CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202428Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA #:	202428
Submission Date:	July 29, 2011
Brand Name:	To Be Determined
Generic Name:	Tazarotene
Dosage Form:	Foam
Dosage Strength:	0.1%
Reviewer:	Chinmay Shukla, Ph.D.
Team Leader:	Doanh Tran, Ph.D.
OCP Division:	DCP-3
OND Division:	Division of Dermatology and Dental Products
Sponsor:	Stiefel Laboratories, Inc.
Relevant IND(s):	105564
Submission Type:	New submission
Indication:	Topical treatment of acne vulgaris in patients 12 years of age or older

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1. Executive Summary

Tazarotene is a retinoid pro-drug which is rapidly hydrolyzed by esterases into its active form tazarotenic acid. Tazarotene gel (Tazorac® Gel) (NDA 020600) was approved on 06/13/1997 and tazarotene cream (Tazorac® Cream) (NDA 021184) was approved on 09/29/2000. Tazorac® Gel, 0.1% is approved for the topical treatment of patients with facial acne vulgaris of mild to moderate severity, while Tazorac® Cream, 0.1% is approved for the topical treatment of acne vulgaris. Tazorac® (0.05% and 0.1%) gel and cream formulations are also approved for the treatment of plaque psoriasis. In addition to this, the 0.1% cream formulation (Avage®) is also approved as an adjunctive agent for use in the mitigation (palliation) of facial fine wrinkling, facial mottled hyper- and hypo

pigmentation, and benign facial lentigines in patients who use comprehensive skin care and sunlight avoidance programs.

With this NDA, the Sponsor is seeking approval for tazarotene foam, 0.1% (w/w) for the topical treatment of (b) (4) acne vulgaris in patients 12 years of age or older. The Division of Dermatology and Dental Products has determined that a more general indication of treatment of acne vulgaris in patients 12 years of age and older will be more appropriate.

Tazarotene foam, 0.1% contains identical active ingredient as Tazorac® Gel, 0.1% and Tazorac® Cream, 0.1%. The Sponsor of this NDA (Stiefel Laboratories, Inc) has obtained full right of reference to the Tazorac NDAs from the holder, Allergan, Inc. The Sponsor provided systemic safety and nonclinical pharmacology/toxicology data via cross-referencing to available data in NDA 020600 (Tazorac Gel) and NDA 021184 (Tazorac Cream). Ultimately, the Sponsor has adopted a 505(b)(1) regulatory pathway for this application.

1.1 Recommendation

From a Clinical Pharmacology Standpoint, the Sponsor has met the requirements under 21 CFR 320 and the application is acceptable provided the labeling comments are adequately addressed by the Sponsor.

1.2 Post-Marketing Requirements/ Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

To support this NDA, the Sponsor conducted 1 pharmacokinetic (PK) trial in subjects with acne vulgaris (Trial W0260-105).

The purpose of this trial was to evaluate the plasma exposure of tazarotene and tazarotenic acid (active metabolite) following once daily administration of tazarotene foam, 0.1% in comparison with Tazorac (tazarotene) Gel, 0.1% in subjects 12 years and older with moderate to severe acne vulgaris (ISGA of 3 or greater) under maximal use conditions.

30 subjects (11 male and 19 female, age range 12 - 33 years) were enrolled and 29 subjects (13 tazarotene foam arm and 16 Tazorac Gel arm) completed the trial. Subject 001-005 in the tazarotene foam arm withdrew consent and did not complete the trial. Approximately 3.7 grams of the study product was applied by the clinical staff once daily in late afternoon or early evening for 22 days to the face, upper chest, upper back and shoulders [approximately 15% body surface area (BSA)].

PK profiles following foam and gel administrations:

Figure 1 and 2 below shows the concentration versus time profile of tazarotenic acid and tazarotene respectively on Day 22 following once daily administration of tazarotene foam, 0.1% and Tazorac® gel, 0.1% Gel. The mean ± SD $AUC_{0\text{-}tau}$ and C_{max} of tazarotenic acid on Day 22 following foam administration were 6.98 ± 3.56 hr*ng/mL and 0.43 ± 0.19 ng/mL and following gel administration were 12.46 ± 5.02 hr*ng/mL and 0.97 ± 0.49 ng/mL respectively. While the mean ± SD $AUC_{0\text{-}tau}$ and C_{max} of the parent compound tazarotene on Day 22 following foam administration were 0.14 ± 0.09 hr*ng/mL and 0.012 ± 0.006 ng/mL and following gel administration were 0.21 ± 0.12 hr*ng/mL and 0.023 ± 0.016 ng/mL respectively.

Figure 1: Concentration versus time profile of tazarotenic acid on Day 22 following once daily administration of tazarotene foam, 0.1% and Tazorac® Gel, 0.1% (dark black line shows the mean)

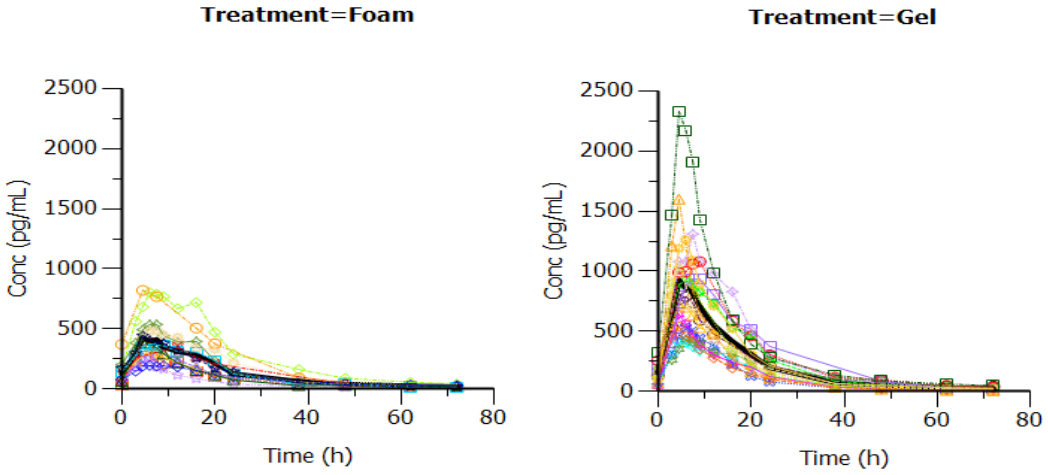
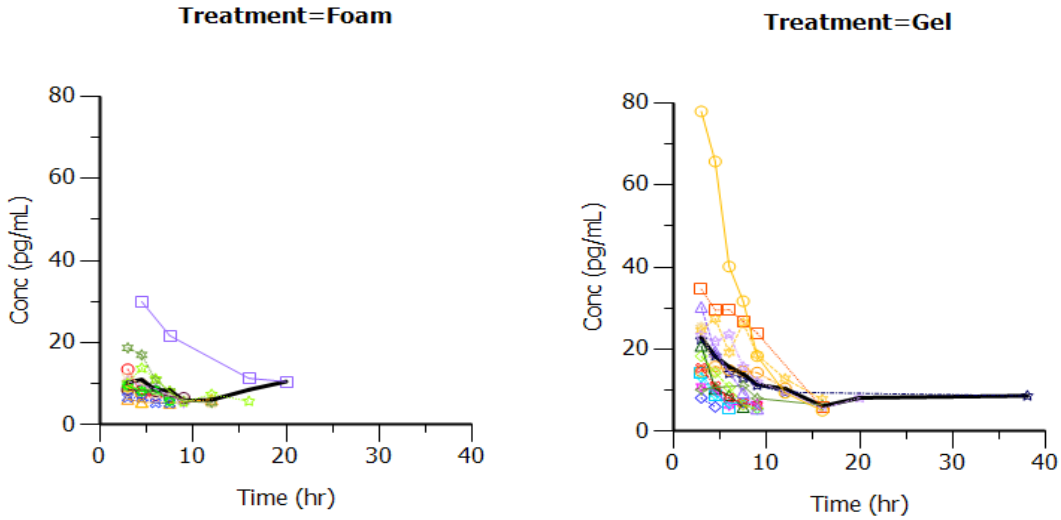


Figure 2: Concentration versus time profile of tazarotene on Day 22 following once daily administration of tazarotene foam, 0.1% and Tazorac Gel, 0.1% formulations (dark black line shows the mean)



Relative BA of tazarotene foam compared to approved Tazorac® Gel

The values of 90% confidence interval (CI) of the ratio of the geometric mean of AUC and C_{max} for tazarotenic acid and tazarotene are shown in Tables 1 and 2 respectively.

Table 1: 90% CI of the ratio of the geometric mean of AUC and C_{max} for tazarotenic acid

PK Parameters	*Reference Formulation*	*Ratio of geometric mean*	*90% CI (Lower)*	*90% CI (Upper)*
$AUC_{0\text{-}tau}$	Gel	0.54	0.41	0.72
C_{max}	Gel	0.46	0.34	0.61

Table 2: 90% CI of the ratio of the geometric mean of AUC and C_{max} for tazarotene

PK Parameters	*Reference Formulation*	*Ratio of geometric mean*	*90% CI (Lower)*	*90% CI (Upper)*
$AUC_{0\text{-}tau}$	Gel	0.72	0.49	1.06
C_{max}	Gel	0.56	0.41	0.77

The results from Tables 1 and 2 show that the bioavailability of tazarotene and tazarotenic acid on Day 22 following once daily administration of the tazarotene foam was lower than once daily administration of Tazorac® Gel.

Specifically the geometric mean values of $AUC_{0\text{-}tau}$ and C_{max} of tazarotenic acid following the administration of the foam formulation were approximately 46% and 54% respectively, lower than those obtained following Tazorac® Gel administration; while the geometric mean values of $AUC_{0\text{-}tau}$ and C_{max} of tazarotene following the administration of the foam formulation were approximately 28% and 44% respectively, lower than those obtained following gel administration.

Clinical Pharmacology Briefing: An optional intra-division level Clinical Pharmacology briefing was conducted on 03/07/2012 with the following in attendance: Doanh Tran, Abimbola Adebowale, Hae-Young Ahn, E. Dennis Bashaw and Chinmay Shukla.

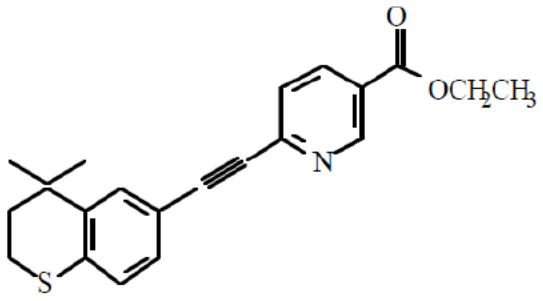
2. Question Based Review

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation?

Drug substance: Tazarotene is a member of acetylenic class of retinoids. It is a prodrug which is converted to its active form tazarotenic acid by deesterification. The molecular formula of tazarotene is $C_{21}H_{21}NO_2S$ and the molecular weight is 351.46. The chemical structure of tazarotene is shown in Figure 3.

Figure 3: Structure of Tazarotene



Formulation: Tazarotene foam, 0.1% (w/w) contains the active pharmaceutical ingredient tazarotene in an aerosol foam vehicle and will be supplied in aluminum containers of 10 g, 50 g and 100 g sizes. The container will be pressurized with a hydrocarbon propellant (propane/n-butane/isobutane). Table 3 below shows the composition of the tazarotene foam, 0.1%.

Table 3: Composition of Tazarotene Foam, 0.1% w/w

Component [a]	Quantity [%w/w] [b]	Function	Reference to Standard
Tazarotene	0.10	API	In-house
Purified Water	(b) (4)		USP
Light Mineral Oil			NF
Diisopropyl Adipate			JP
Macrogol Cetostearyl Ether 12			Ph Eur
Potassium Sorbate			NF
Sorbic Acid			NF
Potassium Citrate, Monohydrate			USP
Butylated Hydroxytoluene			NF
Citric Acid, Anhydrous			USP

Abbreviations: API = Active Pharmaceutical Ingredient; USP/NF = United States Pharmacopoeia/National Formulary, Current Edition; PhEur = European Pharmacopoeia; JP = Japanese Pharmacopoeia

(b) (4)

2.1.2 What are the proposed mechanism of action and the therapeutic indications?

Mechanism of action: The mechanism of action of tazarotene in acne vulgaris is not well defined.

Therapeutic indication: Topical treatment of acne vulgaris in patients 12 years of age or older.

2.1.3 What is the proposed route of administration and dosage?

Proposed route of administration: Topical

Proposed dosage: Tazarotene foam, 0.1% will be applied once daily in the evening after washing the affected area with a mild cleanser and fully drying it. The foam will be labeled to be applied in a quantity sufficient to lightly cover the entire affected area with a thin layer by gently massaging the foam into the skin using fingertips until the foam disappears.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

The development program for tazarotene foam, 0.1% was supported by 7 clinical trials. Among these, 4 dermal safety trials were conducted in healthy subjects and these included a cumulative irritation potential trial (W0260-101), contact sensitization potential trial (W0260-102), phototoxicity potential trial (W0260-103) and a photoallergic potential trial **(**W0260-104). The Sponsor also conducted a relative BA trial (W0260-105) under maximal use conditions in subjects 12 years and older with acne vulgaris (minimum age in the foam arm was 15 years). The purpose of this trial was to evaluate the relative BA of tazarotene foam, 0.1% compared to Tazorac® Gel, 0.1%. In addition to this, the Sponsor also conducted 2 phase 3 safety and efficacy trials in subjects 12 years and older with acne vulgaris (W0260-301 and W0260-302).

This review will focus on the relative BA trial (W0260-105). The 4 dermal safety trials and the 2 Phase 3 safety and efficacy trials will be reviewed by the reviewing medical officer Dr. Denise Cook (see review in DARRTS for more information).

2.2.2 What are the PK results?

The exposure at steady state following administration of foam formulation was lower than Tazorac® Gel. The PK results on Day 22 from the relative BA trial (W0260-105) are shown in Table 4 below. In trial W0260-105, a mean of 3.7 grams of the study product was applied once daily for 22 days to the face, upper chest, upper back and shoulders [approximately 15% BSA].

Table 4: PK parameters on Day 22 following once daily administration of tazarotene foam, 0.1% and Tazorac® Gel, 0.1%

Parameter	Tazarotenic Acid (Mean ± SD)		Tazarotene (Mean ± SD)	
	Foam	***Tazorac® Gel***	***Foam***	***Tazorac® Gel***
$AUC_{0\text{-}tau}$ (hr*ng/mL)	6.98 ± 3.56	12.46 ± 5.02	0.14 ± 0.09	0.21 ± 0.12
C_{max} (ng/mL)	0.43 ± 0.19	0.97 ± 0.49	0.012 ± 0.006	0.023 ± 0.016
$T_{1/2}$ (hr)	21.7 ± 15.7	17.5 ± 7.4	8.1 ± 3.7	9.4 ± 14.2
T_{max} (hr) [Median (range)]	6.0 (4.4 - 12.0)	5.2 (4.5 - 9.0)	3 (2.9 - 4.5)	3 (3.0 - 7.3)

2.2.3 What are the results of relative BA?

The values of 90% confidence interval (CI) of the ratio of the geometric mean of AUC and C_{max} for tazarotenic acid and tazarotene are shown in Table 5 and 6 respectively. The results indicate that the bioavailability of tazarotene and tazarotenic acid on Day 22 following once daily administration of the tazarotene foam was lower than once daily administration of Tazorac® Gel.

Specifically the geometric mean values of $AUC_{0\text{-}tau}$ and C_{max} of tazarotenic acid following the administration of the foam formulation were approximately 46% and 54% respectively, lower than those obtained following Tazorac® Gel administration; while the geometric mean values of $AUC_{0\text{-}tau}$ and C_{max} of the parent compound tazarotene following the administration of the foam formulation were approximately 28% and 44% respectively, lower than those obtained following gel administration.

Table 5: 90% CI of the ratio of the geometric mean of AUC and C_{max} for tazarotenic acid

PK Parameters	***Reference Formulation***	***Ratio of geometric mean***	***90% CI (Lower)***	***90% CI (Upper)***
$AUC_{0\text{-}tau}$	Gel	0.54	0.41	0.72
C_{max}	Gel	0.46	0.34	0.61

Table 6: 90% CI of the ratio of the geometric mean of AUC and C_{max} for tazarotene

PK Parameters	***Reference Formulation***	***Ratio of geometric mean***	***90% CI (Lower)***	***90% CI (Upper)***
$AUC_{0\text{-}tau}$	Gel	0.72	0.49	1.06
C_{max}	Gel	0.56	0.41	0.77

Reviewer comments: ***Trial W0260-105 evaluated the relative BA of the tazarotene foam formulation compared with Tazorac® Gel under maximal use conditions by applying the product to approximately 15% BSA (which included application to face, shoulders, upper chest and upper back). The purpose of this trial was to provide systemic bioavailability data for the foam formulation and provide relative bioavailability to the approved gel formulation to aid in systemic safety assessment.***

Tazorac® Gel is approved for topical treatment of facial acne vulgaris of mild to moderate severity in patients 12 years of age or older. The Division of Dermatology and Dental Products intends to approve tazarotene foam, 0.1% for the general indication of "acne vulgaris" instead of separating the indication by disease severity or by the area of application (face vs. body, etc.). Since trial W0260-105 used Tazorac® Gel off label [i.e. by applying the product to 15% BSA in subjects with acne vulgaris (moderate to severe) compared to the approved indication], the issue of applicability of this trial for the purpose of a clinical bridge for systemic safety was conveyed to the Clinical Division. Since the systemic exposure following foam administration was approximately 50% lower compared to Tazorac® Gel, the Clinical Division concluded that they do not have safety concerns.

Further analysis of the data set of trial W0260-105 revealed that there were 3 subjects with severe acne vulgaris (ISGA 4) in this trial. Specifically these subjects were subject no. 1009 in the foam arm and subject no. 1004 and 1007 in the gel arm (identified in Figures 4 and 5 with a red arrow). All other subjects had moderate acne vulgaris (ISGA 3). Even though there is limited PK data available in subjects with severe acne vulgaris, from the PK profiles shown in the figures below indicate that subjects with severe acne vulgaris did not appear to have higher systemic exposure compared to subjects with moderate acne vulgaris in both the foam and gel arms. Based on the available data, a definitive conclusion should not be inferred due to limited data in subjects with severe acne vulgaris.

Individual subject PK profiles of tazarotenic acid on Day 22 following administration of tazarotene foam, 0.1% and Tazorac® Gel, 0.1% is shown in Figure 4 and 5 respectively (subjects with severe acne vulgaris are identified with a red arrow in the figures).

Figure 4: Individual subject tazarotenic acid concentration versus time plot on Day 22 following once daily administration of tazarotene foam, 0.1%.

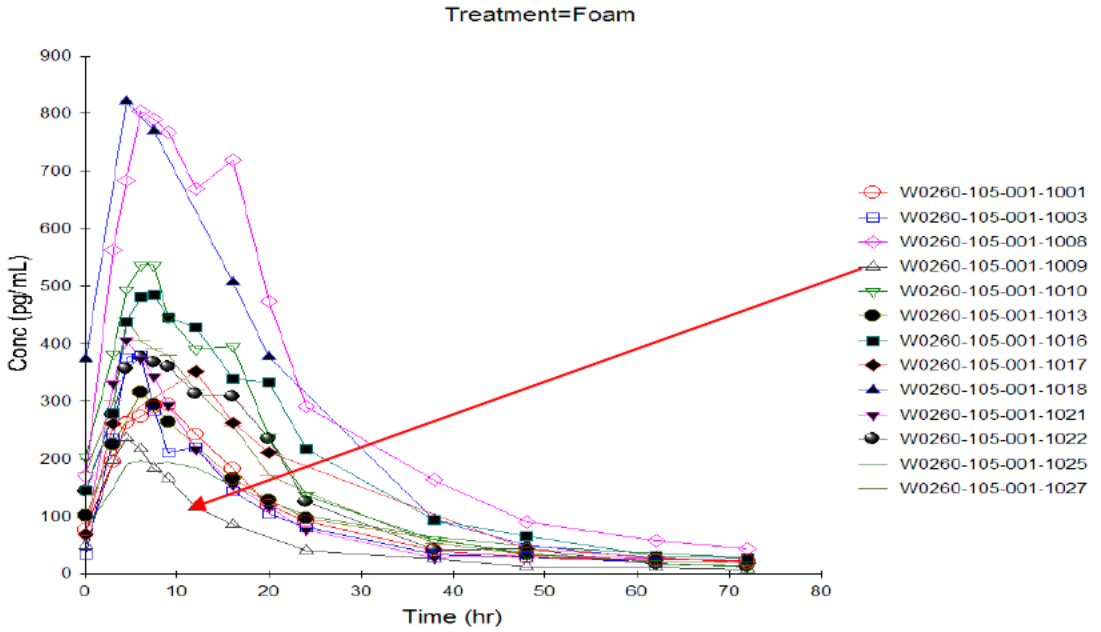
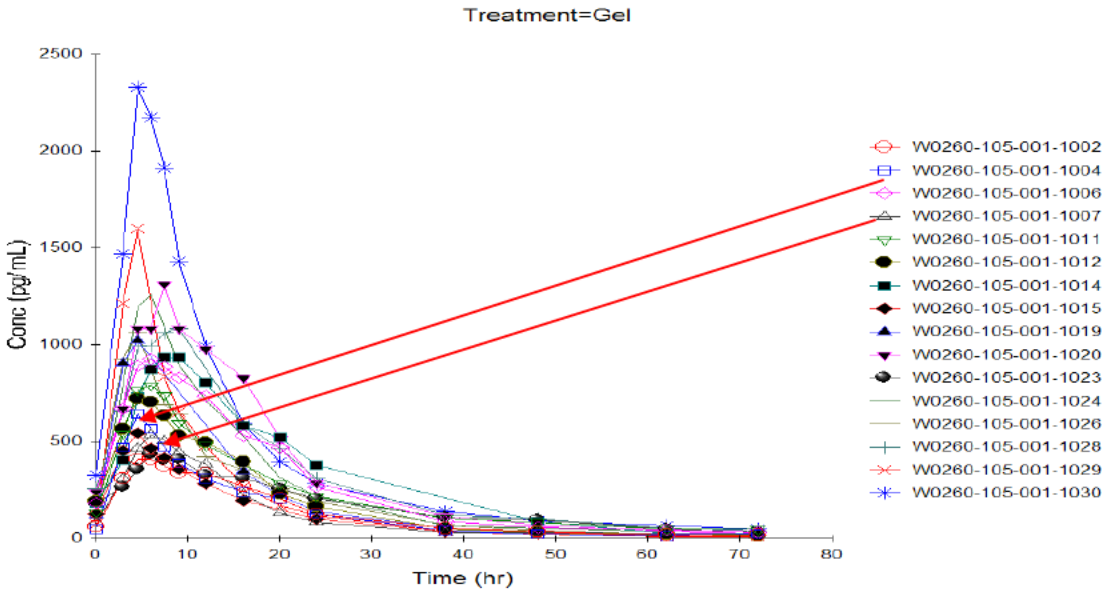


Figure 5: Individual subject tazarotenic acid concentration versus time plot on Day 22 following once daily administration of Tazorac® Gel, 0.1%.



In conclusion, the fact that the systemic exposure of tazarotenic acid with the foam formulation was approximately 50% lower than Tazorac® Gel would indicate that tazarotene foam, 0.1% is unlikely to have any increased systemic safety concerns compared to Tazorac® Gel, 0.1%. This was discussed verbally with the reviewing medical office Dr. Denise Cook, who was in agreement with the overall assessment and conclusions. Furthermore, the human systemic exposure following foam administration under maximal use conditions was considered by the Pharm-Tox reviewer Dr. Jiaqin Yao for the calculation of systemic safety margins and this was considered acceptable (see review in DARRTS dated 02/29/2012).

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.1.1 Effect of Gender

The effect of gender on the PK parameters was not evaluated by the Sponsor in this submission.

2.3.1.2 Pediatric patients

The Sponsor had requested a partial waiver for assessment of tazarotene foam in subjects 11 years old and younger because there are too few children with this disease to study in

this age group. Pediatric Review Committee (PeRC) meeting was held on February 15, 2012 and a waiver for assessment in subjects 11 years and younger was granted.

To address use in patients 12 years of age and older, the Sponsor has submitted results of a relative bioavailability (BA) trial (W0260-105) and 2 Phase 3 trials (W0260-301 and W0260-302) in patients 12 years of age and older. Specifically, in the relative BA trial (W0260-105), the lowest age in the foam arm was 15 years. Furthermore, results of this trial showed a lower systemic exposure with the foam formulation compared to Tazorac® Gel (AUC and Cmax of tazarotenic acid were approximately 50% lower) indicating that 0.1% foam will likely not have any increased systemic safety concern.

2.3.1.3 Renal impairment

No clinical studies have been conducted to evaluate the effect of renal impairment on the PK. Low levels of absorption and the topical indication does not justify the study requirement.

2.3.1.4 Hepatic impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the PK. This study is not justified given the low level of absorption and the topical indication.

2.3.1.5 What pregnancy and lactation use information is there in the application?

The Sponsor has not conducted any studies in pregnant and lactating women. The proposed labeling language for Section 8.1 (Pregnancy) and Section 8.3 (Nursing Mothers) in the proposed labeling is based on the approved labeling of Tazorac®.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure or response?

The influence of extrinsic factors on dose-exposure and/or response was not explored.

2.4.2 Drug-drug interactions

The Sponsor has not conducted any formal drug-drug interaction studies. Most of the proposed labeling language for Section 7 (Drug interactions) of the label has been borrowed from Tazorac label.

(b) (4)

The Sponsor claims that

(b) (4)

(b) (4)

Reviewer comments: An information request (IR) was sent on 02/15/2012 (b) (4) ***The Sponsor responded to this IR on 02/21/2012 and provided two literature references*** (b) (4)***. These references on review were found to be inadequate*** (b) (4) (b) (4) ***and an independent literature search was carried out by this reviewer.***

(b) (4)

Ultimately, this is a chemical reaction between two drugs (b) (4) (b) (4) (b) (4)

References:

(b) (4)

2.5 General Biopharmaceutics

2.5.1 Based on biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Not Applicable

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-marketed formulation was used in the PK trial (W0260-105) and the 2 pivotal Phase 3 clinical trials (W0260-301 and W0260-302).

2.5.2.1 What data support or do not support a waiver of in vivo BE data?

A waiver of BE data is not necessary as the proposed to-be-marketed formulation was used in the 2 pivotal Phase 3 trials (W0260-301 and W0260-302).

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Effect of food on the BA is not evaluated for topical formulations.

2.6 Analytical Section

2.6.1 How are the active moieties identified, and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

High performance liquid chromatography and tandem mass spectrometry (LC with MS/MS detection) was used to quantify tazarotene and tazarotenic acid from plasma samples.

2.6.2 Which metabolites have been selected for analysis and why?

Tazarotene is a prodrug and is converted to its active form tazarotenic acid by rapid de-esterification. The Sponsor has measured both tazarotene and tazarotenic acid.

2.6.3 For all moieties measured, is free, bound, or total measured?

Total plasma concentrations (unbound and bound) of tazarotene and tazarotenic acid were measured.

2.6.4 What is the range of the standard curve?

Analyte	*Range (pg/mL)*
Tazarotene	5 - 1000
Tazarotenic acid	5 - 5000

2.6.5 What are the accuracy, precision, and selectivity at LLOQ?

Analyte	*LLOQ (pg/mL)*	*% Accuracy*		*% Precision*	
		Intraday	*Interday*	*Intraday*	*Interday*
Tazarotene	5	3.60	0.40	3.44	4.54
Tazarotenic acid	5	5.80	0.40	4.26	5.72

2.6.6 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Tazarotene

Stability in plasma at room temperature	At least 25 hours
Long term stability at - 70ºC	384 days
Long term stability at - 20ºC	203 days
Freeze and thaw stability	5 cycles at - 70ºC

Tazarotenic acid

Stability in plasma at room temperature	At least 25 hours
Long term stability at - 70ºC	384 days
Long term stability at - 20ºC	293 days
Freeze and thaw stability	5 cycles at - 70ºC

2.6.6 Were any of the trials conducted by Cetero Research in Houston, Texas?

In response to Agency information request dated September 15, 2011, the Sponsor confirms that there were no studies conducted by Cetero Research in Houston, Texas during the period of concern (April 1, 2005 to June 15, 2010) submitted to NDA 202428 (See communication in DARRTS dated 10/19/2011).

Analysis of samples from trial W0260-105 was performed by (b) (4) (b) (4)

3. Detailed Labeling Recommendations

The following changes are recommended in the Sponsor's proposed labeling (Appendix shows the Drug Interactions and the Clinical Pharmacology sections of Sponsor submitted package insert). The **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates recommended deletion.

7 Drug Interactions

No formal drug-drug interaction studies were conducted with TRADENAME Foam.

Concomitant dermatologic medications and cosmetics that have a strong drying effect should be **avoided** [redacted]. It is recommended to postpone treatment until the effects of these products subside before use of TRADENAME Foam is started.

[redacted] Concomitant use with oxidizing agents, such as benzoyl peroxide, may **cause degradation of tazarotene and may** reduce the clinical efficacy of tazarotene. If combination therapy is required, they should be applied at different times of the day (e.g. one in the morning and the other in the evening).

The impact of tazarotene on the pharmacokinetics of progestin-only oral contraceptives (i.e., minipills) has not been evaluated.

In a study of 27 healthy female subjects between the ages of 20 to 55 years receiving a combination oral contraceptive tablet containing 1 mg norethindrone and 35 mcg ethynyl estradiol, concomitant use of tazarotene did not affect the pharmacokinetics of norethindrone and ethynyl estradiol over a complete cycle.

12.3 Pharmacokinetics

Following topical application, tazarotene undergoes esterase hydrolysis to form its active metabolite, tazarotenic acid. [redacted] Tazarotenic acid was highly bound to plasma proteins (greater than 99%). Tazarotene and tazarotenic acid were metabolized to sulfoxides, sulfones and other polar metabolites which were eliminated through urinary and fecal pathways.

Systemic exposure following topical application of TRADENAME Foam 0.1% was evaluated in one [redacted] **trial**. Patients **aged 15 years and older** with moderate-to-severe acne applied approximately [redacted] **3.7 grams** of TRADENAME Foam 0.1% (N=13) to **approximately** 15% body surface area once daily for 22 days. On day 22, the mean (±SD) tazarotenic acid C_{max} was 0.43 (±0.19) ng/mL, [redacted] the $AUC_{0\text{-}24h}$ was 6.98 (±3.56) ng·hr/mL~~;~~ **and** the half-life was [redacted] -22 **(±16)** hours. **The median T_{max} was 6 hours (range 4 to 12 hours).** [redacted] **- The** [redacted] $AUC_{0\text{-}24h}$ for tazarotenic acid was approximately [redacted] **-50** [redacted]-fold higher compared with **the parent compound** tazarotene~~,~~ [redacted]. **The mean (±SD) half-life of tazarotene was 8 (± 4) hours.**

Accumulation was observed upon repeated once-daily dosing as the tazarotenic acid predose concentrations were measurable in the majority of subjects. Steady state was ~~likely~~ attained within 22 days of daily application. [redacted]

Once-daily dosing resulted in little to no accumulation of tazarotene as predose concentrations were **mostly** below the quantitation limit throughout the study.

4. Detailed Biopharmaceutics Findings

Title: A single-center, randomized, open-label study to evaluate the bioavailability of tazarotene foam, 0.1%, and Tazorac Gel, 0.1%, in subjects with acne vulgaris.

Study No: W0260-105

Study objectives:
Primary: Evaluate plasma exposure and relative bioavailability of tazarotene foam, 0.1%, compared with Tazorac Gel, 0.1%, by measuring circulating plasma concentrations of tazarotenic acid in subjects with acne.
Secondary: Evaluate the safety of tazarotene foam in subjects 12 years of age or older with acne.

Study plan: This was a single-center, randomized, open-label, Phase 1, comparative bioavailability study in subjects with moderate to severe acne. Approximately 30 subjects were planned to be enrolled and randomized to 1 of the 2 study product groups in a 1:1 ratio (tazarotene foam: Tazorac® Gel).

Study product applied once daily for 22 days to the face, upper chest, upper back, and shoulders (approximately 15% BSA). Following the baseline visit, subjects returned to the study center daily for study product application. Table 7 below shows baseline disease characteristics.

Table 7: Baseline disease characteristics

	Tazarotene Foam (N=14)	Tazorac Gel (N=16)
Acne Location		
Face	14 (100)	16 (100)
Shoulders	7 (50)	7 (44)
Upper Chest	6 (43)	8 (50)
Upper Back	8 (57)	12 (75)
Investigator's Static Global Assessment		
Grade 2	0	0
Grade 3	13 (93)	14 (88)
Grade 4	1 (7)	2 (13)
Grade 5	0	0
Missing	0	0

PK blood sampling: Blood samples to determine plasma concentrations of tazarotenic acid and tazarotene were collected before study product application on Days 1, 8, 12, 15, 18, 20, and 22, and collected at multiple time points over a 72-hour period on Day 22.

Specifically on Day 22, the blood sampling time points included 3, 4.5, 6, 7.5, 9, 12, 16, 20, 24, 38, 48, 62, and 72 hours post drug application.

PK parameter estimation: The Sponsor planned to calculate the following PK parameters:

- $AUC_{(0\text{-}t)}$: Area under the plasma concentration-time curve form time 0 to the last time point measurable with analyte
- $AUC_{(0\text{-}tau)}$: Area under the plasma concentration-time curve from time 0 under 1 application interval (24 hours)
- C_{max}: The maximum measured plasma concentration
- T_{max}: time of the maximum measured plasma concentration
- C_{trough}: Pre-application plasma trough concentration
- $T_{1/2}$: The apparent terminal elimination half-life determined on day 22

Treatments:

- Tazarotene foam, 0.1% (Batch No. BDN-2)
- Tazorac® Gel, 0.1% (Batch No. 59655)

The protocol called for approximately 5 grams of the study product to the applied each day. However, the mean amount of study product actually applied was 3.74 g in the foam arm and 3.70 g in the gel arm. The study product were applied by the clinical staff each day in the late afternoon or early evening onto the face, upper chest, upper back, and shoulders (approximately 15% BSA).

Reviewer comments: ***The mean ± SD amount of formulation applied in the Phase 3 trials was approximately 1.2 ± 1.5 grams per day, while the amount of formulation used in the BA trial (W0260-105) was around 3.7 ± 0.5 grams per day (the subjects in the 2 Phas 3 trials were instructed to apply the product only to the face).***

Subject withdrawal: 30 subjects were enrolled with 14 subjects in the tazarotene foam arm and 16 subjects in the Tazorac gel arm. 29 subjects completed the study and subject (001-005) in the tazarotene foam arm withdrew consent and did not complete the study. All 30 subjects were included in the safety analysis, while 29 subjects were included in the PK analysis. Table 8 below shows the disposition of subjects.

Table 8: Disposition of Subjects

Disposition, n (%)	Tazarotene Foam N=14	Tazorac Gel N=16
Completed	13 (93)	16 (100)
Discontinued	1 (7)	0
Reasons for Discontinuation		
Adverse event	0	0
Withdrawal of consent	1 (7)	0

Demographic information and baseline characteristics: The demographic information and baseline characteristics are summarized below in Table 9.

Table 9: Demographic information and baseline characteristics

	Tazarotene Foam N=14	Tazorac Gel N=16
Age (years)		
Mean (SD)	20.6 (4.4)	22.5 (5.8)
Median	19.5	22
Minimum, Maximum	15, 32	12, 33
Sex, n (%)		
Male	4 (29)	7 (44)
Female	10 (71)	9 (56)
Race, n (%)		
American Indian or Alaska Native	0	1 (6)
Asian	0	1 (6)
Black	2 (14)	1 (6)
White	12 (86)	13 (81)
Ethnicity, n (%)		
Hispanic or Latino	10 (71)	6 (38)
Not Hispanic or Latino	4 (29)	10 (63)
Weight (kg)		
Mean (SD)	74.8 (17.5)	78.1 (22.5)
Median	70.55	77.1
Minimum, Maximum	54.4, 108.8	46.3, 118.4
Height (cm)		
Mean (SD)	162.2 (6.9)	168.7 (9.5)
Median	162.6	165.1
Minimum, Maximum	144.8, 175.3	157.5, 182.9
Body mass index (kg/m^2)		
Mean (SD)	28.7 (7.8)	27.6 (8.4)
Median	27.15	24.8
Minimum, Maximum	20.6, 45.4	15.5, 42.9
Acne location(s)		
Face	14 (100)	16 (100)
Shoulders	7 (50)	7 (44)
Upper chest	6 (43)	8 (50)
Upper back	8 (57)	12 (75)
Investigator's Static Global Assessment		
Grade 2	0	0
Grade 3	13 (93)	14 (88)
Grade 4	1 (7)	2 (13)
Grade 5	0	0

<u>Reviewer comments:</u> 4 out of 13 subjects in the foam arm were between 12 to 17 years of age (lowest age was 15 years).

PK results: The PK results shown in Table 10 are for tazarotenic acid and those in Table 11 are for the parent compound tazarotene.

Table 10: PK results of tazarotenic acid on Day 22 following once daily administration of tazarotene foam, 0. 1% and Tazorac® Gel, 0.1%

	Tazarotenic Acid	
Parameter	**Tazarotene Foam N=13**	**Tazorac Gel N=16**
$AUC_{0\text{-}tau}$ (h*pg/mL)		
Mean (SD)	6976.7 (3558.55)	12463.7 (5023.71)
CV_b (%)	50.003	42.105
Geometric mean	6268.8	11556.4
Median	6204	12271
Minimum, Maximum	2913.8, 14348.7	6585.5, 24505.2
C_{max} (pg/mL)		
Mean (SD)	434.1 (192.39)	973.9 (493.92)
CV_b (%)	43.825	50.827
Geometric mean	399.5	873.2
Median	379	931
Minimum, Maximum	196.0, 821.0	405.0, 2330.0
$AUC_{0\text{-}t}$ (h*pg/mL)		
Mean (SD)	9733.3 (4841.24)	15963.2 (6218.88)
CV_b (%)	48.909	40.769
Geometric mean	8788.5	14867.6
Median	8996	14991
Minimum, Maximum	3820.7, 20320.0	8389.3, 30147.8
T_{max} (hours)		
Mean (SD)	6.3 (2.16)	5.6 (1.37)
CV_b (%)	34.0	24.4
Median	6.0	5.2
Minimum, Maximum	4.4, 12.0	4.5, 9.0
$t_{1/2}$ (hours)		
Mean (SD)	21.7 (15.67)	17.5 (7.36)
CV_b (%)	55.312	37.663
Geometric mean	18.6	16.4
Median	14.5	15.7
Minimum, Maximum	12.0, 67.9	10.4, 37.8

Table 11: PK results of tazarotene on Day 22 following once daily administration of tazarotene foam, 0. 1% and Tazorac® Gel, 0.1%

Parameter	Tazarotene	
	Tazarotene Foam N=13	Tazorac Gel N=16
$AUC_{0\text{-}tau}$ (h*pg/mL)		
Mean (SD)	142.3 (87.33) [a]	205.0 (118.56) [b]
CV_b (%)	47.573	61.744
Geometric mean	127.4	176.5
Median	122	164
Minimum, Maximum	80.5, 365.4	67.1, 484.6
C_{max} (pg/mL)		
Mean (SD)	12.1 (6.29)	23.1 (16.43)
CV_b (%)	43.736	58.923
Geometric mean	11.1	19.7
Median	10.0	19.6
Minimum, Maximum	6.3, 30.0	8.1, 77.9
$AUC_{0\text{-}t}$ (h*pg/mL)		
Mean (SD)	85.4 (83.12)[c]	164.8 (134.66)
CV_b (%)	81.360	100.555
Geometric mean	64.9	120.5
Median	59.5	110
Minimum, Maximum	24.1, 330.5	22.9, 466.5
T_{max} (hours)		
Mean (SD)	3.2 (0.54)	3.7 (1.32)
CV_b (%)	16.7	35.8
Median	3.0	3.0
Minimum, Maximum	2.9, 4.5	3.0, 7.3
$t_{1/2}$ (hours)		
Mean (SD)	8.1 (3.66) [a]	9.4 (14.18) [b]
CV_b (%)	53.010	104.687
Geometric mean	7.3	5.8
Median	7.8	5.5
Minimum, Maximum	3.4, 14.3	2.2, 57.4

a: N = 9
b: N = 14
c: N = 12

Reviewer comments:

- ***The T_{max} for tazarotene occurred at the first sampling time point for 11 out of 13 subjects in the foam arm 13 out of 16 subjects in the gel arm. This might under estimate the AUC for tazarotene. But, since tazarotene is a pro-drug which is metabolized to its active form tazarotenic acid, further assessment of tazarotene at earlier time points are not necessary.***
- ***This reviewer reanalyzed the raw PK data set and found PK results very similar to the Sponsor submitted ones. Hence Sponsor submitted PK results are reported in this review.***

Relative BA assessment:

The values of 90% confidence interval (CI) of the ratio of the geometric mean of AUC and C_{max} for tazarotenic acid and tazarotene between foam and gel formulations are shown in Tables 12 and 13 respectively.

Table 12: 90% CI of the ratio of the geometric mean of AUC and C_{max} for tazarotenic acid

PK Parameters	***Reference Formulation***	***Ratio of geometric mean***	***90% CI (Lower)***	***90% CI (Upper)***
$AUC_{0\text{-}tau}$	Gel	0.54	0.41	0.72
C_{max}	Gel	0.46	0.34	0.61

Table 13: 90% CI of the ratio of the geometric mean of AUC and C_{max} for tazarotene

PK Parameters	***Reference Formulation***	***Ratio of geometric mean***	***90% CI (Lower)***	***90% CI (Upper)***
$AUC_{0\text{-}tau}$	Gel	0.72	0.49	1.06
C_{max}	Gel	0.56	0.41	0.77

The PK results show that the bioavailability of tazarotene and tazarotenic acid on Day 22 following administration of tazarotene foam, 0.1% was lower than Tazorac® Gel, 0.1%. Specifically the geometric mean values of $AUC_{0\text{-}tau}$ and C_{max} of tazarotenic acid following the administration of the foam formulation was approximately 46% and 54% respectively, lower than the gel formulation while the geometric mean values of $AUC_{0\text{-}tau}$ and C_{max} of tazarotene following the administration of the foam formulation was approximately 28% and 44% respectively, lower than the gel formulation.

Individual subject PK profiles:

Figure 6 shows the individual subject concentration versus time profile of tazarotenic acid as well as the mean (represented by the dark black line in the figure) on Day 22, following once daily application of the foam and gel formulations. While, Figure 7 shows the mean (± SD) plasma tazarotenic acid concentration versus time profile on Day 22 following once daily administration of tazarotene foam and Tazorac Gel.

Figure 6: Concentration versus time profile of tazarotenic acid on Day 22 following once daily administration of tazarotene foam, 0.1% and Tazorac® Gel, 0.1% (dark black line shows the mean)

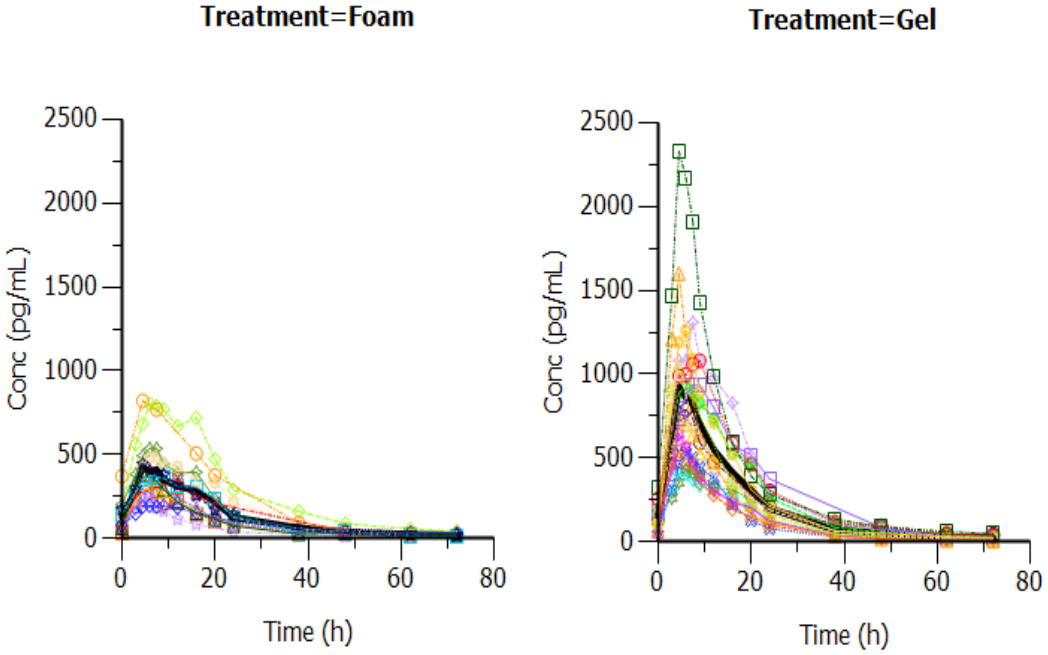


Figure 7: Mean (± SD) plasma tazarotenic acid concentration versus time profile on Day 22 following once daily administration of tazarotene foam and Tazorac® Gel

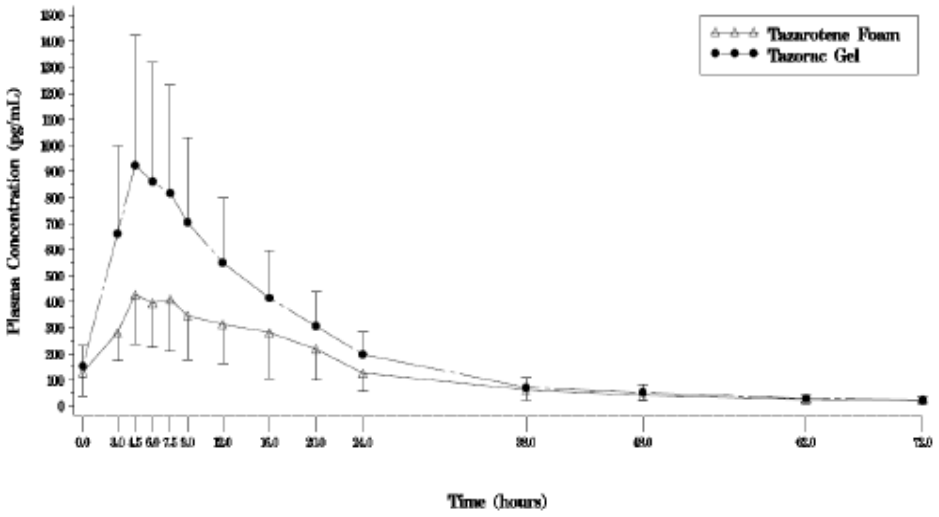


Figure 8 shows the individual subject concentration versus time profile of tazarotene as well as the mean (represented by the dark black line in the figure) on Day 22, following once daily application of tazarotene foam, 0.1% and Tazorac® Gel, 0.1%. While, Figure 9 shows the mean (± SD) plasma tazarotene concentration versus time profile on Day 22 following once daily administration of tazarotene foam and Tazorac® Gel.

Figure 8: Concentration versus time profile of tazarotene on Day 22 following once daily administration of tazarotene foam, 0.1% and Tazorac® Gel, 0.1% gel (dark black line shows the mean)

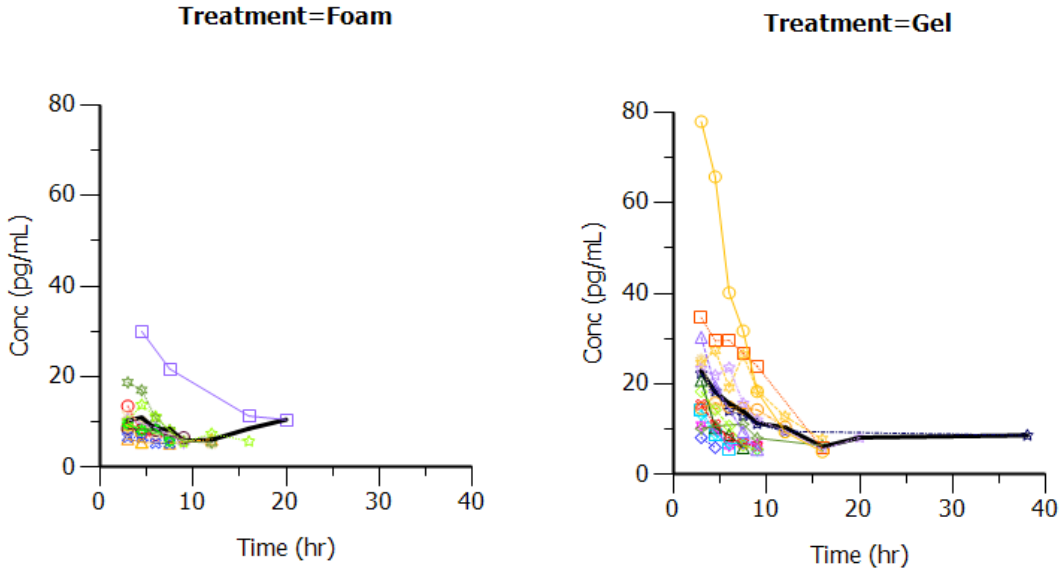


Figure 9: Mean (± SD) plasma tazarotene concentrations versus time profile on Day 22 following once daily administration of tazarotene foam and Tazorac® Gel

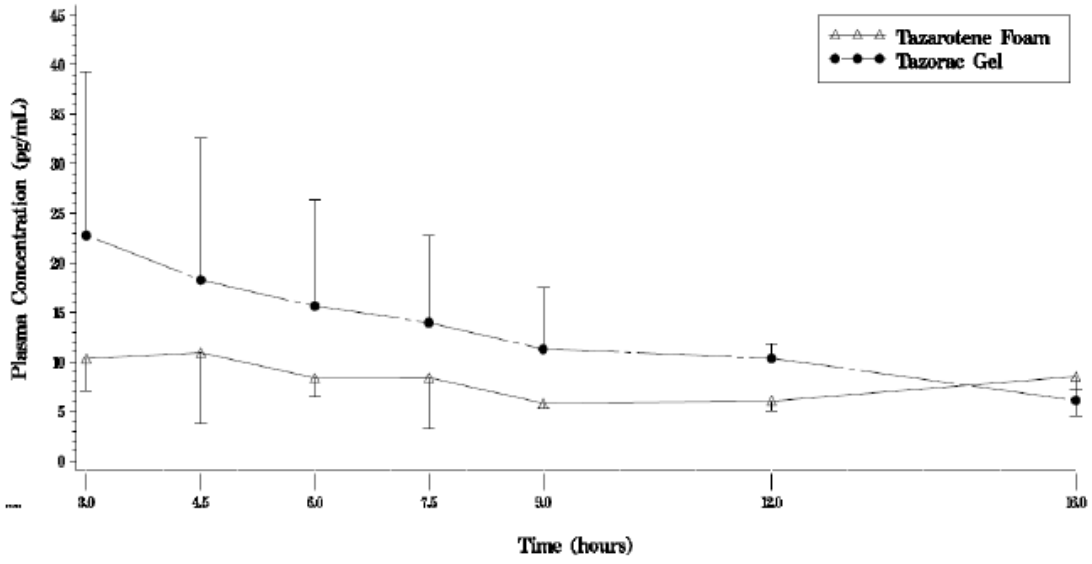


Table 14 and Figure 10 below show the pre-dose concentrations of tazarotenic acid on Days 1, 8, 12, 15, 18, 20, and 22; following once daily administration of tazarotene foam, 0.1% and Tazorac® Gel, 0.1% (Pre-dose concentrations on Day 1 were not quantifiable and hence not shown in the table). The mean (± SD) tazarotenic acid concentration at 24

hours following last dose administration on Day 22 were 127.1 ± 70.92 pg/mL in the tazarotene foam arm and 198.7 ± 85.31 pg/mL in the Tazorac® Gel arm.

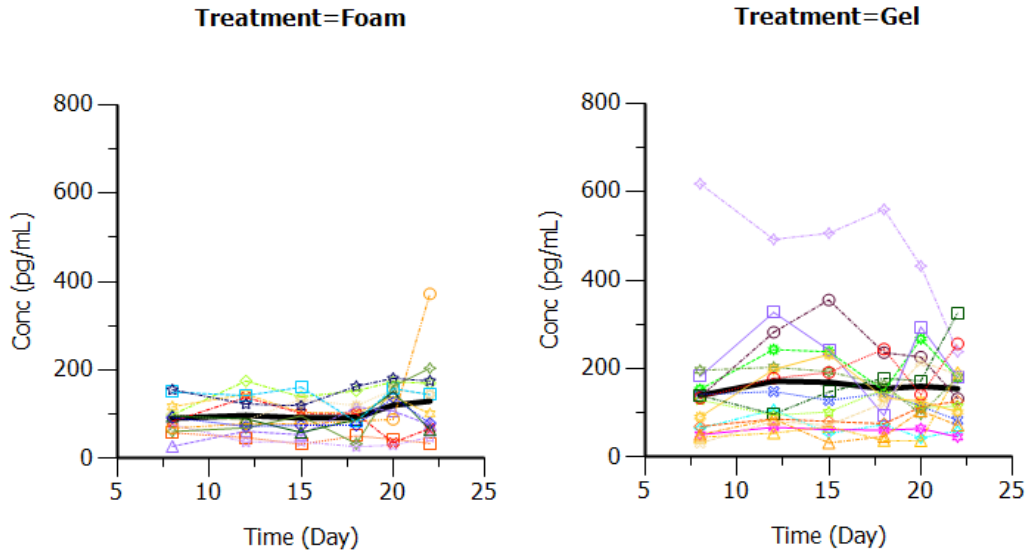
Table 14: Mean trough plasma concentrations of tazarotenic acid by study product

Study Day	Tazarotene Foam N = 13	Tazorac Gel N = 16
	Mean (SD) pg/mL	
8	90.9 (35.61)	139.3 (137.54)
12	97.1 (42.91)	171.4 (118.28)
15	91.5 (40.17)	168.9 (126.72)
18	92.5 (42.74)[a]	154.4 (124.44)
20	120.2 (54.03)	159.9 (104.69)
22	129.3 (90.59)	154.5 (77.35)

a: N = 12

Reviewer comments: ***Trough plasma concentrations suggest that steady state was reached by Day 22.***

Figure 10: Pre-dose concentration versus time profile of tazarotenic acid on Days 1[#], 8, 12, 15, 18, 20, and 22 following once daily administration of tazarotene foam, 0.1% and Tazorac ® Gel, 0.1% (dark black line shows the mean) *([#] Pre-dose concentration of tazarotenic acid on Day 1 was below LLOQ and hence not shown in the figure below)*



The corresponding pre-dose concentrations of tazarotene were quantifiable in 1 subject at a single time point following the foam administration and in 2 subjects at a single time point following the gel administration. These concentrations were 7.04 pg/mL pre-dose on Day 18 following tazarotene foam administration and 5.07 pg/mL and 5.85 pg/mL pre-dose on Day 18 and 12 respectively following Tazorac® Gel administration.

Dosing variability: Summary of missed applications is shown in the Table 15 and information about amount of formulation used is shown in Table 16.

Table 15: Summary of missed applications

Subject Number	Formulation	Day	Reason for Missed Application
001-1002	Tazorac Gel	13 14	AE Application to chest, back, and shoulders only
001-1005	Tazarotene foam	15 19 21, 22	Missed visit Did not apply to face and chest (AE of burning) Withdrew from study
001-1010	Tazarotene foam	16	Application to face and shoulders only – AE of itching on chest and back
001-1017	Tazarotene foam	19	Missed visit
001-1022	Tazarotene foam	2, 10	Missed visit
001-1024	Tazorac Gel	5, 6, 22	Missed visit
001-1026	Tazorac Gel	9	Missed visit
001-1029	Tazorac Gel	7, 8 9 15	Application to chest, back, and shoulders only – AE of burning on face Application to face and back only – AE of burning on chest Application to face, back, and shoulders only – AE of burning on chest
001-1030	Tazorac Gel	5, 6	Missed visit

AE: Adverse event

Table 16: Amount of formulation used

	Tazarotene Foam N = 14	**Tazorac® Gel N=16**
Total amount of study product used (grams)		
Mean (SD)	81.8 (10.6)	81.3 (8.0)
Median	80.3	82.5
Minimum, Maximum	65.7, 102.8	65.3, 93.4
Daily amount of study product used (grams)		
Mean (SD)	3.74 (0.45)	3.70 (0.36)
Median	3.65	3.75
Minimum, Maximum	3.19, 4.67	2.97, 4.25

SD: Standard deviation

Reviewer Comments: ***A mean of approximately 3.7 grams of each study product was applied, although the protocol specified that approximately 5 grams of study product was to be applied to each subject once a day, an amount considered necessary to cover 15% of the body surface area. However according to the Sponsor, 3.7 grams of study product was sufficient to cover 15% of body surface area. The average amount of formulation used in the 2 Phase 3 trials was approximately 1.2 grams/day (the subjects in the 2 Phas 3 trials were instructed to apply the product only to the face).***

Summary of safety: According to the Sponsor, 5 of the 14 subjects (36%) in the tazarotene foam arm and 7 of the 16 subjects (44%) in the Tazorac® Gel arm experienced treatment-emergent adverse events (AEs).

The largest number of AEs reported included upper respiratory tract infection in 2/14 (14%) subjects in the tazarotene foam arm and in 3/16 subjects (19%) in the Tazorac® Gel arm. Nervous system disorders like headache was reported in 3/14 (21%) subjects in

the tazarotene foam arm and in 2/16 (13%) in the Tazorac® Gel arm. These were the only AEs reported by more than 1 subject per group. All AEs according to the Sponsor were mild or moderate in intensity except for 1 severe application site erythema in the Tazorac® Gel group and 1 severe application site irritation in the tazarotene foam group. No Serious AEs or deaths were reported, and no subjects were withdrawn from the study as the result of an AE.

Both groups had 2 subjects (14%) with dosing-related AEs. The Tazorac® Gel dosing-related AEs included severe application site erythema and moderate application site irritation. While, the tazarotene foam dosing-related AEs included application site irritation on 2 occasions (1 severe and 1 moderate) and moderate application site pruritus. Each of the related AEs resulted in interruption of study product application.

Reviewer comments: ***The safety results reported here are those that have been reported by the Sponsor and were not reviewed by this reviewer. For additional information, please refer to Clinical review.***

2 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHINMAY SHUKLA
03/12/2012

DOANH C TRAN
03/12/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**202428**	**Brand Name**	**Pending**
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	**Tazarotene**
Medical Division	**DDDP**	**Drug Class**	**Retinoid**
OCP Reviewer	**Chinmay Shukla, Ph.D.**	**Indication(s)**	**Topical treatment of (b) (4) acne vulgaris in patients 12 years of age or older**
OCP Team Leader	**Doanh Tran, Ph.D.**	**Dosage Form**	**Foam, 0.1%**
Pharmacometrics Reviewer	**NA**	**Dosing Regimen**	**Once daily in the evening**
Date of Submission	**July 29, 2011**	**Route of Administration**	**Topical**
Estimated Due Date of OCP Review	**March 14, 2012**	**Sponsor**	**Stiefel Laboratories, Inc**
Medical Division Due Date	**March 29, 2012**	**Priority Classification**	**Standard**
PDUFA Due Date	**May 29, 2012**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			Long term plasma sample stability report (MC09B-0176) not submitted.
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				

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Patients-				
single dose:				
multiple dose:	**X**	**1**		Trial W0260-105
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**X**	**1**		Trial W0260-105 (12 years and older)
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**1**		Trial W0260-105 – Relative bioavailability of tazarotene foam, 0.1% compared with tazarotene gel, 0.1%
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				

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Total Number of Studies		**7**		**4 Phase 1 trials:** *** W0260-101:** Cumulative irritation potential *** W0260-102:** Contact sensitization potential *** W0260-103:** Phototoxicity potential *** W0260-104:** Photoallergic Potential **1 PK trial:** *** W0260-105:** Relative bioavailability of tazarotene foam, 0.1% compared to tazarotene gel, 0.1% **2 Phase 3 trials:** **W0260-301 and W0260-302**

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	The sponsor stated that all clinical studies were conducted with the to-be-marketed formulation of tazarotene foam.
2	Has the applicant provided metabolism and drug-drug interaction information?	X			Information submitted in Module 2.7.2
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			W0260-105 is a relative bioavailability trial comparing plasma exposure of tazarotene foam, 0.1% with tazarotene gel, 0.1% in subjects with acne vulgaris age 12 years and above under maximal use conditions.
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			The Sponsor stated that the long term stability of plasma PK samples for tazarotene is 196 days and tazarotenic acid is 204 days. This information appears adequate to cover the stability of the max use PK study samples (based on the time of enrollment of the first subject and analysis of the last sample). However, the Sponsor has not submitted the long term plasma sample stability report (MC09B-0176) at this time since the evaluation of frozen sample stability is ongoing.
5	Has a rationale for dose selection been submitted?	X			The Sponsor is developing 0.1% foam formulation of tazarotene and has hypothesized that the foam formulation will have comparable efficacy to tazarotene gel, 0.1% and tazarotene cream, 0.1% in the treatment of acne vulgaris.

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6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the			X	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	pediatric exclusivity data, as described in the WR?				
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			The proposed label appears to contain (b) (4) [redacted] There is no (b) (4) [redacted] information in the label since it was not evaluated.
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	All reports are in English

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? __ __Yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.
- N.A. -

Chinmay Shukla, Ph.D.
Reviewing Clinical Pharmacologist Date

Doanh Tran, Ph.D.
Team Leader Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Memorandum

Clinical Pharmacology Review

NDA: 202428
Compound: Tazarotene Foam, (b) (4)
Indication: Topical treatment of (b) (4) acne vulgaris in patients 12 years of age or older
Sponsor: Stiefel Laboratories, Inc
Date: July 29, 2011
Reviewer: Chinmay Shukla
Related IND: 105564

Background: With this NDA, the Sponsor is seeking approval for tazarotene foam, (b) (4) for the topical treatment of (b) (4) acne vulgaris in patients 12 years of age or older. The Sponsor has adopted a 505(b)(1) pathway.

Tazarotene foam, 0.1% contains the same active ingredient as Tazorac Gel and Tazorac Cream at the same concentration of 0.1%. The Sponsor has obtained full right of reference to the Tazorac NDAs from the holder, Allergan, Inc and plans to provide clinical safety and nonclinical pharmacology/toxicology data via cross-referencing to information in NDA 020600 (Tazorac Gel) and NDA 021184 (Tazorac Cream).

Clinical Trials:

To support the NDA, the Sponsor has submitted two pivotal clinical trials, a systemic bioavailability trial and four dermal safety trials as shown in the table below.

Study Identifier; Type of Study	Number of Centers (Location); Study Dates	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis; Key Inclusion Criteria	Treatment Details: Drug; Form; Dosage; Route; Regimen; Duration	Number of Subjects Entered/ Completed	Sex (M/F); Mean Age (Range)	Study Status; Type of Report; Location
W0260-101 Dermal safety	1 (United States); 29 Mar 2010-26 Apr 2010	To evaluate the cumulative irritation potential of tazarotene foam 0.1%	Randomized, evaluator-blinded, vehicle-controlled with positive and negative controls, single-center	Healthy subjects	Tazarotene foam 0.1%, vehicle foam, sodium lauryl sulfate 0.05% (positive control), and distilled water (negative control); patches with 200 µL study product applied once daily (24 hours); 21 days	39/30	16M/ 23F; 40.9 y (20-65 y)	Complete; Full; m5.3.5.4
W0260-102 Dermal safety	1 (United States); 31 Mar 2010-26 Jun 2010	To evaluate the contact sensitization potential of tazarotene foam 0.1%	Randomized, evaluator-blinded, vehicle-controlled, single-center	Healthy subjects	Tazarotene foam 0.1% and vehicle foam; 10 applications (48-72 hours each) of patches with 200 µL study product: 9 during 3-week Induction Phase & 1 after 2-week Rest Period	254/215	102M/ 152F; 46 y (18-65 y)	Complete; Full; m5.3.5.4
W0260-103 Dermal safety	1 (United States); 31 Mar 2010-10 Apr 2010	To evaluate the phototoxic potential of tazarotene foam 0.1%	Randomized, evaluator-blinded, vehicle-controlled, single-center	Healthy subjects	Tazarotene foam 0.1% and vehicle foam; patches with 200 µL study product applied for 24 hours; 1 day; selected patch sites were exposed to UV radiation or UV plus visible light	38/36	13M/ 25F; 42.7 y (19-65 y)	Complete; Full; m5.3.5.4
W0260-104 Dermal safety	1 (United States); 14 Apr 2010-25 Jun 2010	To evaluate the photoallergic potential of tazarotene foam 0.1%	Randomized, evaluator-blinded, vehicle-controlled, single-center	Healthy subjects	Tazarotene foam 0.1% and vehicle foam; 7 applications (24 hours each) of patches with 200 µL study product: 6 during 3-week Induction Phase & 1 after 2-week Rest Period; selected patch sites were exposed to UV radiation or UV plus visible light	59/51	15M/ 44F; 42.7 y (18-64 y)	Complete; Full; m5.3.5.4
W0260-105 Bioavailability	1 (United States); 08 Oct 2009-19 Nov 2009	Plasma exposure and relative bioavailability of tazarotene foam 0.1% compared with tazarotene gel 0.1%, as measured by circulating plasma concentrations of tazarotenic acid; Evaluate the safety of tazarotene foam	Randomized, open-label, active-controlled, parallel-group, single-center	Subjects with acne vulgaris; ISGA of 3 or greater	Tazarotene foam 0.1% or Tazorac (tazarotene) Gel 0.1%; topical application of approximately 5 grams to face, upper chest, upper back, and shoulders; once daily; 22 days	Overall: 30/29 Tazarotene foam: 14/13 Tazarotene gel: 16/16	11M/ 19F; (12-33 y) Tazarotene foam: 4M/ 10F; 20.6 y (15-32 y) Tazarotene gel: 7M/ 9F; 22.5 y (12-33 y)	Complete; Full; m5.3.1.2
W0260-301 Safety and efficacy	21 centers (18 United States; 3 Canada); 16 Oct 2009-11 Nov 2010	Demonstrate superiority of tazarotene foam versus vehicle foam based on 2 of 3 lesion counts (total, inflammatory, and noninflammatory) and the ISGA; Evaluate the safety of tazarotene foam	Randomized, double-blind, vehicle-controlled, parallel-group, multicenter	Subjects with acne vulgaris; ISGA of 3 or greater; 25-50 inflammatory lesions; 30-125 noninflammatory lesions	Tazarotene foam 0.1% and vehicle foam; once daily; topical application to the face; 12 weeks	Overall: 744/639 Tazarotene foam: 372/306 Vehicle foam: 372/333	Overall: 369M/ 374F; 18.4 y (12-44 y) Tazarotene foam: 189M/ 182F; 18.2 y (12-43 y) Vehicle foam: 180M/ 192F; 18.6 y (12-44 y)	Complete; Full; m5.3.5.1
W0260-302 Safety and efficacy	18 centers (14 United States; 4 Canada); 28 Oct 2009-15 Nov 2010	Demonstrate superiority of tazarotene foam versus vehicle foam based on 2 of 3 lesion counts (total, inflammatory, and noninflammatory) and the ISGA; Evaluate the safety of tazarotene foam	Randomized, double-blind, vehicle-controlled, parallel-group, multicenter	Subjects with acne vulgaris; ISGA of 3 or greater; 25-50 inflammatory lesions; 30-125 noninflammatory lesions	Tazarotene foam 0.1% and vehicle foam; once daily; topical application to the face; 12 weeks	Overall: 742/641 Tazarotene foam: 373/307 Vehicle foam: 369/334	Overall: 360M/ 382F; 19.2 y (12-45 y) Tazarotene foam: 176M/ 197F; 19.2 y (12-45 y) Vehicle foam: 184M/ 185F; 19.2 y (12-45 y)	Complete; Full; m5.3.5.1

Abbreviations: BSA = body surface area; F = female; ISGA = Investigator's Static Global Assessment; M = male; UV = ultraviolet; y = years

Bioavailability Study (W0260-105): There was only 1 PK trial conducted in subjects with acne vulgaris (drug PK was not evaluated in any other trial).

This was a single-center, randomized, open-label study to evaluate the bioavailability of tazarotene foam, 0.1% and Tazorac gel, 0.1% in subjects with acne vulgaris. The purpose of this trial was to evaluate the plasma exposure of tazarotene and tazarotenic acid (active metabolite) following once daily administration of tazarotene foam, 0.1% in comparison with Tazorac (tazarotene) Gel, 0.1% in subjects 12 years and older with acne vulgaris (ISGA of 3 or greater) under maximal use conditions.

A total of 30 subjects (11 male and 19 female, age range 12 - 33 years) were enrolled in the trial. 29 subjects (13 tazarotene foam group and 16 tazarotene gel group) completed the trial.
The protocol specified that approximately 5 grams of the study product was applied once daily in late afternoon or early evening for 22 days to the face, upper chest, upper back and shoulders (~ 15% BSA). The mean amount of study product actually applied per day was 3.74 grams in the tazarotene foam group and 3.70 grams in the tazarotene gel group.

Tazarotene is an acetylenic retinoid and is a prodrug. It is converted in-vivo to its active metabolite tazarotenic acid via hydrolysis. Blood samples to determine plasma concentrations of tazarotene and tazarotenic acid were collected before the study product application on Days 1, 8, 12, 15, 18, 20 and 22, and collected serially over a 72 hour period following drug application on day 22. The results are shown in the table below which indicates that the bioavailability of tazarotene and tazarotenic acid on Day 22 following administration of the foam formulation was lower than that obtained following administration of the reference gel formulation.

Parameters	Tazarotenic Acid		Tazarotene	
	Tazarotene foam N=13	Tazarotene gel N=16	Tazarotene foam N=13	Tazarotene gel N=16
$AUC_{0\text{-}tau}$ (hr*pg/mL), geometric mean	6268.8	11556.4	127.4	176.5
C_{max} (pg/mL), geometric mean	399.5	873.2	11.1	19.7
T_{max} (hours), mean	6.3	5.6	3.2	3.7
$t_{1/2}$ (hours), geometric mean	18.6	16.4	7.3	5.8

Bio-analytical method: Bioanalytical method validation and bioanalysis reports were submitted and are available for review. The long term plasma sample stability report (MC09B-0176) is not submitted at this time because according to the Sponsor, the evaluation of frozen sample stability is ongoing. However, the Sponsor has stated that the long term stability of plasma PK samples for tazarotene is 196 days and tazarotenic acid is 204 days. This information appears to be adequate to cover the stability of the max use PK trial (W0260-105) samples (based on the time of enrollment of the first subject and analysis of the last sample).

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Partial Waiver of Pediatric Studies: The Sponsor has requested a partial waiver for conducting pediatric assessments with tazarotene foam in subjects who are 11 years old and younger because the Sponsor considers that this product will not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in the age range of 0 to 11 years and this product is not likely to be used by a substantial number of pediatric patients in the stated age range.

Recommendation:
The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 202736 is fileable.

Comments to be sent to the Sponsor:

1. Submit report # MC09B-0176 titled "Evaluation of extended stability of tazarotene and tazarotenic acid in human plasma using high-performance liquid chromatography with mass spectrometric detection". This report is needed to support your statement within the bioanalytical report for study W0260-105 that the long-term storage stability has been demonstrated for 196 and 204 days for tazarotene and tazarotenic acid, respectively.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHINMAY SHUKLA
09/13/2011

DOANH C TRAN
09/13/2011