3. Adverse event data from sources other than clinical trials on tazarotene cream in acne patients
4. Clinical laboratory data
5. Systemic bioavailability data and risk of adverse pregnancy outcome

- The studies included in this review have been listed above (Section IV.B). For the phase 3 trials, they are generally considered as a whole here, as they are of almost identical design.
- For adverse event data, the investigator-reported verbatim terms were linked to the COSTART dictionary-preferred terms and body systems.

FINDINGS:

1. DERMAL SAFETY STUDY DATA

Data from dermal safety studies on healthy subjects previously conducted under IND [ ] (for psoriasis) presented in the original submission of NDA 21-184 have been reviewed with the original submission (See Medical Officer's Review of original NDA). These data are derived from studies on healthy skin, but such studies are traditionally acceptable for extrapolation to disease skin. The relevant studies are:

190168-019C. Irritancy
190168-020C. Sensitization
190168-021C. Phototoxicity and photoallergenicity
190168-032C. Photoallergenicity

Tazarotene cream 0.1% has been found to be an irritant, but have low potential for contact sensitization, phototoxicity and photoallergenicity. The irritancy data are reproduced in the following Table:

**Least Squares Mean ± SE[a] Cumulative 21-Day Irritation Scores in 190168-019C**

| Formulation | Cumulative 21-day irritation score |
|---|---|
| vehicle cream | 4.38 ± 1.76 |
| tazarotene cream 0.05% | 35.06 ± 1.76 |
| tazarotene cream 0.1% | 45.09 ± 1.76 |
| sodium lauryl sulfate solution 0.5% | 29.11 ± 1.76 |

a SE = standard error of least squares mean. Between-group comparisons from Tukey test show tazarotene cream 0.1% to be statistically significantly different from vehicle, tazarotene cream 0.05% and SLS solution 0.5% ($p < 0.05$).

2. ADVERSE EVENT DATA IN CLINICAL TRIALS USING TAZAROTENE CREAM 0.1% FOR ACNE

a. Deaths, Serious Adverse Events, and Adverse Events Leading to Discontinuation

i) Deaths and Serious Adverse Events

No deaths were reported. In the phase 3 studies, serious adverse events (SAEs) were reported in 0.5% (2/424) of patients in the tazarotene group, and 0.5% (2/423) of patients in the vehicle group. All SAEs were considered to be unrelated to study drug.

Patients with Serious Adverse Events During the Phase 3 Acne Studies

| BODY SYSTEM preferred term | Tazarotene 0.1% N = 424 | Vehicle N = 423 |
|---|---|---|
| DIGESTIVE/GENERAL | anorexia nervosa 1 | "gastrointestinal disorder" 1 |
| BODY AS A WHOLE | ovarian cyst hemorrhage 1 | accidental shoulder injury 1 |

ii) Discontinuations Due to Adverse Events in Phase 3 Acne Studies

A total of 140 patients (16.5%, 140/847) discontinued participation in the phase 3 acne studies for various reasons. Seventeen patients (2.0%, 17/847) discontinued due to adverse events: 16 of 424 (3.8%) patients in the tazarotene cream group and 1 of 423 (0.2%) in the vehicle group. The specific adverse events leading to discontinuation were mostly dermatological (See Table below).

Number (%) of Adverse Events Leading to Discontinuation During the Phase 3 Acne Studies

| BODY SYSTEM preferred term | Tazarotene 0.1% N = 424 | Vehicle N = 423 |
|---|---|---|
| **SKIN AND APPENDAGES** | | |
| Dry skin | 9 (2.1%) | - |
| Burning sensation on skin | 5 (1.2%) | - |
| Erythema | 6 (1.4%) | - |
| Desquamation | 3 (0.7%) | - |
| Pruritus | 1 (0.2%) | - |
| Acne | 2(0.5%) | 1 (0.2%) |
| Irritation | 2(0.5%) | - |
| **BODY AS A WHOLE** | | |
| Face pain | 1 (0.2%) | - |
| Pain | 1 (0.2%) | - |
| **NERVOUS SYSTEM** | | |
| Hypesthesia | 1 (0.2%) | - |
| **OTHER** | | |
| Pregnancy | 1 (0.2%) | 1 (0.2%) |

Patients reported one or more adverse events as the reason for discontinuation.

Three patients developed positive pregnancy tests during study and 2 were discontinued from study:

Study 190168-031C patient #1384 vehicle - positive pregnancy test at week 4: terminated pregnancy
Study 190168-031C patient #1301 tazarotene - positive pregnancy test at week 8: had a healthy baby
Study 190168-029C patient #1087 tazarotene - positive pregnancy test at the exit visit (week 12, patient completed the study): terminated the pregnancy.

b. Adverse Event Tables

i) Phase 3 Studies

- All Reported Adverse Events Regardless of Causality

There was a significantly higher incidence of adverse events in the tazarotene cream group compared with vehicle in the combined phase 3 acne studies. The most frequently reported adverse events were in the "skin and appendages", "body as a whole", and "respiratory" systems:

**Proportion of Patients with Adverse Events Reported in Phase 3 Acne studies**

| | Tazarotene Cream 0.1% | Vehicle | p-value |
|---|---|---|---|
| 190168-029C | 123/218 (56.4%) | 52/218 (23.9%) | <0.001 |
| 190168-031C | 157/206 (76.2%) | 79/205 (38.5%) | <0.001 |
| Phase 3 Studies Combined | 280/424 (66.0%) | 131/423 (31.0%) | < 0.001 |
| Skin and Appendages | 230/424 (54.2%) | 41/423 (9.7%) | < 0.001 |
| Respiratory | 58/424 (13.7%) | 63/423 (14.9%) | 0.614 |
| Body as a whole* | 56/424 (13.2%) | 35/423 (8.3%) | 0.020 |

*There were no statistically significant differences in the incidences of any of the adverse events within the "body as a whole" overall body system.

Combined adverse event frequencies in each of the other body systems were reported by fewer than 4% of patients, without statistically significant differences between the two treatment groups.

Adverse events reported by >2% of patients in either treatment group are summarized in the following Table. For a full listing of frequencies in the phase 3 studies combined, see Appendix I of this review.

**Number (%) of Patients with 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] |
|---|---|---|---|
| **BODY AS A WHOLE** | | | |
| headache | 21 ( 5.0%) | 13 (3.1%) | 0.164 |
| **RESPIRATORY** | | | |
| infection | 31 ( 7.3%) | 34 (8.0%) | 0.691 |
| pharyngitis | 14 ( 3.3%) | 9 (2.1%) | 0.293 |
| **SKIN AND APPENDAGES** | | | |
| desquamation | 124 (29.2%) | 12 (2.8%) | < 0.001 |
| dry skin | 114 (26.9%) | 11 (2.6%) | < 0.001 |
| erythema | 88 (20.8%) | 9 (2.1%) | < 0.001 |
| skin burning sensation | 60 (14.2%) | 3 (0.7%) | < 0.001 |
| pruritus | 20 ( 4.7%) | 6 (1.4%) | 0.005 |
| irritation skin | 18 ( 4.2%) | 1 (0.2%) | < 0.001 |

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

The following data illustrate the adverse events with frequency of at least 3% in either treatment group in each phase 3 study.

**Number (%) of Patients with Adverse Events, Reported by >3% of Patients in either Treatment Group in Studies 190168-029C and -031C**

| | 190168-029C Data; 190168-031C Data | | |
|---|---|---|---|
| **BODY SYSTEM/ preferred term** | **Tazarotene cream 0.1% N = 218; N = 206** | **Vehicle N = 218; N = 205** | **p-values** |
| **BODY AS A WHOLE*** | | | |
| Headache | 9 (4.1%); 12 (5.8%) | 8 (3.7%); 5 (2.4%) | 0.805; 0.085 |
| **RESPIRATORY SYSTEM*** | | | |
| Infection | 21 (9.6%); 10 (4.9%) | 18 (8.3%); 16 (7.8%) | 0.615; 0.219 |
| **SKIN AND APPENDAGES*** | | | |
| Desquamation | 46 (21.1%); 78 (37.9%) | 2 (0.9%); 10 (4.9%) | < 0.001; <0.001 |
| Dry skin | 46 (21.1%); 68 (33.0%) | 2 (0.9%); 9 (4.4%) | < 0.001; <0.001 |

| | | | |
|---|---|---|---|
| Erythema | 28 (12.8%); 60 (29.1%) | 1 (0.5%); 8 (3.9%) | < 0.001; <0.001 |
| Burning sensation on skin | 16 (7.3%); 44 (21.4%) | 1 (0.5%); 2 (1.0%) | < 0.001; <0.001 |
| Irritation | 11 (5.0%); 7 (3.4%) | 1 (0.5%); 0 (0.0%) | 0.003; 0.015 |

p-value based on Pearson's chi-square test.
*The following events have also been reported by >3% of patients in 190168-031C [tazarotene vs vehicle; p value]: **BODY AS A WHOLE** - Flu syndrome [7 (3.4%) vs 6 (2.9%); 0.785], **RESPIRATORY SYSTEM** - Pharyngitis [11 ( 5.3%) vs 4 (2.0%); 0.067], and **SKIN AND APPENDAGES** - Pruritus [14 ( 6.8%) vs 4 (2.0%); 0.016].

- Treatment-Related Adverse Events

Treatment-related adverse events included those events rated by the investigator as possibly, probably, or definitely related to study medication. In both studies, a significantly greater proportion of patients in the tazarotene 0.1% group than in the vehicle group reported one or more treatment-related adverse events.

**Proportion of Patients with Treatment-Related Adverse Events in Phase 3 Acne studies**

| | Tazarotene Cream 0.1% | Vehicle | p-value |
|---|---|---|---|
| 190168-029C | 91/218 (41.7%) | 9/218 (4.1%) | <0.001 |
| 190168-031C | 134/206 (65.0%) | 26/205 (12.7%) | <0.001 |
| Phase 3 Studies Combined | 225/424 (53.1%) | 35/423 (8.3%) | <0.001 |
| Skin & Appendages | 224/424 (52.8%) | 34/423 (8.0%) | < 0.001 |
| Body as a whole* | 13/424 (3.1%) | 2/423 (0.5%) | 0.004 |

*There were no statistically significant differences in the incidences of any of the adverse events within the "body as a whole" overall body system.

The most common treatment-related adverse events are shown in the following Tables.

**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.

**Number (%) of Patients with Treatment-Related Adverse Events Reported by >3% of Patients in either Treatment Group in Studies 190168-029C and -031C**

| | 190168-029C Data; 190168-031C Data | | |
|---|---|---|---|
| BODY SYSTEM preferred term | Tazarotene cream 0.1% N = 218; N = 206 | Vehicle N = 218; N = 205 | p-value |
| **SKIN AND APPENDAGES*** | | | |
| Desquamation | 46 (21.1%); 78 (37.9%) | 2 (0.9%); 9 (4.4%) | < 0.001; <0.001 |
| Dry skin | 46 (21.1%); 68 (33.0%) | 2 (0.9%); 8 (3.9%) | < 0.001; <0.001 |
| Erythema | 28 (12.8%); 59 (28.6%) | 1 (0.5%); 7 (3.4%) | < 0.001; <0.001 |
| Burning sensation on skin | 15 (6.9%); 44 (21.4%) | 1 (0.5%); 2 (1.0%) | < 0.001; <0.001 |

p-value based on Pearson's chi-square test.
*The following events have also been reported by >3% of patients in 190168-029C [tazarotene vs vehicle; p value]: Irritation [11 (5.0%) vs 1 (0.5%); 0.003], and in 190168-031C [tazarotene vs vehicle; p value]: Pruritus [14 (6.8%) vs 4 (2.0%); 0.016].

- Severity of Adverse Events

The majority of the adverse events were of mild or moderate severity. A total of 41 reported adverse events were rated as severe; most of these were reported in the "skin and appendages" body system. "Severe" adverse events regardless of causality are shown below:

| | Tazarotene Cream 0.1% | Vehicle |
|---|---|---|
| 190168-029C | headache 1, infection 1, pharyngitis 1, burning 1, desquamation 2, dry skin 6, erythema 2, irritation 1, skin pain 1 (total 16 events) | Headache 1, migraine 1, "GI disorder" 1, insomnia 1 (total 4 events) |
| 190168-031C | cyst 1, flu syndrome 1, leg pain 1, acne 2, desquamation 3, dry skin 1, erythema 3, irritation 2, pruritus 1, "testis disorder" 1 (total 16 events) | Accidental injury 1, arm pain 1, fracture 1, acne 1, urinary tract infection 1 (total 5 events) |

Most treatment-related adverse events were mild to moderate in severity. The "severe" events occurred predominantly in the active treatment group and were all in the "skin and appendages" system.

- Study 190168-029C: tazarotene group only: burning (1), desquamation (2), dry skin (6), erythema (2), irritation (1), and skin pain (1).
- Study 190168-031C: tazarotene group: acne (2), desquamation (3), dry skin (1), erythema (3), irritation (2), and pruritus (1); vehicle group: acne (1).

ii) Supportive Study

- Safety Data from PK Study with Tazarotene Cream in Acne Patients (Study 190168-035C)

  Study 190168-035C. "An open-label, single-center, parallel-group, pharmacokinetics study of tazarotene cream 0.1% after a single dose and after 6, 13, 20, and 27 repeat topical applications once daily to either the face only or to an exaggerated body surface area (15%) in female patients with acne vulgaris"

  Investigator: Thomas C. Marbury, M.D. of Orlando, FL 32806

  This was a single-center, open-label, parallel-group study to assess the safety and PK of tazarotene cream 0.1% applied under standard dosing conditions or under exaggerated dosing. A total of 28 applications of tazarotene cream 0.1% were made to the face (9 patients) or to 15% body surface area (BSA) (10 patients) over a period of 33 days.

  - For the standard dosing conditions, a weighed amount of 300 mg per face or approximately 1 mg/cm$^2$ was applied by technical staff to face only (this was observed in the study to be an amount adequate to cover the face with a thin layer).
  - For the exaggerated-dosing conditions, 2 mg/cm$^2$ of tazarotene cream was applied by technical staff to 15% BSA of each patient, including 300 mg of cream applied to the face. The Applicant believes that the amount [2 mg/cm$^2$] is probably higher than that actually applied in real life if patients are instructed to apply a thin layer.

  This was a female-only study. The PK data have been reviewed by Biopharm, and is addressed elsewhere in this review (Section VII.C.5). No serious adverse events or discontinuation from the study due to adverse events were reported. All patients

(100%, 19/19) reported one or more adverse events. Treatment-unrelated adverse events were reported by 66.7% (6/9) of patients in the standard dosing group and by 50% (5/10) of patients in the exaggerated dosing group. The severity of the majority of adverse events was mild; a few were rated as moderate. There was none rated severe.

Almost all reported treatment-related adverse events were in the "skin and appendages" system. Only one such adverse event was reported for another system (cheilitis in the exaggerated dosing group). The frequencies of reported adverse events in the "skin and appendages" system were:

| | Standard Dosing (N=9) | Exaggerated Dosing (N=10) |
|---|---|---|
| Any AE reported | 8 (88.9%) | 10 (100.0%) |
| body desquamation | 7 (77.8%) | 10 (100.0%) |
| dry skin | 6 (66.7%) | 3 (30.0%) |
| burning sensation | 5 (55.6%) | 5 (50.0%) |
| worsened acne | 3 (33.3%) | 3 (30.0%) |
| pruritus | 2 (22.2%) | 8 (80.0%) |
| erythema | 1 (11.1%) | 6 (60.0%) |
| rash | 0 | 4 (40.0%) |

## 3. ADVERSE EVENT DATA FROM SOURCES OTHER THAN CLINICAL TRIALS ON TAZAROTENE CREAM IN ACNE PATIENTS

The safety data from the following have been reviewed:

- Clinical Trials with Tazarotene Cream in Other Indications
- Facial Tolerance Study with Tazarotene Cream 0.1%
- PK Studies with Tazarotene Gel in Acne Patients
- Drug-Drug Interaction Study with Oral Tazarotene
- Postmarketing Adverse Events with Tazarotene Gel

### a. Clinical Trials with Tazarotene Cream in Other Indications

#### i) Psoriasis.

See Medical Officer Review of original NDA 21-184 for safety data for the psoriasis indication.

#### ii) Dose-ranging study on tazarotene creams in patients with photodamage.

- Study 190168-025C. "A multicenter, investigator-masked, randomized, vehicle-controlled, parallel comparison of tazarotene 0.01%, 0.025%, 0.05%, and 0.1% creams and tretinoin 0.05% emollient cream applied once-daily for 24 weeks in patients with photodamaged facial skin"

  This study is submitted in detail in a separate Efficacy Supplement, and will be the subject of review for that supplement. Only an overall picture is presented here in relation to the safety data.

**Incidence of Adverse Event in the Treatment Period of 190168-025C**

| | Tazarotene Cream 0.1% | Vehicle | Tretinoin Emollient Cream* 0.05% |
|---|---|---|---|

| | (N=58) | (N=58) | (N=58) |
|---|---|---|---|
| AE | 87.8% | 53.4% | 69.0% |
| "Treatment-related" AE | 82.8% | 3% | 56.9% |

Data from lower concentrations of tazarotene cream not presented here.
*Renova

The material submitted in the current supplement, S001, has not revealed major differences between the safety data obtained in the treatment of photodamage and those in acne vulgaris, except for a higher incidence of adverse events in general in patients with photodamage. It is not clear whether the higher incidence is the result of lengthier treatment (24 weeks vs 12 weeks) or more susceptible skin in patients with photodamage.

The primary impact is on local toxicity, with desquamation, erythema, burning, and dry skin being the most frequently reported adverse effects. The majority of adverse events related to treatment have been of mild to moderate severity.

For PK data obtained in this study, see Section VII.C.5.

b. Facial Tolerance Study with Tazarotene Cream 0.1%

i) Study 190168-041C. "A single-center, investigator-masked, randomized, balanced, incomplete-block study of the safety and facial tolerance of tazarotene cream 0.1% versus adapalene gel 0.1% and tretinoin gel microsphere 0.1% applied once daily for 4 weeks in healthy volunteers"

Investigator: James J. Leyden, M.D. of Broomall, PA 19008

Data were not yet available at the time of submission of this efficacy supplement. It has since been submitted to IND [redacted] in the form of an abbreviated study report. In this study, healthy volunteers were given 0.1% tazarotene cream, adapalene gel, or tretinoin gel microsphere for daily facial application for 28 days. Each subject applied one product to one side of the face. "Facial tolerance" was evaluated using the signs erythema and dryness, each on a 6-point scale: 0=none, 1=minimal, 2=mild, 3=moderate, 4=severe, 5=very severe. In addition, patients made self-assessment on (a) comfort level and (b) burning/stinging. The results on "facial tolerance" are shown as follows:

| | Tazarotene* (N=32) | Adapalene (N=32) | Tretinoin (N=32) |
|---|---|---|---|
| Erythema | | | |
| Cumulative score over 28 days | 28.0 | 25.3 | 28.5 |
| Average change from baseline over 28 days | 1.41 | 1.27 | 1.43 |
| Dryness | | | |
| Cumulative score over 28 days | 16.3 | 10.7 | 15.7 |
| Average change from baseline over 28 days | 0.78 | 0.51 | 0.74 |

*N refers to the number of sites for application of a drug product and not number of subjects, as this study is of split-face design.

The report concluded that erythema and dryness were clinically similar among the three drugs despite minor differences (analyzed by the least square mean average

change from baseline scores). The evaluation of comfort and burning/stinging did not reveal statistically significant differences between the formulations.

Adverse event data are shown in the following Table. Serious adverse events were not reported. All adverse events were of mild to moderate severity.

| | Tazarotene (N*=32) | Adapalene (N=32) | Tretinoin (N=32) |
|---|---|---|---|
| Total facial AE | 8 (25%) | 6 (18.8%) | 6 (18.8%) |
| Skin and Appendages | 7 (21.9%) | 6 (18.8%) | 5 (15.6%) |
| Puritus | 4 (12.5%) | 3 (9.4%) | 2 (6.3%) |
| Acne | 2 (6.3%) | 1 (3.1%) | 1 (3.1%) |
| Papules | 1 (3.1%) | 1 (3.1%) | 2 (6.3%) |
| Erythema | 1 (3.1%) | 1 (3.1%) | 1 (3.1%) |
| Folliculitis | 0 | 0 | 1 (3.1%) |

*N refers to the number of sites for application of a drug product and not number of subjects, as this study is of split-face design.

Comment This is a single-center, comparative study with arbitrary sample size, bilateral comparison and no placebo control. The small differences between the products in "facial tolerance" evaluated by the Investigator may not necessarily be clinically relevant, especially when the subjective parameters ("comfort level" and burning/stinging) did not reveal statistically significant differences. The adverse event data suggest slightly higher frequencies of facial adverse events with tazarotene cream 0.1% but in view of the small patient numbers, these data are difficult to interpret. In addition, a split-face design is not considered adequate because of potential cross-contamination, application error, and uninterpretable systemic effects.

c. PK Studies with Tazarotene Gel in Acne Patients

i) Study 190168-022. "An open-label, single-center, randomized, parallel-group pharmacokinetics study of tazarotene 0.1% gel qd, tazarotene 0.1% gel qod, tretinoin 0.1% cream qd, and adapalene 0.1% gel qd for one month in female patients with facial acne"

Investigator: Thomas C. Marbury, M.D. of Orlando, FL 32806

This was a second female-only study. Its purpose was to determine the PK profiles of tazarotenic acid, after qd or qod dosing with tazarotene gel 0.1% in females with acne. Other patients were treated with tretinoin cream 0.1% (Retin-A®) qd or adapalene gel 0.1% (Differin®) qd to determine the PK profiles of these agents. See Section VII.C.5, and Biopharm review for more details on PK data.

Forty-two patients were enrolled. In each patient, a total of 28 facial applications of each study medication were made. No serious adverse events or deaths were reported. All patients reported treatment-related adverse events in the "skin and appendages" system. All events were rated as mild to moderate, and none led to discontinuation. The most frequently reported adverse events are shown below:

| | tazarotene gel qd | tazarotene gel qod | tretinoin qd | adapalene qd |
|---|---|---|---|---|
| N | 11 | 10 | 11 | 10 |
| dry skin | 81.8% | 70% | 36.4% | 50% |
| desquamation | 72.7% | 70% | 72.7% | 60% |

| | | | | |
|---|---|---|---|---|
| erythema | 36.4% | 20.0% | 45.5% | 50.0% |
| skin irritation | 36.4% | 10.0% | 18.2% | 20.0% |
| burning skin | 27.3% | 0 | 18.2% | 40.0% |
| worsened acne | 45.5% | 40.0% | 63.6% | 50.0% |
| pruritus | 45.5% | 30.0% | 9.1% | 10.0% |

One patient discontinued due to pregnancy and had a healthy baby (patient treated with tretinoin). Two patients tested positive for pregnancy upon exiting the study. One patient elected to terminate the pregnancy for reasons "unrelated to tazarotene" (patient treated with tazarotene gel 0.1% QOD), and the other patient was lost to follow-up (patient treated with tazarotene gel 0.1% QOD).

Comment This was a single-center, open-label, female-only study on tazarotene gel rather than tazarotene cream. The regulatory utility of this study is limited. The adverse event profile indicates that tazarotene gel 0.1% gives similar cutaneous toxicity as other topical retinoids. However, the observed frequencies suggest that tazarotene gel 0.1% applied qd, when compared to usage with a lower frequency or with other retinoids, may tend to show more frequent local adverse effects.

ii) Study 190168-030. "An open-label, multi-center, pharmacokinetics study of tazarotene gel 0.1% after a single dose and after 6, 13, 26, and 40 repeat topical applications once daily over 15% body surface area in female patients with acne vulgaris"

Investigators:

Sewon Kang, M.D. of Ann Arbor, MI 48109
James J. Leyden, M.D. of Broomall, PA 19008
Nicholas J. Lowe, M.D. of Santa Monica, CA 90404
Jean-Paul Ortonne, M.D. of Nice, France
Tania J. Phillips, M.D. of Boston, MA 02118
Gerald D. Weinstein, M.D. of Irvine, CA 92697

This was a third female-only study. Its purpose was to determine the safety of tazarotene gel 0.1% and the PK of tazarotenic acid under exaggerated use conditions (2 mg/cm$^2$ applied to 15% body surface area (BSA)). See Section VII.C.5, and Biopharm review for more details on PK data.

A total of 41 applications of tazarotene gel 0.1% to 15% BSA was made in 19 women with acne. Overall, 89.5% of patients (17/19) reported one or more adverse events. No serious adverse events were reported. Two patients discontinued due to adverse events, both with moderate burning sensation on skin as the single adverse event. Eight out of 19 patients (42.1%) reported treatment-unrelated events, but the majority of adverse events were treatment-related.

Seventeen of the 19 patients (89.5%) reported treatment-related adverse events in the "skin and appendages" system, and 4 (21.1%) in the "body as a whole" system. No treatment-related adverse events were reported for other body systems. Most frequently reported treatment-related adverse events included:

- burning sensation on skin (15/19, 78.9%)
- pruritus (15/19, 78.9%)
- desquamation (11/19, 57.9%)
- erythema (8/19, 42.1%)
- worsened acne (5/19, 26.3%)
- rash (4/19, 21.1%)
- skin irritation (3/19, 15.8%)
- face edema (2/19, 10.5%)
- headache (2/19, 10.5%)

Comment This was an open-label, female-only study on tazarotene gel rather than tazarotene cream. The regulatory utility of this study is limited. The adverse events observed are consistent with those seen with tazarotene gel 0.1% in previous studies and captured in the label for tazarotene gels. It is difficult to interpret the frequencies in the absence of a comparator.

## d. Drug-Drug Interaction Study with Oral Tazarotene

- PK data from a study with oral tazarotene administered at 1.1 mg daily in 29 healthy females (190168-018P) have been presented to support the low systemic bioavailability and lack of drug-drug interaction with the oral contraceptive norethindrone 1 mg/ethinyl estradiol 0.35 mg (Ortho-Novum 1/35). These data have been previously reviewed when submitted to IND [redacted] With multiple oral dosing of tazarotene at 1.1 mg/d, there did not appear to be sufficient evidence of PK or PD interaction between tazarotene and Ortho-Novum 1/35 in healthy females of child-bearing potential. Systemic retinoid adverse effects cannot be clearly delineated in the safety profile. However, a substantial portion of subjects developed headache of mild to moderate severity.

| | Ortho-Novum 1/35 Dosing Period (N=29) | Ortho-Novum 1/35 + Tazarotene Dosing Period (N=27) | |
|---|---|---|---|
| | ALL Adverse Events | ALL Adverse Events | Treatment-related AE* |
| Headache | 9 (31%) | 9 (33%) | 7 (26%) |
| Infection | 6 (21%) | | |
| Menstrual disorder | 6 (21%) | 4 (15%) | |
| Rhinitis | 5 (17%) | 4 (15%) | |
| Dysmenorrhea | 4 (14%) | | |
| Acne | 3 (10%) | 6 (22%) | 5 (19%) |
| Asthenia | 3 (10%) | | |
| Nausea | 3 (10%) | 6 (22%) | 6 (22%) |
| Dry skin | | 5 (19%) | 5 (19%) |
| Erythema | | 5 (19%) | 3 (11%) |
| Chest pain | | 4 (15%) | |
| "Pain" | | 4 (15%) | |
| Pruritus | | 4 (15%) | 3 (11%) |
| Rash | | 4 (15%) | 4 (15%) |
| Breast pain | | 3 (11%) | |

*No AEs were considered "treatment-related" in the initial Ortho-Novum 1/35 phase, as there was no tazarotene administration. Other treatment-related AEs not listed in this Table included gastroenteritis, oral dryness, urticaria, each in 2 of 27 patients (7%), and abdominal pain, alopecia, diarrhea, dysmenorrhea, face pain, seborrhea, vasodilatation, visual disturbance and vomit, each in 1 of 27 (4%)

## e. Postmarketing Adverse Events with Tazarotene Gel

- In the original NDA, postmarketing adverse event data with tazarotene gels were presented and reviewed. Information has been updated in the current supplement. Since the approval of tazarotene gels through August 31, 2000, there were 515 postmarketing adverse events reported in 217 patients, based on total prescriptions of over 2.6 million, and a total number of samples of over 1.2 million. There are no new findings that would alter previous conclusions concerning adverse effects that have been labeled for tazarotene gels or creams.

## 4. CLINICAL LABORATORY DATA

- There was no clinical laboratory testing in the phase 3 program for acne vulgaris. Previous phase 3 studies on psoriasis did have clinical laboratory testing. Besides possibly triglyceride elevation, there were no consistent clinically significant laboratory findings. As systemic exposure is expected to be probably less in the indication for acne vulgaris, these data are acceptable to support use of tazarotene cream 0.1% in acne.

## 5. SYSTEMIC BIOAVAILABILITY DATA AND RISK OF ADVERSE PREGNANCY OUTCOME

### a. Systemic Bioavailability

The details concerning bioavailability studies to determine PK profile are in the Biopharm review. There are three PK study reports on female subjects in this supplement, one on tazarotene cream 0.1%, and two on tazarotene gel 0.1%. In addition, there are two clinical studies with therapeutic drug monitoring to determine plasma levels of tazarotenic acid arising from clinical use.

### i. Studies on PK profile with Tazarotene Cream 0.1% or Tazarotene Gel 0.1%

The three PK studies are:

- 190168-035C (tazarotene cream): application to face only or to 15% BSA, by study site personnel
- 190168-022 (tazarotene gel): application to face only, by patient under site personnel supervision
- 190168-030 (tazarotene gel): application to 15% BSA, by study site personnel

**Comments**

1. All three studies included only females. It is unclear whether extrapolation to males is valid or not.
2. The studies with application to 15% BSA enrolled patients with moderate to severe acne who had to have lesions on the face, chest, and back at baseline. However, there is no assurance that the area for application (15% BSA, including the face, upper back, upper chest, shoulders ± neck) would actually be an area with acne involvement throughout the course of the study (33 days for 190168-035C and 43 days for 190168-030), or even at baseline. Thus, it is difficult to interpret the PK data, as neither the degree of acne involvement over the area of application nor the achievement of a "steady state" can be ascertained from the study design.

The essence of the data of interest can be displayed in the following Table showing maximum $AUC_{0\text{-}24\ hr}$ values (highest mean value or highest individual value observed during the course of study) for tazarotenic acid, the active metabolite of

tazarotene. The maximum values provide a "worst-case scenario" for conservative estimates when comparison with data from animal studies are made.

**Maximum Exposure Levels to Tazarotenic Acid in Acne Studies on Tazarotene 0.1% Cream or Gel**

| | Tazarotenic Acid $AUC_{0\text{-}24\ hr}$ (ng.hr/mL) | | | |
|---|---|---|---|---|
| | Face Only | | Exaggerated Exposure (15% BSA) | |
| Study | Mean | Individual Maximum | Mean | Individual Maximum |
| 190168-035C (Cream) [Day 15] | 1.538 | 3.132 | 17.007 | 26.591 |
| 190168-022 (Gel) [Day 28]* | 1.576 | 3.354 | - | - |
| 190168-030C (Gel) [Day 15] | - | - | 44.638 | 138.018 |

*Day 15 data not collected

**Comments**

***1. The data indicate that tazarotene cream 0.1% is less bioavailable systemically than tazarotene gel at Day 15 of application over 15% BSA. No comparison can be made with face-only application at Day 15, because of the lack of data collection in 190168-022. At Day 28, tazarotene cream 0.1% is still less bioavailable than tazarotene gel 0.1% with face-only application (tazarotenic acid: 1.259 vs 1.576 ng.hr/mL for mean $AUC_{0\text{-}24\ hr}$, and 1.940 vs 3.354 ng.hr/mL for individual maximum $AUC_{0\text{-}24\ hr}$).***

2. The systemic bioavailability data for tazarotene gel 0.1% in the treatment of acne should be incorporated into the label for tazarotene gels. A labeling supplement to address the new data would be recommended.

ii. Therapeutic Drug Monitoring

The two clinical trials with blood sampling for tazarotenic acid levels are:

- 190168-025C (phase 2 trial on photodamaged skin)
- 190168-029C (phase 3 trial on acne)

Study 190168-025C was a dose-ranging study in patients with photodamaged skin. A subset of 65 patients applied tazarotene cream 0.01%, 0.025%, 0.05%, 0.1%, or vehicle or tretinoin emollient cream 0.05% to photodamaged skin, and had blood sampling for levels of tazarotenic acid. Study 190168-029C used plasma samples from a subset of 48 patients (22 female and 26 male patients) in tazarotene cream 0.1% treatment group, and 40 patients (18 female and 22 male patients) in the vehicle group.

**Levels of Tazarotenic Acid in Patients Using Tazarotene Cream 0.1% in 190168-025C and -029C**

| Study - week | Plasma Concentration (mean ± SD) ng/mL | Highest Level ng/mL |
|---|---|---|
| 025C- week 4 | 0.092 ± 0.032 | 0.141 |
| 025C- week 24 | 0.096 ± 0.092 | 0.339 |
| 029C- week 4 | 0.078 ± 0.073 | 0.406 |
| 029C- week 8 | 0.052 ± 0.037 | 0.169 |

Study 190168-029C: N = 48, Study 190168-025C: N = 15

Plasma tazarotenic acid levels appeared to be independent of gender, age, and body weight. There was no evidence that tazarotenic acid accumulated over time.

**Comments**

1. Data from therapeutic drug monitoring studies may be difficult to interpret because of differences between patients in the skin condition, use of ancillary measures, method of drug application, and time of sampling. However, they appear to be

consistent with the data in the face-only portion of Study 190168-035C (mean Cmax between 0.069 and 0.104 ng/mL; highest level between 0.136 and 0.2 ng/mL).
2. The Applicant believes it is unlikely that the low plasma levels of tazarotenic acid would be associated with systemic adverse events or changes in laboratory data. In this regard, they presented the oral tazarotene study (190168-018P; see Section VII.C.3.d) data for comparison. At an oral dose of 1.1 mg/d, the Cmax on Day 61 was 28.9 ng/mL, which is at least two logs above the mean levels seen with therapeutic drug monitoring. Systemic adverse effects could not be clearly delineated with oral tazarotene at that dose (1.1 mg/d).

b. Risk of Adverse Pregnancy Outcome

This section addresses adverse pregnancy outcome in terms of hazard identification, risk assessment, and risk management. It will also address the Applicant's rationale for proposing Pregnancy Category C for the acne indication.

i. Hazard Identification. Two hazard phenomena can be identified: teratogenesis and elective termination of pregnancy. The severity and seriousness of these adverse events may involve value judgement.

(1) Tazarotene is a retinoid, a teratogen.

- For teratogenesis, human data are more relevant than animal data. Currently, tazarotene is marketed as topical formulations (gel or cream), and no birth defects in association with their use have been reported. On July 24, 2001, Allergan submitted MedWatch reports on two French cases of miscarriage after exposure to tazarotene gel. No details were given in the reports, and it is unclear whether any malformations were observed in the fetuses aborted.
- Preclinical animal data have well documented evidence of reproductive toxicity of tazarotene in several animal species, including rats and rabbits (see Pharm/Tox review). Extrapolation of animal data to humans is routinely done in a regulatory setting, but evidence for validity is not available in most instances. For other retinoids such as isotretinoin, the evidence can be compelling, as there are human data to corroborate the animal data.
- The severity of this hazard for **tazarotene** in **humans** is unknown. Birth defects can be major or minor, and structural or functional. However, teratogenic effect of some retinoids have been shown to be major in **humans** (e.g., isotretinoin). A conservative approach to regard this as a class effect would therefore be appropriate.
- Although the seriousness of this hazard for tazarotene would depend on the type of birth defect and its severity, congenital anomalies/birth defects are classified as "serious adverse experiences" by regulation.

(2) Elective termination of pregnancies exposed to tazarotene is also of public health concern.

- Elective termination has occurred in clinical trials on tazarotene. Although the reports might state that the termination was unrelated to the use of tazarotene, it is often difficult to substantiate such assurances. In the phase 3 acne program for tazarotene cream 0.1%, three pregnancies were observed, two of which ended in elective termination:
  - One vehicle-treated patient had a positive pregnancy test at week 4 (patient #1384, Study 190168-031C) and terminated the pregnancy.
  - One tazarotene cream-treated patient had a positive pregnancy test at week 8 and had a healthy baby (patient #1301, Study 190168-031C).
  - One tazarotene-treated patient had a positive pregnancy test at the exit visit (week 12, patient completed the study) (patient #1087, Study 190168-029C) and terminated the pregnancy.

In addition, in one of the PK studies on tazarotene gel (190168-022) reported in this submission, two patients tested positive for pregnancy upon exiting the study. One patient elected to terminate the pregnancy, and the other patient was lost to follow-up.

- Although the severity and seriousness of death is undisputed, and death is classified under "serious adverse experiences" by regulation, however, society apparently has left the death of fetuses to individual judgment by the pregnant woman.

ii. Risk Assessment. Risk evaluation is often made using the methodology of probability, as a rate or ratio in terms of occurrence, or as a "margin of safety" away from the hazard.

(1) Risk of teratogenesis in humans as an incidence rate.

- As there are no human data on teratogenesis from tazarotene use, risk assessment cannot be addressed as such.

(2) Risk of teratogenesis in humans using the "margin of safety" methodology.

- The Biopharm Reviewer and the Pharm/Tox Reviewer have both contributed to the assessment of human teratogenic risk for tazarotene cream 0.1%.
- The margin of safety can be estimated by comparing the systemic exposure resulting from clinical use in the treatment of acne and that in humans or animals leading to findings of teratogenesis. Because of the uncertainty of extrapolation across species, such estimations are theoretical when the basis for estimation is from experimental animal data. However, as birth defects are serious adverse experiences by regulation, a conservative approach is appropriate, especially since the findings in animals can be profound, including death *in utero*.
- The rat is the more susceptible species for tazarotene-induced reproductive toxicity, and will be used as the species for comparison.
- A conservative approach is also made in selecting the clinical exposure used for estimation. The maximum AUC observed in the human PK study 190168-035C is used as the basis for comparison with animal exposure (AUC) that led to malformations.
- In rats dosed orally at 0.5 mg/kg/day, the AUC of tazarotenic acid achieved was 94 ng.hr/mL, and increased skeletal alterations, including supernumerary ribs, and two litters with cardiac anomalies were observed. At 0.1 mg/kg/day, the AUC was 20.6 ng.hr/mL, and the rats developed decreased fetal body weight. The following Table provides for comparison between human clinical exposure in the treatment of acne and rat exposure associated with reproductive toxicity:

**Comparative Systemic Exposure to Tazarotenic Acid between Treatment of Acne in Humans and Rat Reproductive Toxicity**

| | Face Only | Exaggerated Application (15% BSA) |
|---|---|---|
| Maximal Human Exposure ($AUC_{0\text{-}24\ hr}$) in Acne* | 3.132 ng.hr/mL | 26.591 ng.hr/mL |
| As Multiple of Rat AUC 94 ng.hr/mL | 1/30 | 1/3.5 |
| As Multiple of Rat AUC 20.6 ng.hr/mL | 1/6.6 | 1/0.8 |

*Data from 190168-035C

- Thus, reproductive toxicity can be observed in rats at systemic exposures ranging between 0.8 to 30 times human exposure in the treatment of acne, depending on the clinical dose applied and the type of toxicity observed. **Even with face-only application, the AUC achieved in the treatment of acne may have only a safety margin of 6.6. With exaggerated dosing to facial and non-facial areas, there is an almost vanishing safety margin.**

(3) Risk of elective termination of pregnancy.

- It is beyond the scope of this review to address this issue. There is insufficient information to address it as a rate or a margin of safety in relation to pregnant women exposed to tazarotene. There are also multiple factors unrelated to drug safety and efficacy that impact on a decision for termination. **However, the existence of a risk for termination on the basis of knowing that one's pregnancy has been exposed to tazarotene can never be excluded.**

iii Risk Management. In this instance, the actual human risk for teratogenesis is unknown, and is based on theoretical assumptions. The risk of elective termination of pregnancy also cannot be estimated. Risk management is therefore a balancing act and most challenging, unlike in cases where definitive human data are available for either, or both. Under such circumstances, risk management methodology is primarily through risk communication to enhance safe and effective use of the drug product.

(1) Pregnancy Category.

The Applicant is requesting Pregnancy Category C for this product's acne indication (see Section VII.C.5.b.iv). However, in view of the substantial risk of reproductive toxicity based on animal data, and the availability of other products for the treatment of acne vulgaris of comparable severity, it is reasonable to retain Category X for tazarotene cream 0.1% in the treatment of acne. The regulations require that when the risks clearly outweigh any benefit (for example, safer drugs or other forms of therapy are available), labeling should use Category X. In this case:

- Risk of teratogenesis from use of tazarotene in acne, as based on comparative exposure data between humans and rats, is within the range expected of birth defects and decreased fetal weight in rats. There is little margin of safety, especially with exaggerated application.
- There are many acne drugs on the market, and a search of the PDR gives the following list for "acne vulgaris" (not including those for severe recalcitrant cystic acne, and adjuncts for acne treatment). The list is probably not exhaustive, and I tabulate here under three headings. Although it is difficult to compare safety because the adverse effect profiles of different drugs may not necessarily lend themselves to fair comparison, it is reasonable to conclude that for the type of "acne vulgaris" treatable with tazarotene cream 0.1%, there is no lack of "other forms of therapy", including possibly "safer drugs". For a discussion of other topical retinoids, see below (Section VII.C.5.b.iv).

**Drugs Listed in PDR for the treatment of "Acne Vulgaris"**

| Antimicrobials | Retinoids | Miscellaneous |
|---|---|---|
| Akne-Mycin Ointment | Avita formulations | Ortho Tri-Cyclen 21 or 28 Tablets |
| Benzamycin Topical Gel | Differin formulations | Azelex Cream |
| Cleocin T formulations | Retin-A formulations | Benzyl peroxide (Benzac AC, |
| Clindets Pledgets | Tazorac Gel | Brevoxyl, and Triaz, formulations) |
| Declomycin Tablets | | |
| Doryx Coated Pellet Filled Capsules | | |
| Emgel 2% Topical Gel | | |
| Klaron Lotion 10% | | |
| Monodox Capsules | | |
| Plexion formulations | | |
| Sulfacet-R Lotion | | |
| Vibramycin formulations | | |

(2) Other parts of labeling.

Risk communication involves not only the Pregnancy Category. The package insert as well as the PPI will contain appropriate language advising use of birth control measures in women of child-bearing potential who want to use the product to treat acne, and to start its use after pregnancy test and during a normal menstrual period.

(3) Managing risk of elective termination of pregnancy.

Regarding elective termination of pregnancy, risk management goes beyond risk communication to enhance safe and effective use of the drug product, and cannot be fully addressed here. Some possible steps involving risk communication are:

- The label should provide a balanced account of the available information for the prescriber and patient to "apprise of the potential hazard to the fetus" as well as the negative findings after use in pregnancy. Such findings are in the draft label, and the Applicant should be asked to update them on an ongoing basis.
- It has been amply documented that apart from needed medications used to treat potentially serious, life-threatening conditions in pregnancy, most drug exposures in pregnancy are inadvertent. In actual practice, it is highly unlikely that there will be any planned use of tazarotene cream for acne in pregnancy. Thus, elective termination probably arises from inadvertent exposure, and is possibly associated with the fear of the potential consequences of having a child with birth defects. Education is the key to resolve this problem, and cooperation with the Organization of Teratology Information Services (OTIS) may be useful. How education can allay this fear will form an illuminating chapter of risk communication.
- To some degree, preventing usage in pregnancy by effective risk communication will be expected to reduce the likelihood of exposure in pregnancy, and as a corollary, the likelihood of elective termination. How this can be effectively conveyed without imposing fear leading to elective termination is the challenge. Moreover, as indicated above, most exposures are inadvertent, and not necessarily amenable to such preventive steps.

Ultimately, risk management in the use of topical retinoids should be a fair balance between the need to inform consumers of the risks of teratogenesis and the restraint from creating panic that leads to tragic consequences. "There is a fine line between a fair planning and the possibility that you would be creating panic." (Speech by Bernard A. Schwetz, Ph.D., Acting Deputy Commissioner and Senior Advisor for Science, FDA, on September 17, 2001). However elusive the middle ground may be, it is necessary to keep trying to find it for the sake of public health.

iv. Allergan's Rationale in Proposing Pregnancy Category C for the Acne Indication.

There are four reasons provided:

1. Systemic exposure to tazarotenic acid following topical application of a liberal amount of tazarotene cream, even to an exaggerated body surface area of 15%, is generally low (mean Cmax ± SD: 1.20 ± 0.41 ng/mL), about 4-fold lower than that following application of tazarotene gel 0.1% (mean Cmax ± SD: 4.84 ± 6.05 ng/mL) and at least 5-fold lower than endogenous concentrations of retinoids (total mean plasma concentration 6.63 ng/mL).
2. The concentrations of tazarotenic acid found in plasma following application of tazarotene cream to the face (0.136 ± 0.107 ng/mL) are similar to the concentrations of adapalene and metabolites associated with the topical application of adapalene 0.1% gel (0.045 ± 0.032 ng/mL), and much less (at least 50-fold less) than total levels of endogenous retinoids.

3. The margin of safety for use of tazarotene cream 0.1% in acne *vis a vis* teratogenic risk in animals (rats and rabbits) is at least 5 to 100-fold for application over an exaggerated BSA (15%) in humans, and 60-1600 fold for application to the face only.
4. The developmental toxicity findings in rats and rabbits are supported by the fact that tazarotenic acid is more specific for RARβ and RARγ than for RARα, and has considerably less affinity for RARα than tretinoin. Retinoids with a greater affinity for RARα have been shown to be associated with a wider variety and severity of developmental toxicities in animals.

A comparison between available topical retinoids in the treatment of acne can be shown in the following Table:

**PK Profile and Retinoid Receptor Binding of Topical Retinoids for Acne Treatment**

| | TDM[a] Acne Study Results (ng/mL) | Plasma PK Parameters From PK Studies for Facial Acne Mean ± SD (min, max) | | Plasma Protein Binding | Receptor Affinity, $EC_{50}$ (ng/mL) [ for Induction of Chloramphenicol Acetyl Transferase Expression] Mean ± SD (n = number of assays) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | RAR | | | RXR |
| | | $C_{max}$ (ng/mL) | $AUC_{0-24}$ (ng•hr/mL) | | α | β | γ | α |
| Tazorac 0.1% Gel QD (Tazarotenic Acid) | [b] ≤0.15 detectable 8 in 70 pts | [d]0.136 ± 0.107 (0.014, 0.323) N = 11 | [d]1.58 ± 1.17 (0.16, 3.35) N = 11 | > 99% | 45.9 ± 6.1 (n = 3) | 1.16 ± 0.71 (n = 4) | 7.11 ± 1.62 (n = 4) | No Activity |
| Tazorac Cream 0.1% QD (Tazarotenic Acid) | [c]0.078 ± 0.073 (0.012, 0.406) N = 47 | [e]0.104 ± 0.060 (0.029, 0.200) N = 8 | [e]1.54 ± 1.01 (0.33, 3.13) N = 8 | > 99 % | 45.9 ± 6.1 (n = 3) | 1.16 ± 0.71 (n = 4) | 7.11 ± 1.62 (n = 4) | No Activity |
| Tazorac 0.1% Gel QD (Tazarotene) | [b] ≤0.13 detectable 1 in 70 patients | NA | NA | NA | No Activity | 28.1 ± 19.7 (n = 3) | 38.6 ± 11.2 (n = 3) | No Activity |
| Tazorac Cream 0.1% QD (Tazarotene) | NA | NA | NA | NA | No Activity | 28.1 ± 19.7 (n = 3) | 38.6 ± 11.2 (n = 3) | No Activity |
| Tretinoin 0.1% Cream QD, RETIN-A® (Tretinoin) | [f]NA | [d]2.9 ± 0.4 (2.4, 3.6) N = 10 | [d]60.4 ± 9.9 (47.1, 73.8) N = 10 | 98-99% | 6.00 ± 1.20 (n = 8) | 1.08 ± 0.48 (n = 8) | 0.24 ± 0.09 (n = 8) | 1050 ± 90 (n = 4) |
| Tretinoin 0.1% Cream QD, RETIN-A® (Isotretinoin) | [f]NA | [d]1.2 ± 0.7 (0, 2.1) N = 10 | [d]24.2 ± 18.2 (0, 47.0) N = 10 | 99.9% | NA | NA | NA | NA |
| Tretinoin 0.1% Cream QD, RETIN-A® (Oxoisotretinoin) | [f]NA | [d]1.6 ± 0.6 (0.9, 2.6) N = 10 | [d]35.2 ± 12.9 (18.5, 53.3) N = 10 | NA | NA | NA | NA | NA |
| Adapalene 0.1% Gel QD, DIFFERIN® (Adapalene) | NA | [d]0.045 ± 0.032 (0.016, 0.122) N = 10 | [d]0.637 ± 0.458 (0.177, 1.53) N = 10 | NA | 354 ± 58 (n = 2) | 3.72 ± 2.07 (n = 2) | 5.78 ± 3.72 (n = 2) | No Activity |

[a]Peak plasma drug concentrations in therapeutic drug monitoring studies for acne
[b]Reference: Study R168-221-8606, Report PK-94-102 (gel)
[c]Reference: Study 190168-029C, Report PK-00-084, week 4 (cream)
[d]Reference: Study 190168-022, Report PK-99-123, day 28 (gel)
[e]Reference: Study 190168-035C, Report PK-00-076, from the face only group, day 15 (cream).
[f]NA: Not Applicable/Available
Note: a) tazarotenic acid does not bind to RXRα, RXRβ and RXRγ receptors based on transfected CV-1 cells assay
b) $EC_{50}$ of tretinoin: 927 to 1508 nM for RXRα, RXRβ and RXRγ receptors based on CV-1 cells assay

Comments

1. The Applicant states that tazarotenic acid levels attained in acne treatment are lower than the concentrations of endogenous retinoids (all-*trans*-retinoic acid, 13-*cis*-retinoic acid, and 13-*cis*-4-oxoretinoic acid), which have been reported to be naturally present in plasma at concentrations ranging from 1 to 4 ng/mL. They are also similar to the levels attained with the use of topical adapalene 0.1% gel in acne. This comparison of plasma levels between different retinoids is not informative. As the Applicant clearly points out, they have different properties. Moreover, there is a potential that the endogenous retinoids may actually compete with each other, hence decreasing the net effect despite higher levels. There is inadequate information at

this point to draw conclusions based on comparing plasma levels of different retinoids.
2. The "margin of safety" over teratogenic levels in rats is stated to be 5 and 60 fold for application to 15% BSA and face only, respectively. This was estimated using the mean exposures seen in Study 190168-035C. A more conservative estimate has been shown above, using maximum AUC values achieved in the treatment of acne. This margin can be shown to be as low as 3.5 and 30 fold (for 15% BSA and facial applications, respectively) for clear-cut birth defects, and 0.8 and 6.6 fold (for 15% BSA and facial applications, respectively) for decreased fetal weight. This low margin of safety speaks against use in pregnancy.
3. It is generally difficult to compare safety between drugs. The Applicant has made an argument that the three topical retinoids in the treatment of acne (tretinoin, adapalene, and tazarotene) have similar safety profiles, retinoid receptor affinity, and plasma protein binding. Yet, both adapalene and tretinoin are of Pregnancy Category C. For tretinoin, this substance is made endogenously, there is constant interconversion between isomers, and usage in acne does not appears to affect the levels of endogenous retinoids to a measurable extent. With adapalene, the affinity to RARα is substantially lower (7.7 times less than tazarotenic acid, and 59 times than tretinoin). The DIFFERIN® label also indicates that the maximum recommended human dose is 100 to 200 times lower than that needed for teratogenesis in rats and rabbits, respectively.
4. Receptor affinity is one aspect of the equation on teratogenesis. The situation in vivo is complex, and the interplay between the retinoid ligand, plasma protein binding, receptor, endogenous competitors, antagonists, placental transfer, the transactivation process itself, as well as species differences cannot be simply considered in a vacuum. The fact remains that a hazard has been identified in animal studies, and its risk must be managed conservatively because of the serious nature of the potential consequences.

### D. Adequacy of Safety Testing

- Safety data are adequate in terms of exposure and adequacy of assessments carried out. The PK studies on tazarotene formulations included only females, and the validity of such data for extrapolation to males has not been addressed.

### E. Summary of Critical Safety Findings and Limitations of Data

- 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 in skin.
- As the Applicant is requesting Pregnancy Category C for the acne indication, consideration has been given to systemic bioavailability and to nonclinial data concerning teratogenicity, because there are no human data attesting to teratogenesis due to the administration of tazarotene. Comparative systemic bioavailability data in relation to teratogenicity seen in animals do not support Category C designation for tazarotene cream 0.1% in the treatment of acne. Especially under exaggerated use conditions, systemic exposure to tazarotenic acid may reach levels comparable to teratogenic levels in rats.

## VIII. Dosing, Regimen, and Administration Issues

Recommended dosing, regimen and administration follow what was used in the two adequate and well-controlled phase 3 trials. The clinical program did not include dose-ranging. In order to reflect expected clinical practice, one aspect of the study design in phase 3 was the inclusion of a provision for patients who experienced untoward irritation to temporarily reduce dosing frequency. However, there is no separate analysis for efficacy in those patients who had reduced dosing frequency.

The choice of the dosing regimen studied has been based on what tazarotene gel 0.1% has in the approved label, with some differences. In previous studies with tazarotene gel, efficacy in the treatment of acne vulgaris was not demonstrated at concentrations below 0.1%. Higher concentrations of gel or cream have been difficult to attain because of CMC issues (communications from the Applicant in previous meetings, and confirmation by the CMC Reviewer, Dr. William Timmer). Once-daily dosing appears to be a preferred regimen in the treatment of acne in terms of patient compliance, and for tazarotene cream 0.1%, it is potentially less irritating than more frequent application (based on data with tazarotene gel 0.1%).

The draft label's DOSAGE AND ADMINISTRATION section states:

For tazarotene gel 0.1%, the approved label states:

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

The differences between the labels should be resolved. It is noted that in the TAZORAC Cream label, the recommended dosing for psoriasis treatment includes mentioning of administration in the evening, as well as the approximate measurement of 2 mg/cm$^2$). Evening applications would be preferable because of the potential photoirritant effect of retinoids, and would also be consistent with the practice in the phase 3 acne trials.

## IX. Use in Special Populations

### A. Evaluation of Applicant Gender Effects Analyses and Adequacy of Investigation

Efficacy. See Biometrics Review for details in subset analyses for gender. The following Table provides for significant differences at Week 12 noted in the combined efficacy dataset (ITT) using Studies 190168-029C and -031C, with superiority over vehicle shown as a plus ($p<0.05$):

| | Percent Reduction in Lesion Counts | | | Overall Acne Assessment | |
|---|---|---|---|---|---|
| | Total | Inflammatory | Non-inflammatory | One grade reduction | Minimal or none |
| Female (N=417) | +[1] | + | +[2] | + | + |
| Male (N=430) | + | + | + | + | + |

1 In the tazarotene treatment group, the percent reduction from baseline in total lesion count was significantly higher for female patients than male patients at week 12.

2 In the tazarotene treatment group, the percent reduction from baseline in non-inflammatory lesion count was significantly higher for female patients than male patients at week 12.

Safety. In each of the gender subgroups, there was a significantly higher incidence of total adverse events, and dermatological events, in the tazarotene cream treatment group than in the vehicle group. Neither gender subgroup experienced significantly higher incidences of adverse events than the other.

**Number (%) of Patients per Gender Subgroup with Any Adverse Event in Phase 3 Acne Studies**

| Gender | Tazarotene 0.1% N = 424 | Vehicle N = 423 | p-value [a] |
|---|---|---|---|
| Male | 142/221 (64.3%) | 64/209 (30.6%) | < 0.001 |
| Female | 138/203 (68.0%) | 67/214 (31.3%) | < 0.001 |

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

Both genders treated with tazarotene cream 0.1% experienced significantly more *burning sensation on the skin, desquamation, dry skin, erythema, and skin irritation* than vehicle patients. Male patients treated with tazarotene cream 0.1% also experienced significantly more *pruritus* than vehicle patients.

- These analyses are post-hoc and limited by the fact that the studies were not powered to demonstrate differences between the genders in safety or efficacy.
- From the available data, the differences in the safety and efficacy profiles between the genders appear to be small.
- The Applicant has conducted additional PK studies in females for systemic bioavailability of tazarotene cream and gel 0.1% (See Section VII.C.3.c and VII.C.5.a.i), but not in males. It is not clear whether the PK data on females are generalizable to all.

## B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Efficacy. See Biometrics Review for details in subset analyses for age and race. The following Table provides for significant differences at Week 12 noted in the combined efficacy dataset (ITT) using 190168-029C and -031C, with superiority over vehicle shown as a plus ($p<0.05$).

| | Percent Reduction in Lesion Counts | | | Overall Acne Assessment | |
|---|---|---|---|---|---|
| | Total | Inflammatory | Non-inflammatory | One grade reduction | Minimal or none |
| Age | | | | | |
| ≤17 (N=495) | + | + | + | + | + |
| 18-29 (N=255) | + | + | + | + | |
| ≥30 (N=97) | +[1] | | +[2] | +[3] | |
| Race | | | | | |
| Caucasian (N=614) | + | + | + | + | + |
| Black (N=80) | + | | + | + | |
| Hispanic (N=128) | + | | + | | |
| Asian (N=19) | | | | | |
| Other (N=6) | | | | | |

1 In the tazarotene treatment group, the age subgroup ≥ 30 years showed a significantly higher percent reduction from baseline in total lesion count than the age subgroup ≤17 years.

2 In the tazarotene treatment group, the age subgroup ≥ 30 years showed a significantly higher percent reduction from baseline in non-inflammatory lesion count than age subgroups ≤17 and 18-29 years.
3 In the tazarotene treatment group, the age subgroup ≥ 30 years showed a significantly higher incidence of clinical improvement than age subgroup ≤17 years.

Safety. In each of the age subgroups, there were significantly more total adverse events, and dermatological events, in the tazarotene cream treatment group than in the vehicle group. This was also true for the Caucasian, Black and Hispanic subgroups when analyzed by race.

**Number (%) of Patients per Age & Race Subgroup with Any Adverse Event in Phase 3 Acne Studies**

| Age Category | Tazarotene 0.1% N = 424 | Vehicle N = 423 | p-value [a] |
|---|---|---|---|
| ≤ 17 years | 177/250 (70.8%) | 80/245 (32.7%) | < 0.001 |
| 18 – 29 years | 68/123 (55.3%) | 35/132 (26.5%) | < 0.001 |
| ≥ 30 years | 35/51 (68.6%) | 16/46 (34.8%) | < 0.001 |
| Caucasian | 219/315 (69.5%) | 100/299 (33.4%) | < 0.001 |
| Black | 24/43 (55.8%) | 8/37 (21.6%) | 0.003 |
| Hispanic | 29/53 (54.7%) | 21/75 (28.0%) | 0.003 |
| Asian | 7/10 (70.0%) | 2/9 (22.2%) | 0.070 |
| Other | 1/3 (33.3%) | 0/3 ( 0.0%) | > 0.999 |

a Between group p-value based on Pearson's chi-square test

In the tazarotene cream treatment group, the subgroup of patients ≤17 years old had significantly higher incidences of adverse events than the subgroup of patients aged 18 to 29 (p = 0.003). In all subgroups of patients analyzed by age, those receiving tazarotene experienced significantly more *desquamation and dry skin* than vehicle patients. In addition, the subgroup of patients ≤17 years treated with tazarotene also had significantly more *burning sensation on the skin, erythema, skin irritation, and stinging*, and the 18 to 29 year-old patients similarly treated more *burning sensation and erythema* than vehicle-treated patients.

None of the race subgroups experienced significantly higher incidences of adverse events than other race subgroups. In the Asian and "Other" race subgroups there were no statistically significant between-treatment group differences for any individual adverse event.

Caucasian, Black, and Hispanic patients treated with tazarotene cream 0.1% experienced more *burning sensation on the skin, desquamation, and erythema* than vehicle patients. In addition, Hispanic patients given tazarotene experienced significantly more *dry skin*, and Caucasians more *dry skin and skin irritation* than their vehicle-treated counterparts. There was also a statistically significant between-treatment group difference for the adverse event "*face pain*" among Caucasians.

- These analyses are post-hoc and limited by the fact that the studies were not powered to demonstrate differences between the age or racial groups in safety or efficacy.
- Taking the sample sizes of various subgroups (by age and by race) into consideration, the available data suggest that the differences in the safety and efficacy profiles among the age or race subgroups are small.

### C. Evaluation of Pediatric Program

The pediatric program has included studying pediatric patients above the age of 12 in phase 3 clinical trials. Since acne is very rare before puberty, the program is acceptable. A partial waiver has been requested by the Applicant for studies in neonates, infants and children. This waiver may be granted.

### D. Comments on Data Available or Needed in Other Populations

- Because the drug's action is local for efficacy, and systemic bioavailability is small in the treatment of acne, no special studies in patients with renal or hepatic impairment have been conducted.
- There are no data on planned use in pregnancy, as the clinical studies excluded pregnant women, and women of child-bearing potential had to have acceptable measures of birth control. There have been two reported cases of pregnancy in association with use of tazarotene cream studies for acne, one resulting in elective termination of pregnancy and the other an apparently healthy child. In the 120-day safety update, another case of pregnancy exposure during the use of tazarotene cream 0.1% in a trial for photodamage was reported. An apparently healthy baby was also reported to have been delivered. There is not adequate information to draw conclusions on these reports.
- As discussed above, pediatric population under the age of 12 has not been studied, but as acne is rare in that age group, a partial waiver may be granted for such studies.
- Also discussed above, the PK studies included females and not males. The applicability of the data obtained to males should be addressed.

## X. Conclusions and Recommendations

### A. Conclusions

- The Applicant has demonstrated efficacy of tazarotene cream 0.1% in the topical treatment of acne vulgaris. The adverse effects in the clinical trials are primarily local and due to the irritation effect of the retinoid. The benefits outweigh the risks in the treatment of acne vulgaris, except in pregnant women.

- Although systemic bioavailability appears to be less from tazarotene cream (vs tazarotene gel), the risk of retinoid-induced teratogenesis cannot be completely excluded when tazarotene cream 0.1% is used in the treatment of acne, especially under exaggerated use conditions beyond the face.

### B. Recommendations

1. This Efficacy Supplement is approvable, pending labeling changes.

2. Labeling should be changed to that as recommended below (in the Appendix II).

3. The labeling of tazarotene gels should be updated to include relevant information contained in the current submission.

4. The Applicant should address the applicability of the data from the PK studies in this submission to males.

5. A partial waiver for pediatric study requirements for neonates, infants and children may be granted.

## XI. Appendices

## A. Appendix I. Adverse Events in Phase 3 Clinical Trials on Tazarotene Cream 0.1% in the Treatment of Acne

**All Adverse Events in Phase 3 Trials: Incidence by Body System and Reaction (Safety Population)**

| Body System | COSTART Term | Tazarotene 0.1% (N=424) | Vehicle (N=423) | P-Value [c] |
|---|---|---|---|---|
| Overall | | 280 ( 66.0%) | 131 ( 31.0%) | <0.001 |
| BODY | Overall | 56 ( 13.2%) | 35 ( 8.3%) | 0.020 |
| | ABDOMINAL PAIN | 1 ( 0.2%) | 1 ( 0.2%) | >0.999 [d] |
| | ABSCESS | 1 ( 0.2%) | 0 ( 0.0%) | >0.999 [d] |
| | ACCIDENTAL INJURY | 1 ( 0.2%) | 1 ( 0.2%) | >0.999 [d] |
| | ALLERGIC REACTION | 4 ( 0.9%) | 2 ( 0.5%) | 0.686 [d] |
| | ARM PAIN | 0 ( 0.0%) | 2 ( 0.5%) | 0.249 [d] |
| | BACK PAIN | 2 ( 0.5%) | 4 ( 0.9%) | 0.451 [d] |
| | CYST | 1 ( 0.2%) | 0 ( 0.0%) | >0.999 [d] |
| | FACE PAIN | 8 ( 1.9%) | 2 ( 0.5%) | 0.107 [d] |
| | FEVER | 1 ( 0.2%) | 1 ( 0.2%) | >0.999 [d] |
| | FLU SYNDROME | 8 ( 1.9%) | 7 ( 1.7%) | 0.798 |
| | HEADACHE | 21 ( 5.0%) | 13 ( 3.1%) | 0.164 |
| | INFECTION | 6 ( 1.4%) | 5 ( 1.2%) | 0.765 |
| | KNEE PAIN | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| | LEG PAIN | 1 ( 0.2%) | 0 ( 0.0%) | >0.999 [d] |
| | MALAISE | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| | NECK PAIN | 0 ( 0.0%) | 2 ( 0.5%) | 0.249 [d] |
| | PAIN | 4 ( 0.9%) | 4 ( 0.9%) | >0.999 [d] |
| CV | Overall | 1 ( 0.2%) | 2 ( 0.5%) | 0.624 [d] |
| | MIGRAINE | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| | SYNCOPE | 1 ( 0.2%) | 1 ( 0.2%) | >0.999 [d] |
| DIG | Overall | 11 ( 2.6%) | 14 ( 3.3%) | 0.539 |
| | ANOREXIA | 1 ( 0.2%) | 0 ( 0.0%) | >0.999 [d] |
| | BILIARY PAIN | 1 ( 0.2%) | 0 ( 0.0%) | >0.999 [d] |
| | CHEILITIS | 3 ( 0.7%) | 1 ( 0.2%) | 0.624 [d] |
| | CONSTIPATION | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| | DYSPEPSIA | 2 ( 0.5%) | 1 ( 0.2%) | >0.999 [d] |
| | GASTROENTERITIS | 3 ( 0.7%) | 6 ( 1.4%) | 0.341 [d] |
| | GASTROINTESTINAL | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| | GINGIVITIS | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| | NAUSEA | 2 ( 0.5%) | 1 ( 0.2%) | >0.999 [d] |
| | TOOTH DISORDER | 0 ( 0.0%) | 2 ( 0.5%) | 0.249 [d] |
| | VOMITING | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| ENDO | Overall | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| | HYPOTHYROIDISM | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| MS | Overall | 7 ( 1.7%) | 7 ( 1.7%) | 0.996 |
| | BONE FRACTURE, CAUSE UNKNOWN | 4 ( 0.9%) | 3 ( 0.7%) | >0.999 [d] |
| | JOINT DISORDER | 1 ( 0.2%) | 1 ( 0.2%) | >0.999 [d] |
| | MYALGIA | 3 ( 0.7%) | 0 ( 0.0%) | 0.249 [d] |
| | TENOSYNOVITIS | 0 ( 0.0%) | 2 ( 0.5%) | 0.249 [d] |
| | TRAUMATIC BONE FRACTURE | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| NER | Overall | 2 ( 0.5%) | 5 ( 1.2%) | 0.287 [d] |
| | DEPRESSION | 0 ( 0.0%) | 2 ( 0.5%) | 0.249 [d] |
| | HYPERTONIA | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| | HYPESTHESIA | 1 ( 0.2%) | 0 ( 0.0%) | >0.999 [d] |
| | INSOMNIA | 1 ( 0.2%) | 1 ( 0.2%) | >0.999 [d] |
| | PARESTHESIA | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| RES | Overall | 58 ( 13.7%) | 63 ( 14.9%) | 0.614 |
| | ASTHMA | 1 ( 0.2%) | 1 ( 0.2%) | >0.999 [d] |

| | | | | |
|---|---|---|---|---|
| | BRONCHITIS | 3 ( 0.7%) | 5 ( 1.2%) | 0.506 [d] |
| | COUGH INCREASED | 5 ( 1.2%) | 2 ( 0.5%) | 0.451 [d] |
| | INFECTION | 31 ( 7.3%) | 34 ( 8.0%) | 0.691 |
| | INFECTION SINUS | 4 ( 0.9%) | 4 ( 0.9%) | >0.999 [d] |
| | LUNG DISORDER | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| | PHARYNGITIS | 14 ( 3.3%) | 9 ( 2.1%) | 0.293 |
| | PNEUMONIA | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| | RHINITIS | 3 ( 0.7%) | 8 ( 1.9%) | 0.128 |
| | SINUSITIS | 3 ( 0.7%) | 2 ( 0.5%) | >0.999 [d] |
| SKIN | Overall | 230 ( 54.2%) | 41 ( 9.7%) | <0.001 |
| | ACNE | 5 ( 1.2%) | 3 ( 0.7%) | 0.725 [d] |
| | ALLERGIC CONTACT DERMATITIS | 1 ( 0.2%) | 1 ( 0.2%) | >0.999 [d] |
| | BURNING SENSATION | 60 ( 14.2%) | 3 ( 0.7%) | <0.001 |
| | DERMATITIS | 1 ( 0.2%) | 1 ( 0.2%) | >0.999 [d] |
| | DESQUAMATION | 124 ( 29.2%) | 12 ( 2.8%) | <0.001 |
| | DRY SKIN | 114 ( 26.9%) | 11 ( 2.6%) | <0.001 |
| | ECZEMA | 1 ( 0.2%) | 0 ( 0.0%) | >0.999 [d] |
| | ERYTHEMA | 88 ( 20.8%) | 9 ( 2.1%) | <0.001 |
| | ERYTHEMA | 1 ( 0.2%) | 1 ( 0.2%) | >0.999 [d] |
| | SUN-INDUCED EXCORIATED SKIN | 2 ( 0.5%) | 1 ( 0.2%) | >0.999 [d] |
| | HERPES SIMPLEX | 1 ( 0.2%) | 0 ( 0.0%) | >0.999 [d] |
| | INFLAMMATION SKIN | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| | IRRITATION SKIN | 18 ( 4.2%) | 1 ( 0.2%) | <0.001 |
| | LACERATION SKIN | 3 ( 0.7%) | 0 ( 0.0%) | 0.249 [d] |
| | MACULOPAPULAR RASH | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| | NAIL DISORDER | 1 ( 0.2%) | 0 ( 0.0%) | >0.999 [d] |
| | PAPULES | 1 ( 0.2%) | 0 ( 0.0%) | >0.999 [d] |
| | PRURITUS | 20 ( 4.7%) | 6 ( 1.4%) | 0.005 |
| | RASH | 4 ( 0.9%) | 1 ( 0.2%) | 0.374 [d] |
| | SKIN BURNS | 1 ( 0.2%) | 0 ( 0.0%) | >0.999 [d] |
| | SKIN DISCOLORATION | 4 ( 0.9%) | 0 ( 0.0%) | 0.124 [d] |
| | SKIN PAIN | 1 ( 0.2%) | 0 ( 0.0%) | >0.999 [d] |
| | SKIN TIGHTNESS | 1 ( 0.2%) | 0 ( 0.0%) | >0.999 [d] |
| | STINGING SENSATION SKIN | 7 ( 1.7%) | 1 ( 0.2%) | 0.069 [d] |
| | WORSENED ACNE | 1 ( 0.2%) | 1 ( 0.2%) | >0.999 [d] |
| SS | Overall | 5 ( 1.2%) | 9 ( 2.1%) | 0.279 |
| | CHALAZION | 1 ( 0.2%) | 1 ( 0.2%) | >0.999 [d] |
| | CONJUNCTIVITIS | 0 ( 0.0%) | 2 ( 0.5%) | 0.249 [d] |
| | EAR PAIN | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| | EYE EDEMA | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| | INFECTION EAR | 3 ( 0.7%) | 3 ( 0.7%) | >0.999 [d] |
| | OTITIS MEDIA | 1 ( 0.2%) | 2 ( 0.5%) | 0.624 [d] |
| UG | Overall | 4 ( 0.9%) | 8 ( 1.9%) | 0.243 |
| | BREAST NEOPLASM | 0 ( 0.0%) | 1 ( 0.2%) | 0.499 [d] |
| | DYSMENORRHEA | 1 ( 0.2%) | 2 ( 0.5%) | 0.624 [d] |
| | TESTIS DISORDER | 1 ( 0.2%) | 0 ( 0.0%) | >0.999 [d] |
| | URINARY TRACT INFECTION | 2 ( 0.5%) | 5 ( 1.2%) | 0.287 [d] |

[a] Patient may have had more than one adverse event.
[b] The denominator is the number of patients in the safety population.
[c] P-values were based on Pearson's chi-square or Fisher's exact test if any of the expected cell sizes is < 5.
[d] Fisher's exact test p-values

14 pages redacted from this section of the approval package consisted of draft labeling