# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPROVAL PACKAGE FOR:

# APPLICATION NUMBER

# 21-184/002

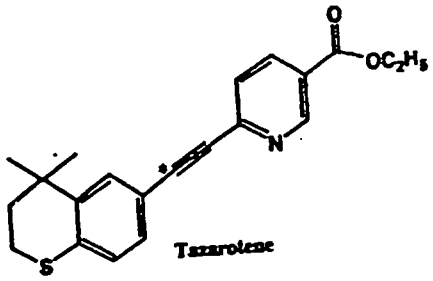
# Clinical Pharmacology and Biopharmaceutics Review

# Clinical Pharmacology/Biopharmaceutics Review

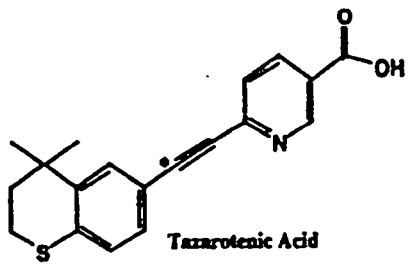
| | |
|---|---|
| **NDA:** | 21-184 |
| **SUBMISSION TYPE:** | Efficacy Supplement (S002) |
| **SUBMISSION DATE:** | June 29, 2001 |
| **PRODUCT:** | Tazorac® (tazarotene topical cream) 0.1% |
| **INDICATION:** | [redacted] |
| **SPONSOR:** | Allergan, Inc., Irvine, CA 92623 |
| **REVIEWER:** | Tapash K. Ghosh, Ph.D. |

## Synopsis

Tazarotene is a member of the acetylenic retinoids. It is intended for topical treatment of psoriasis and acne vulgaris. It is converted to its active form, tazarotenic acid, in biological systems by deesterification. The mechanism of tazarotene action in photodamaged skin is unknown. Improvement in the appearance of photodamaged skin appears to occur in association with increased epidermal thickness, decrease in percentage area of melanin, and compaction of the stratum corneum.



Tazarotene



Tazarotenic Acid

Tazarotene 0.05% and 0.1% gels indicated for the topical treatment of stable plaque psoriasis and Tazarotene 0.1% gel indicated for the topical treatment of acne vulgaris were approved under NDA 20-600 in June, 1997. Tazarotene 0.1% Cream has been approved for plaque psoriasis in September, 2000. Tazarotene 0.1% Cream also has been approved for acne vulgaris in October, 2001.

In this application (NDA 21-184 S002), the sponsor seeks approval of 0.1% tazarotene cream formulation for the topical treatment of photodamaged skin. This is a new indication for which neither tazarotene gel nor tazarotene cream has been approved before..

## Recommendation

One clinical study was conducted to evaluate safety and pharmacokinetics and another clinical study was conducted to evaluate safety and efficacy of tazarotene cream 0.1% to support approval of TAZORAC® (tazarotene) Cream, 0.1% in the once-daily treatment of photodamaged skin. The second study also has an exposure-response component conducted through population pharmacokinetics.The findings from these studies are comparable to findings obtained previously during submission of Tazorac® (tazarotene topical gel) 0.05%, 0.1% gels approved in June, 1997 and TAZORAC® Cream 0.1% approved in September, 2000, and October, 2001 respectively and proven to be safe and effective topical treatment of retinoid responsive dermatoses.

Based on this review, NDA 21-184 S002 is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. A review of the PK data in this submission has resulted in certain changes in the appropriate sections of the product label. The suggested changes are included in the section "Labeling Comments" and have been conveyed to the reviewing division.

## TABLE OF CONTENTS

## Clinical Pharmacology and Biopharmaceutics

### A. Background:

The mechanism of tazarotene action in photodamaged skin is unknown. Improvement in the appearance of photodamaged skin appears to occur in association with increased epidermal thickness, decrease in percentage area of melanin, and compaction of the stratum corneum. A study of the histological safety of tazarotene cream 0.1% applied to photodamaged but otherwise normal skin for 24 weeks showed that tazarotene is not associated with the formation or worsening of keratinocytic atypia or melanocytic atypia. Tazarotene cream 0.1% was associated with significant improvements in the distribution/severity of melanocytic atypia when compared with vehicle. Furthermore, tazarotene cream 0.1% was shown to be associated with (i) significant increases in epidermal thickness and (ii) significantly greater proportions of patients who showed an increase from baseline in the number of granular cell layers. Tazarotene cream 0.1% was also associated with significantly greater proportions of patients who showed an increase from baseline in epidermal edema. The clinical significance of these changes is unknown.

Tazarotene is converted to its active form, tazarotenic acid, by rapid deesterification upon reaching the systemic circulation. The metabolic pathways of tazarotene include hydrolysis to form the free acid and oxidation to form sulfoxide and sulfone metabolites. The primary metabolites of tazarotene consists of the free acid (tazarotenic acid, active metabolite) in plasma, and the sulfoxide and tazarotenic acid in urine. In fecal excretion, polar metabolites (59%) (one of which was identified as an oxygenated derivative of tazarotenic acid) were found in addition to the above two metabolites. In studies using radiolabeled drug, both urinary and fecal excretion pathways were found to be equally important. Following topical application, tazarotene undergoes esterase hydrolysis to form its active metabolite, tazarotenic acid. Little parent compound could be detected in the plasma. Tazarotenic acid is highly bound to plasma proteins (>99%).

### B. Regulatory Summary of Approved Gel and Cream Formulations of Tazarotene by Indications

| Formulation | NDA | Indication | BSA | Regulatory Status | Parameters | |
|---|---|---|---|---|---|---|
| | | | | | Cmax (ng/ml) | $AUC_{0-24}$ (ng.h/ml) |
| 0.1% Cream | 21-184 S002 | Photodamaged Skin | 15% | Under review | 1.75±0.53 | 23.75±7.0 |
| 0.1% Cream | 21-184 S001 | Acne | 15% | Approved (Oct/2001) | 1.20±0.41 | 17.0±6.1 |
| 0.1% Gel | 20-600 | Acne | 15% | Approved (June/1997) | 4.84±6.05 | 44.6±38.9 |
| 0.1% Cream | 21-184 | Psoriasis | 14±11% | Approved (Sep/2000) | 2.31±2.78 | 31.2±35.2 |
| 0.1% Gel | 20-600 | Psoriasis | 13±5% | Approved (June/1997) | 12±7.6 | 105±55 |

Based on the above Summary Table the following conclusions were drawn:

- Compared to 0.1% Gel, 0.1% Cream always showed lesser systemic exposure under similar condition.

- Systemic exposure in photodamaged skin is less than that in psoriasis but more than that in acne under similar condition from 0.1% cream formulations.

- Plasma concentration of tazarotenic acid after exaggerated dosing were toward the lower end of the range for the endogenous concentrations of tretinoin and its metabolites, which have been reported to range from 1 to 4 ng/ml.

**C. Formulation:**

The following table describes the composition of the approved cream presently under consideration for new photodamage indication:

| **Ingredients** | **0.1% Cream (#9087X)** |
|---|---|
| Tazarotene | 0.10 |
| Benzyl Alcohol | 1.0 |
| Sodium Thiosulfate USP | |
| | - |
| | - |
| | - |
| Disodium EDTA | |
| Mineral Oil USP | |
| Medium Chain Triglycerides | |
| Carbomer 1342 NF | |
| Sorbital Monooleate NF | |
| | - |
| | - |
| Carbomer 934P | |
| | - |
| | - |
| | - |
| NaOH NF | |
| Purified Water | |

**D. Analytical:**

Tazarotenic acid plasma concentrations in both clinical PK studies were assayed using a validated — method (Allergan report PK-95-044). The method employed — internal standard of tazarotenic acid. employing — columns. Tazarotenic acid was with — . After the sample was — — in — and injected onto a — . The lower limit of quantitation (LLOQ) of tazarotenic acid was —pg/mL. All concentrations were interpolated from calibration curves with a nominal concentration range of 5 to 500 pg/mL. The analysis was performed by —

**E. Pharmacokinetic Studies**

The sponsor listed the following studies to provide ***in vivo*** pharmacokinetics data in support of 0.1% tazarotene cream for photodamaged skin. The above formulation (#9087X) was used in all these studies. The first study is considered pivotal for this application whereas population PK part of the second study is supportive. The studies have been reviewed individually and the reports have been included in the Appendix.

1. **Study 190168-038C:** An open-label, single-center, parallel-group, safety and 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 patients with photodamaged facial skin

2. **Study 190168-033C:** An *Exposure-Response Report* of Tazarotenic Acid Based on Weeks 36 and 52 Data Collected from Allergan Study 190168-033C-00 Titled, "A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Comparison of the Safety and Efficacy of Tazarotene Cream 0.1% Applied Once Daily for 24 Weeks Followed by Treatment with Tazarotene Cream 0.1% (Open-Label) for 28 Weeks in Patients with Photodamaged Facial Skin"

**F. General Clinical Pharmacology Issues**

- Tazarotenic acid is considered a weak inhibitor of cytochrome P450 enzyme with Ki values ranging from 4800 to 26000 ng/mL. Following topical dosing in humans, the tazarotenic acid concentration in plasma is several thousand times lower than these Ki values and therefore, the potential for a tazarotenic acid mediated drug-drug interaction is minimal following topical dosing.

- Being a topical dosage form, the characteristics of the exposure-response relationships for efficacy and safety is not defined. The therapeutic drug monitoring (190169-029C) had both PK and efficacy components. However, plasma concentration did not correlate with the efficacy outcome, which may be expected from topical therapy where improved efficacy may mean improvement of barrier function of the skin, which leads to lower plasma concentration in subsequent weeks.

**G. Are the designs of the PK studies adequate to evaluate PK parameters and to demonstrate safety at the maximum usage condition to the right patient population?**

Yes. Two clinical studies were conducted to evaluate pharmacokinetics to support approval of TAZORAC® (tazarotene) Cream, 0.1% in the once-daily treatment of photodamaged skin. The findings from these studies are comparable to findings obtained previously during submission of Tazorac® (tazarotene topical cream) 0.1%

cream approved in Sep, 2000 for psoriasis and TAZORAC® Cream 0.1% approved in October, 2001 for acne vulgaris.

## LABELING COMMENTS

Please refer to the **Pharmacokinetics** section under **Clinical Pharmacology** of proposed Tazorac® Cream labeling . ~~Strikeout~~ suggests deletion and *italics* suggests insertion.

**Pharmacokinetics:** Following topical application, tazarotene undergoes esterase hydrolysis to form its active metabolite, tazarotenic acid. Little parent compound could be detected in the plasma. Tazarotenic acid was highly bound to plasma proteins (>99%). Tazarotene and tazarotenic acid were metabolized to sulfoxides, sulfones and other polar metabolites which were eliminated through urinary and fecal pathways. The half-life of tazarotenic acid

/S/ 3/19/02

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CC: NDA 21-184 (S002)
HFD-540/Div File
HFD-540/CSO/Bhatt
HFD-880(Bashaw/Ghosh)
HFD-880 (Lazor)

# APPENDIX

NDA: 21-184 SN2/Study 190168-038C Study Date: Oct' 00 – Nov' 00

**An Open-label, Single-center, Parallel-group, Safety and 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 Patients with Photodamaged Facial Skin**

## Objectives

The study objectives were (1) to compare the pharmacokinetics of tazarotenic acid under standard (face only) dosing and exaggerated-dosing conditions after a single dose and after 6, 13, 20, and 27 repeat topical applications once daily of tazarotene cream 0.1% to patients with photodamaged facial skin, and (2) to demonstrate the safety of tazarotene cream 0.1% after a single application and after 6, 13, 20, and 27 repeat applications under standard and exaggerated-dosing conditions to patients with photodamaged facial skin.

## Study Design

This was a single-center, open-label, parallel-group, pharmacokinetics study to assess the pharmacokinetics of tazarotene cream 0.1% (9087X, lot number 11311D) when used on an exaggerated dosing area or only on the face in patients with photodamaged facial skin according to the following schedule.

BODY LOAD ESTIMATE FOR STANDARD DOSING GROUP (FACE ONLY) AND EXAGGERATED-DOSING GROUP (15% BSA)

| | Face-Only | 15% BSA |
|---|---|---|
| Area of Application | – | 2445 $cm^2$* |
| Application rate | – | 2 $mg/cm^2$ |
| Amount of cream applied | 0.30 g | 4.89 g |
| Drug concentration | 0.1% | 0.1% |
| Amount of drug applied per application | 0.3 mg | 4.89 mg |
| Applications per day | 1 | 1 |
| Number of dosing days | 28 | 28 |
| Total dose of drug during study | 8.4 mg | 136.92 mg |
| Drug during study (for a 59 kg person) | 0.14 mg/kg | 2.32 mg/kg |
| Drug per day (for a 59 kg person) | 0.005 mg/kg/day | 0.083 mg/kg/day |

* Assuming that patient is 5'-4" tall and 130 lb (16,300 $cm^2$ skin x 15% = 2,445 $cm^2$)

For one group of 16 patients (8 females and 8 males) with photodamage, treatment was to a total area of approximately 15% body surface area, including the entire face (i.e., whole face from the mandibular line to the hairline edge), the chest, back, shoulders (the neck was optional depending on the patient's need), arms and the backs of the hands. For another group of 8 patients (6 females and 2 males) with photodamage, treatment was to

the entire face only (i.e., whole face from the mandibular line to the hairline edge). A total of 28 doses were applied over a period of 33 days. The mean ± SD number of days of exposure in the exaggerated-dosing group was 28.0 ± 0.0 days, and in the face-only group it was 27.0 ± 2.83 days (range 20 – 28). In the exaggerated-dosing group, all patients (100.0%, 16/16) were exposed to 28 doses, whereas in the face-only group 87.5% (7/8) of patients were exposed to 28 doses. Each dose was applied in the late afternoon/early evening at the investigational site on day 0 and days 3 through 29. All doses were applied by the investigational site personnel to ensure uniformity of application. Each patient had blood withdrawn for measurement of tazarotenic acid on the following days:

- Prior to the first dose on Day 0, and at 3, 6, 9, 12, 16, 20, 24, 36, 48, 60, and 72 hours post-dose
- Prior to the doses (trough) on Days 8, 15, and 22, and at 3, 6, 9, 12, 16, 20, and 24 hours post-dose on Days 8, 15, and 22
- Prior to the last dose (Day 29, trough) and at 3, 6, 9, 12, 16, 20, 24, 36, 48, 60, and 72 hours post-dose.

**Pharmacokinetic and Statistical Assessments**

The parameters $K_e$ and $T_{1/2}$ were calculated for the day 0 and 29 tazarotenic acid data while $AUC_{0\text{-}inf}$ was calculated for the day 0 data only. The parameters $AUC_{0\text{-}24}$, $C_{max}$ and $T_{max}$ were calculated for data from days 0, 8, 15, 22, and 29. Descriptive statistics including mean, standard deviation (SD), minimal value (Min), median, maximal value (Max), coefficient of variation (CV), standard error (SE), 95% confidence levels (Conf. Level, CL) for the mean, 25% and 75% quantiles were calculated for each pharmacokinetic parameter. Potential gender and time effects on $C_{max}$ and AUC ($AUC_{0\text{-}inf}$ on day 0, $AUC_{0\text{-}24}$ on days 8, 15, 22 and 29) in the exaggerated-dosing group were investigated using a multivariate repeated-measures analysis approach (SAS PROC GLM, REPEATED statement). This analysis was also performed to evaluate time effect for the face-only treatment group. The null hypothesis was that there was no difference in the mean $C_{max}$ and AUC values between female and male patients and that time had no effect on systemic drug exposure. Differences were considered statistically significant when the p-value associated with the multivariate test F statistics was less or equal to 0.05.

**Results**

Tables 1a, 1b, 1c, 1d, and 1e present the list and summary of tazarotenic acid concentration values from patients in the face only and exaggerated dosing group at each sampling time on days 0, 8, 15, 22, and 29, respectively.

**Table 1a: List of plasma tazarotenic acid concentrations (pg/ml) prior to topical application of tazarotene cream 0.1% to the face only and exaggerated dosing group on day 0, and at 3, 6, 9, 12, 16, 20, 24, 36, 48, 60, and 72 hours post-dose on days 0 to 3.**

## Days 0 - 3

| Obs | Pt# | Trt | Sex | 0hr | 3hr | 6hr | 9hr | 12hr | 16hr | 20hr | 24hr | 36hr | 48hr | 60hr | 72hr | Cmax | Ctrough |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3001 | 15% | F | 0 | | | | | | | | | | | | 274 | 0 |
| 2 | 3002 | 15% | F | 0 | | | | | | | | | | | | 1113 | 0 |
| 3 | 3003 | 15% | F | 0 | | | | | | | | | | | | 128 | 0 |
| 4 | 3004 | 15% | F | 0 | | | | | | | | | | | | 125 | 0 |
| 5 | 3005 | 15% | F | 0 | | | | | | | | | | | | 171 | 0 |
| 6 | 3006 | 15% | F | 0 | | | | | | | | | | | | 139 | 0 |
| 7 | 3007 | 15% | F | 0 | | | | | | | | | | | | 129 | 0 |
| 8 | 3008 | 15% | M | 0 | | | | | | | | | | | | 191 | 0 |
| 9 | 3009 | 15% | M | 0 | | | | | | | | | | | | 109 | 0 |
| 10 | 3010 | 15% | M | 0 | | | | | | | | | | | | 279 | 0 |
| 11 | 3011 | 15% | M | 0 | | | | | | | | | | | | 121 | 0 |
| 12 | 3012 | 15% | M | 0 | | | | | | | | | | | | 143 | 0 |
| 13 | 3013 | 15% | M | 0 | | | | | | | | | | | | 244 | 0 |
| 14 | 3014 | 15% | M | 0 | | | | | | | | | | | | 362 | 0 |
| 15 | 3015 | 15% | M | 0 | | | | | | | | | | | | 171 | 0 |
| 16 | 3016 | 15% | M | 0 | | | | | | | | | | | | 329 | 0 |
| | | | Mean | 0 | 55 | 200 | 232 | 223 | 182 | 137 | 115 | 74 | 41 | 20 | 13 | 252 | 0 |
| | | | SD | 0 | 45 | 252 | 213 | 180 | 151 | 95 | 77 | 46 | 21 | 10 | 7 | 243 | 0 |
| | | | CV% | 0 | 82 | 126 | 92 | 81 | 83 | 69 | 67 | 62 | 50 | 50 | 55 | 97 | 0 |
| | | | Min | | | | | | | | | | | | | | 0 |
| | | | Max | | | | | | | | | | | | | | 0 |
| | | | Median | 0 | 38 | 124 | 171 | 170 | 130 | 104 | 99 | 66 | 40 | 19 | 11 | 171 | 0 |
| 17 | 3017 | Face | F | 0 | | | | | | | | | | | | 88 | 0 |
| 18 | 3018 | Face | F | 0 | | | | | | | | | | | | 97 | 0 |
| 19 | 3019 | Face | F | 0 | | | | | | | | | | | | 103 | 0 |
| 20 | 3020 | Face | F | 0 | | | | | | | | | | | | 59 | 0 |
| 21 | 3023 | Face | F | 0 | | | | | | | | | | | | 63 | 0 |
| 22 | 3024 | Face | F | 0 | | | | | | | | | | | | 199 | 0 |
| 23 | 3021 | Face | M | | | | | | | | | | | | | 72 | 0 |
| 24 | 3022 | Face | M | | | | | | | | | | | | | 58 | 0 |
| | | | Mean | 0 | 32 | 76 | 86 | 75 | 50 | 36 | 27 | 13 | 5 | 1 | 0 | 92 | 0 |
| | | | SD | 0 | 12 | 35 | 47 | 38 | 20 | 16 | 14 | 7 | 5 | 3 | 0 | 46 | 0 |
| | | | CV% | 0 | 38 | 46 | 54 | 51 | 39 | 45 | 50 | 53 | 100 | 186 | 0 | 50 | 0 |
| | | | Min | | | | | | | | | | | | | | 0 |
| | | | Max | | | | | | | | | | | | | | 0 |
| | | | Median | 0 | 30 | 62 | 74 | 64 | 44 | 30 | 22 | 11 | 5 | 0 | 0 | 80 | 0 |

**Table 1b: List of plasma tazarotenic acid concentrations (pg/ml) prior to topical application of tazarotene cream 0.1% to the face only and exaggerated dosing group on day 8**

**Days 8 - 9**

| Obs | Pt# | Trt | Sex | 0hr | 3hr | 6hr | 9hr | 12hr | 16hr | 20hr | 24hr | Cmax | Ctrough |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3001 | 15% | F | | | | | | | | | 450 | 191 |
| 2 | 3002 | 15% | F | | | | | | | | | 1049 | 366 |
| 3 | 3003 | 15% | F | | | | | | | | | 478 | 137 |
| 4 | 3004 | 15% | F | | | | | | | | | 377 | 179 |
| 5 | 3005 | 15% | F | | | | | | | | | 327 | 62 |
| 6 | 3006 | 15% | F | | | | | | | | | 316 | 185 |
| 7 | 3007 | 15% | F | | | | | | | | | 570 | 244 |
| 8 | 3008 | 15% | M | | | | | | | | | 535 | 104 |
| 9 | 3009 | 15% | M | | | | | | | | | 335 | 65 |
| 10 | 3010 | 15% | M | | | | | | | | | 469 | 266 |
| 11 | 3011 | 15% | M | | | | | | | | | 158 | 57 |
| 12 | 3012 | 15% | M | | | | | | | | | 253 | 93 |
| 13 | 3013 | 15% | M | | | | | | | | | 1373 | 400 |
| 14 | 3014 | 15% | M | | | | | | | | | 826 | 185 |
| 15 | 3015 | 15% | M | | | | | | | | | 688 | 183 |
| 16 | 3016 | 15% | M | | | | | | | | | 928 | 139 |
| | | | Mean | 213 | 376 | 549 | 521 | 484 | 365 | 247 | 210 | 571 | 179 |
| | | | SD | 117 | 215 | 330 | 275 | 294 | 229 | 146 | 115 | 327 | 101 |
| | | | CV% | 55 | 57 | 60 | 53 | 61 | 63 | 59 | 55 | 57 | 57 |
| | | | Min | | | | | | | | | | |
| | | | Max | | | | | | | | | | |
| | | | Median | 192 | 313 | 459 | 474 | 431 | 320 | 226 | 188 | 474 | 181 |
| 17 | 3017 | Face | F | | | | | | | | | 210 | 20 |
| 18 | 3018 | Face | F | | | | | | | | | 105 | 32 |
| 19 | 3019 | Face | F | | | | | | | | | 151 | 31 |
| 20 | 3020 | Face | F | | | | | | | | | 94 | 19 |
| 21 | 3023 | Face | F | | | | | | | | | 73 | 21 |
| 22 | 3024 | Face | F | | | | | | | | | 249 | 52 |
| 23 | 3021 | Face | M | | | | | | | | | 198 | 62 |
| 24 | 3022 | Face | M | | | | | | | | | 118 | 31 |
| | | | Mean | 40 | 112 | 142 | 125 | 103 | 83 | 49 | 40 | 150 | 34 |
| | | | SD | 22 | 64 | 66 | 55 | 54 | 46 | 20 | 18 | 63 | 16 |
| | | | CV% | 54 | 57 | 46 | 44 | 53 | 56 | 42 | 44 | 42 | 47 |
| | | | Min | | | | | | | | | | |
| | | | Max | | | | | | | | | | |
| | | | Median | 38 | 76 | 108 | 112 | 84 | 64 | 43 | 34 | 135 | 31 |

**Table 1c: List of plasma tazarotenic acid concentrations (pg/ml) prior to topical application of tazarotene cream 0.1% to the face only and exaggerated dosing group on day 15**

## Days 15 -16

| Obs | Pt# | Trt | Sex | 0hr | 3hr | 6hr | 9hr | 12hr | 16hr | 20hr | 24hr | Cmax | Ctrough |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3001 | 15% | F | | | | | | | | | 892 | 426 |
| 2 | 3002 | 15% | F | | | | | | | | | 1552 | 346 |
| 3 | 3003 | 15% | F | | | | | | | | | 1459 | 118 |
| 4 | 3004 | 15% | F | | | | | | | | | 1266 | 546 |
| 5 | 3005 | 15% | F | | | | | | | | | 1170 | 223 |
| 6 | 3006 | 15% | F | | | | | | | | | 1951 | 225 |
| 7 | 3007 | 15% | F | | | | | | | | | 1792 | 382 |
| 8 | 3008 | 15% | M | | | | | | | | | 1303 | 289 |
| 9 | 3009 | 15% | M | | | | | | | | | 479 | 120 |
| 10 | 3010 | 15% | M | | | | | | | | | 720 | 168 |
| 11 | 3011 | 15% | M | | | | | | | | | 896 | 168 |
| 12 | 3012 | 15% | M | | | | | | | | | 1603 | 229 |
| 13 | 3013 | 15% | M | | | | | | | | | 1512 | 352 |
| 14 | 3014 | 15% | M | | | | | | | | | 1935 | 352 |
| 15 | 3015 | 15% | M | | | | | | | | | 1315 | 354 |
| 16 | 3016 | 15% | M | | | | | | | | | 1575 | 236 |
| | | | Mean | 297 | 1073 | 1339 | 1114 | 912 | 677 | 447 | 342 | 1339 | 283 |
| | | | SD | 132 | 434 | 425 | 328 | 282 | 196 | 143 | 129 | 425 | 118 |
| | | | CV% | 45 | 40 | 32 | 29 | 31 | 29 | 32 | 38 | 32 | 42 |
| | | | Min | | | | | | | | | | |
| | | | Max | | | | | | | | | | |
| | | | Median | 294 | 991 | 1387 | 1168 | 973 | 675 | 457 | 327 | 1387 | .263 |
| 17 | 3017 | Face | F | | | | | | | | | 95 | 13 |
| 18 | 3018 | Face | F | | | | | | | | | 126 | 26 |
| 19 | 3019 | Face | F | | | | | | | | | 835 | 30 |
| 20 | 3020 | Face | F | | | | | | | | | 113 | 22 |
| 21 | 3023 | Face | F | | | | | | | | | 223 | 57 |
| 22 | 3024 | Face | F | | | | | | | | | 100 | 24 |
| 23 | 3021 | Face | M | | | | | | | | | 78 | 34 |
| 24 | 3022 | Face | M | | | | | | | | | 321 | 57 |
| | | | Mean | 37 | 127 | 236 | 131 | 104 | 72 | 47 | 33 | 236 | 33 |
| | | | SD | 19 | 65 | 255 | 75 | 60 | 37 | 23 | 16 | 255 | 16 |
| | | | CV% | 52 | 51 | 108 | 58 | 57 | 52 | 50 | 48 | 108 | 49 |
| | | | Min | | | | | | | | | | |
| | | | Max | | | | | | | | | | |
| | | | Median | 32 | 99.5 | 120 | 94.5 | 83 | 54.5 | 38.5 | 28 | 119.5 | 28 |

**Table 1d: List of plasma tazarotenic acid concentrations (pg/ml) prior to topical application of tazarotene cream 0.1% to the face only and exaggerated dosing group on day 22**

## Days 22 - 23

| Obs | Pt# | Trt | Sex | 0hr | 3hr | 6hr | 9hr | 12hr | 16hr | 20hr | 24hr | Cmax | Ctrough |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3001 | 15% | F | | | | | | | | | 1660 | 381 |
| 2 | 3002 | 15% | F | | | | | | | | | 1583 | 306 |
| 3 | 3003 | 15% | F | | | | | | | | | 1876 | 224 |
| 4 | 3004 | 15% | F | | | | | | | | | 2127 | 671 |
| 5 | 3005 | 15% | F | | | | | | | | | 1183 | 237 |
| 6 | 3006 | 15% | F | | | | | | | | | 1833 | 220 |
| 7 | 3007 | 15% | F | | | | | | | | | 1801 | 442 |
| 8 | 3008 | 15% | M | | | | | | | | | 1780 | 331 |
| 9 | 3009 | 15% | M | | | | | | | | | 989 | 178 |
| 10 | 3010 | 15% | M | | | | | | | | | 1190 | 52 |
| 11 | 3011 | 15% | M | | | | | | | | | 960 | 215 |
| 12 | 3012 | 15% | M | | | | | | | | | 2849 | 151 |
| 13 | 3013 | 15% | M | | | | | | | | | 2325 | 504 |
| 14 | 3014 | 15% | M | | | | | | | | | 2515 | 269 |
| 15 | 3015 | 15% | M | | | | | | | | | 1459 | 369 |
| 16 | 3016 | 15% | M | | | | | | | | | 1881 | 168 |
| | | | Mean | 326 | 1230 | 1736 | 1444 | 1048 | 787 | 531 | 396 | 1751 | 295 |
| | | | SD | 186 | 452 | 523 | 500 | 425 | 271 | 172 | 139 | 533 | 153 |
| | | | CV% | 57 | 37 | 30 | 35 | 41 | 34 | 32 | 35 | 30 | 52 |
| | | | Min | | | | | | | | | | |
| | | | Max | | | | | | | | | | |
| | | | Median | 302 | 1182 | 1791 | 1336 | 1075 | 762 | 494 | 374 | 1791 | 253 |
| 17 | 3017 | Face | F | | | | | | | | | 105 | 11 |
| 18 | 3018 | Face | F | | | | | | | | | 124 | 32 |
| 19 | 3019 | Face | F | | | | | | | | | 169 | 23 |
| 20 | 3020 | Face | F | | | | | | | | | 118 | 16 |
| 21 | 3023 | Face | F | | | | | | | | | 73 | 26 |
| 22 | 3024 | Face | F | | | | | | | | | 334 | 61 |
| 23 | 3021 | Face | M | | | | | | | | | 218 | 47 |
| | | | Mean | 34 | 116 | 156 | 131 | 105 | 81 | 50 | 34 | 163 | 31 |
| | | | SD | 18 | 70 | 95 | 80 | 58 | 27 | 30 | 19 | 89 | 18 |
| | | | CV% | 54 | 60 | 61 | 61 | 55 | 33 | 61 | 56 | 54 | 57 |
| | | | Min | | | | | | | | | | |
| | | | Max | | | | | | | | | | |
| | | | Median | 32 | 88 | 124 | 109 | 88 | 68 | 35 | 26 | 124 | 26 |

**Table 1e: List of plasma tazarotenic acid concentrations (pg/ml) prior to topical application of tazarotene cream 0.1% to the face only and exaggerated dosing group on day 29, and at 3, 6, 9, 12, 16, 20, 24, 36, 48, 60, and 72 hours post-dose on days 29 to 32.**

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| Obs | Pt# | Trt | Sex | 0hr | 3hr | 6hr | 9hr | 12hr | 16hr | 20hr | 24hr | 36hr | 48hr | 60hr | 72hr | Cmax | Ctrough |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3001 | 15% | F | | | | | | | | | | | | | 1386 | 452 |
| 2 | 3002 | 15% | F | | | | | | | | | | | | | 1886 | 395 |
| 3 | 3003 | 15% | F | | | | | | | | | | | | | 1567 | 132 |
| 4 | 3004 | 15% | F | | | | | | | | | | | | | 2773 | 965 |
| 5 | 3005 | 15% | F | | | | | | | | | | | | | 708 | 127 |
| 6 | 3006 | 15% | F | | | | | | | | | | | | | 3429 | 392 |
| 7 | 3007 | 15% | F | | | | | | | | | | | | | 1699 | 332 |
| 8 | 3008 | 15% | M | | | | | | | | | | | | | 1067 | 308 |
| 9 | 3009 | 15% | M | | | | | | | | | | | | | 721 | 136 |
| 10 | 3010 | 15% | M | | | | | | | | | | | | | 508 | 89 |
| 11 | 3011 | 15% | M | | | | | | | | | | | | | 920 | 179 |
| 12 | 3012 | 15% | M | | | | | | | | | | | | | 1495 | 84 |
| 13 | 3013 | 15% | M | | | | | | | | | | | | | 1352 | 330 |
| 14 | 3014 | 15% | M | | | | | | | | | | | | | 2477 | 284 |
| 15 | 3015 | 15% | M | | | | | | | | | | | | | 1429 | 324 |
| 16 | 3016 | 15% | M | | | | | | | | | | | | | 1714 | 277 |
| | | | Mean | 309 | 1096 | 1552 | 1331 | 1062 | 760 | 541 | 395 | 214 | 128 | 88 | 64 | 1571 | 300 |
| | | | SD | 214 | 451 | 810 | 618 | 511 | 339 | 254 | 217 | 143 | 87 | 54 | 38 | 785 | 212 |
| | | | CV% | 69 | 41 | 52 | 46 | 48 | 45 | 47 | 55 | 67 | 68 | 62 | 60 | 50 | 71 |
| | | | Min | | | | | | | | | | | | | | |
| | | | Max | | | | | | | | | | | | | | |
| | | | Median | 301 | 1156 | 1462 | 1332 | 1053 | 767 | 519 | 327 | 148 | 94 | 72 | 53.5 | 1462 | 296 |
| 17 | 3017 | Face | F | | | | | | | | | | | | | 169 | 19 |
| 18 | 3018 | Face | F | | | | | | | | | | | | | 159 | 25 |
| 19 | 3019 | Face | F | | | | | | | | | | | | | 187 | 26 |
| 20 | 3020 | Face | F | | | | | | | | | | | | | 91 | 23 |
| 21 | 3023 | Face | F | | | | | | | | | | | | | 98 | 27 |
| 22 | 3024 | Face | F | | | | | | | | | | | | | 233 | 49 |
| 23 | 3021 | Face | M | | | | | | | | | | | | | 178 | 48 |
| | | | Mean | 36 | 113 | 158 | 134 | 114 | 80 | 50 | 32 | 18 | 11 | 7 | 2 | 159 | 31 |
| | | | SD | 15 | 38 | 50 | 50 | 44 | 28 | 21 | 12 | 6 | 4 | 3 | 4 | 50 | 12 |
| | | | CV% | 43 | 34 | 31 | 38 | 39 | 36 | 42 | 38 | 36 | 35 | 52 | 173 | 31 | 39 |
| | | | Min | | | | | | | | | | | | | | |
| | | | Max | | | | | | | | | | | | | | 9 |
| | | | Median | 29 | 108 | 168 | 122 | 113 | 69 | 49 | 27 | 17 | 10 | 7 | 0 | 169 | 26 |

Mean ± SD plasma tazarotenic acid concentrations on days 0, 8, 15, 22, and 29 plotted as a function of time in the face only dosing group and in the exaggerated dosing group are presented in Figures 1 and 2, respectively. The non-compartmental pharmacokinetic

parameters of tazarotenic acid from patients in the face only dosing group and the exaggerated dosing group are presented in Tables I and II, respectively. Table III represents a descriptive statistical summary of pharmacokinetic parameters for tazarotenic acid for days 0, 8, 15, 22 and 29 from female patients in the exaggerated-dosing group. Table IV represents a descriptive statistical summary of pharmacokinetic parameters from male patients in the exaggerated-dosing group.

**Table I: Mean ± SD (Maximum, Median) Pharmacokinetic Parameters of Tazarotenic Acid on Study Days 0, 8, 15, 22, and 29 from Patients in the Face-Only Dosing Group (N = 8, 6 Females, 2 Males)**

| Study Day | $C_{max}$ (pg/mL) | $C_{trough}$ (pg/mL) | $T_{max}$ (hr) | AUC[a] (pg·hr/mL) | $T_{½}$ (hr) |
|---|---|---|---|---|---|
| 0 | 92 ± 46 (199, 80) | BLQ | 8.6 ± 1.9 (12.0, 9.0) | 1698 ± 728 (3353, 1376) | 10.7 ± 1.9 (12.5, 11.2) |
| 8 | 150 ± 63 (249, 135) | 34 ±1 6 (62, 31) | 8.0 ± 3.5 (16.0, 6.0) | 2165 ± 956 (3685, 1936) | NA |
| 15 | 236 ± 255 (835, 120) | 33 ±1 6 (57, 28) | 6.0 ± 0.0 (6.0, 6.0) | 2442 ± 1378 (4441, 1646) | NA |
| 22[b] | 163 ± 89 (334, 124) | 31 ±1 8 (61, 26) | 6.0 ± 1.7 (9.0, 6.0) | 2224 ± 1148 (4493, 1934) | NA |
| 29[b] | 159 ± 50 (233, 169) | 31 ±1 2[c] (49, 26) | 6.4 ± 1.1 (9.0, 6.0) | 2248 ± 755 (3465, 2299) | 18.8 ± 3.7 (26.2, 17.6) |

[a] AUC: $AUC_{0\text{-}inf}$ at day 0, and $AUC_{0\text{-}24hr}$ at days 8, 15, 22, and 29
[b] N = 7 at days 22 and 29
[c] Based on data up to 24 hours
NA Not Applicable

**Table II: Mean ± SD (Maximum, Median) Pharmacokinetic Parameters of Tazarotenic Acid on Study Days 0, 8, 15, 22, and 29 from Patients in the Exaggerated-Dosing Group (N = 16, 8 Females, 8 Males)**

| Study Day | $C_{max}$ (pg/mL) | $C_{trough}$ (pg/mL) | $T_{max}$ (hr) | AUC (pg·hr/mL) | $T_{½}$ (hr) |
|---|---|---|---|---|---|
| 0 | 252 ± 243 (1113, 171) | BLQ | 9.6 ± 2.3 (12.0, 9.0) | 6455 ± 4512 (22136, 5300) | 15.1 ± 5.0 (29.5, 13.9) |
| 8 | 571 ± 327 (1373, 474) | 179 ± 101 (400, 181) | 7.7 ± 1.9 (12.0, 7.5) | 9222 ± 5164 (21389, 8102) | NA |
| 15 | 1339 ± 425 (1951, 1387) | 285 ± 118 (546, 263) | 6.0 ± 0.0 (6.0, 6.0) | 19397 ± 5741 (27656, 20257) | NA |
| 22 | 1751 ± 533 (2849, 1791) | 295 ± 153 (671, 253) | 6.0 ± 1.1 (9.0, 6.0) | 23754 ± 6967 (35034, 23493) | NA |
| 29 | 1571 ± 785 (3429, 1462) | 300 ± 212[a] (965, 296) | 6.2 ± 1.3 (9.0, 6.0) | 22110 ± 9962 (43971, 21742) | 23.8 ± 13.0 (51.3, 17.7) |

AUC $AUC_{0\text{-}inf}$ at day 0, and $AUC_{0\text{-}24hr}$ at days 8, 15, 22, and 29
NA Not Applicable
[a] Based on data up to 24 hours

In the face-only dosing group, the maximum average $C_{max}$ and AUC values of tazarotenic acid occurred on day 15. The mean ± SD values of $C_{max}$ and $AUC_{0\text{-}24}$ of tazarotenic acid on day 15 were 0.236 ± 0.255 ng/mL (N = 8) and 2.44 ± 1.38 ng·hr/mL (N = 8), respectively. The single highest $C_{max}$ was 0.835 ng/mL on day 15.
In the exaggerated-dosing group, the maximum average $C_{max}$ and AUC values of tazarotenic acid occurred on day 22. The mean ± SD values of $C_{max}$ and $AUC_{0\text{-}24}$ of tazarotenic acid on day 22 were 1.75 ± 0.53 ng/mL (N = 16) and 23.8 ± 7.0 ng·hr/mL (N = 16), respectively. The single highest $C_{max}$ was 3.43 ng/mL on day 29.

In general, when drug were applied to the face only, $C_{trough}$ values are very low and are similar among days 8, 15, 22, and 29, suggesting that the steady state might have been reached by day 8. When drug were applied to the 15% body surface area, $C_{trough}$ values are usually similar among days 15, 22, 29 and 42, suggesting that the steady state might have been reached by day 15.

**Table III: Mean ± SD (Maximum, Median) Pharmacokinetic Parameters of Tazarotenic Acid on Study Days 0, 8, 15, 22, and 29 from Female Patients in the Exaggerated-Dosing Group (N = 8)**

| Study Day | $C_{max}$ (pg/mL) | $T_{max}$ (hr) | AUC (pg·hr/mL) | $T_{½}$ (hr) |
|---|---|---|---|---|
| 0 | 284 ± 339 (1113, 155) | 9.0 ± 2.8 (12.0, 9.0) | 7198 ± 6133 (22136, 4935) | 17.2 ± 5.5 (29.5, 15.4) |
| 8 | 513 ± 235 (1049, 464) | 7.9 ± 2.2 (12.0, 7.5) | 8696 ± 4352 (18633, 7874) | NA |
| 15 | 1423 ± 342 (1951, 1381) | 6.0 ± 0 (6.0, 6.0) | 21167 ± 4576 (27656, 19962) | NA |
| 22 | 1730 ± 273 (2127, 1791) | 6.0 ± 0 (6.0, 6.0) | 24209 ± 4313 (32551, 23756) | NA |
| 29 | 1814 ± 892 (3429, 1633) | 6.0 ± 0.0 (6.0, 6.0) | 25613 ± 11502 (43971, 23806) | 27.4 ± 14.1 (51.3, 24.0) |

AUC $AUC_{0\text{-}inf}$ at day 0, and $AUC_{0\text{-}24hr}$ at days 8, 15, 22, and 29
NA Not Applicable

**Table IV: Mean ± SD (Maximum, Median) Pharmacokinetic Parameters of Tazarotenic Acid on Study Days 0, 8, 15, 22, and 29 from Male Patients in the Exaggerated-Dosing Group (N = 8)**

| Study Day | $C_{max}$ (pg/mL) | $T_{max}$ (hr) | AUC (pg·hr/mL) | $T_{½}$ (hr) |
|---|---|---|---|---|
| 0 | 220 ± 98 (362, 208) | 10.1 ± 1.6 (12.0, 9.0) | 5712 ± 2179 (9096, 5736) | 13.1 ± 3.6 (21.5, 12.3) |
| 8 | 629 ± 407 (1373, 579) | 7.5 ± 1.6 (9.0, 7.5) | 9748 ± 6130 (21389, 10186) | NA |
| 15 | 1254 ± 503 (1935, 1414) | 6.0 ± 0.0 (6.0, 6.0) | 17628 ± 6522 (24974, 20257) | NA |
| 22 | 1771 ± 731 (2849, 1670) | 6.0 ± 1.6 (9.0, 6.0) | 23299 ± 9216 (35034, 22450) | NA |
| 29 | 1327 ± 623 (2477, 1391) | 6.4 ± 1.9 (9.0, 6.0) | 18607 ± 7233 (28998, 20328) | 20.2 ± 11.7 (42.2, 16.4) |

AUC $AUC_{0\text{-}inf}$ at day 0, and $AUC_{0\text{-}24hr}$ at days 8, 15, 22, and 29
NA Not Applicable

In the exaggerated-dosing group, the $C_{max}$ and AUC values of tazarotenic acid for female and male patients were similar.

**Figure 1: Mean plasma tazarotenic acid concentration – time profiles following topical application of tazarotene cream 0.1% once-daily to the entire face of eight patients with photodamaged skin**

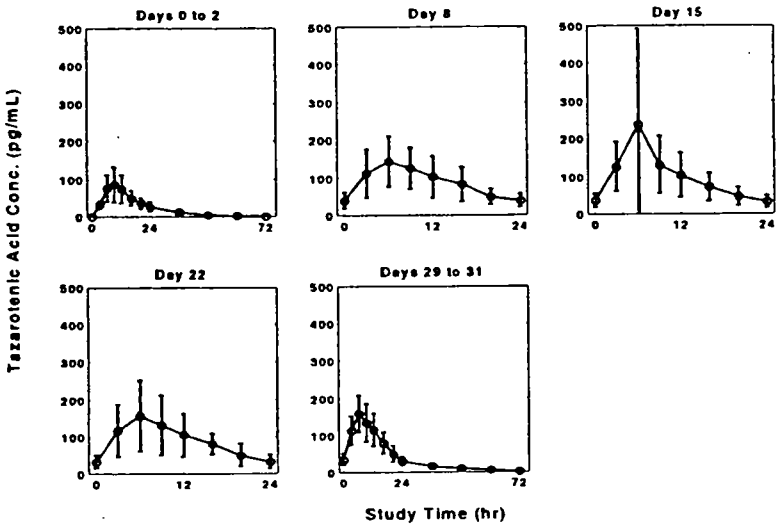
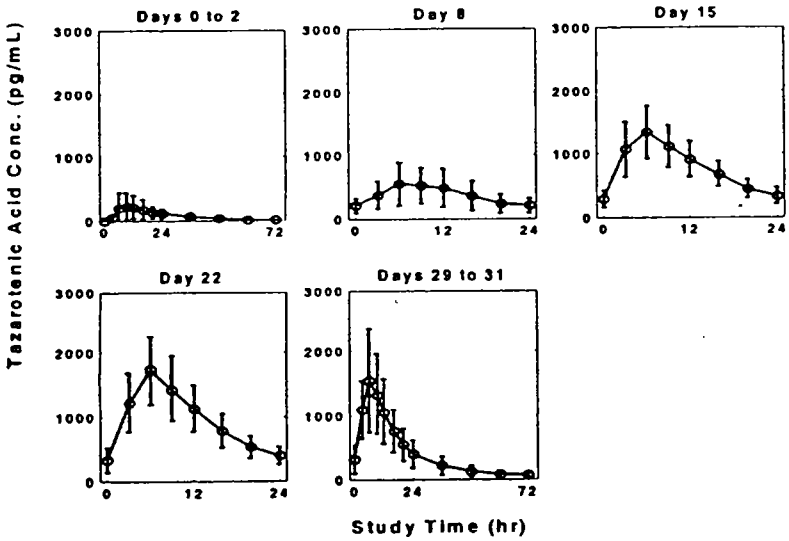



**Figure 2. Mean plasma tazarotenic acid concentration – time profiles following topical application of tazarotene cream 0.1% once-daily to 15 % total body surface area of 16 male and female patients with photodamaged skin**




A summary of the multivariate analysis of potential gender effect on $C_{max}$ and AUC from patients in the exaggerated-dosing group is presented in Table V. The results suggested that gender difference had no influence on systemic drug exposure. A summary of the multivariate analysis of potential time effect on $C_{max}$ and AUC from patients in the two treatment groups is presented in the TablesVI and VII, respectively. These results suggest there were no time effects on the $C_{max}$ and AUC values of tazorotenic acid when the cream was applied to the face only. However, time effects became significant when

the cream was applied to 15% of total body surface area, ie. AUC and $C_{max}$ values reached a steady level on day 22 and beyond.

**Table V: Summary of Multivariate Repeated-measures Analyses of Pharmacokinetic Parameters $C_{max}$ and AUC from patients in the Exaggerated-dosing Group**

| Comparison Group | p value associated with the F Statistics for the hypothesis of no gender effect | |
|---|---|---|
| | $C_{max}$ | AUC |
| Days 0, 8, 15, 22, and 29 | 0.5290 | 0.3440 |
| Days 8, 15, 22, and 29 | 0.5618 | 0.3727 |
| Days 15, 22, and 29 | 0.4389 | 0.2661 |

**Table VI: Summary of Multivariate Repeated-measures Analyses of $C_{max}$ and AUC to Evaluate Time Effect in the Face-only Dosing Group**

| Comparison Group | p value associated with the F Statistics for the hypothesis of no time effect | |
|---|---|---|
| | $C_{max}$ | AUC |
| Days 0, 8, 15, 22, and 29 | 0.0977* | 0.1713 |
| Days 8, 15, 22, and 29 | 0.8654 | 0.8596 |
| Days 15, 22, and 29 | 0.6632 | 0.6533 |

*: $C_{max}$ values from single dose data included

**Table VII: Summary of Multivariate Repeated-measures Analyses of $C_{max}$ and AUC to Evaluate Time Effect in the Exaggerated-dosing Group**

| Comparison Group | p value associated with the F Statistics for the hypothesis of no time effect | |
|---|---|---|
| | $C_{max}$ | AUC |
| Days 0, 8, 15, 22, and 29 | <0.0001* | <0.0001 |
| Days 8, 15, 22, and 29 | <0.0001 | <0.0001 |
| Days 15, 22, and 29 | 0.0021 | 0.0148 |

*: $C_{max}$ values from single dose data included

## Discussion

This study has characterized the plasma concentration versus time profile of tazarotenic acid following administration of up to 28 multiple doses of tazarotene cream 0.1% applied daily to an exaggerated body surface area (15% BSA) or to the face only in patients with facial photodamage. All patients had at least moderate fine wrinkling or mottled hyperpigmentation on the face. Patients in the exaggerated-dosing group also had fine wrinkling or mottled hyperpigmentation of at least minimal severity on chest, back, neck, shoulders, arms, and back of hands. Application to 15% BSA results in an estimated body load that is calculated to be approximately 17 times higher than the estimated body load resulting from application to the face only. In the exaggerated-dosing group, the maximum average $C_{max}$ and AUC values of tazarotenic acid occurred

on day 22. The mean ± SD values of $C_{max}$ and $AUC_{0-24}$ of tazarotenic acid on day 22 were 1.75 ± 0.53 ng/mL (N = 16) and 23.8 ± 7.0 ng·hr/mL (N = 16), respectively. The single highest $C_{max}$ was 3.43 ng/mL on day 29. In the face-only dosing group, the maximum average $C_{max}$ and AUC values of tazarotenic acid occurred on day 15. The mean ± SD values of $C_{max}$ and $AUC_{0-24}$ of tazarotenic acid on day 15 were 0.236 ± 0.255 ng/mL (N =8) and 2.44 ± 1.38 ng·hr/mL (N = 8), respectively. The single highest $C_{max}$ was 0.835 ng/mL on day 15.

In a previous study, tazarotene 0.1% cream was applied once daily to patients with acne vulgaris. Comparison of the data from these two studies, as tabulated below, suggest that systemic availability of tazarotenic acid is higher in patients with photodamaged skin than in patients with acne vulgaris following once daily topical application of the 0.1% cream under both face-only (127% increase in Cmax and 59% increase in AUC) and exaggerated-dosing (46% increase in Cmax and 40% increase in AUC) conditions. However percentage increases calculated here are based on mean values of the parameters. Overall statistical significance of these apparent increases are not known. Nonetheless, it appears that under similar conditions, patients with photodamaged skin show higher systemic exposure of tazarotene as compared to acne patients.

| Indication | Face only (Mean ± SD) | | 15% BSA (Mean ± SD) | |
|---|---|---|---|---|
| | Cmax (ng/ml) | AUC (ng.hr/ml) | Cmax (ng/ml) | AUC (ng.hr/ml) |
| Acne | 104 ± 60 | 1540 ± 1010 | 1200 ± 410 | 17000 ± 6100 |
| Photodamaged skin | 236 ± 255 | 2442 ± 1378 | 1751 ± 533 | 23754 ± 6967 |
| % increase | 127 | 59 | 46 | 40 |

The severity of the majority of adverse events was rated mild or moderate. Five adverse events in the exaggerated-dosing group were rated as severe: 1 patient with severe edema, 2 patients with severe erythema, and 2 patients with severe rash.

In summary, topical application of tazarotene cream 0.1% to 15% body surface area resulted in higher plasma concentrations of tazarotenic acid than after application to the face only. Nevertheless, the plasma concentrations of tazarotenic acid after exaggerated-dosing were toward the lower end of the range for the endogenous concentrations of tretinoin and its metabolites, which have been reported to range from 1 to 4 ng/mL, with the total concentration up to a much as 6.63 ng/mL (Eckhoff & Nau, 1990). Adverse events were limited to signs and symptoms of local skin irritation, predominantly of mild or moderate severity and were more common in the exaggerated-dosing group.

**Conclusions**

1. In the exaggerated-dosing group, the maximum average $C_{max}$ and AUC values of tazarotenic acid occurred on day 22 during a 33-day study period. The mean ± SD values of $C_{max}$ and $AUC_{0-24}$ of tazarotenic acid on day 22 were 1.75 ± 0.53 ng/mL (N = 16) and 23.8 ± 7.0 ng·hr/mL (N = 16), respectively. The single highest $C_{max}$ was 3.43 ng/mL on day 29.

2. In the face-only dosing group, the maximum average $C_{max}$ and AUC values of tazarotenic acid occurred on day 15 during a 33-day study period. The mean ± SD values of $C_{max}$ and $AUC_{0-24}$ of tazarotenic acid on day 15 were 0.236 ± 0.255 ng/mL (N = 8) and 2.44 ± 1.38 ng·hr/mL (N = 8), respectively. The single highest $C_{max}$ was 0.835 ng/mL on day 15.

3. In the exaggerated-dosing group, the $C_{max}$ and AUC values of tazarotenic acid between males and females were similar.

**Reviewer's Comments:**

*Apparently there was increase in both Cmax and AUC values under both face only and exaggerated dosing group of patients with photodamaged skin compared to similar group of patients with acne vulgaris. A statistical comparison of the data from two different disease states could verify the significance of the differences.*

*Based on Ctrough data, steady state appears to have been reached by day 15 in the exaggerated dosing group. However, statistical analysis show that it was reached by day 22.*

NDA: 21-184 SN2/Study 190168-033C Study Date: Sep'99 – Mar'01

**An *Exposure-Response Report* of Tazarotenic Acid Based on Weeks 36 and 52 Data Collected from Allergan Study 190168-033C-00 Titled, "A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Comparison of the Safety and Efficacy of Tazarotene Cream 0.1% Applied Once Daily for 24 Weeks Followed by Treatment with Tazarotene Cream 0.1% (Open-Label) for 28 Weeks in Patients with Photodamaged Facial Skin"**

**Objectives:**

1. Examine plasma tazarotenic acid (AGN 190299) concentrations after once daily application to the faces of patients with photodamaged skin at weeks 36, and 52.
2. Evaluate population pharmacokinetics of tazarotenic acid.

**Study Design:**

The current study was a 52-week multi-center study with a 24-week double-blind, randomized, vehicle-controlled, parallel-group comparison phase followed by a 28-week open-label phase.

During the 24-week double-blind period, patients with photodamaged facial skin applied either tazarotene cream 0.1% or tazarotene cream vehicle once daily to their faces. Blood samples were collected from 125 patients from five selected sites at week 2, 12, and 24 visits for the determination of plasma tazarotenic acid concentrations (Study 190168-033C, Report PK-01-012). Pharmacokinetic analyses were performed on data collected from 60 patients (54 females and 6 males) in the tazarotene cream 0.1% treatment group, and from 65 patients (56 females and 9 males) in the tazarotene cream vehicle treatment group.

During the 28-week open-label period, all patients with photodamaged facial skin applied tazarotene cream 0.1% once daily to their faces. Blood samples were collected from 106 patients from five selected sites at weeks 36 and 52 visits for the determination of plasma tazarotenic acid (TA) concentrations. Among these 106 patients, 48 patients (42 females and 6 males) were in the tazarotene cream 0.1% treatment group, and 58 patients (49 females and 9 males) were in the tazarotene cream vehicle treatment group during the 24-week double-blind period. On the designated visit day, patients received the morning dose in the clinic and were instructed to return 3 to10 hours later for the collection of a pharmacokinetic blood sample.

The log-transformed plasma tazarotenic acid concentrations were compared between weeks 36 and 52, using a paired T-Test approach (SAS PROC MEANS) to evaluate if

drug concentrations might have changed from weeks 36 to 52. Exploratory analyses were also performed to examine if tazarotenic acid concentrations might correlate with patient age, body weight, body surface area, blood sampling time, and amount of tazarotene cream applied. Log-transformed plasma tazarotenic acid concentrations at weeks 36 and 52 were treated as the response (dependent) variables, while age, body weight, body surface area, blood sampling time, and amount of tazarotene cream applied were treated as independent variables. Gender effect was not formally investigated due to unbalanced sample size (male = 14, female = 84 to 86; Table I).



**Results:**

***Double blind 24-week Study***

The average amount of tazarotene cream applied to the face of patients in the tazarotene cream 0.1% treatment group was approximately 300 mg (median amount is 255 mg, mean $\pm$ SD = 328 $\pm$ 267 mg).

All but six (173 out of 179 samples) plasma tazarotenic acid concentrations in samples from the vehicle cream treatment group were below LLOQ of tazarotenic acid ( pg/mL). In general, these six above LLOQ concentrations were very close to the LLOQ and are considered background noise. Patient 1173 (site 3259 at week 24) had a tazarotenic acid concentration of 109 pg/mL. This study site permitted patients to apply the cream under open-labeled conditions rather than under blinded conditions. This might have contributed to this finding and the study result is questionable.

All plasma tazarotenic acid concentrations were quantifiable in the tazarotene cream 0.1% treatment group (159 samples). The single highest plasma tazarotenic acid concentration throughout the study period was 423 pg/mL at week 24 from patients 1070 and 1430).

Mean±SD (Maximum, Median) plasma tazarotenic acid concentrations (ng/mL) from the tazarotene cream 0.1% treatment group at weeks 2, 12, and 24 are summarized in the following Table I. There were no significant differences among week 2, 12, and 24 tazarotenic acid concentrations. Exploratory analysis indicated a possible correlation between patient age and tazarotenic acid plasma concentration but not with patient weight and body surface area. The drug concentration appeared to be similar between male and female patients.

**Table I: Mean±SD (Maximum, Median) plasma tazarotenic acid concentrations (ng/mL) from the tazarotene cream 0.1% treatment group at weeks 2, 12, and 24**

| | Week 2 | Week 12 | Week 24 |
|---|---|---|---|
| **From all female and male patients** | 0.092 ± 0.073<br>(N = 55)<br>Median = 0.072<br>Max = 0.310 | 0.108 ± 0.081<br>(N = 54 )<br>Median = 0.079<br>Max = 0.385 | 0.108 ± 0.098<br>(N = 50)<br>Median = 0.072<br>Max = 0.423 |
| **From all female patients** | 0.095 ± 0.075<br>(N = 50)<br>Median = 0.070<br>Max = 0.310 | 0.109 ± 0.082<br>(N = 48)<br>Median = 0.079<br>Max = 0.385 | 0.104 ± 0.089<br>(N = 44)<br>Median = 0.072<br>Max = 0.423 |
| **From all male patients** | 0.071 ± 0.054<br>(N = 5)<br>Median = 0.073<br>Max = 0.144 | 0.107 ± 0.078<br>(N = 6)<br>Median = 0.105<br>Max = 0.209 | 0.135 ± 0.161<br>(N = 6)<br>Median = 0.059<br>Max = 0.423 |

Relationship between plasma tazarotenic acid concentration versus blood sampling time and versus the amount of tazarotene cream 0.1% applied in patients in the active drug treatment group were investigated.

The summary of results of linear regression analyses of age, body weight, body surface area, blood sampling time, amount of cream applied with plasma tazarotenic acid concentrations are presented in Table II: Exploratory analyses indicate a possible correlation between patient age and amount of cream applied with tazarotenic acid plasma concentration. There was no apparent correlation between drug concentrations and patient weight, body surface area and the blood sampling time.

**Table II. Summary of linear regression analyses results relating tazarotenic acid concentrations to other variables of patients with photodamaged skin receiving tazarotene cream 0.1%to the face once-daily up to 24 weeks**

| Dependent Variable | Independent Variable | p-value for the slope |
|---|---|---|
| tazarotenic acid at week 2 | age | 0.0228 (N = 55) |
| tazarotenic acid at week 12 | age | 0.0308 (N = 54) |
| tazarotenic acid at week 24 | age | 0.0555 (N = 50) |
| tazarotenic acid at week 2 | body weight | 0.7598 (N = 55) |
| tazarotenic acid at week 12 | body weight | 0.7344 (N = 54) |
| tazarotenic acid at week 24 | body weight | 0.6318 (N = 50) |
| tazarotenic acid at week 2 | body surface area | 0.5079 (N = 55) |
| tazarotenic acid at week 12 | body surface area | 0.6491 (N = 54) |
| tazarotenic acid at week 24 | body surface area | 0.6904 (N = 50) |
| tazarotenic acid at weeks 2, 12, and 24 | Blood sampling time | 0.4625 (N = 159) |
| tazarotenic acid at weeks 2, 12, and 24 | Amount of cream applied | 0.0013 (N = 156) |

*Open-label 28-week Study*

Pharmacokinetic analyses were performed on data collected from 106 patients (91 females and 15 males) during the 28-week open-label period. Among these 106 patients, 103 were Caucasian, one was Asian, and two were Hispanic. The demographics data summary is presented below. Among these 106 patients, 48 patients (42 females and 6 males) were in the tazarotene cream 0.1% treatment group, and 58 patients (49 females and 9 males) were in the tazarotene cream vehicle treatment group during the 24-week double-blind period. The average amount of tazarotene cream applied to the face of all patients at weeks 36 and 52 visits was approximately 350 mg (median amount is 240 mg; mean ± SD = 350 ± 350 mg, N = 200).

**Demographics Data Summary for Weeks 36 and 52**

| Variable | N | Mean | SD | %Coeff of Variation | Minimum | Maximum | Median |
|---|---|---|---|---|---|---|---|
| Age (year) | 106 | 56.59 | 11.86 | 20.95 | 33.00 | 81.00 | 57.00 |
| Weight (Kg) | 106 | 69.65 | 14.63 | 21.01 | 44.00 | 117.94 | 68.04 |
| Height (cm) | 106 | 165.91 | 8.40 | 5.06 | 147.32 | 193.04 | 165.10 |
| BSA ($m^2$) | 106 | 1.77 | 0.20 | 11.12 | — | — | 1.75 |
| Sampling Time (Hr) | 197 | 4.25 | 1.19 | 27.91 | — | — | 4.00 |
| Amount Applied (g) | 200 | 0.35 | 0.35 | 100.69 | — | — | 0.24 |

**List of plasma tazarotenic acid concentration, blood sampling time, and amount of cream applied at weeks 36 and 52 in patients with photodamaged skin receiving tazarotene cream 0.1% to the face once daily is presented below.**

Listing of Time and Amount of Dose Applied, and Plasma Tazarotenic Acid Concentrations (pg/mL) at Weeks 36 and 52

| Obs | WEEK | Study SITE ID | Patient Number | Time after Dosing (hr) | Amount of Cream Applied (gram) | Tazarotenic Acid Concentration (pg/mL) |
|---|---|---|---|---|---|---|
| 1 | 36 | 1964 | 1041 | 7.00 | 0.23 | 146 |
| 2 | 36 | 1964 | 1042 | 3.83 | 0.43 | 62.0 |
| 3 | 36 | 1964 | 1043 | 4.58 | 0.28 | 140 |
| 4 | 36 | 1964 | 1047 | 4.00 | 0.34 | 54.0 |
| 5 | 36 | 1964 | 1048 | 3.92 | 0.11 | 112 |
| 6 | 36 | 1964 | 1049 | 4.08 | 0.69 | 415 |
| 7 | 36 | 1964 | 1050 | 7.83 | 0.20 | 65.0 |
| 8 | 36 | 1964 | 1051 | 3.25 | 0.57 | 155 |
| 9 | 36 | 1964 | 1052 | 4.42 | 0.18 | 79.9 |
| 10 | 36 | 1964 | 1053 | 3.00 | 0.46 | 150 |
| 11 | 36 | 1964 | 1055 | 4.50 | 0.24 | 41.2 |
| 12 | 36 | 1964 | 1058 | 3.08 | 0.21 | 93.6 |
| 13 | 36 | 1964 | 1059 | 4.75 | 0.33 | 60.2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 14 | 36 | 1964 | 1401 | 9.33 | 0.32 | 115 |
| 15 | 36 | 1964 | 1402 | 3.33 | 0.40 | 37.2 |
| 16 | 36 | 1964 | 1403 | 4.42 | 0.36 | 226 |
| 17 | 36 | 1964 | 1404 | 3.00 | 0.24 | 66.8 |
| 18 | 36 | 1964 | 1405 | 3.17 | 0.32 | 146 |
| 19 | 36 | 1964 | 1406 | 3.33 | 0.31 | 16.6 |
| 20 | 36 | 1964 | 1411 | 4.17 | 0.78 | 64.8 |
| 21 | 36 | 1964 | 1412 | 3.33 | 0.20 | 74.6 |
| 22 | 36 | 1964 | 1417 | 4.75 | 0.95 | 300 |
| 23 | 36 | 1964 | 1419 | 3.92 | 0.58 | 128 |
| 24 | 36 | 1964 | 1420 | 3.92 | 0.21 | 65.2 |
| 25 | 36 | 1964 | 1422 | 6.08 | 0.34 | 97.6 |
| 26 | 36 | 1964 | 1426 | 3.08 | 0.10 | 111 |
| 27 | 36 | 1964 | 1427 | 5.28 | 0.15 | 111 |
| 28 | 36 | 1964 | 1429 | 4.00 | 0.20 | 111 |
| 29 | 36 | 1964 | 1430 | 3.42 | 0.90 | 705 |
| 30 | 36 | 1964 | 1431 | 5.58 | 0.32 | 68.1 |
| 31 | 36 | 2420 | 1001 | 3.57 | 0.35 | 66.5 |
| 32 | 36 | 2420 | 1002 | 3.10 | 1.49 | 83.0 |
| 33 | 36 | 2420 | 1003 | 3.83 | 0.25 | 118 |
| 34 | 36 | 2420 | 1004 | 3.00 | 0.53 | 19.9 |
| 35 | 36 | 2420 | 1007 | 4.72 | 0.86 | 536 |
| 36 | 36 | 2420 | 1008 | 4.72 | 0.48 | 90.1 |
| 37 | 36 | 2420 | 1010 | 4.28 | 0.06 | 12.1 |
| 38 | 36 | 2420 | 1011 | 4.05 | 0.22 | 170 |
| 39 | 36 | 2420 | 1014 | 4.25 | 0.14 | 48.4 |
| 40 | 36 | 2420 | 1015 | 3.67 | 0.22 | 383 |
| 41 | 36 | 2420 | 1017 | 4.42 | 0.15 | 159 |
| 42 | 36 | 2420 | 1019 | 4.62 | 0.20 | 80.6 |
| 43 | 36 | 2420 | 1020 | 4.22 | 0.41 | 140 |
| 44 | 36 | 2420 | 1021 | 3.47 | 0.12 | 110 |
| 45 | 36 | 2420 | 1022 | 4.92 | 0.36 | 268 |
| 46 | 36 | 2420 | 1024 | 3.32 | 0.17 | 98.9 |
| 47 | 36 | 2420 | 1028 | 4.67 | 0.06 | 29.4 |
| 48 | 36 | 2420 | 1031 | 3.98 | 0.26 | 123 |
| 49 | 36 | 2420 | 1032 | 6.55 | 0.18 | 20.2 |
| 50 | 36 | 2420 | 1034 | 6.00 | 0.43 | 385 |
| 51 | 36 | 2420 | 1035 | 5.08 | 0.31 | 44.5 |
| 52 | 36 | 2420 | 1036 | 3.60 | 0.52 | 40.9 |
| 53 | 36 | 2420 | 1037 | 5.38 | 0.24 | 221 |
| 54 | 36 | 2420 | 1038 | 3.15 | 0.15 | 36.0 |
| 55 | 36 | 2420 | 1039 | 5.08 | 0.31 | 115 |
| 56 | 36 | 3244 | 1221 | 3.00 | 0.20 | 41.7 |
| 57 | 36 | 3244 | 1222 | 3.13 | 0.20 | 56.4 |
| 58 | 36 | 3244 | 1224 | 5.08 | 0.10 | 69.9 |
| 59 | 36 | 3244 | 1225 | 3.03 | 0.20 | 50.5 |
| 60 | 36 | 3244 | 1227 | 5.00 | 0.30 | 199 |
| 61 | 36 | 3244 | 1229 | 4.00 | 0.10 | 34.7 |
| 62 | 36 | 3244 | 1232 | 3.53 | 0.20 | 68.2 |
| 63 | 36 | 3244 | 1233 | 3.22 | 0.10 | 83.1 |
| 64 | 36 | 3244 | 1234 | 3.50 | 0.10 | 51.1 |
| 65 | 36 | 3244 | 1236 | 3.25 | 0.10 | 6.86 |
| 66 | 36 | 3244 | 1237 | 4.58 | 0.10 | 156 |
| 67 | 36 | 3244 | 1238 | 3.42 | 0.20 | 55.1 |
| 68 | 36 | 3244 | 1239 | 3.08 | 0.30 | 20.2 |
| 69 | 36 | 3244 | 1240 | 3.33 | 0.10 | 6.43 |
| 70 | 36 | 3244 | 1533 | 4.42 | 0.10 | 30.2 |
| 71 | 36 | 3244 | 1534 | 2.67 | 0.50 | 62.7 |
| 72 | 36 | 3244 | 1536 | 2.63 | 0.20 | 54.4 |
| 73 | 36 | 3244 | 1541 | 5.00 | 0.10 | 43.1 |
| 74 | 36 | 3244 | 1544 | 4.00 | 0.20 | 87.0 |
| 75 | 36 | 3259 | 1162 | 5.30 | 0.16 | 64.7 |
| 76 | 36 | 3259 | 1173 | 2.42 | 0.19 | 161 |
| 77 | 36 | 3259 | 1174 | 3.00 | 0.30 | 50.2 |
| 78 | 36 | 3259 | 1175 | 3.92 | 0.38 | 43.8 |
| 79 | 36 | 3259 | 1176 | 5.20 | 0.14 | 37.7 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 80 | 36 | 3259 | 1179 | 4.92 | 0.12 | 41.3 |
| 81 | 36 | 3259 | 1558 | 2.92 | 0.16 | 10.9 |
| 82 | 36 | 3260 | 1061 | 5.93 | 0.54 | 131 |
| 83 | 36 | 3260 | 1062 | 3.62 | 0.24 | 174 |
| 84 | 36 | 3260 | 1063 | 3.67 | 0.21 | 49.6 |
| 85 | 36 | 3260 | 1066 | . | 0.40 | 211 |
| 86 | 36 | 3260 | 1068 | 3.68 | 0.62 | 194 |
| 87 | 36 | 3260 | 1070 | 4.25 | 0.11 | 35.0 |
| 88 | 36 | 3260 | 1072 | 3.08 | 0.44 | 66.4 |
| 89 | 36 | 3260 | 1075 | 2.67 | 0.10 | 41.6 |
| 90 | 36 | 3260 | 1077 | 3.25 | 0.14 | 65.5 |
| 91 | 36 | 3260 | 1078 | 3.00 | 0.40 | 119 |
| 92 | 36 | 3260 | 1080 | 3.92 | 0.33 | 51.9 |
| 93 | 36 | 3260 | 1435 | 4.17 | 1.09 | 22.5 |
| 94 | 36 | 3260 | 1438 | 4.77 | 0.43 | 58.3 |
| 95 | 36 | 3260 | 1440 | 8.67 | 0.19 | 57.7 |
| 96 | 36 | 3260 | 1441 | 3.47 | 0.42 | 281 |
| 97 | 36 | 3260 | 1443 | 4.50 | 0.94 | 61.9 |
| 98 | 36 | 3260 | 1445 | 4.08 | 1.07 | 313 |
| 99 | 52 | 1964 | 1041 | 5.63 | 0.24 | 193 |
| 100 | 52 | 1964 | 1042 | 7.92 | 0.35 | 76.6 |
| 101 | 52 | 1964 | 1043 | 3.70 | 0.43 | 72.0 |
| 102 | 52 | 1964 | 1044 | 3.25 | 0.16 | 8.53 |
| 103 | 52 | 1964 | 1047 | 3.67 | 0.85 | 129 |
| 104 | 52 | 1964 | 1048 | 3.15 | 0.18 | 62.5 |
| 105 | 52 | 1964 | 1049 | 3.83 | 0.66 | 340 |
| 106 | 52 | 1964 | 1050 | 7.08 | 0.25 | 120 |
| 107 | 52 | 1964 | 1051 | 3.17 | 0.49 | 31.3 |
| 108 | 52 | 1964 | 1052 | 3.33 | 0.09 | 37.7 |
| 109 | 52 | 1964 | 1053 | 3.83 | 0.62 | 191 |
| 110 | 52 | 1964 | 1054 | 3.42 | 0.11 | 33.4 |
| 111 | 52 | 1964 | 1055 | 3.00 | 0.12 | 82.6 |
| 112 | 52 | 1964 | 1058 | 3.17 | 0.10 | 22.4 |
| 113 | 52 | 1964 | 1059 | 3.28 | 0.52 | 188 |
| 114 | 52 | 1964 | 1401 | 8.50 | 0.24 | 63.6 |
| 115 | 52 | 1964 | 1402 | 3.25 | 0.18 | 51.5 |
| 116 | 52 | 1964 | 1403 | 5.00 | 0.29 | 176 |
| 117 | 52 | 1964 | 1404 | 3.25 | 0.23 | 38.4 |
| 118 | 52 | 1964 | 1405 | 3.00 | 0.26 | 193 |
| 119 | 52 | 1964 | 1406 | 3.75 | 0.34 | 18.4 |
| 120 | 52 | 1964 | 1407 | 3.75 | 0.49 | 96.1 |
| 121 | 52 | 1964 | 1408 | 3.92 | 0.39 | 168 |
| 122 | 52 | 1964 | 1411 | 3.75 | 0.86 | 60.7 |
| 123 | 52 | 1964 | 1412 | 3.92 | 0.12 | 61.4 |
| 124 | 52 | 1964 | 1413 | 5.00 | 0.35 | 131 |
| 125 | 52 | 1964 | 1417 | 5.25 | 0.48 | 160 |
| 126 | 52 | 1964 | 1420 | 4.08 | 0.20 | 27.7 |
| 127 | 52 | 1964 | 1422 | 5.50 | 0.08 | 30.5 |
| 128 | 52 | 1964 | 1426 | 5.27 | 0.24 | 82.5 |
| 129 | 52 | 1964 | 1427 | 3.83 | 0.66 | 72.6 |
| 130 | 52 | 1964 | 1429 | 3.00 | 0.51 | 70.7 |
| 131 | 52 | 1964 | 1430 | 6.33 | 0.72 | 583 |
| 132 | 52 | 1964 | 1431 | 3.42 | 0.23 | 71.5 |
| 133 | 52 | 2420 | 1001 | 4.08 | 0.54 | 21.0 |
| 134 | 52 | 2420 | 1002 | 3.83 | 0.25 | 87.5 |
| 135 | 52 | 2420 | 1003 | 4.30 | 0.21 | 113 |
| 136 | 52 | 2420 | 1004 | 4.33 | 0.27 | 78.7 |
| 137 | 52 | 2420 | 1007 | 5.75 | 0.24 | 318 |
| 138 | 52 | 2420 | 1008 | 5.53 | 0.25 | 65.9 |
| 139 | 52 | 2420 | 1010 | 5.17 | 0.12 | 25.7 |
| 140 | 52 | 2420 | 1011 | 5.07 | 0.15 | 237 |
| 141 | 52 | 2420 | 1014 | 4.48 | 0.21 | 120 |
| 142 | 52 | 2420 | 1015 | 4.00 | 0.15 | 203 |
| 143 | 52 | 2420 | 1017 | 4.33 | 0.23 | 226 |
| 144 | 52 | 2420 | 1019 | 5.25 | 0.29 | 85.3 |
| 145 | 52 | 2420 | 1020 | 3.28 | 1.35 | 85.2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 146 | 52 | 2420 | 1022 | 5.83 | 1.17 | 486 |
| 147 | 52 | 2420 | 1024 | 4.08 | 0.15 | 62.4 |
| 148 | 52 | 2420 | 1028 | 4.17 | 0.22 | 20.4 |
| 149 | 52 | 2420 | 1031 | 4.08 | 0.26 | 76.8 |
| 150 | 52 | 2420 | 1032 | 4.88 | 1.19 | 56.5 |
| 151 | 52 | 2420 | 1033 | 7.25 | 0.41 | 57.8 |
| 152 | 52 | 2420 | 1034 | 4.70 | 0.36 | 263 |
| 153 | 52 | 2420 | 1035 | 4.50 | 0.29 | 40.3 |
| 154 | 52 | 2420 | 1036 | 4.13 | 0.12 | 17.1 |
| 155 | 52 | 2420 | 1037 | 4.67 | 0.32 | 146 |
| 156 | 52 | 2420 | 1038 | 3.58 | 0.16 | 33.6 |
| 157 | 52 | 2420 | 1039 | 4.00 | 0.31 | 56.2 |
| 158 | 52 | 3244 | 1221 | 3.75 | 0.30 | 51.5 |
| 159 | 52 | 3244 | 1222 | 4.03 | 0.30 | 17.0 |
| 160 | 52 | 3244 | 1224 | 3.25 | 0.20 | 128 |
| 161 | 52 | 3244 | 1225 | 3.92 | 0.10 | 42.8 |
| 162 | 52 | 3244 | 1227 | 3.33 | 0.50 | 116 |
| 163 | 52 | 3244 | 1229 | 3.95 | 0.10 | 17.4 |
| 164 | 52 | 3244 | 1232 | 4.30 | 0.20 | 46.5 |
| 165 | 52 | 3244 | 1233 | 3.70 | 0.20 | 103 |
| 166 | 52 | 3244 | 1234 | 4.63 | 0.30 | 78.7 |
| 167 | 52 | 3244 | 1236 | 3.42 | 0.10 | 24.9 |
| 168 | 52 | 3244 | 1237 | 4.17 | 0.10 | 46.3 |
| 169 | 52 | 3244 | 1238 | 3.67 | 0.30 | 72.3 |
| 170 | 52 | 3244 | 1239 | 4.50 | 0.10 | BLQ |
| 171 | 52 | 3244 | 1240 | 4.20 | 0.10 | 19.0 |
| 172 | 52 | 3244 | 1533 | 4.08 | 0.10 | 22.0 |
| 173 | 52 | 3244 | 1534 | 3.00 | 0.10 | 29.2 |
| 174 | 52 | 3244 | 1536 | 2.92 | 0.20 | 60.7 |
| 175 | 52 | 3244 | 1541 | 4.17 | 0.10 | 60.4 |
| 176 | 52 | 3244 | 1544 | 5.33 | 0.10 | 151 |
| 177 | 52 | 3259 | 1162 | 3.50 | 0.21 | 45.9 |
| 178 | 52 | 3259 | 1173 | 2.97 | 0.26 | 131 |
| 179 | 52 | 3259 | 1174 | 3.83 | 0.19 | 170 |
| 180 | 52 | 3259 | 1175 | 5.33 | 0.30 | 53.6 |
| 181 | 52 | 3259 | 1176 | 3.42 | 0.18 | 18.5 |
| 182 | 52 | 3259 | 1179 | 6.33 | 0.35 | 33.5 |
| 183 | 52 | 3259 | 1180 | 3.27 | 0.38 | 14.6 |
| 184 | 52 | 3260 | 1061 | 5.83 | 0.95 | 159 |
| 185 | 52 | 3260 | 1062 | 3.23 | 0.11 | 101 |
| 186 | 52 | 3260 | 1063 | 3.17 | 0.23 | 38.2 |
| 187 | 52 | 3260 | 1066 | 3.17 | 0.07 | 13.0 |
| 188 | 52 | 3260 | 1068 | 4.33 | 0.03 | 151 |
| 189 | 52 | 3260 | 1070 | 5.22 | 0.52 | 179 |
| 190 | 52 | 3260 | 1072 | . | 0.51 | 137 |
| 191 | 52 | 3260 | 1075 | 5.50 | 0.07 | 55.0 |
| 192 | 52 | 3260 | 1077 | . | 0.00 | BLQ |
| 193 | 52 | 3260 | 1078 | 4.37 | 0.95 | 59.7 |
| 194 | 52 | 3260 | 1080 | 3.75 | 0.92 | 60.7 |
| 195 | 52 | 3260 | 1435 | 7.00 | 1.10 | 16.6 |
| 196 | 52 | 3260 | 1438 | 6.23 | 0.69 | 105 |
| 197 | 52 | 3260 | 1440 | 3.50 | 0.24 | 20.8 |
| 198 | 52 | 3260 | 1443 | 5.92 | 0.34 | 58.7 |
| 199 | 52 | 3260 | 1444 | 3.08 | 1.09 | 115 |
| 200 | 52 | 3260 | 1445 | 6.17 | 3.57 | 151 |

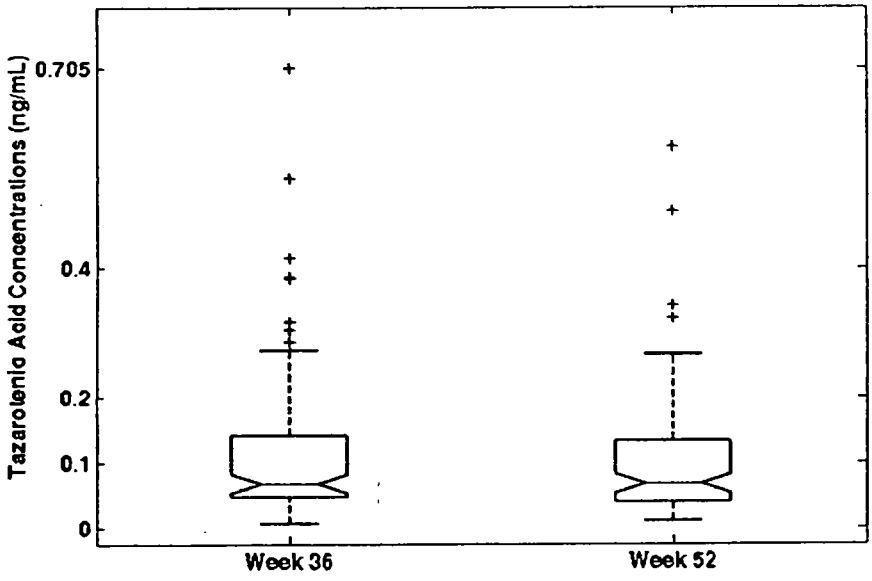
The single highest plasma tazarotenic acid concentration throughout the study period was 0.705 ng/mL at week 36 from patient 1430 who was in the tazarotene cream 0.1% treatment group during the 24-week double-blind period. Observed plasma tazarotenic acid concentrations from different collection periods are illustrated in Figure 1. Mean plasma tazarotenic acid concentrations were not statistically significantly different

between weeks 36 and 52, indicating tazarotenic acid concentrations were steady over the 28-week open-label time period (p = 0.1124). Further analysis of the data stratified by gender and by patients entered in the open-label study from tazarotene treatment group or vehicle group from the preceding 24-week double blind study is summarized in Table III.

**Table III: Mean±SD (Maximum, Median) plasma tazarotenic acid concentrations (ng/mL) at Weeks 36 and 52**

| | Week 36 | Week 52 |
|---|---|---|
| **From all female and male patients** | 0.112 ± 0.112 (N = 98)<br>Median = 0.068, Max = 0.705 | 0.097 ± 0.093 (N = 100)<br>Median = 0.068, Max = 0.583 |
| **From all female patients** | 0.115 ± 0.115 (N = 84)<br>Median = 0.072, Max = 0.705 | 0.096 ± 0.088 (N = 86)<br>Median = 0.072, Max = 0.583 |
| **From all male patients** | 0.090 ± 0.091 (N = 14)<br>Median = 0.062, Max = 0.313 | 0.102 ± 0.121 (N = 14)<br>Median = 0.063, Max = 0.486 |
| **From all patients in the taz cream group during the 24-week double-blind period** | 0.127 ± 0.142 (N = 46)<br>Median = 0.067, Max = 0.705 | 0.110 ± 0.104 (N = 47)<br>Median = 0.073, Max = 0.583 |
| **From all patients in the vehicle group during the 24-week double-blind period** | 0.098 ± 0.076 (N = 52)<br>Median = 0.069, Max = 0.385 | 0.085 ± 0.081 (N = 53)<br>Median = 0.061, Max = 0.486 |

**Figure 1. Summary of plasma tazarotenic acid concentrations at weeks 36 and 52 in patients with photodamaged skin receiving tazarotene cream 0.1% to the face once daily during 28 weeks open-label study period**




1. The lower and upper lines of the "box" are the 25th and 75th percentiles of the sample. The distance between the top and bottom of the box is the interquartile range.
2. The line in the middle of the box is the sample median. If the median is not centered in the box, that indicates that the data are skewed.
3. The "whiskers" are lines extending above and below the box. They show the extent of the rest of the sample (unless there are outliers). Assuming no outliers, the maximum of the sample is the top of the upper whisker. The minimum of the sample is the bottom of the lower whisker. By default, an outlier is a value that is more than 1.5 times the interquartile range away from the top or bottom of the box.
4. The plus sign at the top or bottom of the plot is an indication of an outlier in the data.

Mean±SD (Maximum, Median) plasma tazarotenic acid concentrations (ng/mL) at Weeks 2, 12, 24, 36 and 52 from all patients who received tazarotene cream 0.1% treatment during both 24-week double-blind period and 28-week open-label period are summarized in Table IV below.

**Table IV: Mean±SD (Maximum, Median) plasma tazarotenic acid concentrations (ng/mL) at Weeks 2, 12, 24, 36 and 52 from all patients who received tazarotene cream 0.1% treatment during both 24-week double-blind period and 28-week open-label period**

| Week 2 | Week 12 | Week 24 | Week 36 | Week 52 |
|---|---|---|---|---|
| 0.092 ± 0.073<br>(N = 55)<br>Median = 0.072<br>Max = 0.310 | 0.108 ± 0.081<br>(N = 54 )<br>Median = 0.079<br>Max = 0.385 | 0.108 ± 0.098<br>(N = 50)<br>Median = 0.072<br>Max = 0.423 | 0.127 ± 0.142<br>(N = 46)<br>Median = 0.067<br>Max = 0.705 | 0.110 ± 0.104<br>(N = 47)<br>Median = 0.073<br>Max = 0.583 |

In all patients who received tazarotene cream 0.1% treatment during both 24-week double-blind period and 28-week open-label period, plasma tazarotenic acid concentrations at weeks 2, 12, 24, 36 and 52 were similar, indicating topical dosing of tazarotene cream 0.1% does not result in systemic accumulation of drug over 52 weeks.

The regression plots of age, body weight, body surface area, blood sampling time, and amount of tazarotene cream applied with plasma tazarotenic acid concentrations are presented in Figures 2, 3, 4, 5 and 6 respectively. The summary of results linear regression analyses are presented in Table V: Exploratory analyses indicate possible correlations between tazarotenic acid plasma concentration and patient age, blood sampling time, and amount of cream applied. There was no apparent correlation between drug concentrations and patient weight, and to body surface area.

**Table V: Summary of linear regression analyses results relating tazarotenic acid concentrations to while age, body weight, body surface area, blood sampling time, and amount of tazarotene cream applied of patients with photodamaged skin receiving tazarotene cream 0.1% to the face once-daily during the 28 weeks open-label period.**

| Dependent Variable | | Independent Variable | Slope | p-value for the slope |
|---|---|---|---|---|
| Log-transformed tazarotenic acid concentration at | Week 36 | Age (yr) | 0.0206 | 0.0057 (N = 98) |
| | Week 52 | Age (yr) | 0.0173 | 0.0171 (N = 100) |
| | Week 36 | Body weight (kg) | -0.0064 | 0.2826 (N = 98) |
| | Week 52 | Body weight (kg) | -0.0019 | 0.7458 (N = 100) |
| | Week 36 | Body surface area ($m^2$) | -0.5498 | 0.2178 (N = 98) |
| | Week 52 | Body surface area ($m^2$) | -0.1305 | 0.7661 (N = 100) |
| | Weeks 36 and 52 | Blood sampling time (hr) | 0.1317 | 0.0114 (N = 200) |
| | Weeks 36 and 52 | Amount dose applied (g) | 0.6661 | 0.0001 (N = 200) |

Figure 2. Regression plots of *age* with plasma tazarotenic concentrations at weeks 36 and 52 in patients with photodamaged skin receiving tazarotene cream 0.1% to the face once daily during 28 weeks open-label study period

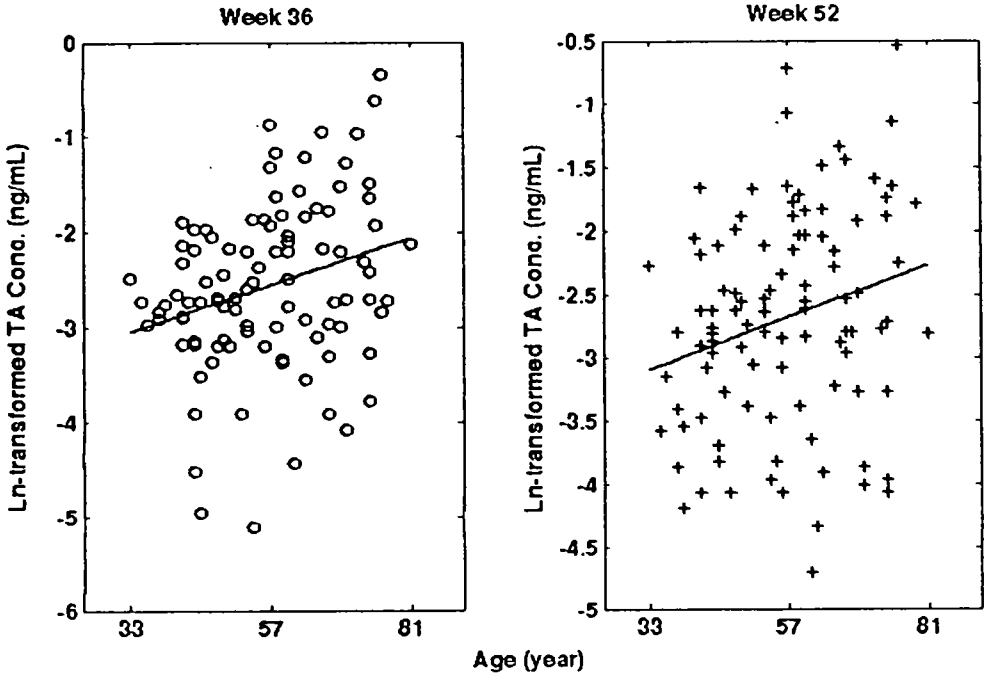



Figure 3. Regression plots of *body weight* with plasma tazarotenic concentrations at weeks 36 and 52 in patients with photodamaged skin receiving tazarotene cream 0.1% to the face once daily during 28 weeks open-label study period

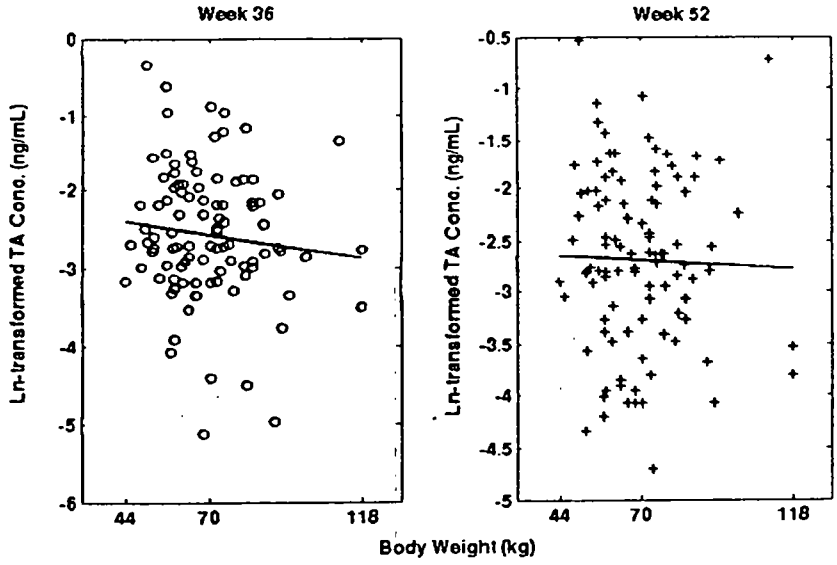


Figure 4. Regression plots of ***body surface area*** with plasma tazarotenic concentrations at weeks 36 and 52 in patients with photodamaged skin receiving tazarotene cream 0.1% to the face once daily during 28 weeks open-label study period

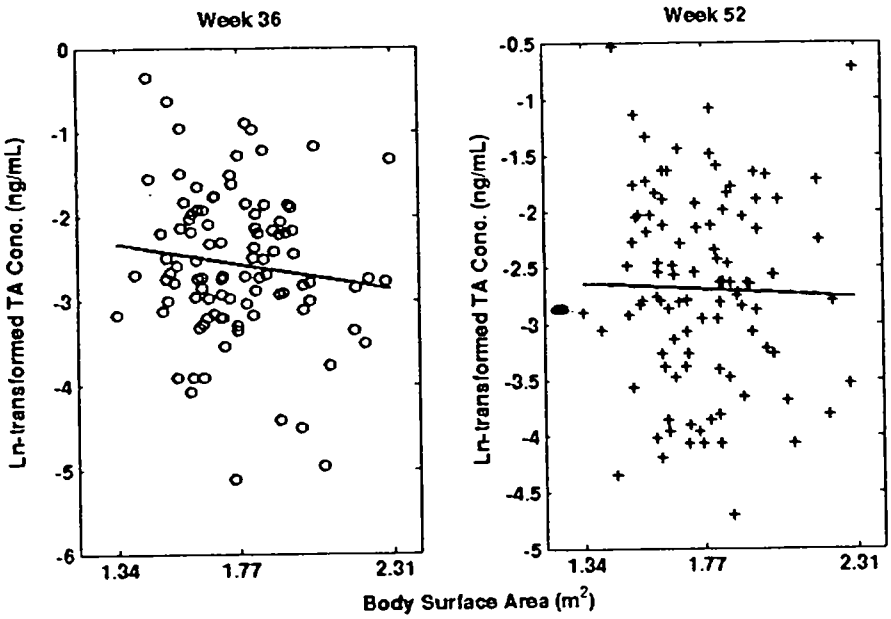



Figure 5. Relationships between plasma tazarotenic acid concentration and ***blood sampling time*** in patients with photodamaged skin receiving tazarotene cream 0.1% to the face once daily during 28 weeks open-label study period

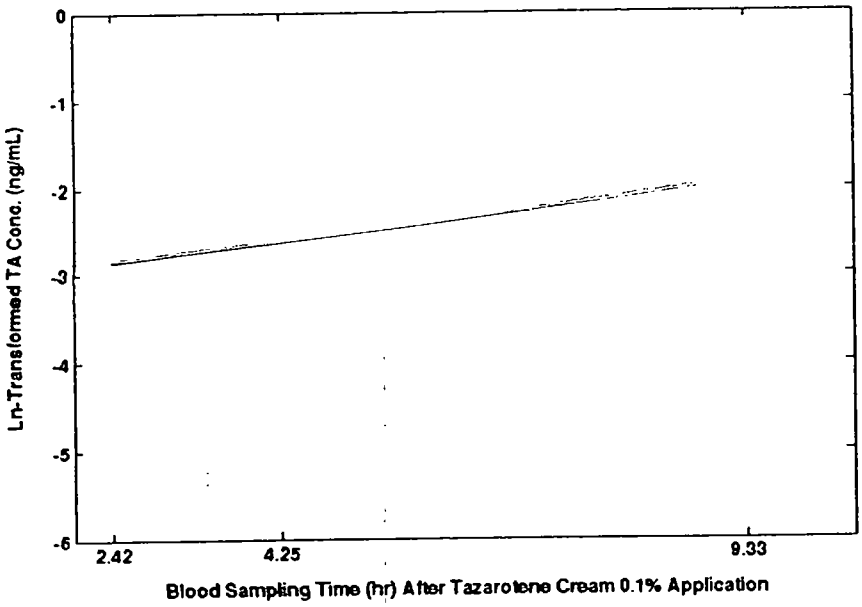
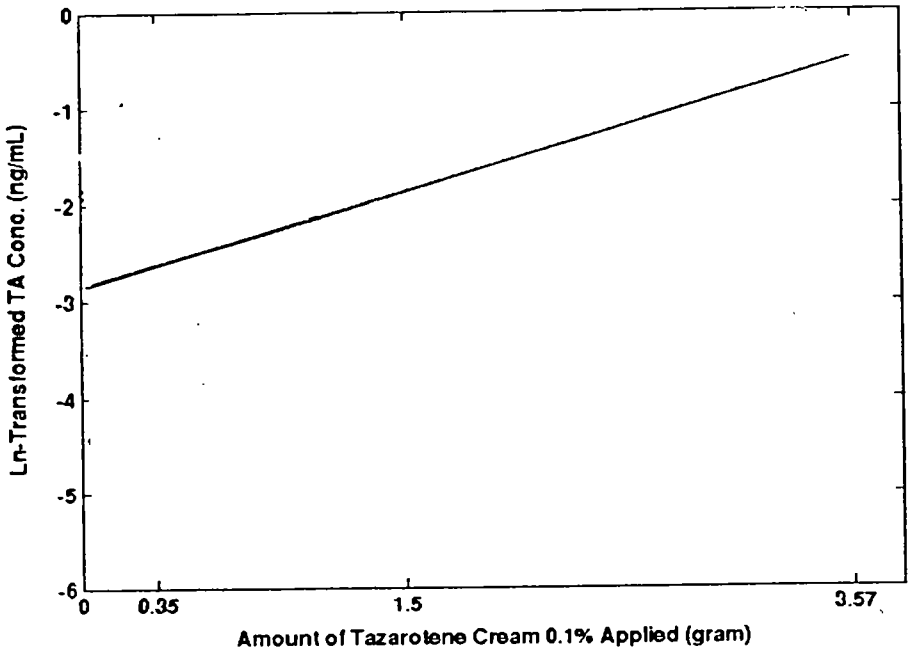


**Figure 6. Relationships between plasma tazarotenic acid concentration and *amount of tazarotene cream* 0.1% applied in patients with photodamaged skin receiving tazarotene cream 0.1% to the face once daily during 28 weeks open-label study period**




## Discussion

Plasma drug concentration is an indicator of systemic drug exposure after dosing. The current Therapeutic Drug Monitoring (TDM) report characterizes the 3 to 10 hour tazarotenic acid plasma concentrations after once-daily application to the faces of patients with photodamaged skin at weeks 36, and 52 during the 28-week open-label period, and evaluates the population pharmacokinetics of tazarotenic acid.
The study results demonstrate that the plasma tazarotenic acid concentration is very low following topical application of tazarotene cream 0.1% in patients with photodamaged skin. The magnitude of systemic exposure to tazarotenic acid from topical tazarotene application is lower than endogenous tretinoin and active metabolite concentrations which are approximately 1 to 4 ng/mL in humans. Fairly constant tazarotenic acid concentration over 52-week period suggests little potential for drug accumulation during long-term therapy.

A comparison of systemic tazarotenic acid concentrations observed in this study with acne vulgaris study in an similar dosing regimen (Allergan PKDM Report PK-00-084) is summarized below. In the acne study, the plasma tazarotenic acid concentrations in selected patients at weeks 4 and 8 were 0.078 ± 0.073 ng/mL (N = 47) and 0.052 ± 0.037 ng/mL (N = 42), respectively. The highest individual plasma tazarotenic acid concentration was 0.41 ng/mL at Week 4. In the current study, tazarotenic acid concentrations at weeks 36 and 52 were 0.112 ± 0.112 (N = 98) and 0.097 ± 0.093 ng/mL (N = 100), respectively. The highest individual concentration was 0.705 ng/mL. In the acne study, there was an apparent drop in plasma concentration between weeks 4 (78 ±

73 pg/mL) and week 8 (52 ± 37 pg/mL) of tazarotenic acid, which may be expected from topical therapy where improved efficacy may mean improvement of barrier function of the skin, which leads to lower plasma concentration in subsequent weeks. In the current study, no such drop is apparent between week 2 to week 52. Plasma concentration remains fairly constant across the study period. In absence of respective efficacy data, it is not possible to correlate plasma concentration with efficacy outcome. Though from the mean tazarotenic concentration data it appears that drug absorption from patients with photodamaged skin is little higher than patients with acne vulgaris, the extent of large variability in all those data makes the differences indistinguishable.

| Indication | Area | Mean ± SD Concentration (ng/mL) at | |
|---|---|---|---|
| Acne vulgaris | Face only | Week 4 | Week 8 |
| | | 0.078 ± 0.073 (N = 47) | 0.052 ± 0.037 (N = 42) |
| Photodamaged skin | Face only | Week 36 | Week 52 |
| | | 0.112 ± 0.112 (N = 98) | 0.097 ± 0.093 (N = 100) |

The lack of correlation with body weight and surface area further support that systemic drug exposure to tazarotenic acid is low and predictable.

**Conclusions**

After topical application of tazarotene cream 0.1% once daily for 28 weeks in 106 patients with photodamaged facial skin during the 28-week open-label period:

- Topical dosing of tazarotene cream 0.1% does not result in systemic accumulation of drug over time.

- The single highest observed tazarotenic acid concentration throughout the 28 weeks study period was 0.705 ng/mL on week 36 from one female patient. The mean ± SD values of tazarotenic acid at weeks 36 and 52 were 0.112 ± 0.112 ng/mL (N = 98) and 0.097 ± 0.093 ng/mL (N = 100), respectively.

**Reviewer's Comments:**

- *An apparently significant correlation between drug concentration and patient age has been found in both double-blind and open-label phases. However, maximum individual patient concentrations in double-blind and open-label phases were 0.423 0.705 ng/ml respectively. Therefore, such finding has no practical significance.*

- *Another apparently significant correlation has been found between drug concentration and amount of tazarotene cream 0.1% applied in both double-blind and open-label phases. However, respective proviles reveal very few isolated cases of higher amount (~3.5 g) which may have skewed the correlation outcome. Taking that point out of the graphs as outlier should make the correlation look insignificant. Nevertheless, direction for use of any topical cream always emphasizes that a thin layer should be applied to the affected area.*

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