; 12 wks	n=29; 4 wks	n=31; <u>3 wks</u> (p=0.003)	n=34; 6 wks

*Highlighted data show significant difference in completion rates between tazarotene 0.1% and 0.05% gels (p=0.013); and double-underlined data show significant differences between vehicle or active control with tazarotene gels (p<0.05%). Single-underlined data show significant difference in drug exposure of dropouts between vehicle or active control with tazarotene (p<0.05).

Two studies showed significant dropout rates in tazarotene-treated groups vs vehicle/active control group in the posttreatment period: R168-120 and R168-125:

Table 2.6.6B Significant Dropout Rates in Tazarotene Trials: Posttreatment Period

	Patients Completing Follow-up			Patients Dropping out of Follow-up		
	Taz 0.1%	Taz 0.05%	Veh/Active	Taz 0.1%	Taz 0.05%	Veh/Active
R168-120	<u>35/80 (44%)</u>	<u>37/80 (46%)</u>	23/81 (28%)	<u>45/80 (56%)</u>	<u>43/80 (54%)</u>	58/81 (72%)
R168-125	<u>57/79 (72%)</u>	57/89 (64%)	59/107 (55%)	<u>22/79 (28%)</u> (p=0.022)	32/89 (36%)	48/107 (45%)

Underlined data show significant difference in drug exposure of dropouts between vehicle or active control with tazarotene (p<0.05).

Comment Very significant dropout rates in tazarotene-treated patient groups vs control-treated groups are observed in the active-controlled trials (R168-125-8606, R168-126-8606 and R168-145-8606). This may be due to greater irritation effect or lesser effectiveness of tazarotene vs the active control (Lidex or Dovonex). Duration of drug exposure among tazarotene dropouts was also generally shorter except in one vehicle-controlled acne trial (R168-220-8606).

2.6.7 Bias among Treatment Groups in Posttreatment Periods of Psoriasis Studies.

Owing to the disproportionate sample sizes of treatment groups in the posttreatment periods of psoriasis trials, the Applicant was requested to reanalyze the data to see whether there was bias introduced in this type of postrandomization selection

of subjects. The following information has been furnished for subjects entered into the posttreatment phase of those trials that had such a phase:

<u>AGE</u>	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.01%</u>	<u>Vehicle/Active Control</u>
R168-120	n=80, mean±S.D.=46±14	n=80, mean±S.D.=46±15	n=81, mean±S.D.=47±16
R168-125	n=79, mean±S.D.=45±14	n=89, mean±S.D.=46±15	n=106, mean±S.D.=46±16
R168-126	n=74, mean±S.D.=50±13	n=74, mean±S.D.=49±15	n=95, mean±S.D.=52±15
R168-145	n=52, mean±S.D.=40±15*	n=47, mean±S.D.=45±15	n=66, mean±S.D.=50±15

*Tazarotene 0.1% group significantly different from control group (Dovonex), p=0.001.

<u>SEX (% female)</u>	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.01%</u>	<u>Vehicle/Active Control</u>
R168-120	33	38	32
R168-125	39	46	39
R168-126	32	38	34
R168-145	40	30	33

<u>RACE (% nonwhite)</u>	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.01%</u>	<u>Vehicle/Active Control</u>
R168-120	9	18	9
R168-125	8	6	9
R168-126	3	8	5
R168-145	2	2	3

% Body

<u>Involvement</u>	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.01%</u>	<u>Vehicle/Active Control</u>
R168-120	n=80, mean=7, range=1-20	n=80, mean=7, range=1-20	n=81, mean=6, range=1-20
R168-125	n=79, mean=9, range=1-20	n=89, mean=7, range=1-20	n=106, mean=8, range=1-20
R168-126	n=74, mean=7, range=1-20	n=74, mean=6, range=1-20	n=95, mean=6, range=1-18

Duration (mths)

<u>of Psoriasis</u>	<u>Tazarotene 0.1%</u>	<u>Tazarotene 0.01%</u>	<u>Vehicle/Active Control</u>
R168-120	n=80, mean=16, range=0.4-58	n=80, mean=18, range=2-50	n=81, mean=21, range=0.8-56
R168-125	n=79, mean=14, range=0.8-40	n=89, mean=17, range=1-50	n=106, mean=16, range=0.4-50
R168-126	n=74, mean=20, range=2-60	n=74, mean=20, range=0.5-54	n=95, mean=18, range=0.3-44

Comments

1. Only age comparison showed a significant difference in one study (between tazarotene 0.1% group and Dovonex group in R168-145-8606). Other comparisons of baseline data did not show statistical significance.

2. These are baseline demographic data before randomization. The possibility of postrandomization selection bias after treatment is of serious concern. The Applicant has not addressed this issue. The comparability of "baselines" of the posttreatment period between treatment groups cannot be easily established.

2.7. Distinguishability of the two Concentrations of Tazarotene Gel

The Applicant provided the following information for the differences between tazarotene 0.1% and 0.05% gels:

2.7.1 Psoriasis

Efficacy and safety data from psoriasis trials are summarized in the following Table:

Table 2.7.1 Distinguishability of Tazarotene 0.1% and 0.5% Gels in Psoriasis Trials

Study	Earlier Superiority over Veh* (Taz 0.1% vs Taz 0.05%)	Taz 0.1% superior to Taz 0.05%				Safety (Taz 0.1% vs Taz 0.05%)
		Scores for Response to Treatment	Treatment Success	Reduction in Clinical Scores	Overall Severity Grade	
R168-120	S _{TAL} wk1 vs wk2 E _{TAL} wk8 vs wk12 E _{KE} wk4 vs wk12 TS _{KE} wk2 vs wk4	TAL wk2 ALL wk2	TAL wk4 KE wk2 All wk2		All wk2	Tr-rel AE 42% vs 32% ¹ AE Termination 12% vs 10%
R168-121				S _{KE} wk8		Tr-rel AE 65% vs 46% ² AE Termination 19% vs 9%
R168-125	NOT APPLICABLE	TAL wk1 wk2 All wk1	KE wk2	PE _{TAL} wk1 PE _{KE} wk1 S _{TAL} wk1 wk2 SS _{TAL} wk1 wk2	TAL wk1 wk2 All wk2	Tr-rel AE 68% vs 56% ³ AE Termination 18% vs 12%
R168-126	NOT APPLICABLE	TAL wk8 KE wk8 All wk8	TAL wk8 wk12 KE wk8 All wk8	PE _{TAL} wk8 S _{TAL} wk1 wk8 wk12 SS _{TAL} wk1 wk8 SS _{KE} wk8	TAL wk1 wk8 All wk8	Tr-rel AE 61% vs 54% ⁴ AE Termination 23% vs 19%
R168-145	NOT APPLICABLE			PE wk4 wk8 S _(UK) wk4 S _(Germany) wk1 SS wk1 wk2 wk4 wk8		Tr-rel AE 47% vs 40% ⁵ AE Termination 20% vs 18%
R168-128	NOT APPLICABLE	mth1	4 mths earlier	PE mth1 S mth4		Tr-rel AE 75% vs 71% ⁶ AE Termination 12% vs 10%

¹ predominantly mild to moderate local irritation consisting of pruritus, burning or erythema. Nearly all terminations due to AE were related to local irritation.

² predominantly mild to moderate local irritation including pruritus, burning or erythema. Nearly all terminations due to AE were related to local irritation.

³ predominantly mild to moderate local irritation. Nearly all terminations due to AE were related to local irritation.

⁴ predominantly mild to moderate local irritation. Nearly all terminations due to AE were related to local irritation.

⁵ predominantly erythema, burning, irritation, pain and pruritus. Terminations for AE mainly due to local irritation.

⁶ predominantly local events as shown below -

	Pruritus	Burning	Erythema	Irritation
Tazarotene 0.1%	36%	25%	24%	20%
Tazarotene 0.05%	31%	19%	17%	20%

*Veh=vehicle, Taz=tazarotene, Tr-rel=treatment-related, AE=adverse event(s), TS="treatment success", PE=plaque elevation, S=scaling, E=erythema, SS=sum of clinical scores TAL=trunk/arm/leg lesions, KE=knee/elbow lesions

In addition, the following differences (tazarotene 0.1% vs 0.05% gel) for "Treatment Success" were noted by the Applicant:

R168-120-8606 Times to "Treatment Success" for KE and all lesions significantly different between the two gels.

R168-121-8606 "Treatment success" rates numerically superior in general with the 1% gel, e.g. week-12: TAL

R168-128-8606 55% vs 47%, KE 49% vs 43% and all lesions 52 vs 42%.
 "Treatment success" rates at month-12 were 53% vs 42% (tazarotene 0.1% vs 0.05% gel).
 Maximum "Success" rates were 56% (mth-7) vs 45% (mth-9).
 Throughout the 12-month study, the 0.1% gel consistently showing greater "treatment success" rates.

Throughout the 12-month in the long-term R168-128-8606 study, tazarotene 0.1% gel also consistently showed greater reduction for plaque elevation and scaling and gave a lower rate of lack of efficacy as reason for termination (11%, vs 17% with the 0.05% gel).

Conclusions drawn by Applicant for Differences between Tazarotene Gels in Psoriasis:

1. Tazarotene 0.1% gel - More effective
2. Tazarotene 0.1% gel - Earlier response to treatment
3. Tazarotene 0.1% gel - Incidence and severity of local irritation higher

2.7.2 Acne

Efficacy and safety data from acne trials are summarized in the following Table:

Table 2.7.2 Distinguishability of Tazarotene 0.1% and 0.5% Gels in Acne Trials

Studies R168-220-7997* R168-221-8606	0.1% gel vs veh**	0.05% gel vs veh**	0.1% gel vs 0.05% gel	
			Significant differences	Not significant differences at Endpoint (wk12)
I noninflammatory lesion counts	weeks 4, 8, 12	weeks 8, 12	wk4 (55% vs 45%) wk12(55% vs 45%) wk12(43% vs 38%)	
I inflammatory lesion counts	week 12 weeks 8, 12			42% vs 39% 47% vs 37%
I total lesion counts	weeks 4, 8, 12	weeks 8, 12	wk12(52% vs 44%)	45% vs 39%
Global	weeks 4, 8, 12 weeks 4, 8, 12	week 12 weeks 8, 12	Week 12 week 12	
Treatment success	weeks 8, 12 weeks 4, 8, 12	week 8	wk12(68% vs 51%)	48% vs 40%
Safety	NOT APPLICABLE	NOT APPLICABLE	Tr-rel AE 35% vs 25% ¹ Tr-rel AE both 58% ²	

*Data from R168-220-7997 are shaded.

**For vehicle comparisons, only significant differences given.

¹ predominantly mild to moderate local adverse events such as burning, desquamation or dryness.

² predominantly mild to moderate local irritation: burning, dryness, desquamation (38% vs 29% given by tazarotene 0.1% vs 0.05% gel) and erythema (22% vs 17% given by tazarotene 0.1% vs 0.05% gel): both desquamation and erythema more severe in 0.1% group.

Conclusions by Applicant for Differences between Tazarotene Gels in Acne: same as those for psoriasis trials.

2.7.3 Significant Differences in Adverse Event Incidence between the 0.1% and 0.05% Gels in Phase 3 Clinical Trials of Tazarotene and Termination due to Adverse Events

The Applicant provided an analysis of the incidence of adverse events in phase 3 trials and terminations due to adverse events. This is summarized in the following two Tables.

Table 2.7.3A Significant Differences in Adverse Event Incidence between Tazarotene 0.1% and 0.05% Gels in Phase 3 Clinical Trials of Tazarotene

	Tazarotene 0.1%	Tazarotene 0.05%	p-value
All Trials*			
Dermatologic (total)	432/690 (63%)	377/690 (55%)	0.003
skin pain	69/432 (10%)	38/432 (6%)	0.002
All Acne Trials*			
None with significant difference			
All Psoriasis Trials*			
Dermatologic (total)	575/989 (58%)	506/987 (51%)	0.002
erythema	183/989 (19%)	137/987 (14%)	0.006
desquamation	128/989 (13%)	85/987 (9%)	0.002
irritation	116/989 (12%)	82/987 (8%)	0.013
skin pain	74/989 (8%)	39/987 (4%)	0.001
R168-120			
None with significant difference			
R168-121			
Nervous System	0/112	5/111 (5%)	0.029
Dermatologic (total)	77/112 (69%)	60/111 (54%)	0.028
R168-125			
Dermatologic			
pruritus	40/116 (35%)	24/117 (21%)	0.019
skin pain	11/116 (10%)	3/117 (3%)	0.030
R168-126			
None with significant difference			
R168-145			
<u>Treatment period</u>			
Body (total)	10/122 (8%)	2/122 (2%)	0.034
Flu syndrome	6/122 (5%)	0/122	0.029
<u>Posttreatment period</u>			
Body (total)	0/70	5/63 (8%)	0.022
R168-128			
Dermatologic			
"Allergic" contact dermatitis	6/122 (5%)	0/121	0.029
dry skin	4/122 (3%)	13/122 (11%)	0.025
R168-220			
Dermatologic			
erythema	22/150 (15%)	8/148 (5%)	0.011
R168-221			
None with significant difference			

* For data combined across trials, p-values of 0.0158 or less are considered significant based on modified Bonferroni adjustment.

Table 2.7.3B Termination due to Adverse Events*

Study	Tazarotene 0.1%		Tazarotene 0.05%		Vehicle
	Rate	p (vs vehicle)	Rate	p (vs vehicle)	
R168-120	13/108 (12%)	0.017	11/108 (10%)	0.050	3/108 (3%)
R168-121	21/112 (19%)	0.019	10/111 (9%)	N/S	9/113 (8%)
R168-125	21/116 (18%)	<0.001	14/117 (12%)	0.003	2/115 (2%)
R168-126	25/110 (23%)	<0.001	21/111 (19%)	<0.001	2/110 (2%)
R168-145	24/123 (20%)	0.001	22/122 (18%)	0.001	5/124 (4%)
R168-128	30/122 (25%)	N/A	29/121 (24%)	N/A	(No vehicle)
R168-220	13/150 (9%)	0.006	12/148 (8%)	0.011	2/148 (1%)
R168-221	9/149 (6%)	N/S	10/149 (7%)	0.035	2/149 (1%)

*Treatment period only. No statistically significant difference between the 0.1% and 0.05% gels in these incidences.

Comment These data are consistent with a more irritating effect of the tazarotene 0.1% gel vs the 0.05% gel. As well, only differences in local adverse events could properly be attributed to differences between the two gels in the comparisons for safety shown in Sections 2.7.1 and 2.7.2.

2.7.4 Overall Conclusions by Applicant on Differences between Tazarotene 0.1% and 0.05% Gels

1. a. Efficacy - tazarotene 0.1% gel more effective consistently (0.05% gel never significantly more effective than 0.1%) and earlier onset of action
- b. Safety - tazarotene 0.1% gel more local irritation
2. Needs of physicians and patients for two concentrations
3. Precedent of multiple concentrations of other topical agents
4. FDA agreement of 12/10/92 - the Applicant stated that there was an agreement with the Agency that Allergan not be required to show statistically significant differences between the two concentrations for efficacy in order to gain approval.

Comment

1. Psoriasis. Reanalysis of the submitted data confirms the previous review opinion that despite the existence of some differences in both efficacy and safety between the two concentrations of tazarotene, these differences are in general minor. However, it does appear that the 0.1% gel is associated with an earlier onset of effect and this extra benefit may be valuable. With more prolonged use as shown in the 12-month study (R168-128-8606), the two preparations seem to be indistinguishable.

2. Acne. Tazarotene 0.05% gel is clearly less effective than the 0.1% gel and is not significantly superior to vehicle in "treatment success" in one of the two pivotal studies. It should not be approvable for this indication.

3. Conclusions

Materials in the current submissions have confirmed the conclusions drawn previously except that tazarotene 0.1% gel may have merit in earlier achievement of a therapeutic response in psoriasis. Other conclusions as arrived at in the original review are summarized below:

3.1. 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.

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) 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.

iii) 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.

3.2 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 previously 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.

4. Labeling Review

The Applicant has indicated in the latest submissions that no changes are being proposed in the labeling previously submitted. The draft version of August 10, 1995 has been reviewed and suggested changes are shown as follows: additions being highlighted (██████████) and deletions with strikeout (x————x).

10 Pages (35-44)

Deleted

Comments

The label should be modified as suggested above. Specifically, the following major changes are suggested:

1. Tazarotene 0.05% gel is indicated only for the treatment of stable plaque psoriasis.
2. A CLINICAL STUDY section giving informative efficacy data on the pivotal trials is to be added.
3. Adverse events Tables separating the adverse event incidences for the two indications are to be created.