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# 21-184/S-001

# Medical Review(s)

# CLINICAL REVIEW of NDA 21-184 Efficacy Supplement SE1-001

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| APPLICATION NUMBER: | | 21-184<br>Efficacy Supplement SE1-001<br>Division Tracking Number 017267 |
| SUBMISSION/REVIEW DATES | | |
| | SUBMISSION DATE: | 12/8/00 |
| | CDER STAMP DATE: | 12/11/00 |
| | ASSIGNED DATE: | 12/21/00 |
| | FILING DATE: | 2/9/01 |
| | REVIEW COMPLETION DATE: | 10/3/01 |
| APPLICANT | NAME: | Allergan, Inc. |
| | ADDRESS: | 2525 Dupont Drive<br>P.O. Box 19534<br>Irvine, CA 92623-9534 |
| NOMENCLATURE | | |
| | TRADE (GENERIC) NAME: | TAZORAC® (tazarotene) Cream 0.1% |
| | CHEMICAL NAME: | Ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)-ethynyl] nicotinate |
| MOLECULAR FORMULA: | | $C_{21}H_{21}NO_2S$ |
| MOLECULAR WEIGHT: | | 351.46 |
| DOSAGE FORM: | | Cream |
| ADMINISTRATION ROUTE: | | Topical |
| REVIEWER | NAME: | Hon-Sum Ko |
| | TITLE: | Medical Officer |
| | DIVISION: | Dermatologic and Dental Drug Products |
| DOCUMENTS REVIEWED: | | NDA 21-184 SE1-001 volumes 1, 21-31<br>Electronic Case Report Forms<br>Electronic Case Report Tabulations<br>NDA 21-184 SE1-001 120-day Safety Update |

# CLINICAL REVIEW of NDA 21-184 Efficacy Supplement SE1-001

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# CLINICAL REVIEW of NDA 21-184 Efficacy Supplement SE1-001

## Executive Summary Section

### I. Recommendations

#### A. Recommendation on Approvability

- This Efficacy Supplement is approvable, pending labeling changes.
- Labeling should be changed to that as recommended in Appendix II.

#### B. Recommendation on Phase 4 Studies and/or Risk Management Steps

- The labeling of tazarotene gels should be updated to include relevant information contained in the current submission.
- The Applicant should address the applicability of the data from the PK studies in this submission to males.
- A partial waiver of pediatric study requirements for neonates, infants and children may be granted.

### II. Summary of Clinical Findings

#### A. Brief Overview of Clinical Program

Tazarotene creams was developed initially for the indication of plaque psoriasis. This indication has been approved on September 29, 2000. The indication of acne vulgaris was studied upon IND submission ( ) on March 30, 1999. The Applicant also pursued studies for manifestations of photodamage for this product, and reports on the completed studies for photodamage have recently been submitted in June, 2001.

The clinical program for tazarotene cream 0.1% in the treatment of acne vulgaris consists of two adequate and well-controlled phase 3 studies to demonstrate safety and efficacy. It is supplemented by a pharmacokinetic study on tazarotene cream 0.1% in female acne patients, and a "facial tolerance study" in healthy volunteers. Additional studies were performed with tazarotene gel in female acne patients, and the PK data from (a) a phase 2 dose-ranging study of tazarotene cream in photodamage, and (b) a drug-drug interaction study between oral tazarotene and Ortho-Novum 1/35 were used to support this application. The studies on tazarotene gel 0.1% were conducted to determine whether there was comparable bioavailability between topical retinoids in the treatment of acne.

The program can be summarized in the following Table:

| Study | Nature of Study | Utility |
|---|---|---|
| Tazarotene Cream 0.1% | | |
| 190168-029C | Phase 3 vehicle-controlled safety and efficacy trial | Substantial evidence; TDM* |
| 190168-031C | Phase 3 vehicle-controlled safety and efficacy trial | Substantial evidence |
| 190168-035C (female only) | PK profile for face only and exaggerated application | Systemic bioavailability |
| 190168-041C (healthy subjects) | Facial tolerance | Safety data |
| 190168-025C | Phase 2 dose-ranging study on photodamage | Safety data; TDM |
| Tazarotene Gel 0.1% | | |
| 190168-022 (female only) | PK profile for face-only application | Systemic bioavailability of gel formulation |
| 190168-030 (female only) | PK profile for exaggerated application (15% BSA**) | |
| Tazarotene oral formulation | | |
| 190168-018P | Drug-drug interaction with Ortho-Novum 1/35 | Safety in women of child-bearing potential |

*TDM = therapeutic drug monitoring; ** BSA = body surface area.

Reports for dermal safety studies (irritancy, sensitization, phototoxicity and photoallergenicity) had previously been submitted to the original NDA when the indication for plaque psoriasis was sought.

## B. Efficacy

In two almost identical* adequate and well controlled studies, the Applicant studied patients aged 12 or older with acne vulgaris, who applied tazarotene cream 0.1% to facial acne, once a day, for 12 weeks. The primary efficacy parameters included the percent reduction in lesion counts: total, non-inflammatory, and inflammatory, as well as a dichotomized static global evaluation, with no acne or minimal acne at week 12 considered as success. The results are shown in the following Table:

**Efficacy Results after Twelve Weeks of Treatment in Two Controlled Clinical Trials for Acne**

| | TAZORAC® 0.1% Cream | | Vehicle Cream | |
|---|---|---|---|---|
| | 190168-029C N=218 | 190168-031C N=206 | 190168-029C N=218 | 190168-031C N=205 |
| **Median Percent Reduction in** | | | | |
| • Noninflammatory lesions | 46%* | 41%* | 27% | 21% |
| • Inflammatory lesions | 41%* | 44%* | 27% | 25% |
| • Total lesions | 44%* | 42%* | 24% | 21% |
| **Percent of Subjects with No Acne or Minimal Acne** | 18%* | 20%* | 11% | 6% |

*Denotes statistically significant difference compared with vehicle.

These trials independently demonstrate substantial evidence of effectiveness in reducing acne lesion counts (total, non-inflammatory, and inflammatory) by tazarotene cream 0.1%, and its superiority over vehicle in the proportion of patients showing no acne or minimal acne at the end of treatment for 12 weeks.

## C. Safety

Studies on tazarotene cream 0.1% in the treatment of acne have included an adequate database in the phase 3 trials for exposure to the drug product.

*The only difference between the adequate and well-controlled phase 3 trials was the collection of PK data in one, 190168-029C but not the other, 190168-031C.

**Patient Exposure in Phase 3 Studies (190168-029C and -031C)**

| | Exposure Duration (days) | | Patient Numbers (%) | | | | |
|---|---|---|---|---|---|---|---|
| | Mean/Median | Range | Week 0 | Week 2 | Week 4 | Week 8 | Week 12 |
| Taz 0.1% Cream | 75.64/84.00 | | 424 (100%) | 395 (93.2%) | 392 (92.4%) | 363 (85.6%) | 306 (72.1%) |
| Vehicle | 78.00/84.00 | | 423 (100%) | 397 (93.8%) | 395 (93.4%) | 374 (88.4%) | 318 (75.2%) |

There is no major difference between the Applicant's assessment of data from that in this review in terms of clinical findings of adverse effects. The adverse effects of tazarotene cream 0.1% observed in clinical trials are primarily local, including desquamation, dryness, erythema and burning sensation. These are frequently seen and expected adverse events with topical retinoid treatment

**Number (%) of Patients with Treatment-Related Adverse Events Reported by > 2% of Patients in either Treatment Group During the Phase 3 Acne Studies**

| BODY SYSTEM preferred term | Tazarotene 0.1% N = 424 | Vehicle N = 423 | p-value [a] |
|---|---|---|---|
| **SKIN AND APPENDAGES** | | | |
| desquamation | 124 (29.2%) | 11 ( 2.6%) | < 0.001 |
| dry skin | 114 (26.9%) | 10 ( 2.4%) | < 0.001 |
| skin burning sensation | 59 (13.9%) | 3 ( 0.7%) | < 0.001 |
| erythema | 87 (20.5%) | 8 ( 1.9%) | < 0.001 |
| pruritus | 19 ( 4.5%) | 6 ( 1.4%) | 0.009 |
| irritation skin | 17 ( 4.0%) | 1 ( 0.2%) | < 0.001 |

a p-value based on the Pearson's chi-square test.

A pharmacokinetic study, 190168-035C, demonstrates that with both face-only or exaggerated application over 15% body surface area (BSA), the maximal systemic bioavailability occurs on Day 15 of treatment (both Cmax and AUC).

Comparative systemic bioavailability data in relation to teratogenicity seen in animals demonstrate that, especially under exaggerated use conditions, systemic exposure to tazarotenic acid may reach levels comparable to teratogenesis levels in animals.

## D. Dosing

The recommended dose for tazarotene cream in the treatment of acne is that as used in the phase 3 clinical trials, and the following is appropriate for labeling:

> "Cleanse the face gently. After the skin is dry, apply a thin layer ($2mg/cm^2$) of TAZORAC® Cream 0.1% once per day, in the evening, to the skin areas where acne lesions appear. Use enough to cover the entire affected area. TAZORAC® Cream 0.1% was investigated for up to 12 weeks during clinical trials for acne."

## E. Special Populations

Analyses for both safety and efficacy have been performed in terms of gender, age, and race for the phase 3 clinical trials. Since acne is rare before puberty and in the elderly, the age subsets analyzed were ≤17, 18-29, and ≥30 (patients actually enrolled in phase 3 trials being aged 12-52). There are no major differences between demographic

subsets in the treatment effects regarding (a) effectiveness or (b) reported adverse events.

The Applicant conducted one PK study with tazarotene cream 0.1% (190168-035C) and two with tazarotene gel 0.1% (190168-022 and 190168-030) to determine systemic bioavailability in female acne patients only. The applicability of these data to males is assumed albeit not definitively. In previous PK studies during the development program for the psoriasis indication, there were only 4 male patients with reliable data. Thus, no meaningful conclusion on gender effect can be drawn at this point.

A study on drug-drug interaction with Ortho-Novum 1/35 upon oral dosing of tazarotene (1.1 mg/day) in female subjects for two cycles did not appear to show interaction or systemic retinoid adverse effects. Therapeutic drug monitoring in clinical trials show that the systemic exposure to tazarotenic acid, the active metabolite of tazarotene, in acne treatment with tazarotene cream 0.1% is two logs below that attained in the oral tazarotene study. In view of the low systemic bioavailability arising from topical use, there has been no analysis of data for special populations with organ impairment (hepatic, cardiac, or renal).

# CLINICAL REVIEW of NDA 21-184 Efficacy Supplement SE1-001

## Clinical Review Section

### I. Introduction and Background

#### A. Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

- Trade Name: TAZORAC®
- Drug Class: retinoid
- Proposed Indication (for current supplement): topical treatment of patients with acne vulgaris [the product being already approved for the indication plaque psoriasis]
- Dose and Regimen: The DOSAGE AND ADMINISTRATION section of the draft label has added the following to the approved language*:

  Cleanse the face gently. After the skin is dry, apply a thin layer of TAZORAC® Cream 0.1% once per day to the skin where acne lesions appear. Use enough to cover the entire affected area.
- Proposed Indicated Age Group: The Pediatric Use subsection in the PRECAUTIONS section of the draft label:

  The safety and efficacy of tazarotene cream have not been established ..... in patients with acne under the age of 12 years.

#### B. State of Armamentarium for Indication

The mainstay of treatment for acne vulgaris includes:

- Systemic Antibiotics: antibiotics that are concentrated in sebum, such as tetracycline, minocycline, and erythromycin for inflammatory acne
- Oral Retinoids: currently only isotretinoin
- Topical Antibiotics: such as topical erythromycin solutions
- Topical Retinoids and Other Agents: including tretinoin (retinoic acid; Retin-A), tazarotene, adapalene, benzoyl peroxide gel, and azelaic acid
- Avoidance of oil-based cosmetics and hair spray that aggravate obstruction of partially occluded sebaceous follicles: may alleviate the comedonal component of acne
- Patient Education

#### C. Important Milestones in Product Development

Upon the marketing approval of tazarotene (TAZORAC®) gels 0.05% and 0.1% in the treatment of plaque psoriasis and 0.1% for acne vulgaris in 1997, the Applicant started to develop tazarotene creams 0.05% and 0.1% for the treatment of plaque psoriasis. The following are milestones for the development of tazarotene cream 0.1% in the treatment of acne vulgaris:

11/23/98 Pre-IND/EOP2 meeting for tazarotene cream 0.1% in the treatment of acne

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* Current approved language in the DOSAGE AND ADMINISTRATION Section on dosing regimen for plaque psoriasis:
It is recommended that treatment start with TAZORAC® 0.05% Cream, with strength increased to 0.1% if tolerated and medically indicated. Apply TAZORAC® cream once per day, in the evening, to psoriatic lesions, using enough (2mg/cm$^2$) to cover only the lesion with a thin film. If a bath or shower is taken prior to application, the skin should be dry before applying the cream.

| | |
|---|---|
| 3/30/99 | Submission of IND { } (tazarotene cream 0.1%) with phase 3 protocols for acne studies |
| 10/13/99 | Submission of phase 3 clinical protocol amendments with static global endpoint |
| 1/12/00 | Submission of PK protocol (190168-035C) |
| 9/11/00 | Pre-NDA meeting |
| 9/29/00 | NDA 21-184 approved for tazarotene creams in the treatment of plaque psoriasis |
| 12/8/00 | Submission of Efficacy Supplement (SE1/001) for acne indication to NDA 21-184 |

**D. Other Relevant Information**

Tazarotene cream 0.1% has not been approved for the treatment of acne in the U.S. or any other country. As indicated in the above section, tazarotene creams 0.05% and 0.1% have been approved in 2000 for the treatment of plaque psoriasis.

**E. Important Issues with Pharmacologically Related Agents**

The use of retinoids in the treatment of acne vulgaris poses the important issue of balancing the physical and psychological benefits to the patient against the potential adverse effects, including teratogenicity. Topical retinoids yielding lower systemic exposure might have better benefit/risk ratios by reducing potential systemic toxicity. Currently the available topical retinoids for acne include tretinoin, adapalene and tazarotene in various dosage forms.

Among these three topical retinoids, tazarotene gel 0.1% is the only product of Pregnancy Category X, while the other two are of Category C. At the time of approval of tazarotene gels, there were no formal studies in acne patients to fully document systemic exposure with PK profiles. Systemic exposure data for tazarotene gels were primarily obtained in psoriasis patients and normal individuals. In the current submission, the Applicant is presenting systemic exposure data for tazarotene cream 0.1% in the treatment of acne, and trying to make a point that tazarotene cream 0.1% should be of Category C for the acne indication.

**II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews**

- Chemistry CMC information has been cross-referenced to data in the original submission of NDA 21-184.
- Pharm/Tox The Pharm/Tox Reviewer is of the opinion that new studies (in dogs, rats and rabbits) submitted have not changed the previous conclusions on the safety of tazarotene cream. She recommends retaining the Pregnancy Category as X, and provides other labeling changes to the Applicant's draft label.
- Microbiology Not applicable
- Biopharm The Biopharm Reviewer deems the human clinical pharmacology and biopharmaceutics data acceptable for approval of this supplement, pending labeling changes.

- Statistics The Biometrics Reviewer has concluded that the data "support the sponsor's claim of efficacy of tazarotene cream 0.1% in the treatment of acne vulgaris. Each study has demonstrated that (i) tazarotene can reduce significantly more lesions (inflammatory, non-inflammatory, and total lesions) over a 12 week period than its vehicle, and (ii) a significantly higher percentage of tazarotene patients than vehicle patients are classified as having no acne or minimal acne at Week 12. Thus the sponsor has met the Division's usual requirements for establishing efficacy in acne trials."

## III. Human Pharmacokinetics and Pharmacodynamics

### A. Pharmacokinetics

Basic PK properties of tazarotene, including half-life, metabolism and excretion, linearity, potential for PK interactions, effects of impaired renal and hepatic function, and effects of size, body weight, gender, and race have previously been provided for in the NDA for tazarotene gels (20-600) and in the original application of NDA 21-184 (for plaque psoriasis treatment).

PK data are reviewed by Biopharm. See Section IV for the list of PK studies presented in this supplement. For tazarotene cream 0.1%, there is one formal PK study in acne treatment (190168-035C), and one therapeutic drug monitoring study from each type of clinical trial involving patients with: a) acne (190168-29C) and b) photodamage (190168-025C). In addition, there are two studies on the pharmacokinetics of tazarotene gel 0.1% in female acne patients:

- Comparison of the PK profiles of tazarotene gel 0.1%, tretinoin cream 0.1% & adapalene gel 0.1% (190168-022), and
- PK profile of tazarotene gel 0.1% applied to 15% body surface area (BSA) (190168-030).

For more detailed discussion of the PK data, see Sections VII.C.3.c and VII.C.5.a.

### B. Pharmacodynamics

- See Section VI and VII for efficacy and safety information respectively.
- There are no PD studies specifically addressing tazarotene's mechanism of action in acne. The Applicant's proposed mechanism of action is theoretical.
- Dose selection is based on information from tazarotene gels. The 0.1% gel is the only concentration documented to be successful in the treatment of acne, and approved for this indication. There have been no formal dose-ranging studies.
- The Applicant cross-references to the dermal safety studies in the original application of NDA 21-184. Briefly, tazarotene cream 0.1%, like other topical retinoids, is a mild to moderate dermal irritant, but is by itself of low sensitization, phototoxic or photoallergenic potential. This supplement also presents the protocol of a single-center study of tazarotene cream 0.1% on facial tolerance (190168-041C). An abbreviated study report has been submitted subsequently to IND[ ]

- In this submission, the Applicant presents a drug-drug interaction study between oral tazarotene and Ortho-Novum® 1/35 oral contraceptive in healthy female volunteers to support the lack of interaction between tazarotene and oral contraceptive medication (190168-018P). For further discussion, see Section VII.

## IV. Description of Clinical Data and Sources

### A. Overall Data

- The clinical database supporting safety and efficacy consists primarily of two adequate and well-controlled, multi-center, vehicle-controlled trials comparing tazarotene cream 0.1% to vehicle in the treatment of mild to moderate acne vulgaris. Both studies were conducted by the Applicant.
- An overview of the supportive PK and PD studies is given in Section III.
- The Table of clinical studies is shown below in Section IV.B.

### B. Tables Listing the Clinical Trials

1. PHASE 3 CONTROLLED CLINICAL TRIALS OF TAZAROTENE CREAM IN ACNE

**Phase 3 Controlled Clinical Trials of Tazarotene Cream in Acne**

| Study Number | Study Design | Treatment Dose | Duration | No. of Patients | Mean Age (Range) | Sex | Race |
|---|---|---|---|---|---|---|---|
| 190168-029C | multicenter, double-blind, randomized, vehicle-controlled | tazarotene cream 0.1% or vehicle cream a thin layer applied to the entire face | once daily 12 weeks treatment phase | 436: tazarotene =218 vehicle =218 | 19.9 years (12 to 51) | M: 52% F: 48% | C: 67% B: 9% A: 2% H: 21% O: <1% |
| 190168-031C | multicenter, double-blind, randomized, vehicle-controlled | tazarotene cream 0.1% or vehicle cream a thin layer applied to the entire face | once daily 12 weeks | 411: tazarotene =206 vehicle =205 | 18.6 years (11 to 52) | M: 50% F: 50% | C: 78% B: 10% A: 2% H: 9% O: <1% |

M = male, F = female; C = Caucasian, B = black, A = Asian, H = Hispanic, O = other

## 2. HUMAN PHARMACOKINETIC STUDY OF TAZAROTENE CREAM IN ACNE

**Human Pharmacokinetic Study of Tazarotene Cream in Acne**

| Study Number | Study Design | Treatment Dose | Duration | No. of Patients | Mean Age (Range) | Sex | Race |
|---|---|---|---|---|---|---|---|
| 190168-035C | open-label, single-center, parallel-group, stratified by BSA involvement & severity | a) tazarotene cream 0.1% to face only (300 mg/face)<br>b) tazarotene cream 0.1% to 15% body surface area (2 mg/cm$^2$; PLUS 300 mg to face) | 28 applications over 33-day period | a) face only - 9 females (moderate acne)<br>b) 15% BSA - 10 females (severe acne) | a) 26.9 (16 to 44)<br>b) 25.5 (17-34) | M: 0% F:100% | a) Face only C: 33% B: 67%<br>b) 15% BSA C: 50% B: 20% H: 30% |

M = male, F = female; C = Caucasian, B = black, A = Asian, H = Hispanic, O = other, BSA = body surface area involvement

## 3. HUMAN PHARMACOKINETIC STUDIES OF TAZAROTENE GEL IN ACNE

**Human Pharmacokinetic Studies of Tazarotene Gel in Acne**

| Study Number | Study Design | Treatment Dose | Duration | No. of Patients | Mean Age (Range) | Sex | Race |
|---|---|---|---|---|---|---|---|
| 190168-022 | open-label, single center, randomized, parallel-group | tazarotene gel 0.1% qd or 0.1% qod or tretinoin 0.1% cream qd or adapalene 0.1% gel qd: a thin layer applied to the entire face | 28 days | 42 female patients with mild to moderate acne | 24.4 years (16 to 43) | M: 0% F: 100% | C: 54.8% B: 21.4% A: 4.8% H: 16.7% O: 2.4% |
| 190168-030 | Open-label, single center, double-blind | Tazarotene gel 0.1% applied to 15% body surface area (2 mg/ cm$^2$) | 41 applications over 46-day period | 19 female patients with moderate to severe acne | 26.9 years (16 to 43) | M: 0% F: 100% | C: 53% B: 37% A: 0% H: 11% |

M = male, F = female; C = Caucasian, B = black, A = Asian, H = Hispanic, O = other

## 4. PHASE 2 DOSE-RANGING STUDY OF TAZAROTENE CREAM IN PHOTODAMAGE

**Phase 2 Dose-Ranging Study of Tazarotene Cream in Photodamage**

| Study Number | Study Design | Treatment Dose | Duration | No. of Patients | Mean Age (Range) | Sex | Race |
|---|---|---|---|---|---|---|---|
| 190168-025C | multicenter, investigator-masked, randomized, vehicle-controlled, parallel-comparison | tazarotene cream 0.01% or 0.025% or 0.05% or 0.1% or vehicle or tretinoin emollient cream 0.05%: a thin layer applied to entire face | 24 weeks 2 weeks post-treatment follow-up | 349 subjects with photodamaged facial skin | 54.1 years (27 to 87) | M: 10% F: 90% | C: 95% B: <1% A: <1% H: 3% O: <1% |

M = male, F = female; C = Caucasian, B = black, A = Asian, H = Hispanic, O = other

## 5. PHARMACOKINETIC AND PHARMACODYNAMIC STUDY OF THE DRUG-DRUG INTERACTION OF ORAL TAZAROTENE AND ORAL CONTRACEPTIVES

**Pharmacokinetic and Pharmacodynamic Study of the Drug-Drug Interaction of Oral Tazarotene and Oral Contraceptives**

| Study Number | Study Design | Treatment Dose | Duration | No. of Patients | Mean Age (Range) | Sex | Race |
|---|---|---|---|---|---|---|---|
| 190168-018P | single center, open label, randomized | Oral tazarotene 1.1 mg norethindrone: 1 mg and ethinyl estradiol: 0.35 mg | 64 days | 29 healthy female subjects | 33.1 ± 8.70 years (20-55) | F: 100% M: 0% | C: 86.2% B: 3.5% A; 3.5% H: 6.9% O: 0% |

M = male, F = female; C = Caucasian, B = black, A = Asian, H = Hispanic, O = other

## 6. FACIAL TOLERANCE STUDY COMPARING TAZAROTENE CREAM, ADAPALENE GEL AND TRETINOIN GEL IN THE TREATMENT OF ACNE

The Applicant lists an additional study on facial tolerance of tazarotene 0.1% cream in 48 healthy subjects:

> 190168-041C. Single center, investigator-masked, randomized, balanced incomplete block study comparing tazarotene cream 0.1% vs adapalene gel 0.1%, and tretinoin gel microsphere 0.1%, once daily for 4 weeks (with 2 of the 3 medications per patient and applied to contralateral sides of face)

No data were presented in the original submission of this supplement. An abbreviated study report has been submitted subsequently to IND[illegible]

### C. Postmarketing Experience

- Tazarotene creams 0.05% and 0.1% were approved at the end of September, 2000 for the treatment of plaque psoriasis. Postmarketing experience on tazarotene

creams has been limited and not included in the submission of this supplement, and by the time of the 120-day safety update.

- Tazarotene gels have been approved for 4 years for psoriasis (0.05% and 0.1% formulations) and acne (0.1% formulation) treatment. In the Integrated Summary of Safety (p. 21-136), the Applicant summarizes information through 8/31/00 with 515 postmarketing adverse events in 217 patients, 11 of which were believed to be related to tazarotene gel use: burning 1, desquamation 2, dry skin 1, erythema 3, irritation 1, misuse 1, puritus 1, and skin discoloration 1. There were no reports requiring prescription drug treatment, injury, disability, in-patient hospitalization, or death.

### D. Literature Review

- Although there is a fair amount of information on tazarotene gels in the literature, published references on tazarotene cream in the treatment of acne are lacking at this time.

## V. Clinical Review Methods

### A. How the Review was Conducted

This review was conducted in concert with the Pharm/Tox, Biopharm and Biometrics Reviewers. The focus has been on the two adequate and well-controlled phase 3 trials (190168-029C and -031C). The PK data have been primarily under the review of Biopharm. Input from the Pharm/Tox and Biopharm Reviewers has been considered in the review of the proposed Pregnancy Category in the draft label.

### B. Overview of Materials Consulted In Review

Besides material submitted under NDA 21-184 (paper and electronic) this review also includes -
a) verifying material submitted to IND[ ]
b) checking minutes of pre-IND/EOP2 and pre-NDA meetings, and
c) reviewing the labels and supporting data on topical tretinoin and adapalene products.

### C. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI audit of 3 selected sites from the phase 3 trials to evaluate data quality and integrity has been completed without adverse findings. The Investigators audited were: Dr. Lloyd G. Wickboldt (and Dr. Thomas C. Marbury) of Study 190168-29C, and Drs. Ann W. Lucky and Keith H. Loven, both of Study 190168-031C. As there were 15 sites for Study 190168-029C and 14 sites for 190168-31C, and no single site had more than 12% of subjects in either study, it is not expected that data quality from any one site would affect the overall data significantly. In addition, treatment-by-investigator interaction has been sought in the Biometrics review.

Financial disclosure information shows that _____ had received funds from the Applicant. Both Investigators participated in Study _____ and together had 55 out of the total _____ patients in that study (12.6%). However, significant treatment-by-Investigator interaction has not been noted.

### D. Were Trials Conducted in Accordance with Accepted Ethical Standards?

The protocols for the studies in this submission all contain statements of compliance with GCP regulations and guidelines, e.g. ICH guideline on GCP, and protection of human subjects, including compliance with -

- Informed consent regulations (21 CFR 50),
- IRB or IEC regulations (21 CFR 56.103), and
- Declaration of Helsinki.

### E. Evaluation of Financial Disclosure

See Section V.C.

## VI. Integrated Review of Efficacy

### A. Brief Statement of Conclusions

In two adequate and well-controlled phase 3 studies, the Applicant has demonstrated effectiveness of tazarotene 0.1% cream in the treatment of acne vulgaris by showing superiority over vehicle cream. The studies support the claim in the draft label, which has this in the INDICATIONS AND USAGE section:

> TAZORAC® (tazarotene) Cream 0.1% is also indicated for the topical treatment of patients with acne vulgaris.

Comment The draft label contrasts with the approved label for TAZORAC® Gels, which has: "TAZORAC® (tazarotene topical gel) 0.1% is also indicated for the topical treatment of patients with facial acne vulgaris of mild to moderate severity." In the tazarotene cream development program, patient enrollment was not confined to mild to moderate disease, and baseline severity shows that both studies have approximately half of patients with moderate disease, and one-quarter each with mild or severe disease (see below). As well, the Applicant undertook PK studies on exaggerated application in patients with severe disease not confined to the face, to determine systemic exposure. Thus, the labeling claim appears to be acceptable.

### B. General Approach to Review of the Efficacy of the Drug

The efficacy database consists of two adequate and well-controlled trials on acne:

> Study 190168-029C. A multi-center, double-blind, randomized, vehicle-controlled, parallel-group study of the safety and efficacy of tazarotene cream 0.1% applied once daily for 12 weeks in patients with acne vulgaris (conducted 9/30/99 to 6/2/00);

and

Study 190168-031C. A multi-center, double-blind, randomized, vehicle-controlled, parallel-group study of the safety and efficacy of tazarotene cream 0.1% applied once daily for 12 weeks in patients with acne vulgaris (conducted 9/30/99 to 4/25/00).

These are virtually identical studies other than the collection of PK data by therapeutic drug monitoring in 190168-029C at selected sites. The patient numbers in this database are:

| Study | Tazarotene | Vehicle | Total |
|---|---|---|---|
| 190168-029C | 218 | 218 | 436 |
| 190168-031C | 206 | 205 | 411 |

Both studies were reviewed in detail and presented in Section VI.C.

### C. Detailed Review of Trials by Indication

## INDICATION: ACNE VULGARIS

Two adequate and well-controlled trials, 190168-029C and -031C, support the indication of treatment of acne vulgaris for tazarotene cream 0.1%. The design of these studies are almost identical and presented together here. The results will be discussed separately.

PROTOCOL DESIGN FOR STUDIES 190168-029C AND -031C

OBJECTIVE: To assess the safety and efficacy of tazarotene cream 0.1% versus vehicle cream applied once daily for 12 weeks in the treatment of acne vulgaris

NUMBER OF SUBJECTS: Approximately 400 patients at 8-15 centers

PATIENT SELECTION:

Inclusion criteria

1) Male or female, 12 years of age or older, with facial acne vulgaris (of a severity that is suitable for monotherapy with a topical agent)
2) Minimum of 10 facial inflammatory lesions (papules and pustules)
3) Minimum of 25 facial (excluding nose) non-inflammatory lesions (open/closed comedones)
4) No more than four facial nodular cystic lesions (≥ 5 mm in diameter)
5) No more than 200 facial lesions, excluding open and closed comedones on the nose
6) Anticipated ability to complete the study and comply with appropriate instructions
7) Negative urine pregnancy test on entry for female patients of childbearing potential
8) Written informed consent has been obtained.

Exclusion criteria

1) Known sensitivity to any of the ingredients in the study medication
2) Systemic therapy with antibiotics during the 4 weeks immediately prior to study start
3) Systemic therapy with retinoids during the 6 months immediately prior to study start
4) Topical use of antibiotics and/or other topical acne products (e.g., erythromycin, benzoyl peroxide, adapalene, tretinoin, tazarotene) during the 2 weeks immediately prior to study start
5) History or evidence of other skin conditions that would interfere with the evaluation of the study medication
6) Use of hormones for 12 weeks or less immediately preceding study entry; patients treated with hormonal therapy for more than 12 consecutive weeks immediately prior to study entry need not be excluded unless the patient expects to discontinue or change their hormonal therapy during the study
7) Anticipated need for surgery or hospitalization during the study
8) Uncontrolled systemic disease

9) Patients who require or desire excessive or prolonged exposure to ultraviolet light (e.g., sunlight, tanning beds) during the study
10) Concurrent involvement in another investigational study or participation within 30 days prior to the start of this study
11) Females who are pregnant, nursing, or planning a pregnancy
12) Females of childbearing potential not using reliable means of contraception during the study
13) Any condition or situation which, in the investigator's opinion, may put the patient at significant risk, could confound the study results, or interfere significantly with the patient's participation in the study.

Withdrawal criteria

Significant worsening or any of the following:
1) Adverse events
2) Protocol violations
3) Lack of efficacy
4) Administrative reasons (e.g., inability to continue, lost to follow-up)
5) Pregnancy

DESIGN: Multi-center, double-blind, randomized, vehicle-controlled, parallel-group study of 12 weeks duration comparing tazarotene 0.1% cream qd vs vehicle cream qd, with 4 scheduled visits: Weeks 0 (baseline), 4, 8, and 12. The Study Flow Chart is shown as follows

**SCHEDULE OF VISITS AND MEASUREMENTS:**

| | Week 0 | Week 4 | Week 8 | Week 12 |
|---|---|---|---|---|
| Informed Consent, Medical History, and Baseline Exam | X | | | |
| Urine Pregnancy Test (if applicable) | X | X | X | X[b] |
| Evaluate Lesions | X | X | X | X[b] |
| Photography[a] | X | | | X[b] |
| Dispense Study Medication | X | X | X | |
| Cosmetic Acceptability Questionnaire | | | | X[b] |
| Collect Study Medication | | X | X | X[b] |

[a] at selected sites; [b] Week 12 or earlier if the patient discontinues the study prior to Week 12

TREATMENT PROCEDURES:

Application of Study Medication and Restrictions during Study

- Patients will be instructed to apply a thin layer of the study medication once a day to the entire face as delineated by the hairline, jawline, and ears.
- Patients will avoid bringing the study medication in contact with their eyes, eyelids, and mouth. If contact with these areas occurs, patients should rinse the area thoroughly with water.
- Patients will wash their hands after applying the study medication.
- Patients will cleanse their face in the evening and they will be instructed to apply the study medication after they have allowed their skin to dry. After the medication has thoroughly dried, cosmetics may be applied.
- Patients who have been using antibacterial soaps prior to study entry will continue to use them throughout the study.
- Patients will avoid excessive sun exposure (e.g., sunlight, tanning booths) and use protective measures when exposed to sunlight (e.g., hat, visor, sunscreen).
- During the study, patients will be allowed to use their own non-medicated moisturizers and cleansers. Sunscreens and moisturizers should be non-comedogenic.
- Prohibited concomitant medications include any topical or systemic therapy that might alter the course of acne, including topical therapy with antibiotics or other anti-acne medications and systemic antibiotic therapy of greater than two weeks duration for infections. Therapy considered necessary for the patient's welfare may be given.
- Patients will avoid excessive or prolonged periods of sun exposure and extremes in weather, such as wind or cold. Patients should be instructed to wear protective clothing (e.g., hat, visor) and/or sunscreen when they go out in the sun.

EVALUATIONS:

Efficacy measures

- Total facial acne lesions [non-inflammatory (open and closed comedones) and inflammatory (papules, pustules, and nodules)] at Weeks 0, 4, 8 and 12.
- Non-inflammatory lesions (sum of open and closed comedones) at Weeks 0, 4, 8 & 12.
- Inflammatory lesions (sum of papules, pustules, and nodules) at Weeks 0, 4, 8 & 12.
- Global response to treatment (0 = completely cleared; 1 = almost cleared; 2 = marked response; 3 = moderate response; 4 = slight response; 5 = condition unchanged; 6 = condition worsened) at Weeks 4, 8 and 12.
- Overall acne assessment (OAA), a static global assessment for acne to be performed at Weeks 0, 4, 8 and 12, with the following grading:
  0=none: no evidence of facial acne vulgaris
  1=minimal: a few non-inflammatory lesions (comedones) are present, a few inflammatory lesions (papules/pustules) may be present
  2= mild: several to many noninflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) are present
  3= moderate: many noninflammatory lesions (comedones) and inflammatory lesions (papules/pustules) are present; no nodulocystic lesions are allowed
  4= severe: significant degree of inflammatory disease; papules/pustules are a prominent feature; a few nodulocystic lesions may be present
  5= very severe: aggressive nodulocystic disease; nodulocystic lesions predominate; includes acne conglobata; comedones and papules/pustules may be present
  Areas other than the face are not included in assessment.

Comment This "overall acne assessment" was amended to the protocol (submission 001 of IND [redacted] dated 10/13/99) upon FDA recommendation to introduce a static global evaluation. However, this grading system using the terms "a few", "several to many", etc. is too subjective and may introduce intra- and inter-observer variability.

## Safety measures

- Adverse events elicited by non-direct questioning in the original protocol, but modified upon FDA recommendation to be by queries including whether patients experienced any form of face irritancy.
- Urine pregnancy tests (females of childbearing potential) at Weeks 0, 4, 8, 12
- Follow-up in the event of pregnancy

## Other measures

- Color facial photographs at Weeks 0 and 12 at selected sites
- Patient cosmetic acceptability questionnaires at Week 12 (or earlier if the exit prior to Week 12) including:
  appearance of the study cream before application, feel of the study cream before application, ability to apply and spread the study cream, ability of the study cream to blend into the skin, appearance of the study cream after application, feel of the study cream after application, smell or odor of the study cream after application, and overall acceptability of the study cream, with 5-point scale for answers to each question: 1 = Highly favorable, 2 = Favorable, 3 = Neutral, 4 = Unfavorable, 5 = Highly unfavorable.
- Investigator evaluation of overall appearance of the patient's facial skin on the following 6-point scale at each visit:
  1 = Oily, 2 = Normal to Oily, 3 = Normal, 4 = Normal to Dry, 5 = Dry, 6 = Mixed (oily/dry).

## PK measures

- Therapeutic drug monitoring at selected centers: tazarotene and tazarotenic acid plasma concentrations to be determined at Weeks 4 and 8. The PK study was limited to 190168-029C and was amended to the protocol in submission 001 to IND [redacted] dated 10/13/99. The lower limit of quantitation was 5 pg/mL for tazarotenic acid.

# DATA ANALYSIS:

## Hypotheses

- Tazarotene cream 0.1% is more effective than vehicle as measured by a 15-percentage point or greater difference between groups at Week 12 in the mean percent reduction in total lesion counts from baseline.
- Tazarotene cream 0.1% has an acceptable safety profile.

Population for analysis

- For efficacy and safety variables, an intent-to-treat analysis will be performed, with last observation carried forward to Week 12 (including baseline data for those with no post-baseline visits).

Statistical methods

- Acne lesion count data and global response to treatment data will be analyzed by nonparametric (i.e., CMH, Kruskal-Wallis) or parametric tests (ANOVA). Adverse event data will be summarized by frequency tables and analyzed by appropriate statistical methods such as chi-square test. In addition, for lesion count reductions, the protocol specifies that the data will be transformed using a rank transformation to normalize them.

Criteria for effectiveness

- The primary endpoint will be Week 12. The primary efficacy variable will be ***total lesion counts***. "A 15-percentage point difference between treatment groups in the mean percent reduction in total lesion counts from baseline at Week 12 is considered clinically significant."
- "Treatment success", which is a derived variable of global response to treatment, will be defined as a treatment response of moderate or better. This derived variable will be analyzed by the CMH test using table scores or logistic regression or exact categorical variables.
- Clinical improvement is to be defined as a one-grade reduction from baseline (Week 0) for the OAA.

Comment The Applicant had been told at the pre-IND meeting that the primary variables should include a static global evaluation with dichotomization, and reduction in lesion counts in two out of three of the following: total, noninflammatory and inflammatory lesion counts.

RESULTS:

1. Investigators, Enrollment, Patient Disposition and Baseline Comparability

a. Investigators:

Name and location of the Investigators in Studies 190168-029C and -031C are listed in the Table under "Enrollment Information". The investigators in these two studies are qualified. For financial disclosure information and comments, see Section V.C.

b. Enrollment Information:

**Patient Numbers Stratified by Site and Treatment**

| Investigator Name | Location | Inv ID* | Taz* | Veh* | | Total |
|---|---|---|---|---|---|---|
| 190168-029C | | | | | | |
| Jerry Bagel, M.D. | East Windsor, NJ 08520 | 2927 | 12 | 14 | | 26 |
| Jon M. Hanifin, M.D. | Portland, OR 97201 | 1185 | 4 | 4 | | 8 |
| Adelaide A. Herbert, M.D. | Houston, TX 77030 | 1593 | 11 | 10 | | 21 |
| Steven R. Hong, M.D. | Boulder, CO 80304 | 2168 | 24 | 24 | | 48 |
| Steven E. Kempers, M.D. | Fridley, MN 55432 | 2912 | 16 | 17 | | 33 |
| Youn Kim, M.D. | Stanford, CA 94305 | 3285 | 2 | 2 | | 4 |
| Jack L. Lesher, Jr, M.D. | Augusta, GA 30912 | 1562 | 8 | 7 | | 15 |
| James J. Leyden, M.D. | Broomall, PA 19008 | 0084 | 8 | 8 | | 16 |
| Toivo Rist, M.D. | Knoxville, TN 37917 | 2926 | 13 | 13 | | 26 |
| Alan R. Shalita, M.D. | Paramus, NJ 07652 | 0626 | 20 | 19 | | 39 |
| Linda F. Stein, M.D. | Detroit, MI 48202 | 3256 | 12 | 11 | | 23 |
| Diane M. Thiboutot, M.D. | Hershey, PA 17033 | 2148 | 16 | 16 | | 32 |
| Eduardo H. Tschen, M.D. | Albuquerque, NM 87106 | 1104 | 24 | 24 | | 48 |
| Lloyd G. Wickboldt, M.D. | Orlando, FL 32806 | 3197 | 26 | 26 | | 52 |
| Hector Wiltz, M.D. | Miami, FL 33144 | 3257 | 22 | 23 | | 45 |
| 190168-031C | | | | | | |
| Ernst Ast, M.D. | Great Neck, NY 11021 | 2187 | 13 | 13 | | 26 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Richard S. Berger, M.D. | East Brunswick, NJ 08816 | 1962 | 19 | 19 | | 38 |
| Scott D. Clark, M.D. | Longmont, CO 80501 | 2995 | 15 | 14 | | 29 |
| Steven A. Davis, M.D. | San Antonio, TX 78229 | 2925 | 18 | 19 | | 37 |
| Craig A. Elmets, M.D. | Birmingham, AL 35294 | 3218 | 6 | 7 | | 13 |
| Rebat M. Halder, M.D. | Washington, DC 20060 | 2677 | 7 | 7 | | 14 |
| Terry M. Jones, M.D. | Bryan, TX 77801 | 1967 | 20 | 20 | | 40 |
| Paul A. Krusinski, M.D. | Burlington, VT 05401 | 2181 | 14 | 15 | | 29 |
| Mark R. Ling, M.D. | Newman, GA 30263 | 2427 | 19 | 18 | | 37 |
| Keith H. Loven, M.D. | Goodlettsville, TN 37072 | 3278 | 20 | 20 | | 40 |
| Ann W. Lucky, M.D. | Cincinnati, OH 45230 | 1900 | 20 | 20 | | 40 |
| Leslie A. Mark, M.D. | San Diego, CA 92117 | 2990 | 15 | 15 | | 30 |
| M. Alan Menter, M.D. | Dallas, TX 75230 | 2137 | 3 | 2 | | 5 |
| Glenn G. Russo, M.D. | New Orleans, LA 70112 | 2679 | 17 | 16 | | 33 |
| | | | 206 | 205 | | 411 |

*Inv ID=Investigator Identification Number, Taz=tazarotene cream 0.1%, veh=vehicle cream

c. Patient Disposition:

**Patient Disposition (Intent-to-Treat Analysis)**

| Study | 190168-029C | | 190168-031C | |
|---|---|---|---|---|
| Treatment Arm | Tazarotene 0.1% | Vehicle | Tazarotene 0.1% | Vehicle |
| Enrolled | 218 (100.0%) | 218 (100.0%) | 206 (100.0%) | 205 (100.0%) |
| Completed | 182 ( 83.5%) | 192 ( 88.1%) | 167 ( 81.1%) | 166 ( 81.0%) |
| Discontinued | | | | |
| • Non-compliance | 4 ( 1.8%) | 3 ( 1.4%) | 2 ( 1.0%) | 2 ( 1.0%) |
| • "Personal Reasons" | 9 ( 4.1%) | 2 ( 0.9%) | 14 ( 6.8%) | 13 ( 6.3%) |
| • Lack of Efficacy | 3 ( 1.4%) | 9 ( 4.1%) | 2 ( 1.0%) | 3 ( 1.5%) |
| • Adverse Event | 7 ( 3.2%) | 0 ( 0.0%) | 9 ( 4.4%) | 1 ( 0.5%) |
| • Relocated | 1 ( 0.5%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) |
| • Improper Entry of Subject | 2 ( 0.9%) | 0 ( 0.0%) | 0 ( 0.0%) | 2 ( 1.0%) |
| • Lost to Follow-up | 10 ( 4.6%) | 12 ( 5.5%) | 11 ( 5.3%) | 17 ( 8.3%) |
| • Positive Pregnancy Test | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.5%) | 1 ( 0.5%) |
| Total Discontinued | 36 ( 16.5%) | 26 ( 11.9%) | 39 ( 18.9%) | 39 ( 19.0%) |

No details of the "personal reasons" for discontinuation are available. The following Table shows the adverse events leading to discontinuation:

| | 190168-029C | 190168-031C |
|---|---|---|
| Tazarotene 0.1% | • Dry skin<br>• Burning /dry skin<br>• Burning /dry skin/erythema<br>• Dry skin<br>• Dry skin<br>• Dry skin/erythema<br>• Desquamation/irritation | • Burning/erythema/pruritus<br>• Dry skin<br>• Dry skin/erythema<br>• Acne<br>• Burning/desquamation/erythema<br>• Acne<br>• Hyperesthesia/irritation/dry skin<br>• Pain<br>• Burning/desquamation/erythema/pain |
| Vehicle | | • Acne |

d. Baseline Comparability:

**Baseline Comparability (Intent-to-Treat Analysis)**

| Study | 190168-029C | | 190168-031C | |
|---|---|---|---|---|
| Treatment Arm | Tazarotene 0.1% | Vehicle | Tazarotene 0.1% | Vehicle |

| | | | | | |
|---|---|---|---|---|---|
| Enrolled | | 218 (100.0%) | 218 (100.0%) | 206 (100.0%) | 205 (100.0%) |
| Age | Mean | 20.3 | 19.5 | 17. 9 | 19.3 |
| | Median | 17.0 | 17.0 | 16.0 | 16.0 |
| | Range | 12-51 | 12-46 | 12-52 | 11-52 |
| Age group | ≤17 | 113 ( 51.8%) | 119 ( 54.6%) | 137 ( 66.5%) | 126 ( 61.5%) |
| | 18-29 | 68 ( 31.2%) | 78 ( 35.8%) | 55 ( 26.7%) | 54 ( 26.3%) |
| | ≥30 | 37 ( 17.0%) | 21 ( 9.6%) | 14 ( 6.8%) | 25 ( 12.2%) |
| Gender | Male | 113 ( 51.8%) | 112 ( 51.4%) | 108 ( 52.4%) | 97 ( 47.3%) |
| | Female | 105 ( 48.2%) | 106 ( 48.6%) | 98 ( 47.6%) | 108 ( 52.7%) |
| Race | Caucasian | 151 ( 69.3%) | 142 ( 65.1%) | 164 ( 79.6%) | 157 ( 76.6%) |
| | Black | 22 ( 10.1%) | 17 ( 7.8%) | 21 ( 10.2%) | 20 ( 9.8%) |
| | Asian | 6 ( 2.8%) | 4 ( 1.8%) | 4 ( 1.9%) | 5 ( 2.4%) |
| | Hispanic | 37 ( 17.0%) | 53 ( 24.3%) | 16 ( 7.8%) | 22 ( 10.7%) |
| | Other | 2 ( 0.9%) | 2 ( 0.9%) | 1 ( 0.5%) | 1 ( 0.5%) |
| Year with Acne | Mean | 6.2 | 5.5 | 4.8 | 5.6 |
| | Median | 3.3 | 3.2 | 3.0 | 3.0 |
| | Range | | | | |

There are no statistically significant differences between the treatment groups for the above demographic parameters at baseline in each study.

2. Primary Endpoint Data

The primary endpoint for efficacy analysis is at the end of treatment at Week 12, using the intent-to-treat population. The primary parameters are: Percent change in lesion counts: total, noninflammatory and inflammatory, PLUS a dichotomized global evaluation, which in this case is the "overall acne assessment" (OAA).

The preferred dichotomization for OAA is to regard "none" or "minimal" as success. In this review, two additional analyses are also presented: a) "none", "minimal" and "mild" as success, and b) a change in one grade as success. The protocol defines b) as "clinical improvement". However, this kind of dichotomization using a derived score (change of one grade) is not generally accepted.

a. Lesion Counts

**Total Lesions – Median and Mean Percent Change From Baseline**

| Study week | Study 190168-029C | | | Study 190168-031C | | | 029C and 031C Combined | | |
|---|---|---|---|---|---|---|---|---|---|
| | Taz 0.1% N=218 | Vehicle N=218 | P-value[a] | Taz 0.1% N=206 | Vehicle N=205 | P-value[a] | Taz 0.1% N=424 | Vehicle N=423 | P-value[a] |
| 4 | -21.51%<br>-21.31% | -14.52%<br>-15.44% | 0.034 | -15.33%<br>-12.99% | -9.23%<br>-7.02% | 0.163 | -18.28%<br>-17.31% | -12.94%<br>-11.36% | 0.015 |
| 8 | -36.27%<br>-34.15% | -20.93%<br>-21.48% | <0.001 | -33.33%<br>-25.28% | -15.53%<br>-10.09% | <0.001 | -35.56%<br>-29.91% | -19.60%<br>-15.98% | <0.001 |
| 12 | -43.90%<br>-38.85% | -23.97%<br>-24.80% | <0.001 | -41.76%<br>-30.10% | -20.92%<br>-9.61% | <0.001 | -43.02%<br>-34.60% | -22.78%<br>-17.44% | <0.001 |

In each cell under a treatment group, median change value is followed by mean value (given under the median value).
Taz = tazarotene cream. N = number of patients at baseline; subsequent sample sizes may vary due to missing values.
a P-values based on two-way analysis of variance using a rank transformation*

* For both Studies 29C and 31C, the p-values for the Shapiro-Wilk test for all three types of lesions were all less than 0.001, providing evidence of non-normality. The Biometrics Reviewer considers the rank transformation as appropriate.

**Inflammatory Lesions – Median and Mean Percent Change From Baseline**

| Study week | Study 190168-029C | | | Study 190168-031C | | | 029C and 031C Combined | | |
|---|---|---|---|---|---|---|---|---|---|
| | Taz 0.1% N=218 | Vehicle N=218 | P-value[a] | Taz 0.1% N=206 | Vehicle N=205 | P-value[a] | Taz 0.1% N=424 | Vehicle N=423 | P-value[a] |
| 4 | -16.33%<br>-11.52% | -14.29%<br>-9.17% | 0.712 | 0.00%<br>+8.52% | -15.38%<br>-9.21% | 0.007 | -9.76%<br>-1.89% | -14.29%<br>-9.19% | 0.055 |
| 8 | -29.71%<br>-25.98% | -23.21%<br>-20.87% | 0.103 | -30.22%<br>-16.83% | -23.30%<br>-18.14% | 0.241 | -30.00%<br>-21.61% | -23.21%<br>-19.55% | 0.110 |
| 12 | -40.69%<br>-32.09% | -27.43%<br>-21.44% | 0.010 | -44.49%<br>-30.56% | -25.00%<br>-18.86% | 0.001 | -43.05%<br>-31.34% | -26.67%<br>-20.19% | <0.001 |

In each cell under a treatment group, median change value is followed by mean value (given under the median value).
Taz = tazarotene cream. N = number of patients at baseline
a P-values based on two-way analysis of variance using a rank transformation

**Non-Inflammatory Lesions – Median and Mean Percent Change From Baseline**

| Study week | Study 190168-029C | | | Study 190168-031C | | | 029C and 031C Combined | | |
|---|---|---|---|---|---|---|---|---|---|
| | Taz 0.1% N=218 | Vehicle N=218 | P-value[a] | Taz 0.1% N=206 | Vehicle N=205 | P-value[a] | Taz 0.1% N=424 | Vehicle N=423 | P-value[a] |
| 4 | -20.57%<br>-24.01% | -13.89%<br>-17.90% | 0.037 | -23.33%<br>-17.60% | -6.67%<br>-5.13% | 0.001 | -21.24%<br>-20.93% | -12.50%<br>-11.72% | <0.001 |
| 8 | -39.36%<br>-36.50% | -21.68%<br>-20.80% | <0.001 | -34.22%<br>-26.07% | -12.77%<br>-6.55% | <0.001 | -37.79%<br>-31.52% | -19.14%<br>-13.93% | <0.001 |
| 12 | -46.32%<br>-41.10% | -26.67%<br>-24.77% | <0.001 | -41.32%<br>-28.71% | -20.83%<br>-6.37% | <0.001 | -44.26%<br>-35.08% | -24.49%<br>-15.85% | <0.001 |

In each cell under a treatment group, median change value is followed by mean value (given under the median value).
Taz = tazarotene cream. N = number of patients at baseline
a P-values based on two-way analysis of variance using a rank transformation

## b. Overall Acne Assessment (Static Global)

**Incidence of Patients Achieving Overall Acne Assessment of "None" or "Minimal"**

| Study week | Study 190168-029C* | | | Study 190168-031C | | |
|---|---|---|---|---|---|---|
| | Taz 0.1% N=218 | Vehicle N=218 | P-value[b] | Taz 0.1% N=206 | Vehicle N=205 | P-value[b] |
| 12 | 40/218=<br>18.35% | 25/218=<br>11.47% | 0.039 | 41/206=<br>19.90% | 13/205=<br>6.34% | <0.001 |

Taz = tazarotene cream. N = number of patients at baseline *Taz 0.1% cream also superior at Weeks 4 and 8 in 190168-029C (Taz vs vehicle being 5% vs 1% (p=0.03) at Week 4, and 13% vs 4% (p=0.001) at Week 8)

**Incidence of Patients Achieving Overall Acne Assessment of "None", "Minimal" or "Mild"**

| Study week | Study 190168-029C | | | Study 190168-031C | | |
|---|---|---|---|---|---|---|
| | Taz 0.1% N=218 | Vehicle N=218 | P-value[b] | Taz 0.1% N=206 | Vehicle N=205 | P-value[b] |
| 8 | 87/209=<br>41.63% | 66/206=<br>34.20% | 0.034 | 90/192=<br>46.88% | 69/192=<br>35.94% | 0.033 |
| 12 | 119/218=<br>54.59% | 79/218=<br>36.24% | <0.001 | 110/206=<br>53.40% | 74/205=<br>36.10% | <0.001 |

Taz = tazarotene cream. N = number of patients at baseline

**Incidence of "Clinical Improvement"[a]**

| Study week | Study 190168-029C | | | Study 190168-031C | | | 029C and 031C Combined | | |
|---|---|---|---|---|---|---|---|---|---|
| | Taz 0.1% N=218 | Vehicle N=218 | P-value[b] | Taz 0.1% N=206 | Vehicle N=205 | P-value[b] | Taz 0.1% N=424 | Vehicle N=423 | P-value[b] |
| 4 | 25.94% | 22.64% | 0.429 | 22.96% | 30.65% | 0.086 | 24.51% | 26.52% | 0.512 |
| 8 | 36.36% | 26.70% | 0.029 | 40.63% | 36.98% | 0.410 | 38.40% | 31.66% | 0.045 |
| 12 | 49.08% | 33.49% | 0.001 | 48.06% | 32.68% | 0.001 | 48.58% | 33.10% | <0.001 |

Taz = tazarotene cream. N = number of patients at baseline

a Clinical Improvement: % of patients whose overall acne assessment improved by at least one grade from baseline.

b P-values based on Cochran-Mantel-Haenszel test

## 3. Secondary Endpoint Data

### Global Response to Treatment

**Global Response to Treatment[a] – "Treatment Success"[b]**

| Study week | Study 190168-029C | | | Study 190168-031C | | |
|---|---|---|---|---|---|---|
| | Taz 0.1% N=218 | Vehicle N=218 | P-value[c] | Taz 0.1% N=206 | Vehicle N=205 | P-value[c] |
| 4 | 24.06% | 13.68% | 0.004 | 15.82% | 14.57% | 0.687 |
| 8 | 44.98% | 23.30% | <0.001 | 36.98% | 21.88% | 0.001 |
| 12 | 59.17% | 33.94% | <0.001 | 48.54% | 26.83% | <0.001 |

Taz = tazarotene cream. N = number of patients at baseline

a Completely cleared – 100% improved; almost cleared – approx. 90% improved; marked response – approx. 75% improvement; moderate response = approx. 50% improvement; slight response – approx. 25% improvement; condition unchanged; condition worsened

b Treatment success: response of moderate, marked, almost cleared, or completely cleared

c P-values based on Cochran-Mantel-Haenszel test

## 4. Other Measures

Other measures include color facial photographs at selected investigational sites, patient cosmetic acceptability questionnaires, and Investigator evaluation of overall appearance of the patient's facial skin on oiliness/dryness. These parameters are of limited regulatory value in terms of efficacy and will not be deliberated upon.

## 5. Subset Analysis

See Section IX for subset analysis using gender, age, and race as criteria. Analysis based on baseline severity on the combined data from 190168-029C and -031C is shown in the following Table:

**Lesion Count Reduction* and Overall Acne Assessment of "None" or "Minimal"** at Week 12**

| BL severity | Mild | | Moderate | | Severe | |
|---|---|---|---|---|---|---|
| | Tazarotene (N=93) | Vehicle (N=76) | Tazarotene (N=235) | Vehicle (N=229) | Tazarotene (N=96) | Vehicle (N=115) |
| NI lesions | -46% | -32% | -46% | -23% | -42% | -26% |
| Infl lesions | -43% | -31% | -48% | -27% | -40% | -22% |
| Total lesions | -44% | -32% | -45% | -21% | -40% | -21% |
| OAA=0 or 1 | 33 (35%) | 12 (16%) | 36 (15%) | 20 (9%) | 12 (13%) | 3 (3%) |

*Percent reduction; ** patient number (% patients). BL=baselikne, NI=non-inflammatory, Infl=inflammatory, OAA=overall acne assessment: 0=none, 1=minimal, 2=mild, 3=moderate, 4=severe, 5=very severe.

Comment This analysis of Week 12 data has been performed by the Biometrics Reviewer, Dr. K. Fritsch. It is a post-hoc analysis, and statistical significance is not explored. The following may be observed:
a. The reductions in lesion counts appear to be consistent across baseline disease severity, although in patients starting with mild acne, the vehicle effect appears to be larger in general. The greater vehicle effect also shows up with the dichotomized static global ("none" or "minimal" with overall acne assessment), but in these mild cases, the active drug works best (35% vs 15% and 13% with moderate or severe cases, respectively).
b. However, in moderate and severe acne, the lesser active drug effect is balanced by the lower vehicle effect (9% and 3% of vehicle-treated patients with no/mimimal acne at Week 12 for the moderate and severe cases, respectively).
c. Thus, using the types of analyses shown above, and based on vehicle comparison, tazarotene cream 0.1% seems to show efficacy for mild, moderate, as well as severe acne.

### 6. PK Data

PK data from therapeutic drug monitoring at selected sites in 190168-029C will be discussed in Section VII.C.5.

### D. Efficacy Conclusions

Indication: Acne vulgaris.
Regulatory -

- There are two adequate and well-controlled studies showing effectiveness of tazarotene cream 0.1% in the treatment of acne.
- Independent substantiation of effectiveness has been achieved in these two trials.

Scientific -

- Appropriate clinical endpoints have been evaluated for the indication. These include the change in lesion counts: total, noninflammatory, and inflammatory PLUS a static physician global (OAA) analyzed by appropriate dichotomization.
- The data demonstrate success in all of the required endpoints for acne, and no multiplicity adjustment is necessary.

## VII. Integrated Review of Safety

### A. Brief Statement of Conclusions

- Tazarotene cream 0.1% in the treatment of acne presents with the anticipated retinoid irritant effects, including primarily desquamation, dry skin, erythema, and burning.
- Systemic bioavailability of tazarotenic acid exposure (AUC) is low when tazarotene cream 0.1% is used in the treatment of acne, but may be comparable to levels consistent with teratogenesis in rats, especially under exaggerated use conditions.

### B. Description of Patient Exposure

Patient exposure in the treatment of acne vulgaris occurred primary in the phase 3 adequate and well-controlled studies. As the two studies in phase 3 had virtually identical design, the exposure information can be presented as a whole:

**Patient Exposure in Phase 3 Studies (190168-029C and -031C)**

| | Exposure Duration (days) | | Patient Numbers (%) | | | | |
|---|---|---|---|---|---|---|---|
| | Mean/Median | Range | Week 0 | Week 2 | Week 4 | Week 8 | Week 12 |
| Taz 0.1% Cream | 75.64/84.00 | 1-114 | 424 (100%) | 395 (93.2%) | 392 (92.4%) | 363 (85.6%) | 306 (72.1%) |
| Vehicle | 78.00/84.00 | 1-128 | 423 (100%) | 397 (93.8%) | 395 (93.4%) | 374 (88.4%) | 318 (75.2%) |

Thus, over 300 patients had been exposed to tazarotene cream 0.1% in the phase 3 clinical studies. In addition, the PK study (Study 190168-035C) enrolled 19 acne patients to use tazarotene cream 0.1% for 4 weeks, and 88.9% (18/19) of patients completed this study.

A phase 3b study was performed in which the safety and facial tolerance of tazarotene cream 0.1% was compared with those of adapalene gel 0.1% and tretinoin gel microsphere 0.1% (Study 190168-041C) upon 4 weeks of treatment. A total of 48 healthy patients were enrolled in the study and 45 completed the study. As this study used a split-face design, 32 subjects received each treatment, including tazarotene cream 0.1%.

To support safety, this supplement also uses the phase 2 dose-ranging study for photodamage (Study 190168-025C) in which 4 tazarotene creams (0.01%, 0.025%, 0.05%, and 0.1%) were compared with vehicle cream and Renova® cream (0.05%). Each of 58 to 59 subjects in each treatment group applied one of the 6 products daily for a maximum of 24 weeks. Of the patients using any of the 4 tazarotene creams, 88.8% (207/233) completed the study including the 2-week post-treatment period.

In the phase 3 studies in acne, the body load given a putative application rate of 2 mg/cm$^2$ can be calculated to be 0.60 to 0.70 mg of tazarotene/day (0.01 mg/kg/day), translating to a total dose of 50 to 60 mg.

Comment The above assumed application rate (2 mg/cm$^2$) may be more generous than the actual rate of usage by acne patients. In a PK study (190168-035C), a pre-weighed amount of 300 mg tazarotene cream 0.1% adequately covered the face with a thin layer (300 mg/face gives approximately 1 mg/cm$^2$).

For information on demographics, see Section VI.C, "Detailed Review of Trials by Indication", under "Integrated Review of Efficacy".

### C. Methods and Specific Findings of Safety Review

METHODS:
The safety data are reviewed in the following manner:
1. Dermal safety study data
2. Adverse event data in the clinical trials using tazarotene cream 0.1% for acne