CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202428Orig1s000

MEDICAL REVIEW(S)

Addendum to NDA 202-428

Date: May 8, 2012

To: NDA 202-428 in DARRTS
3/20/12

From: Denise Cook, M.D.
Medical Officer, DDDP

Through: Gordana Diglisic, M.D.
Clinical Team Leader, DDDP

RE: Outstanding Issues for NDA 202-428

The clinical review in DARRTS dated 3/20/12 stated that the following issues from CMC were outstanding:

- "Overall Summary" of approval for inspections from the Office of Compliance
- Adequate carton/container labels

The trade name for tazarotene foam was also pending at the close of the review on 3/20/12.

CMC, in an addendum, in DARRTS dated 5/5/12 has deemed the carton and container labels as adequate and received an overall "Acceptable" recommendation from the Office of Compliance. Thus, from a CMC perspective, the NDA is now recommended for approval.
DMEPA has also, in a review in DARRTS dated 5/8/12, all of the issues concerning the container and carton labeling as well as the prescribing information addressed.

The applicant's request for the trade name for tazarotene foam to be Fabior has also been approved.

From a clinical perspective, there are no remaining outstanding issues to impede the approval of NDA 202-428.

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/s/

DENISE COOK
05/08/2012

GORDANA DIGLISIC
05/08/2012

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202428
Priority or Standard	Standard
Submit Date(s)	July 29, 2011
Received Date(s)	July 29, 2011
PDUFA Goal Date	May 29, 2012
Division / Office	DDDP/ODE III
Reviewer Name(s)	Denise Cook, M.D.
Review Completion Date	March 21, 2012
Established Name	tazarotene
(Proposed) Trade Name	Pending
Therapeutic Class	retinoid
Applicant	Stiefel Laboratories, Inc.
Formulation(s)	foam
Dosing Regimen	Once daily at bedtime
Proposed Indication(s)	For the topical treatment of (b) (4) acne vulgaris
Intended Population(s)	Males and females ages 12 years and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended, from a clinical perspective, that tazarotene foam, 0.1% be approved for the treatment of acne vulgaris in patients 12 years of age and older.

1.2 Risk Benefit Assessment

Tazarotene foam, 0.1% has been shown in two randomized, double-blind, vehicle-controlled clinical trials to be statistically significantly superior to vehicle ($p<0.001$) in the treatment of moderate to severe acne vulgaris. The most common adverse reactions were related to the integument and were not unexpected for a topical retinoid. Most reactions were mild to moderate and most subjects did not discontinue because of these application site reactions.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are none.

1.4 Recommendations for Postmarket Requirements and Commitments

There are none.

2 Introduction and Regulatory Background

2.1 Product Information

Tazarotene foam contains the compound tazarotene, a member of the acetylenic class of retinoids. It is for topical use only. Tazarotene is a pale yellow to yellow substance. The foam formulation contains tazarotene, 1 mg/g in an aqueous-based white to off-white foam vehicle consisting of butylated hydroxytoluene, ceteareth-12, citric acid anhydrous, diisopropyl adipate, light mineral oil, potassium citrate monohydrate, potassium sorbate, purified water, and sorbic acid. The foam is

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dispensed from an aluminum can pressurized with a hydrocarbon (propane/n-butane/isobutane) propellant.

Reviewer's Comment: *DMEPA has denied the applicant's initial proprietary name, of* (b) (4) *Fabior, a second proposed proprietary name by the application is currently under review by DMEPA.*

2.2 Tables of Currently Available Treatments for Proposed Indications

There are a number of other topical and systemic drugs available for the treatment of acne vulgaris. These include topical as well as oral antibiotics, retinoids of various strengths, and benzoyl peroxide in monotherapy or in combination drug products. The oral formulation of isotretinoin is also available for severe, recalcitrant, nodular acne.

Table 1: Topical Antimicrobials

Medications	Dose	List of Preparations
Benzoyl peroxide†	Twice daily	Multiple 2.5% to 10% gels, lotion, creams, pads, masks, cleansers
Clindamycin	Twice daily	1% gel, lotion, solution, foam
Erythromycin	Twice daily	2% gel, solution
Dapsone	Twice daily	5% gel
Sodium sulfacetamide (KLARON®)	Twice daily	10% lotion, wash, suspension, pad plus 10% urea

Source: Adapted from a review of UpToDate Online 18.1 Acne Medications 2; 2010
† Benzoyl peroxide is non-prescription

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Table 2: Topical Combination Products

Medications	Dose	List of Preparations
Benzoyl peroxide 5% - Clindamycin 1% (BENZACLIN® and DUAC®)	Twice daily	Gel
Benzoyl peroxide 5% - Erythromycin 3% (BENZAMYCIN®)	Twice daily	Gel
Benzoyl peroxide 2.5% - Clindamycin 1.2% (ACANYA®)	Once daily	Gel
Clindamycin 1.2% - Tretinoin 0.025% (ZIANA®)	Once daily, at bedtime	Gel
Benzoyl peroxide 2.5% - Adapalene 0.1% (EPIDUO®)	Once daily	Gel
Azelaic acid (FINACEA® and AZELEX®)	Twice daily	20% cream, 15% gel

Source: Adapted from a review of UpToDate Online 18.1 Acne Medications 2; 2010

Table 3: Retinoids (Topical and Oral)

Medications	Dose	List of Preparations
Topical Retinoids		
Tretinoin	Once daily, at bedtime	**Creams:** 0.025%, 0.05%, 0.1% **Gels:** 0.01%, 0.025%, 0.05% **Microsphere gels:** 0.04%, 0.1% **Prepolyolprepolymer gel:** 0.025%
Adapalene	Once daily, at bedtime	**Cream:** 0.1% **Gels:** 0.1%, 0.3%
Tazarotene	Once daily, at bedtime	**Creams:** 0.05%, 0.1% **Gels:** 0.05%, 0.1%
Oral Retinoid		
Oral isotretinoin	0.5mg/kg/day, increasing to 1mg/kg/day; total dose 120 to 150mg/kg over 20 weeks	**oral**

Source: Adopted from a review of UpToDate Online 18.1 Acne Medications 2; 2010

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Table 4: Oral Antibiotics

Medications	Dose
Tetracycline	500mg twice daily
Doxycycline	50 to 100mg twice daily or 150mg once daily
Minocycline	50 to 100mg twice daily or 1mg/kg.day or the extended release formulation
Erythromycin	500mg twice daily
Trimethoprim-sulfamethoxazole	160mg/800mg once to twice daily
Azithromycin [a]	Intermittent dosing due to long drug half life; optimum regimen unknown

Source: Adapted from a review of UpToDate Online 18.1 Acne Medications 2; 2010
Note: Antibiotics are frequently used in clinical practice, but may not be approved for the indication.
[a] Katsambas A, Dessinioti C. New and emerging treatments in dermatology: acne. Dermatol Ther. 2008;21(2):86-95

Table 5: Hormonal Agents

Medications	Dose
Combination oral contraceptives (estrogen/progestin)	Once daily
Spironolactone	25 to 200mg/day; doses of 50 to 100mg/day may be as effective as higher doses and reduce side effects

Source: Adapted from a review of UpToDate Online 18.1 Acne Medications 2; 2010

2.3 Availability of Proposed Active Ingredient in the United States

Tazorac is currently marketed in two formulations, cream and gel, both at 0.05% and 0.1%. The cream formulation is approved for the treatment of plaque psoriasis at both strengths and the 0.1% cream is approved for facial acne vulgaris and as an adjunctive agent for use in the mitigation (palliation) of facial fine wrinkling, facial mottled hyper- and hypopigmentation, and benign facial lentigines in patients who use comprehensive skin care and sunlight avoidance programs. The 0.05% gel formulation is also approved for plaque psoriasis while the 0.1% gel formulation is approved for the treatment of facial acne vulgaris of mild to moderate severity.

2.4 Important Safety Issues With Consideration to Related Drugs

Tazarotene in all of its formulations is a probable teratogen and therefore, is labeled as a pregnancy category X drug product. The label recommends that baseline pregnancy testing is obtained and that females of childbearing potential take the drug during a

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normal menstrual cycle. It also advises that females of childbearing potential should use adequate birth control measures when using the drug.
All topical retinoid drug products, including tazarotene formulations, cause cutaneous irritation and have the potential to cause photosensitivity reactions (see sections 7.3.5 and 7.4.1 and 7.4.5). Most of these reactions are mild and are reversible.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

• PreNDA meeting – June 15, 2011

This was conducted as a teleconference between the applicant and the Agency. Content and format were discussed at this meeting. In this meeting, the applicant was also reminded of the following advice letters sent and advised to consider the contents of these letters in preparing the NDA submission:

• December 28, 2010: Biostatistics Advice Letter

This Agency letter gave the sponsor final advice on the primary endpoint analysis as follows:

> *"The two analyses on the ISGA are likely to have substantial overlap. Although listed separately in the Agency's previous comments, to simplify the endpoint structure, the concept of two grade reduction as well as achieving a score of 0 or 1 at the end of the study could be combined into a single ISGA endpoint with success defined as 0 or 1 with two grades reduction. It should also be noted that because the inclusion criteria specify that the baseline ISGA will be 3 or higher, that in this case the combined endpoint will be the same as achieving 0 or 1."*

• August 3, 2010: Nonclinical Advice Letter

The Agency had the following nonclinical advice for the sponsor:

> "*It appears that a 90-day repeat-dose dermal toxicity study in rats treated with tazarotene foam and other available nonclinical information on tazarotene will be appropriate to support an NDA for tazarotene foam, 0.1%. The adequacy of the 90-day repeat-dose dermal toxicity study in rats will be a review issue."*

• May 25, 2010: Nonclinical Advice Letter

The Agency had the following nonclinical advice for the sponsor:

> "*A three-month dermal toxicity study in minipigs using the clinical formulation should be conducted to support the proposed 12-week phase 3 clinical studies as well as an NDA. This nonclinical study should be conducted instead of the proposed* [redacted] (b) (4)*.*
> *Provide the level of* [redacted] (b) (4) *(a possible carcinogen) contained in your propellant."*

Reviewer's Comment: *In the pharm/tox review, the sponsor did a 28 day dermal toxicity study in minipigs and coupled with a 90-day repeat dose dermal toxicity study in rats, this was found to be acceptable from a pharm/tox perspective to support the NDA. The pharm/tox review also states that the sponsor stated that* [redacted] (b) (4) *is not contained in the propellant of tazarotene foam.*

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- December 4, 2009: Multidiscipline Advice Letter

There were no other regulatory meetings with the sponsor.

2.6 Other Relevant Background Information

There is no other relevant background information. The United States is the first country in which an application for marketing of tazarotene foam has been submitted.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was well organized and in a reviewable format. The Division did not request any DSI investigations of any of the centers in the trial.

3.2 Compliance with Good Clinical Practices

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCP), ethical principles that have their origins in the Declaration of Helsinki, and all applicable laws and regulations. Prior to the start of the study, the study protocol and other relevant study documents were submitted to the institutional review boards (IRB). The IRBs reviewed and approved the required documents; copies of the approval letters were provided to Stiefel. Consistent with both IRB requirements and all applicable regulations, the investigator periodically provided study updates to the committees.

3.3 Financial Disclosures

The applicant filled out form 3454 and did not have any financial disclosures.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

From a chemistry perspective, the applicant has submitted sufficient information to assure the identity, strength, purity, and quality of the drug product. The to-be-marketed formulation is the same formulation used in all the clinical trials and registration stability batches. However, chemistry has two outstanding issues: it needs an overall

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"acceptable" recommendation from the Office of Compliance for the facilities involved and issues on labels/labeling need to be satisfactorily resolved. The latter have been sent to the sponsor and this reviewer does not perceive that the changes proposed for the label will be an issue.

4.2 Clinical Microbiology

There was no clinical microbiology.

4.3 Preclinical Pharmacology/Toxicology

The following are the findings regarding the preclinical program for tazarotene foam from the review of Dr. Jiaqin Yao.

"The sponsor has obtained the right to refer to the information in NDAs 20600 and 21184 from Allergan to support this NDA with a new dosage form (Foam, 0.1%) containing the same active ingredient for acne vulgaris. Topical treatment with Tazarotene Foam (up to 0.2%) in minipigs for 28 days caused only local dermal irritation associated with histopathological findings in the skin at the treatment site. The extent of dermal irritation elicited by topical treatment with Tazarotene Foam was less severe than the dermal irritation caused by topical treatment with Tazarotene Gel. The exposure levels of tazarotenic acid, the major metabolite of tazarotene, following topical treatment with Tazarotene Foam in rats or minipigs were comparable to or less than those following topical treatment with Tazarotene Gel. Tazarotene is not a genotoxic or carcinogenic compound. However, tazarotene is a teratogen in rats and rabbits." From a pharmacology/toxicology perspective, according to Dr. Yao, the NDA should be approved.

***Reviewer's Comment**: From a clinical perspective, the non-clinical studies support the clin/pharm trial in regards to the safety profile of this new formulation of tazarotene. The foam has less systemic availability and also from a cutaneous perspective is less irritating.*

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Tazarotene is a retinoid prodrug that is converted to its active form, the cognate carboxylic acid of tazarotene, by rapid deesterification in animals and man. Tazarotenic acid binds to all three members of the retinoic acid receptor (RAR) family: RARα, RARβ,

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and RARγ but shows relative selectivity for RARβ, and RARγ and may modify gene expression. The clinical significance of these findings is unknown.

The mechanism of tazarotene action in acne vulgaris is not defined. However, the basis of tazarotene's therapeutic effect in acne may be due to its anti-hyperproliferative, normalizing-of-differentiation and anti-inflammatory effects. Tazarotene inhibited corneocyte accumulation in rhino mouse skin and cross-linked envelope formation in cultured human keratinocytes. The clinical significance of these findings is unknown.

4.4.2 Pharmacodynamics

The pharmacodynamics of tazarotene foam are unknown.

4.4.3 Pharmacokinetics

The applicant conducted one pharmacokinetic trial. 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: approximately 5 grams to face, upper chest, upper back and shoulders (~15% BSA) for 22 days.
The reader is referred to the biopharmaceutics review by Dr. Chinmay Shukla for the details of the trial design and detailed results. In summary, Dr. Shukla deemed that the trial was adequate to evaluate the stated objective. Subjects in the trial had acne vulgaris, were ethnically diverse, with more females than males in each arm. The youngest subject in the trial was 15 years of age.
The geometric mean values of AUC and Cmax of the tazarotenic acid of tazarotene foam was ~50% less than that of tazarotene gel. The results show that the bioavailability of tazarotene and tazarotenic acid from the foam formulation on day 22 (end of treatment) was lower than the gel formulation.

Reviewer's Comment: *The results of this trial suggest that with less bioavailability than tazarotene gel, one would expect the safety profile of this new formulation to be no worse or better than the currently marketed tazarotene gel. Thus, the results of this trial form an adequate clinical bridge such that the applicant can rely on the Agency's finding of both systemic and long-term safety for tazarotene gel for this product, tazarotene foam.*

5 Sources of Clinical Data

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5.1 Tables of Studies/Clinical Trials

Table 6
Description of Clinical Efficacy and Safety Studies

Study Identifier; Type of Study	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis	Treatment Details: Drug; Form; Dosage; Route; Regimen; Duration	Number of Subjects Entered/ Completed	Study Status; Type of Report; Location
W0260-101 Dermal safety	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 hrs); 21 days	39/30	Complete; Full; m5.3.5.4
W0260-102 Dermal safety	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 hrs each) of patches with 200 µL study product: 9 during 3-week Induction & 1 after 2-week Rest	254/215	Complete; Full; m5.3.5.4
W0260-103 Dermal safety	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 hrs; 1 day; selected patch sites were exposed to UV or UV plus visible light	38/36	Complete; Full; m5.3.5.4
W0260-104 Dermal safety	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 hrs each) of patches with 200 µL study product: 6 during 3-week Induction & 1 after 2-week Rest; selected patch sites were exposed to UV or UV plus visible light	59/51	Complete; Full; m5.3.5.4

Source: NDA 202-428, Module 2: Clinical Overview, Section 1.5, page 13

Study Identifier; Type of Study	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis	Treatment Details: Drug; Form; Dosage; Route; Regimen; Duration	Number of Subjects Entered/ Completed	Study Status; Type of Report; Location
W0260-105 Bioavailability	Plasma exposure and relative bioavailability of tazarotene foam 0.1% compared with tazarotene gel 0.1%; Evaluate the safety of tazarotene foam	Randomized, open-label, active-controlled, parallel-group, single-center	Subjects with moderate-to-severe acne (ISGA ≥3)	Tazarotene foam 0.1% or 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	Complete; Full; m5.3.1.2
W0260-301 Safety and efficacy	Demonstrate superiority of tazarotene foam versus vehicle foam based on 2 of 3 lesion counts and the ISGA; Evaluate the safety of tazarotene foam	Randomized, double-blind, vehicle-controlled, parallel-group, multicenter	Subjects with moderate-to-severe acne (ISGA ≥3)	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	Complete; Full; m5.3.5.1
W0260-302 Safety and efficacy	Demonstrate superiority of tazarotene foam versus vehicle foam based on 2 of 3 lesion counts and the ISGA; Evaluate the safety of tazarotene foam	Randomized, double-blind, vehicle-controlled, parallel-group, multicenter	Subjects with moderate-to-severe acne (ISGA ≥3)	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	Complete; Full; m5.3.5.1

Abbreviations: ISGA = Investigator's Static Global Assessment; UV = ultraviolet
Source: NDA 202-428, Module 2: Clinical Overview, Section 1.5, page 14

5.2 Review Strategy

The pivotal trials, W0260-301 and W0250-302 were reviewed in detail, as these two trials were the bases for efficacy and safety of tazarotene foam. The four dermal safety trials, W0620-101, -102, -103, and -104 were also reviewed.

Trial W0260-05, a comparative bioavailability trial with a marketed formulation of tazarotene, tazarotene gel, provided the basis for a bridge to the Agency's finding of systemic and long-term safety for this formulation, tazarotene foam. This trial was reviewed in detail by the clinical pharmacologist, Dr. Chinmay Shukla. Efficacy was verified by the biostatistician, Dr. Kathleen Fritsch. In addition, the applicant obtained a letter of cross reference from Allergan, Inc., the owners of NDA 20-600, tazarotene gel and NDA 21-184, tazarotene cream on 7/5/11 for right of reference to the information contained in these NDAs, which provided the bulk of the non-clinical data to support this NDA.

Consults were submitted to the following:

- DMEPA – carton and immediate container labels, PI, PPI, proprietary name
- OPDP – all labeling
- DMPP – PPI

5.3 Discussion of Individual Studies/Clinical Trials

Reviewer's Comment: *The two pivotal trials, W0260-301 and W0260-302 had identical trial designs.*

The trials were multicentered, randomized, double-blind, vehicle-controlled, parallel group trials to evaluate the safety and efficacy of tazarotene foam, 0.1% in subjects with acne vulgaris. Together the trials had 39 centers, 32 in the United States and 7 in Canada.

The key inclusion criteria were as follows:

- Male or female between 12 and 45 years of age, inclusive, in general good health
- Has ISGA score of 3 or greater (moderate to severe disease)
- Lesion counts meeting both of the following criteria:
  a. A minimum of 25 but not more than 50 facial inflammatory lesions (papules plus pustules), including nasal lesions, and no more than 1 facial nodular lesion (<5 mm), with NO cystic lesions.
  b. A minimum of 30 but not more than 125 facial noninflammatory lesions (open and closed comedones), excluding nasal lesions.
- Negative urine pregnancy test for females of childbearing potential
- Sexually active females of childbearing potential participating in the trial must agree to use a medically acceptable method of contraception while receiving protocol-assigned product.

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The key exclusion criteria were as follows:

- Female who is pregnant, trying to become pregnant, or breast feeding
- History of lupus, dermatomyositis, rosacea, seborrheic dermatitis, beard folliculitis, or perioral dermatitis. Seb derm cannot have been active for at least 1 year or not involve the face.
- Use of topical antibiotics on the face within the past 2 weeks
- Use of systemic antibiotics for acne treatment within the past 4 weeks
- Concurrent use of medications known to be photosensitizers
- Use of topical corticosteroids on the face within the past 2 weeks or systemic corticosteroids within the past 4 weeks
- Treatment with hormonal therapy for 12 weeks or less immediately prior to the trial enrollment
- Use of systemic retinoids (e.g. isotretinoin) within the past 6 months
- Use of topical acne medications with in the past 2 weeks
- Facial procedures within the past 4 weeks
- Require or desire excessive or prolonged exposure to ultraviolet light during the study

Subjects in the trial were randomized 1:1 to either tazarotene foam, 0.1% or vehicle foam. The trial product was applied to the face once daily in the evening for 12 weeks. Subjects washed the face with a mild non-antimicrobial soap or soap-free cleanser, and allowed the area to fully dry before applying study product. Study product was dispensed from the canister by gently squeezing down on the actuator and dispensing the foam product through the nozzle; the canister was oriented in an upright or near upright position during actuation.
A sufficient amount of study product was gently massaged to cover the entire face until it disappeared. Subjects avoided application around the eyes and in the nose and mouth. It was recommended that subjects apply oil-free and noncomedogenic facial moisturizer and sunscreen as needed. Table 7 shows the schedule of assessments throughout the trial.

Reference ID: 3109305

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Table 7
Schedule of Assessments*

		Study Period			
Visit	1	2	3	4	5
	Baseline Week 0 / Day 1	Week 2 / Day 15 ±3 days	Week 4 / Day 29 ±5 days	Week 8 / Day 57 ±5 days	Week 12 / Day 85 ±5 days or ET
Informed consent/assent	X				
Demographics, medical history	X				
Inclusion/exclusion criteria	X				
Concomitant medication query	X	X	X	X	X
Adverse event query	X	X	X	X	X
Subject's Global Assessment	X	X	X	X	X
Investigator's Static Global Assessment [a]	X	X	X	X	X
Lesion count [a]	X	X	X	X	X
Local tolerability assessment [a, b]	X	X	X	X	X
Urine pregnancy test (females of childbearing potential)	X	X	X	X	X
DLQI or CDLQI	X	X	X	X	X
Randomization	X				
Weigh and dispense study product container	X			X [d]	
Collect and weigh study product container		X	X	X	X
Redispense study product container		X	X		
Dispense Subject Compliance Log	X	X	X	X	
Collect and review Subject Compliance Log		X	X	X	X
Subject's post-study questionnaire					X
Clinical photography [c]	X				X

Abbreviations: ET = early termination/discontinuation; DLQI = Dermatology Life Quality Index; CDLQI = Children's Dermatology Life Quality Index

[a] The same investigator/designee is strongly recommended to perform all acne assessments for each subject at each visit.

[b] Erythema, dryness, and peeling will be assessed by the investigator; burning/stinging and itching will be assessed by the subject.

[c] Clinical photography will be performed at selected sites and is not required of subjects for participation in the study.

[d] A new study product container may be dispensed at an earlier visit as needed.

*Source: NDA 202-428, Module 5: Study Protocol, Table 1, page 17

Efficacy assessments included the following variables, investigator's static global assessment (IGSA), lesion counts, and subject's global assessment (SGA). The ISGA was performed at baseline and at weeks 2, 4, 8, and 12. The ISGA severity scale is shown in table 8. The investigator/designee performed a count of inflammatory lesions (papules and pustules and nodules), noninflammatory lesions (open and closed comedones), and total lesions at baseline and at weeks 2, 4, 8, and 12. Lesion counts were confined to the face (including forehead, nose, cheeks, and chin). The SGA of the facial skin, excluding the scalp, was performed by subjects at baseline and at weeks 2, 4, 8, and 12. That scale is shown in table 9.

Reviewer's Comment: *The efficacy variables that we considered when reviewing this application and that were agreed on with the sponsor was the ISGA and lesion counts. The SGA was not used to determine efficacy of tazarotene foam.*

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Table 8
Investigator's Static Global Assessment

ISGA Assessment Scale		
0	=	Clear skin with no inflammatory or noninflammatory lesions
1	=	Almost clear: rare noninflammatory lesions with no more than rare papules
2	=	Mild severity: greater than Grade 1, some noninflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	=	Moderate severity: greater than Grade 2, up to many noninflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4	=	Severe: greater than Grade 3, up to many noninflammatory and inflammatory lesions, but no more than a few nodular lesions
5	=	Very severe: many noninflammatory and inflammatory lesions and more than a few nodular lesions. May have cystic lesions

NDA 202-428: Module 5, Clinical Study Protocol, Appendix 1, page 57

Table 9
Subject's Global Assessment

Subject's Global Assessment Scale		
0	=	My face is basically free of acne, with only an occasional blackhead and/or whitehead
1	=	My face has several blackheads and/or whiteheads and small pimples, but there are no tender deep-seated bumps or cysts
2	=	My face has several to many blackheads and/or whiteheads and small- to medium-sized pimples, and may have one deep-seated bump or cyst
3	=	My face has many blackheads and/or whiteheads, many medium- to large-sized pimples, and perhaps a few deep-seated bumps or cysts
4	=	My face has blackheads and/or whiteheads, and several to many medium- to large-sized pimples and deep-seated bumps or cysts dominate

NDA 202-428: Module 5, Clinical Study Protocol, Appendix 3, page 59

An additional assessment that occurred at each visit was that of local tolerability. This assessment included scales that assessed the erythema, dryness, and peeling by the investigator at each visit and a scale in which the subject assessed burning/stinging and itching at each visit. Tables 10 and 11 show these scales.

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Table 10
Evaluator-Assessed Erythema, Dryness, and Peeling

Grade	Severity	Erythema	Dryness	Peeling
0	Absent	No redness	None	No peeling
1	Slight	Faint red or pink coloration, barely perceptible	Barely perceptible dryness with no flakes or fissure formation	Mild localized peeling
2	Mild	Light red or pink coloration	Easily perceptible dryness with no flakes or fissure formation	Mild and diffuse peeling
3	Moderate	Medium red coloration	Easily noted dryness and flakes but no fissure formation	Moderate and diffuse peeling
4	Severe	Beet red coloration	Easily noted dryness with flakes and fissure formation	Moderate to prominent, dense peeling

NDA 202-428: Module 5, Clinical Study Protocol, Appendix 2, page 58

Table 11
Subject-Assessed Itching and Burning/Stinging

Grade	Itching	Burning/Stinging
0	None	None
1	Slight	Slight
2	Moderate	Moderate
3	Strong	Strong

NDA 202-428: Module 5, Clinical Study Protocol, Appendix 2, page 58

Reviewer's Comment: *These last two assessment scales may provide useful information for patients in what to expect with use of the drug product. The subject's global assessment scale was not reviewed, as the Division relies on objective scales (such as those associated with lesion counts) for efficacy assessments along with an overall assessment by an experienced investigator (e.g. as with the ISGA).*

Safety assessments included recording in the case report form (CRF) all adverse events encountered or spontaneously reported by the subject and/or elicited by investigators or designees at any time throughout the study (prior to and after receiving study product). Causality, defined as a reasonable possibility that a causal relationship existed between the study product and adverse event was determined by the investigator. Adverse events were also graded on a 3-point scale as follows:

- Mild – no disruption to activities of daily living
- Moderate – interferes with activities of daily living
- Severe – significantly impacts activities of daily living

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Tazarotene foam, 0.1% is indicated for the topical treatment of (b) (4) acne vulgaris in patients 12 years of age or older.

Reviewer's Comment: *This is the applicant's proposed indication. The indication will be modified to "the topical treatment of acne vulgaris in patients 12 years of age or older," rather than (b) (4) acne vulgaris. Acne vulgaris is the same disease whether it manifests itself solely on the face or whether it involves the upper back, shoulders, and upper chest. The applicant performed a comparative pk trial between tazarotene gel and tazarotene foam under maximal use conditions (see section 4.4.3, page 14) and the bioavailability of tazarotene foam was lower than Tazorac gel. As will be described below, tazarotene foam was found to be efficacious in the treatment of moderate to severe acne vulgaris in 2 vehicle controlled trials. Thus, with lower bioavailability, even though the trials only study the face, there will not be a safety issue in approving the drug product for the indication of acne vulgaris without regard to the anatomical surface that it may involve.*

6.1.1 Methods

The two pivotal phase 3 trials, W0260-301 and W0260-302 were reviewed along with the clinical summary of efficacy to support the proposed indication of the applicant. These trials were double-blind, placebo controlled, multicentered trials (see section 5.1).

6.1.2 Demographics

A total of 1486 subjects were enrolled in the phase 3 trials across 39 study centers in Canada and the U.S.A. The mean age was similar between tazarotene foam and its vehicle, 18.7 years and 18.9 years, respectively. More than half of the subjects were age 12 to 17 years in both arms, at 58%. Subjects were approximately evenly distributed in terms of sex, 49% male and 51% female. The majority of the subjects were White (76%) and not Hispanic or Latino. Table 12 describes the demographics of the Intent-to-Treat (ITT) population. These percentages were consistent across the individual trials, also (see statistical review, table 7, page 10, DARRTS 3/14/12).

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Table 12
Demographics Phase 3 Trials
W0260-301 and W0260-302 (ITT Population)

Demographics	Tazarotene Foam N=744	Vehicle Foam N=741	All Subjects N=1485
Age (years)			
Mean (standard deviation)	18.7 (6.1)	18.9 (6.6)	18.8 (6.4)
Median (minimum, maximum)	17 (12, 45)	17 (12, 45)	17 (12, 45)
Age Category, n (%)			
12 to 17 years	428 (58)	432 (58)	860 (58)
18 to 25 years	221 (30)	207 (28)	428 (29)
26 to 35 years	73 (10)	70 (9)	143 (10)
36 to 45 years	22 (3)	32 (4)	54 (4)
Sex, n (%)			
Male	365 (49)	364 (49)	729 (49)
Female	379 (51)	377 (51)	756 (51)
Ethnicity, n (%)			
Hispanic or Latino	133 (18)	127 (17)	260 (18)
Not Hispanic or Latino	611 (82)	614 (83)	1225 (82)
Race, n (%)[a]			
American Indian or Alaska Native	14 (2)	5 (1)	19 (1)
Asian	38 (5)	25 (3)	63 (4)
Black	112 (15)	107 (14)	219 (15)
Native Hawaiian or Other Pacific Islander	0	5 (1)	5 (<1)
White	563 (76)	587 (79)	1150 (77)
Other	17 (2)	12 (2)	29 (2)

NDA 202-428: ISE, table 17, page 37

6.1.3 Subject Disposition

Both trials were multicentered trials. In trial W0260-301, there were a total of 21 centers (18 in the United States and 3 in Canada). The first subject's first visit was on October 16, 2009 and the last subject completed the trial on November 11, 2010. In trial W0260-302, there were a total of 18 centers (14 in the United States and 4 in Canada). The first subject's first visit was on October 28, 2009 and the last subject completed the trial on November 15, 2010. Tables 13 and 14 describe the Intent-to-Treat Population and the Per-Protocol Population for the pivotal trials.

Table 13
Disposition Summary of Analysis Data Sets
Pivotal Trial W0260-301

Analysis Set, n (%)	Tazarotene Foam (N=372)	Vehicle Foam (N=372)	Total (N=744)
Intent-to-Treat analysis set	371 (100)[a]	372 (100)	743 (100)
Per-Protocol analysis set	270 (73)	318 (85)	588 (79)
Subjects excluded from the Per-Protocol analysis set	102 (27)	54 (15)	156 (21)

aSubject 106-0027 was randomized to the tazarotene foam group but discontinued due to pregnancy and did not receive any drug product
Source: NDA 202-428: W0260-301, Final Study Report, table 8, page 46.

Table 14
Disposition Summary of Analysis Data Sets
Pivotal Trial W0260-302

Analysis Set, n (%)	Tazarotene Foam (N=373)	Vehicle Foam (N=369)	Total (N=742)
Intent-to-Treat analysis set	373 (100)	369 (100)	742(100)
Per-Protocol analysis set	276 (74)	311 (84)	587 (79)
Subjects excluded from the Per-Protocol analysis set	97 (26)	58 (16)	155 (21)

Source: NDA 202-428: W0260-302, Final Study Report, table 8, page 46.

Reviewer's Comment: *There is very little difference between the two trials in terms of the population sets.*

In both phase 3 trials, nearly twice as many subjects in the tazarotene foam group discontinued the study compared with the vehicle foam group (66 versus 39 in trial W260 -301 and 66 versus 35 in trial W0260-302), mostly due to withdrawal by subject (32 tazarotene versus 16 vehicle in trial -301 and 39 versus 21 in trial -302) and discontinuation due to an AE (11 tazarotene versus 1 vehicle in trial -301 and 9 versus 0 in trial -302). Examples of reasons for subject withdrawal included scheduling conflicts, dissatisfaction with speed of improvement, and disliking facial dryness. Table 15 shows the disposition for trial W0260-301 and table 16 describes the disposition of subjects for trial W0260-302.

Reference ID: 3109305

Table 15
Disposition of Subjects
ITT Population – W0260-301

	Tazarotene Foam (N=371)	Vehicle Foam (N=372)	Total (N=743)
Completed Study, n (%)	306 (82)	333 (90)	639 (86)
Discontinued, n (%)	66 (18)	39 (10)	104 (14)
Reasons for discontinuation, n (%)			
Adverse event	11 (3)	1 (<1)	12 (2)
Lost to follow-up	14 (4)	14 (4)	28 (4)
Noncompliance with study product	1 (<1)	1 (<1))	2 (<1)
Withdrawal by subject	32 (9)	16 (4)	48 (6)
Other	7 (2)	7 (2)	14 (2)
Source: NDA 202-428: W0260-301, Final Study Report, table 8, page 47.			

Table 16
Disposition of Subjects
ITT Population – W0260-302

	Tazarotene Foam (N=373)	Vehicle Foam (N=369)	Total (N=742)
Completed Study, n (%)	307 (82)	334 (91)	641 (86)
Discontinued, n (%)	66 (18)	35 (9)	101 (14)
Reasons for discontinuation, n (%)			
Adverse event	9 (2)	0	9 (1)
Lost to follow-up	13 (3)	11 (3)	24 (3)
Noncompliance with study product	1 (<1)	0	1 (<1)
Withdrawal by subject	39 (10)	21 (6)	60 (8)
Other	4 (1)	3 (1)	7 (1)
Source: NDA 202-428: W0260-302, Final Study Report, table 8, page 47.			

Protocol Deviations

Both trials, W0260-301 and W0260-302, had a similar number of subjects with protocol deviations, 156 subjects and 155 subjects, respectively. The most commonly reported deviation resulting in per protocol (PP) exclusion was not having the required efficacy evaluations, 18% in both trials for the tazarotene arm and 11% and 10%, respectively for the vehicle foam arm. More subjects missed more than 16 applications in the tazarotene arm than in the vehicle arm in both trials, between 5-7% in the tazarotene arm and between 1-3% in the vehicle arm. No other protocol deviation was greater than 3% for either of the phase 3 trials. Tables 17 and 18 describe the reasons for exclusion in the PP analysis population.

Reference ID: 3109305

Table 17
Disposition of Subjects
PP Population – W0260-301

Analysis Set n (%)	Tazarotene Foam (N=372)	Vehicle Foam (N=372)	Total (N=744)
Subjects excluded from the Per-Protocol analysis set	102 (27)	54 (15)	156 (21)
Reasons for exclusion			
Subject did not have required efficacy evaluations	68 (18)	42 (11)	110 (15)
Subject enrolled in error regarding inclusion/exclusion criteria	3 (1)	3 (1)	6 (1)
Subject did not have first treatment date	1 (<1)	0	1 (<1)
Subject is excluded for other reason	2 (1)	1 (<1)	3 (<1)
Subject missed >16 applications	20 (5)	5 (1)	25 (3)
Subject used a prohibited concomitant medication	11 (3)	5 (1)	16 (2)
Subject was misrandomized to treatment	2 (1)	0	2 (<1)
Subject's final efficacy evaluations were >6 days after After last dose date	8 (2)	3 (1)	1 (1)
Source: NDA 202-428: Final Study Report W0260-301 – table 10, page 48			

Table 18
Disposition of Subjects
PP Population – W0260-302

Analysis Set n (%)	Tazarotene Foam (N=373)	Vehicle Foam (N=369)	Total (N=742)
Subjects excluded from the Per-Protocol analysis set	97 (26)	58 (16)	155 (21)
Reasons for exclusion			
Subject did not have required efficacy evaluations	66 (18)	38 (10)	104 (14)
Subject enrolled in error regarding inclusion/exclusion criteria	2 (1)	2 (1)	4 (1)
Subject did not have first treatment date	1 (<1)	0	1 (<1)
Subject missed >16 applications	25 (7)	10 (3)	35 (5)
Subject used a prohibited concomitant medication	6 (2)	5 (1)	11 (1)
Subject was misrandomized to treatment	1 (<1)	1 (<1)	2 (<1)
Subject's final efficacy evaluations were >6 days after After last dose date	3 (1)	4 (1)	7 (1)
Source: NDA 202-428: Final Study Report W0260-302 – table 10, page 48			

Reviewer's Comment: *These protocol deviations are not major and will not adversely effect the efficacy evaluation of the drug product, which is determined by the intent-to-treat population (all subjects who were dispensed study product). Compliance may be an issue for some patients, given the percentage of subjects who missed applications (up to 7%).*

Baseline Disease Characteristics

In the pivotal trials, the distribution of disease in terms of severity and lesion counts was similar between the tazarotene foam and vehicle foam arms. For the ISGA, 81% of subjects in the tazarotene foam arm and 80% of subjects in the vehicle foam arm had moderate (grade 3) disease, while 19% and 20%, respectively had severe (grade 4) disease. No subjects in either arm had very severe (grade 5) disease. The two arms were also very similar in distribution of lesion counts. The mean noninflammatory lesion count was 47.7 for the tazarotene arm and 48.0 in the vehicle arm while the mean inflammatory lesion count was 31.7 for the tazarotene arm and 32.2 for the vehicle arm. Table 19 describes the baseline disease characteristics for the integrated ITT population.

Reference ID: 3109305

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Table 19
Baseline Disease Characteristics
ITT Population – Integrated Pivotal Trials

Baseline Disease Characteristics	Tazarotene Foam N=744	Vehicle Foam N=741	All Subjects N=1485
Lesion Counts			
Total[a]			
Mean (standard deviation)	79.4 (21.8)	80.2 (21.8)	79.8 (21.8)
Median (minimum, maximum)	73 (55, 165)	75 (55, 174)	74 (55, 174)
Noninflammatory[b]			
Mean (standard deviation)	47.7 (19.7)	48.0 (19.4)	47.8 (19.6)
Median (minimum, maximum)	40 (30, 125)	42 (30, 125)	41 (30, 125)
Open Comedones			
Mean (standard deviation)	15.8 (15.9)	16.0 (15.1)	15.9 (15.5)
Median (minimum, maximum)	13 (0, 94)	13 (0, 120)	13 (0, 120)
Closed Comedones			
Mean (standard deviation)	31.9 (17.7)	32.0 (16.9)	31.9 (17.3)
Median (minimum, maximum)	29 (0, 119)	29 (0, 125)	29 (0, 125)
Inflammatory[c]			
Mean (standard deviation)	31.7 (6.8)	32.2 (6.9)	31.9 (6.9)
Median (minimum, maximum)	29 (25, 51)	30 (25, 51)	29 (25, 51)
Papules			
Mean (standard deviation)	24.1 (7.4)	24.3 (8.1)	24.2 (7.7)
Median (minimum, maximum)	24 (7, 46)	24 (4, 50)	24 (4, 50)
Pustules			
Mean (standard deviation)	7.5 (6.6)	7.7 (6.5)	7.6 (6.5)
Median (minimum, maximum)	7 (0, 38)	6 (0, 42)	6 (0, 42)
Nodules, n (%)			
0	665 (89)	650 (88)	1315 (89)
1	79 (11)	91 (12)	170 (11)
≥2	0	0	0
Investigator's Static Global Assessment, n (%)			
Grade 3	599 (81)	593 (80)	1192 (80)
Grade 4	145 (19)	148 (20)	293 (20)
Grade 5	0	0	0

Source: NDA 202-428, ISE, adapted from table 18, page 38.

Reviewer's Comment: *The integrated analysis of baseline demographics and disease characteristics accurately reflect an even distribution of these characteristics across both trials as can be seen in table 20.*

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Table 20
Baseline Demographics and Disease Characteristics
ITT Population – Individual Phase 3 Trials

	W0260-301		W0260-302	
	Tazarotene Foam N=371	Vehicle Foam N=372	Tazarotene Foam N=373	Vehicle Foam N=369
Age (years)				
Mean (SD)	18.2 (5.7)	18.6 (6.4)	19.2 (6.5)	19.2 (6.8)
Median (minimum, maximum)	17 (12, 43)	16 (12, 44)	17 (12, 45)	17 (12, 45)
Age Category, n (%)				
12 to 17 years	223 (60)	227 (61)	205 (55)	205 (56)
18 to 25 years	104 (28)	99 (27)	117 (31)	108 (29)
26 to 35 years	38 (10)	33 (9)	35 (9)	37 (10)
36 to 45 years	6 (2)	13 (3)	16 (4)	19 (5)
Sex, n (%)				
Male	189 (51)	180 (48)	176 (47)	184 (50)
Female	182 (49)	192 (52)	197 (53)	185 (50)
Ethnicity, n (%)				
Hispanic or Latino	62 (17)	55 (15)	71 (19)	72 (20)
Not Hispanic or Latino	309 (83)	317 (85)	302 (81)	297 (80)
Race, n (%)				
American Indian or Alaska Native	12 (3)	3 (1)	2 (1)	2 (1)
Asian	11 (3)	4 (1)	27 (7)	21 (6)
Black	53 (14)	50 (13)	59 (16)	57 (15)
Native Hawaiian or Other Pacific Islander	0	1 (<1)	0	4 (1)
White	285 (77)	307 (83)	278 (75)	280 (76)
Other	10 (3)	7 (2)	7 (2)	5 (1)
Baseline Lesion Counts				
Total Lesions				
Mean (SD)	81.5 (23.3)	81.7 (23.0)	77.3 (20.0)	78.7 (20.4)
Median (minimum, maximum)	75 (55, 165)	76 (55, 173)	71 (56, 164)	74 (55, 174)
Noninflammatory Lesions				
Mean (SD)	50.1 (20.9)	49.8 (20.5)	45.2 (18.2)	46.2 (18.1)
Median (minimum, maximum)	43 (30, 125)	43 (30, 125)	39 (30, 124)	40 (30, 125)
Inflammatory Lesions				
Mean (SD)	31.4 (6.8)	31.9 (7.0)	32.1 (6.8)	32.4 (6.9)
Median (minimum, maximum)	29 (25, 51)	29 (25, 51)	29 (25, 50)	30 (25, 51)
Baseline ISGA, n (%)				
Grade 3	282 (76)	282 (76)	317 (85)	311 (84)
Grade 4	89 (24)	90 (24)	56 (15)	58 (16)

Source: NDA 202-428: Clinical Overview, table 5, page 24 and statistical review, tables 7 & 8 page 10.

6.1.4 Analysis of Primary Endpoint(s)

The applicant evaluated 3 co-primary efficacy endpoints:

1) the absolute change in 2 out of 3 lesion counts (inflammatory, non-inflammatory and total) from baseline to week 12 (end of treatment)

2) the proportion of subjects who had a score of 0 – 1 (clear or almost clear) on the ISGA (Investigator's Severity Global Assessment) and

3) a minimum 2-grade improvement at week 12

Table 21 describes the co- primary endpoints.

Table 21
Week 12 Efficacy Results
Pivotal Trials – ITT Population

Endpoint	**Trial W0260-301**			**Trial W0260-302**		
	Tazarotene N=371	Vehicle N=372	p-value	Tazarotene N=373	Vehicle N=369	p-value
Baseline Count						
Inflammatory	31.4	31.9		32.1	32.4	
Non-inflammatory	50.1	49.8		45.2	46.2	
Total	81.5	81.7		77.3	78.7	
Absolute Change						
Inflammatory	-18.0	-14.1	<0.001	-17.8	-14.7	<0.001
Non-inflammatory	-27.9	-16.7	<0.001	-25.6	-18.2	<0.001
Total	-45.8	-30.8	<0.001	-43.3	-32.9	<0.001
ISGA						
Clear or Almost Clear (grade 0 or1)	132 (36%)	89 (24%)	<0.001	120 (32%)	67 (18%)	<0.001
2-Grade Improvement	107 (29%)	60 (16%)	<0.001	103 (28%)	49 (13%)	<0.001
ISGA of Clear or Almost Clear ***and*** a minimum 2-grade Improvement	107 (29%)	60 (16%)	<0.001	103 (28%)	49 (13%)	<0.001

Source: NDA 202-428: Modified from tables 6 & 7, Clinical Overview, pages 25-26; Statistical Review, table 9, page 12.

Reviewer's Comment: *As noted by the advice letter sent to the* applicant*, 12/28/10, the Division would consider the criteria for success for efficacy would be the proportion of subjects who had a score of 0 – 1 (clear or almost clear) on the ISGA (Investigator's Severity Global Assessment)* ***and*** *a minimum 2-grade improvement at week 12 along with the absolute change in 2 out of 3 lesion counts (inflammatory, non-inflammatory and total) from baseline to week 12 (end of treatment). Both trials met statistical significance of (p<0.001) for all endpoints and the definition of success.*

6.1.5 Analysis of Secondary Endpoints(s)

The applicant evaluated the lesion counts based on the percent change from baseline to weeks 2 through week 12. The mean decreases were greater for the tazarotene foam group compared with the vehicle foam group, reaching statistical significance for noninflammatory and total lesions at all time points, and, for inflammatory lesions, at Weeks 8 and 12 (see table 22).

Table 22
Percentage Change from Baseline in Lesion Counts
ITT Population Pivotal Trials

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	Inflammatory		Noninflammatory		Total	
	Tazarotene Foam N= 744	Vehicle Foam N=741	Tazarotene Foam N= 744	Vehicle Foam N=741	Tazarotene Foam N= 744	Vehicle Foam N=741
Baseline						
Mean (SD)	31.7 (6.78)	32.2 (6.94)	47.7 (19.70)	48.0 (19.43)	79.4 (21.78)	80.2 (21.77)
Week 2 Change						
Mean (SD)	-18.2 (31.33)	-19.2 (30.18)	-24.1 (26.00)	-16.9 (26.88)	-22.0 (21.95)	-18.0 (21.32)
Adjusted LS mean	-18.2	-19.2	-24.1	-16.9	-22.0	-18.0
Difference (SE)		1.05 (1.60)		-7.20 (1.37)		-4.05 (1.12)
p-value[a]		0.509		**<0.001**		**<0.001**
Week 4 Change						
Mean (SD)	-33.0 (31.47)	-33.1 (31.92)	-37.9 (27.96)	-26.2 (30.91)	-36.1 (24.43)	-29.1 (25.22)
Adjusted LS mean	-32.9	-33.1	-37.9	-26.2	-36.0	-29.2
Difference (SE)		0.19 (1.65)		-11.7 (1.53)		-6.88 (1.28)
p-value[a]		0.910		**<0.001**		**<0.001**
Week 8 Change						
Mean (SD)	-49.1 (31.25)	-41.6 (34.06)	-49.7 (28.28)	-33.6 (32.66)	-49.6 (25.41)	-37.0 (27.98)
Adjusted LS mean	-49.1	-41.6	-49.6	-33.6	-49.6	-37.0
Difference (SE)		-7.51 (1.70)		-16.0 (1.58)		-12.6 (1.38)
p-value[a]		**<0.001**		**<0.001**		**<0.001**
Week 12 Change						
Mean (SD)	-56.0 (33.10)	-45.3 (34.89)	-55.9 (29.87)	-37.7 (37.43)	-56.1 (27.63)	-40.8 (30.88)
Adjusted LS mean	-56.0	-45.3	-55.9	-37.8	-56.1	-40.9
Difference (SE)		-10.7 (1.77)		-18.1 (1.75)		-15.2 (1.52)
p-value[a]		**<0.001**		**<0.001**		**<0.001**

Source:: NDA 202-428: ISE , table 21, page 42

Reviewer's Comment: *The percentage reduction of inflammatory lesions, non-inflammatory lesions, and total lesions at week 12 supports the primary efficacy endpoints in the efficacy of tazarotene foam to treat acne vulgaris. This is consistent with the statistical review, where the mean percent reduction in inflammatory lesions was approximately 55% for tazarotene versus 44% for vehicle in both studies, while the mean percent reduction in non-inflammatory lesions was approximately 56% versus 34% in Study 301 and 56% versus 41% in Study 302. In addition, the median time to 50% reduction in total lesions was 8 weeks for tazarotene and 12 weeks for vehicle.*[1]

6.1.6 Other Endpoints

Dr. Kathleen Fritsch discusses the sensitivity analyses that the applicant completed in her review on pages 15-16. She states that all of the p values for the imputation sensitivity analyses [observed case analysis, LOCF, regression imputation (for lesion count endpoints), and missing as failure (for ISGA endpoints)] are <0.001. Even though this was the case, she would not recommend the sponsor's sensitivity analysis for future trials. Results obtained from analyses of the primary endpoints utilizing the PP analysis set also showed tazarotene foam was statistically superior to vehicle foam for the primary endpoints (see table 23). This is also supported by the statistical review by our statistician, Dr. Kathleen Fritsch (see table 23a below).

Table 23a – Primary Efficacy Endpoints at Week 12 (PP)

Endpoint	Study 301		Study 302	
	Tazarotene N=270	Vehicle N=318	Tazarotene N=276	Vehicle N=311
Absolute change: Least Squares Means				
Inflammatory	-20.4	-14.6	-20.4	-15.5
Non-inflammatory	-31.3	-17.0	-29.0	-18.5
Total	-51.8	-31.2	-49.6	-33.7
ISGA:				
2-Grade Improvement	112 (41%)	83 (26%)	106 (38%)	62 (20%)
Clear or Almost Clear	91 (34%)	56 (18%)	93 (34%)	48 (15%)

Source: Biostatics Review: Table 10, page 12, DARRTS 3/14/12.

1 Biostatistic Review: Dr. Kathleen Fritsch, pages 18, DARRTS, 3/14/12.

Reference ID: 3109305

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Table 23
Supportive Analyses of Primary Endpoints
Integrated Analysis

		Intent-to-Treat Analysis Set			Per-Protocol Analysis Set[a]		
	Imputation method:	Tazarotene Foam N=744	Vehicle Foam N=741	p-value	Tazarotene Foam N=546	Vehicle Foam N=629	p-value
ISGA 2-grade Improvement							
Success[b], % subjects	LOCF	33.9%	21.1%	**<0.001[d]**	39.9%	23.1%	**<0.001[d]**
	failure	32.9%	20.4%	**<0.001[d]**			
ISGA Score of 0 or 1							
Success[c], % subjects	LOCF	28.2%	14.7%	**<0.001[d]**	33.7%	16.5%	**<0.001[d]**
	failure	27.7%	14.3%	**<0.001[d]**			
Inflammatory Lesions							
Adjusted LS mean change	LOCF	-18.0	-14.3	**<0.001[e]**	-20.6	-15.0	**<0.001[e]**
	predicted mean sub[f]	-20.7	-15.1	**<0.001[e]**			
Noninflammatory Lesions							
Adjusted LS mean change	LOCF	-26.8	-17.4	**<0.001[e]**	-29.8	-18.7	**<0.001[e]**
	predicted mean sub[f]	-30.2	-19.0	**<0.001[e]**			
Total Lesions							
Adjusted LS mean change	LOCF	-44.7	-31.7	**<0.001[e]**	-50.5	-33.7	**<0.001[e]**
	predicted mean sub[f]	-50.8	-34.2	**<0.001[e]**			

Source: m5.3.5.3, Integrated Analysis, Table 2.1.1, Table 2.1.2, Table 2.2.1, Table 2.2.2, Table 2.3.1, Table 2.3.2, Table 2.4.1, Table 2.4.2, Table 2.5.1, and Table 2.5.2

Abbreviations: ISGA = Investigator's Static Global Assessment; LOCF = last observation carried forward; LS = least squares; sub = substitution

a. Subjects were excluded from the Per-Protocol analysis set if they did not have Week 12 efficacy data; therefore, no imputations were made for missing data.
b. Success was defined as at least a 2-grade improvement in ISGA score from Baseline to Week 12.
c. Success was defined as an ISGA score of 0 or 1 at Week 12.
d. p-value from Cochran-Mantel-Haenszel test
e. p-value was based on analysis of covariance (ANCOVA) with Baseline value, treatment, study, and interaction of treatment-study. If the treatment-study interaction was not significant at 0.1 level, it was excluded in the ANCOVA model.
f. Based on an ordinary least-squares multiple regression model of the predicted mean for missing data.

6.1.7 Subpopulations

Subgroup analyses were performed for the primary endpoints on the basis of age (12 to

17 years, 18 to 25 years, 26 to 35 years, and 36 to 45 years), sex (male and female), race (Black, White, and other than Black or White), ethnicity (Hispanic or Latino, and not Hispanic or Latino), and Baseline ISGA (3 and 4) utilizing the ITT analysis set and the LOCF method of imputation for missing Week 12 data. At Baseline, subjects who were Black and subjects 12 to 17 years of age had more noninflammatory lesions than subjects who were not Black and subjects 18 to 45 years of age; subjects with a Baseline ISGA of 4 had more inflammatory, noninflammatory, and total lesions than subjects with a Baseline ISGA of 3; there were no notable differences between subjects based on sex or ethnicity (see table 24).

Table 24
Mean Lesion Counts at Baseline by Age, Sex, Ethnicity, Race and Baseline Investigator's Global Assessment
ITT Population

Best Available Copy

		Inflammatory		Noninflammatory		Total Lesions	
		Tazarotene Foam N=744	Vehicle Foam N=741	Tazarotene Foam N=744	Vehicle Foam N=741	Tazarotene Foam N=744	Vehicle Foam N=741
Age:							
12 to 17 years	(n=860)	32.5	32.4	50.9	51.2	83.4	83.6
18 to 25 years	(n=428)	30.7	32.5	43.7	44.2	74.4	76.8
26 to 35 years	(n=143)	30.6	30.0	42.8	42.2	73.3	72.1
36 to 45 years	(n=54)	30.4	31.0	41.2	42.0	71.6	73.0
Sex:							
Male	(n=729)	32.8	33.3	49.2	48.6	82.0	81.9
Female	(n=756)	30.7	31.0	46.2	47.4	76.9	78.5
Ethnicity:							
Hispanic or Latino	(n=260)	30.9	31.2	46.5	44.3	77.4	75.5
Not Hispanic or Latino	(n=1225)	31.9	32.4	47.9	48.8	79.8	81.1
Race:							
Black	(n=219)	30.7	30.9	54.3	55.6	85.0	86.6
White	(n=1150)	32.2	32.4	46.1	46.3	78.2	78.6
Other [a]	(n=116)	29.8	32.3	50.0	52.3	79.8	84.6
Baseline ISGA:							
3	(n=1192)	30.7	31.0	45.5	46.1	76.1	77.1
4	(n=293)	36.2	36.9	56.7	55.6	92.9	92.5

a "Other" also includes American Indian or Alaskan Native, Asian, and Native Hawaiian or Other Pacific Islander.
Source: NDA 202-428: ISE, table 28, page 51.

Reviewer's Comment: *The subgroup population analysis of these two trials at baseline is reflective of the general population with acne vulgaris; namely that acne vulgaris is primarily a disease of adolescents and young adults, that it affects males and females fairly equally, that the more severe the disease, the more lesions, and that Blacks tend to have more noninflammatory lesions than those that are not Black.*

Minor variations in treatment effects within subgroup categories were observed, although these variations did not indicate any substantial patterns or trends associated with differing efficacy of tazarotene foam based on age, sex, race, ethnicity, or baseline disease severity. Greater efficacy was consistently observed with tazarotene foam relative to vehicle foam within each subgroup analysis, with the exception of subjects 36 to 45 years of age (N=54). Within this age group, numerical reductions in lesion counts were similar for the tazarotene foam and vehicle foam groups (see Table 26); however, the proportions of subjects with a 2-grade improvement in ISGA and with an ISGA score of 0 or 1 were lower in the tazarotene foam group than in the vehicle foam group; the differences were not statistically significant (see Table 25). The reason for this is not clear, but appears to be associated with a higher vehicle response rate for this age group compared with vehicle response rates observed for the younger age groups.
For the subgroup of race other than Black or White (N=116), greater efficacy was observed with tazarotene foam relative to vehicle foam for all endpoints; however, the proportion of subjects with a 2-grade improvement in ISGA was not significantly different between groups (see Table 25).

Reference ID: 3109305

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Table 25
Proportion of Subjects with Treatment Success at Week 12
By Age, Sex, Ethnicity, Race, and Baseline ISGA
ITT Population

		ISGA 2-grade Improvement			ISGA Score of 0 or 1		
		Tazarotene Foam N=744	Vehicle Foam N=741	p-value[b]	Tazarotene Foam N=744	Vehicle Foam N=741	p-value[b]
		n/n (%)	n/n (%)		n/n (%)	n/n (%)	
Age:							
12 to 17 years	(n=860)	134/428 (31.3)	73/432 (16.9)	**<0.001**	108/428 (25.2)	45/432 (10.4)	**<0.001**
18 to 25 years	(n=428)	80/221 (36.2)	51/207 (24.6)	**0.009**	70/221 (31.7)	39/207 (18.8)	**0.002**
26 to 35 years	(n=143)	30/73 (41.1)	17/70 (24.3)	**0.040**	26/73 (35.6)	12/70 (17.1)	**0.015**
36 to 45 years	(n=54)	8/22 (36.4)	15/32 (46.9)	0.443	6/22 (27.3)	13/32 (40.6)	0.329
Sex:							
Male	(n=729)	108/365 (29.6)	81/364 (22.3)	**0.025**	86/365 (23.6)	49/364 (13.5)	**<0.001**
Female	(n=756)	144/379 (38.0)	75/377 (19.9)	**<0.001**	124/379 (32.7)	60/377 (15.9)	**<0.001**
Ethnicity:							
Hispanic or Latino	(n=260)	51/133 (38.3)	32/127 (25.2)	**0.028**	43/133 (32.3)	20/127 (15.7)	**0.002**
Not Hispanic or Latino	(n=1225)	201/611 (32.9)	124/614 (20.2)	**<0.001**	167/611 (27.3)	89/614 (14.5)	**<0.001**
Race:							
Black	(n=219)	32/112 (28.6)	16/107 (15.0)	**0.015**	25/112 (22.3)	11/107 (10.3)	**0.017**
White	(n=1150)	192/563 (34.1)	128/587 (21.8)	**<0.001**	163/563 (29.0)	92/587 (15.7)	**<0.001**
Other[a]	(n=116)	28/69 (40.6)	12/47 (25.5)	0.139	22/69 (31.9)	6/47 (12.8)	**0.026**
Baseline ISGA:							
3	(n=1192)	179/599 (29.9)	102/593 (17.2)	**<0.001**	179/599 (29.9)	102/593 (17.2)	**<0.001**
4	(n=293)	73/145 (50.3)	54/148 (36.5)	**0.017**	31/145 (21.4)	7/148 (4.7)	**<0.001**

a. "Other" also includes American Indian or Alaskan Native, Asian, and Native Hawaiian or Other Pacific Islander.
b. p-value from Cochran-Mantel-Haenszel test
Source: NDA 202-428: ISE, table 29, page 53.

Table 26
Absolute Change in Lesion Counts from Baseline to Week 12
By Age, Sex, Ethnicity, Race, and Baseline ISGA
ITT Population

Best Available Copy

		Inflammatory			Noninflammatory			Total Lesions		
		Tazarotene Foam N=744	Vehicle Foam N=741	p-value[a]	Tazarotene Foam N=744	Vehicle Foam N=741	p-value[a]	Tazarotene Foam N=744	Vehicle Foam N=741	p-value[a]
Age:										
12 to 17 yrs	(n=860)	-17.3	-13.0	**<0.001**	-27.6	-16.1	**<0.001**	-44.9	-29.1	**<0.001**
18 to 25 yrs	(n=428)	-18.5	-16.0	**0.010**	-26.1	-18.4	**<0.001**	-44.4	-34.5	**<0.001**
26 to 35 yrs	(n=143)	-19.7	-15.0	**0.003**	-24.6	-19.1	**0.019**	-44.3	-34.1	**0.002**
36 to 45 yrs	(n=54)	-21.1	-19.6	0.565	-27.3	-26.4	0.796	-48.6	-46.1	0.625
Sex:										
Male	(n=729)	-16.9	-13.7	**<0.001**	-26.6	-16.8	**<0.001**	-43.5	-30.5	**<0.001**
Female	(n=756)	-19.0	-14.8	**<0.001**	-27.0	-18.0	**<0.001**	-46.0	-32.9	**<0.001**
Ethnicity:										
Hispanic or Latino	(n=260)	-18.9	-16.7	**0.042**	-25.2	-16.7	**<0.001**	-44.1	-33.4	**<0.001**
Not Hispanic or Latino	(n=1225)	-17.7	-13.8	**<0.001**	-27.2	-17.6	**<0.001**	-44.9	-31.4	**<0.001**
Race:										
Black	(n=219)	-19.8	-14.6	**<0.001**	-29.7	-13.4	**<0.001**	-49.4	-28.0	**<0.001**
White	(n=1150)	-17.7	-14.4	**<0.001**	-25.8	-18.0	**<0.001**	-43.5	-32.5	**<0.001**
Other [b]	(n=116)	-17.4	-12.5	**0.012**	-30.4	-17.9	**0.001**	-47.7	-30.7	**0.001**
Baseline ISGA:										
3	(n=1192)	-17.8	-14.5	**<0.001**	-25.4	-16.6	**<0.001**	-43.2	-31.2	**<0.001**
4	(n=293)	-19.0	-13.8	**0.001**	-32.4	-20.5	**<0.001**	-51.4	-34.3	**<0.001**

a. p-value was based on analysis of covariance (ANCOVA) with baseline value, treatment, and study.
b. "Other" also includes American Indian or Alaskan Native, Asian, and Native Hawaiian or Other Pacific Islander.
Source: NDA 202-428: ISE, table 30, page 54.

Reviewer's Comment: *The subgroup analyses did not reveal any clinical concerns regarding the efficacy of tazarotene foam, 0.1% in the treatment of acne vulgaris. On discussion of age group differences with Dr. Kathleen Fritsch, the biostat reviewer, we agree that the age group categories are somewhat arbitrary and in the age group 36-45, the number of patients (54) is so small that the difference found is not clinically meaningful. The same could be said for the racial group classified as "Other" where the number of patients is small (116). Furthermore, this group did win on all other efficacy*

endpoints. Thus, overall, there were no clinically meaningful differences in the subgroup analysis that would rise to the level to necessitate comment in the labeling.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There was no formal analysis for this formulation of tazarotene foam. The applicant relied on the concentration and frequency of dosing for the approved products of tazarotene gel and tazarotene cream. The applicant also relied on the comparative bioavailability study with tazarotene gel, 0.1% (see section 4.4.3). The tazarotene topical products are dosed on a frequency of once daily at bedtime over a 12 week period and have been found to be efficacious, as has this formulation of tazarotene.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

There was no evidence over the 12 weeks of treatment that tolerance developed to tazarotene foam. Lesion counts continued to decrease over each evaluation period from weeks 2 through 12. See table 27.

Reference ID: 3109305

Table 27
Absolute Change from Baseline in Lesion Counts
ITT Population

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	Inflammatory		Noninflammatory		Total	
	Tazarotene Foam N= 744	Vehicle Foam N=741	Tazarotene Foam N= 744	Vehicle Foam N=741	Tazarotene Foam N= 744	Vehicle Foam N=741
Baseline						
Mean (SD)	31.7 (6.78)	32.2 (6.94)	47.7 (19.70)	48.0 (19.43)	79.4 (21.78)	80.2 (21.77)
Week 2 Change						
Mean (SD)	-5.7 (10.28)	-6.0 (10.52)	-11.6 (14.61)	-8.1 (14.49)	-17.4 (18.74)	-14.2 (18.17)
Adjusted LS mean	-5.7	-6.0	-11.7	-8.1	-17.4	-14.1
Difference (SE)		0.28 (0.54)		-3.58 (0.72)		-3.30 (0.94)
p-value[a]		0.606		**<0.001**		**<0.001**
Week 4 Change						
Mean (SD)	-10.4 (10.42)	-10.5 (10.88)	-17.7 (15.83)	-12.0 (16.51)	-28.1 (20.88)	-22.6 (21.44)
Adjusted LS mean	-10.5	-10.5	-17.8	-12.0	-28.2	-22.5
Difference (SE)		0.01 (0.54)		-5.77 (0.80)		-5.70 (1.08)
p-value[a]		0.991		**<0.001**		**<0.001**
Week 8 Change						
Mean (SD)	-15.6 (10.73)	-13.2 (11.34)	-23.6 (17.67)	-15.6 (18.34)	-39.2 (23.13)	-28.8 (24.57)
Adjusted LS mean	-15.7	-13.1	-23.6	-15.6	-39.3	-28.7
Difference (SE)		-2.59 (0.55)		-8.08 (0.85)		-10.6 (1.18)
p-value[a]		**<0.001**		**<0.001**		**<0.001**
Week 12 Change						
Mean (SD)	-17.9 (11.41)	-14.4 (11.55)	-26.7 (19.50)	-17.5 (18.76)	-44.6 (26.15)	-31.9 (25.58)
Adjusted LS mean	-18.0	-14.3	-26.8	-17.4	-44.7	-31.7
Difference (SE)		-3.66 (0.57)		-9.39 (0.89)		-13.0 (1.26)
p-value[a]		**<0.001**		**<0.001**		**<0.001**

Source: NDA 202-428: ISE, table 20, page 41.

Persistence of efficacy was not evaluated beyond the 12 weeks of the clinical trials. However, the applicant offers the following in support of maintenance therapy and persistence of effects with topical tazarotene gel, 0.1%:

> "Topical retinoids are recommended as maintenance treatment for acne to inhibit formation of the microcomedone, thus preventing the development of new comedones and inflammatory lesions [Gollnick 2003a; Thiboutot 2009]. A study evaluating the

maintenance effect of tazarotene gel 0.1% monotherapy, minocycline 100 mg monotherapy, or a combination of both products for 12 weeks, after completing 12-weeks of combination treatment (total of 6 months of treatment), found maintenance treatment with tazarotene monotherapy to be effective in sustaining improvements in acne that were achieved with the initial combination treatment [Leyden 2006].

After discontinuation of retinoid therapy, reductions in comedone counts have been shown to continue during a 4-week follow-up period; however, the number of microcomedones increases almost immediately signaling that new acne lesions develop even while older lesions resolve [Thiboutot 2009; Thielitz 2001]."[2]

Reviewer's Comment: *Given that the efficacy of tazarotene foam in its clinical trials against vehicle appears to be about the same as the efficacy of tazarotene gel in its clinical trials against vehicle in terms of percent reduction in lesion counts (see table 22, page 31 and table 28 below) , there is every reason to believe that the maintenance of effect of tazarotene foam will be comparable to that of tazarotene gel and that the relapse of the disease will also probably be the same upon discontinuation of tazarotene foam as with tazarotene gel.*

Table 28 – Tazorac® 0.1% Gel[3]

Reduction in Lesion Counts after Twelve Weeks of Treatment in Two Controlled Clinical Trials for Acne

	TAZORAC® 0.1% Gel		**Vehicle Gel**	
	N=150	N=149	N=148	N=149
Noninflammatory lesions	55%	43%	35%	27%
Inflammatory lesions	42%	47%	30%	28%
Total lesions	52%	45%	33%	27%

2 NDA 202-428: Integrated Summary of Efficacy: pages 54-55., dated 7/29/11.
3 Tazorac Gel, 0.1% Package Insert Label, revised 2/2011: Clinical Studies Section.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Pivotal trials, W0260-301 and W0260-302, which were double-blind placebo controlled trials of 12 weeks duration, were reviewed to evaluate the safety of this formulation of topical tazarotene, tazarotene foam. The biopharmacology pk trial, W0206-206, which was a relative bioavailability trial between tazarotene foam, 0.1% and the approved drug product, Tazorac (tazarotene) Gel, 0.1% provides a bridge to our findings of systemic safety of Tazorac Gel, 0.1% to tazarotene foam, 0.1% (see section 4.4.3).
Four dermal safety studies were conducted to evaluate the potential of tazarotene foam to cause skin irritation (W0260-101), skin sensitization (W0260-102), skin phototoxicity (W0260-103), and skin photoallergy (W0260-104)

7.1.2 Categorization of Adverse Events

Adverse events in the trials were described by diagnosis and not by symptoms when possible (e.g. common cold or seasonal allergy instead of runny nose). The applicant also listed adverse events by site and subject and also by system organ class and preferred term. In review, the verbatim term and preferred terms were consistent. For example, verbatim term of “peeling on face” was coded as preferred term “application site exfoliation”.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data from the two vehicle-controlled trials in subjects with acne vulgaris were combined for the integrated analysis of safety. The integrated Intent-To-Treat (ITT) analysis set consists of all randomized subjects in these two trials that were dispensed study product. Adverse events in the treatment arm will be compared to those in the vehicle arm.

Reference ID: 3109305

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall, within the ITT analysis set, 83% to 91% of subjects in each group, the tazarotene arm and the vehicle arm, applied study product for at least 8 weeks and 81% to 89% applied study product for at least 11 weeks (inclusive of missed applications). The percentage remains close to the same when missing applications are excluded for at least 8 weeks, 80% and 91%, respectively for tazarotene foam and vehicle, but falls somewhat at the greater than or equal to 11 weeks time mark at 59% and 75%, respectively. The mean number of days of study product use was 68 days for tazarotene foam and 77 days for vehicle foam. In the phase 3 trials, subjects in the tazarotene foam group were exposed to a mean of 1.22 grams of study drug each day and the highest cumulative exposure to tazarotene foam for an individual subject was 251.4 grams over 12 weeks (see Table 29).

Table 29
Extent of Exposure
Intent to Treat Population – Trials W0260-301 and -302

Best Available Copy

	Tazarotene Foam N=744	Vehicle Foam N=741
Duration in days[a]		
n	738	726
Mean (SD)	73.0 (25.8)	79.8 (16.6)
Median	84	84
Minimum, Maximum	1, 98	1, 103
Duration by weeks of exposure,[a] n (%)		
≥1 day	738 (99)	726 (98)
≥2 weeks	681 (92)	714 (96)
≥4 weeks	643 (86)	697 (94)
≥8 weeks	618 (83)	675 (91)
≥11 weeks	603 (81)	659 (89)
Missing	6 (1)	15 (2)
Use in days[b]		
n	738	726
Mean (SD)	67.9 (25.2)	76.6 (16.6)
Median	79	82
Minimum, Maximum	1, 97	1, 102
Use by weeks of exposure,[b] n (%)		
≥1 day	738 (99)	726 (98)
≥2 weeks	668 (90)	714 (96)
≥4 weeks	638 (86)	693 (94)
≥8 weeks	597 (80)	671 (91)
≥11 weeks	436 (59)	559 (75)
Missing	6 (1)	15 (2)
Total amount of study product used (grams)		
n	710	717
Mean (SD)	87.7 (47.56)	107.2 (45.30)
Median	90.1	108.6
Minimum, Maximum	1.4, 251.4	1.2, 307.9
Daily amount of study product used (grams)		
n	710	717
Mean (SD)	1.22 (1.46)	1.34 (0.52)
Median	1.17	1.32
Minimum, Maximum	0.13, 37.50[c]	0.20, 3.95

Source: NDA 202-428: Clinical Summary of Safety, table 8, page 16.
[a]Duration is inclusive of missed applications (Date of the last application – date of furst application) +1 day
[b]Use is exclusive of missed applications (i.e. only included days study product was applied)
[c]Subject 302-203-0074 only reported applying product on 1 day before withdrawing from the study; however, the container was not returned to the center until Week 12; the weight at that time showed a total of 37.50 grams of study product had been used.

Demographics

The demographics of the two phase 3 pivotal trials were about the same. The majority of the subjects (55-61%) were in the 12-17 year old age range, with another 37-40% of subjects included in the 18-35 year old age group. The genders were approximately equal with the majority of the subjects being Caucasian and not Hispanic or Latino. All of the subjects had either moderate or severe acne (see table 30)

Table 30
Demographics of the Phase 3 Pivotal Trials
ITT Population

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	W0260-301 N=743	W0260-302 N=742	Integrated N=1485
Number of study centers	21	18	39
Number of subjects enrolled	744	742	1486
Subjects completed the study, n (%)	639 (86)	641 (86)	1280 (86)
Subjects in Intent-to-Treat analysis set, n (%)	743 (100)[a]	742 (100)	1485 (100)
Subjects in Per-Protocol analysis set, n (%)	588 (79)	587 (79)	1175 (79)
Age (years)			
Mean (standard deviation)	18.4 (6.1)	19.2 (6.6)	18.8 (6.4)
Median (minimum, maximum)	16 (12, 44)	17 (12, 45)	17 (12, 45)
Age Category, n (%)			
12 to 17 years	450 (61)	410 (55)	860 (58)
18 to 25 years	203 (27)	225 (30)	428 (29)
26 to 35 years	71 (10)	72 (10)	143 (10)
36 to 45 years	19 (3)	35 (5)	54 (4)
Sex, n (%)			
Male	369 (50)	360 (49)	729 (49)
Female	374 (50)	382 (51)	756 (51)
Ethnicity, n (%)			
Hispanic or Latino	117 (16)	143 (19)	260 (18)
Not Hispanic or Latino	626 (84)	599 (81)	1225 (82)
Race, n (%)[a]			
American Indian or Alaska Native	15 (2)	4 (1)	19 (1)
Asian	15 (2)	48 (6)	63 (4)
Black	103 (14)	116 (16)	219 (15)
Native Hawaiian or Other Pacific Islander	1 (<1)	4 (1)	5 (<1)
White	592 (80)	558 (75)	1150 (77)
Other	17 (2)	12 (2)	29 (2)
Investigator's Static Global Assessment, n (%)			
Grade 3 – moderate	564 (76)	628 (85)	1192 (80)
Grade 4 – severe	179 (24)	114 (15)	293 (20)

Source: NDA 202-428: Clinical Summary of Safety, table 11, page 23

7.2.2 Explorations for Dose Response

As a topical drug product, there were no explorations for dose response. The sponsor did not perform phase 2 dose ranging trials, relying instead on the dosing frequency of previously approved formulations of topical tazarotene, the gel and the cream and the relative bioavailability study to support using the regimen approved for tazarotene gel.

7.2.3 Special Animal and/or In Vitro Testing

There were no special animal and/or in vitro testing.

7.2.4 Routine Clinical Testing

The only routine clinical testing performed was that of urine pregnancy tests for female subjects of childbearing potential in all of the tazarotene foam trials, as tazarotene is a teratogenic substance. In the phase 1 dermal safety trials urine pregnancy testing was performed as follows:

- W0260-101: Baseline, Day 14, and Day 22.
- W0260-102: Screening (~Day -14); Day 12 and Day 22 of Induction Phase; and Day 1 and Day 6 of Challenge and Repeat Challenge Phases.
- W0260-103: Screening Visit 1 (~Day -6) and Day 5.
- W0260-104: Screening Visit 1 (~Day -5); Day 11 and Day 22 of Induction Phase; and Day 1 and Day 5 of Challenge and Repeat Challenge Phases.

In the bioavailability trial, urine pregnancy tests were performed for female subjects of childbearing potential at Baseline (Day 1) and on Days 8, 15, 20, and 25. For the phase 3 pivotal trials, urine pregnancy testing was performed at baseline and weeks 2, 4, 8, and 12.
Other routine clinical testing was not done in this trial, as the sponsor provided a head-to-head comparative pk study report which demonstrated that tazarotene foam, 0.1% had lower mean plasma concentrations of tazarotene and tazarotenic acid than the approved product, tazarotene gel, 0.1%. Thus, the systemic safety of tazarotene foam is not expected to be different from that of tazarotene gel.

7.2.5 Metabolic, Clearance, and Interaction Workup

Non-applicable.

Reference ID: 3109305

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Again, no formal evaluation was performed, as the sponsor borrowed the findings of safety from two approved NDAs for topical tazarotene, 0.1%.

7.3 Major Safety Results

7.3.1 Deaths

There was one death, subject 102-2090 in trial W0260-102, that occurred but that injury was blunt force trauma sustained in an automobile accident. This incident occurred on day 20 of the trial for this subject.

7.3.2 Nonfatal Serious Adverse Events

There were 2 nonfatal serious adverse events in the dermal safety studies. These occurred in trial W0260-102 (see table 31). None of these adverse events were related to tazarotene foam.

Table 31
Serious Adverse Events – Dermal Safety Studies

Subject Number	Preferred Term	Severity	Causality	Study Day Start/Stop	Action Taken with Product
102-2104	Contusion	Moderate	No	14/20	Withdrawn
102-2151	Post procedural hemorrhage	Severe	No	2/10	Withdrawn
Source: NDA 202-428: ISS – adapted from table 26, page 37					

There were 3 nonfatal serious adverse events experienced by subjects in the pivotal trials. None were considered related to study drug (see table 32)

Reference ID: 3109305

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Table 32
Serious Adverse Events – ITT Population
Pivotal Trials

Subject Number	Study Group	Preferred Term	Severity	Causality	AE Day Start/ Stop	Action Taken with Product
Study W0260-301						
108-0040	Tazarotene foam	Adjustment disorder with mixed disturbance of emotion and conduct	Moderate	No	3 / 7	Interrupted
		Depression	Moderate	No	3 / 7	Interrupted
111-0035	Vehicle foam	Brain contusion	Severe	No	74 (1) / ong	Withdrawn
		Intracranial pressure increased	Severe	No	74 (1) / ong	Withdrawn
Study W0260-302						
209-0021	Tazarotene foam	Convulsion	Severe	No	15 / 19	No action

Source: NDA 202-428: ISS, table 27, page 40.

Reviewer's Comment: *Agree with the applicant that these events were not related to tazarotene foam. Specifically, on review of the CRF and patient narrative for subject #108-0040, the subject's incident of hospitalization occurred (b) days after start of study drug and for a topical drug product with low systemic absorption, I agree that this 16 year old's diagnosis of depression with adjustment disorder with mixed disturbance of emotion and conduct was not due to tazarotene foam. The subject's medication was interrupted for those few days of hospitalization, then resumed upon his release and the subject finished the trial. His treatment for the psychiatric disorder was intensive family therapy.*
The subject who had the seizure disorder was a 19 y/o who had been on tazarotene foam for 14 days prior to the event. The subject had a history of head trauma and was also found to be a recreational drug user. Workup did not reveal an epileptic focus but because of the history of severe head trauma, the subject was treated with anti-seizure medication. The subject was discontinued from the trial due not to this event but to non-compliance with the protocol (prohibited recreational drug use reported on hospital records).

7.3.3 Dropouts and/or Discontinuations

In the dermal safety trials, there were 5 discontinuations. None of them were due to study drug (see table 33).

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Table 33
Discontinuations in the Dermal Safety Studies

Subject Number	Preferred Term	Severity	Causality	AE Day Start/ Stop	Serious
Study W0260-102					
102-2090	Injury	Severe	No	20 / 20	Yes (Death)
102-2104	Contusion	Moderate	No	14 / 20	Yes
102-2151	Post procedural haemorrhage	Severe	No	2 / 10	Yes
	Anaemia	Severe	No	2 / ong	No
	Atelectasis	Severe	No	2 / 2	No
	Tachycardia	Severe	No	2 / 3	No
	Syncope	Severe	No	2 / 2	No
102-2247	Dizziness	Moderate	No	32 / 33	No
Study W0260-104					
104-4032	Viral infection	Mild	No	18 / 42	No

Source: NDA 202-428: ISS, table 28, page 41.

Reviewer's Comment: *Agree with the applicant that none of these discontinuations were due to the drug product, tazarotene foam.*

Table 34 denotes the subjects who discontinued in the phase 3 pivotal trials. A total of 12 subjects in Study W0260-301 and 9 subjects in Study W0260-302 discontinued from the trial due to an AE. Of these 21 subjects, 20 subjects were in the tazarotene foam group and discontinued due to an application site reaction (primarily irritation and/or erythema) that was considered to be study product related. The onset was within the first 8 days of tazarotene foam application for 16 subjects and was within the first 2 to 3 weeks for 4 other subjects. The majority of events were moderate in severity, although 4 subjects experienced severe application site irritation. The only AEs resulting in discontinuation in the vehicle foam group were SAEs (2 events in 1 subject) with an onset of Day 74 that were not study product-related.

Table 34
Discontinuations in the Pivotal Trials – ITT Population

SYSTEM ORGAN CLASS Preferred Term	Tazarotene Foam N=744	Vehicle Foam N=741
Subjects with any adverse event resulting in discontinuation, n (%)	20 (3)	1 (<1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	20 (3)	0
Application site dermatitis	2 (<1)	0
Application site discoloration	1 (<1)	0
Application site dryness	3 (<1)	0
Application site erythema	8 (1)	0
Application site exfoliation	4 (1)	0
Application site irritation	13 (2)	0
Application site oedema	1 (<1)	0
Application site pain	2 (<1)	0
Application site pruritus	1 (<1)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (<1)
Brain contusion	0	1 (<1)
NERVOUS SYSTEM DISORDERS	0	1 (<1)
Intracranial pressure increased	0	1 (<1)

Source: NDA 202-428: ISS, table 29, page 42.

Reviewer's Comment: *Overall, 2.6% (20/744) of subjects discontinued from the pivotal trials due to the adverse reactions under the category of general disorders and administration site conditions. While these adverse reactions are expected adverse reactions for a topical retinoid product, it should be noted in the labeling that these reactions were severe enough to cause 2.6% of subjects to discontinue the drug product, particularly application site irritation, which was responsible for 2% of the discontinuations.*

7.3.4 Significant Adverse Events

Table 35 describes the incidence of severe treatment-emergent adverse events in the phase 3 pivotal trials. Subjects with a severe adverse event represented 3% of the intent-to-treat population. As expected for a topical retinoid, general disorders and administration site conditions represented 20/26 of the severe reactions, with application site irritation occurring in 13/26 or 2% of these subjects. These reactions are due to study drug. The other severe reactions listed in table 35 are not treatment related adverse events with the exception of application site dryness in the vehicle foam group that the investigator attributed to the product.

Table 35
Incidence of Severe Treatment-Emergent Adverse Events
In the Phase 3 Studies – ITT Population

Best Available Copy

SYSTEM ORGAN CLASS Preferred Term	Tazarotene Foam N=744	Vehicle Foam N=741
Subjects with any severe adverse event, n (%)	26 (3)	2 (<1)
GASTROINTESTINAL DISORDERS	2 (<1)	0
Abdominal pain upper	1 (<1)	0
Toothache	1 (<1)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	20 (3)	1 (<1)
Application site dryness	6 (1)[a]	1 (<1)[a]
Application site erythema	4 (1)[a]	0
Application site exfoliation	3 (<1)[a]	0
Application site irritation[b]	13 (2)[a]	0
Application site pain	1 (<1)[a]	0
Application site pruritus	1 (<1)[a]	0
INFECTIONS AND INFESTATIONS	2 (<1)	0
Chronic sinusitis	1 (<1)	0
Tonsillitis	1 (<1)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3 (<1)	1 (<1)
Brain contusion	0	1 (<1)
Procedural pain	2 (<1)	0
Tooth injury	1 (<1)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (<1)	0
Muscle spasms	1 (<1)	0
NERVOUS SYSTEM DISORDERS	1 (<1)	1 (<1)
Convulsion	1 (<1)	0
Intracranial pressure increased	0	1 (<1)

Source: NDA 202-428: ISS, table 24, page 36.

Of those experiencing severe adverse reactions, the applicant reports that only 4 subjects discontinued as a result of severe application site irritation and 10 subjects did complete the trials. Table 36 lists the subjects who had severe reactions in the trials and their disposition.

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Table 36
List of Severe Adverse Reactions to Study Product
Phase 3 Trials – ITT Population

Subject Number	Sex/Age/ Race	Study Group	Preferred Term	Action Taken	AE Day Start/Stop	Subject Disposition[a]
Study W0260-301						
104-0010	M/17/WH	Tazarotene foam	Application site irritation	NC	1 / 3	Completed
			Application site irritation	INT	42 / 43	
111-0011	M/17/WH	Tazarotene foam	Application site erythema	INT	5 / ong	WD – D5
			Application site exfoliation	INT	5 / ong	
			Application site irritation	INT	5 / ong	
112-0031	F/15/WH	Tazarotene foam	Application site dryness	INT	20 / ong	Completed
112-0034	F/22/WH	Tazarotene foam	Application site irritation	INT	6 / 7	LTFU – D56
115-0056	F/25/NA	Tazarotene foam	Application site irritation	DC	2 / ong	DC-AE – D3
116-0006	F/24/WH	Tazarotene foam	Application site irritation	INT	60 / 63	Completed
			Application site pain	INT	60 / 63	
116-0020	F/29/WH	Tazarotene foam	Application site irritation	INT	2 / 5	Completed
116-0036	F/13/BL	Tazarotene foam	Application site irritation	INT	5 / 8	WD – D14
			Application site irritation	INT	11(1)/15 (5)	
118-0008	F/24/WH	Tazarotene foam	Application site irritation	DC	1 / ong	DC-AE – D29
Study W0260-302						
202-0014	M/16/WH	Tazarotene foam	Application site irritation	DC	1 / 13 (4)	DC-AE – D13
202-0020	M/15/WH	Tazarotene foam	Application site irritation	DC	1 / 12 (7)	DC-AE – D38
203-0006	M/12/WH	Tazarotene foam	Application site dryness	INT	4 / 11	Completed
203-0010	F/35/WH	Tazarotene foam	Application site erythema	INT	4 / 14 (10)	Other – D15[b]
			Application site exfoliation	INT	4 / 12 (8)	
			Application site irritation	INT	4 / 10 (6)	
203-0018	M/45/WH	Tazarotene foam	Application site dryness	NC	3 / 22	Completed
203-0019	M/20/WH	Tazarotene foam	Application site dryness	INT	17 / 28	Completed
			Application site exfoliation	INT	17 / 28	
203-0030	M/23/WH	Tazarotene foam	Application site dryness	INT	6 / 9	Completed
			Application site erythema	INT	6 / 9	
207-0020	M/14/WH	Tazarotene foam	Application site irritation	INT	18 / 20	WD – D56
211-0038	F/13/BL	Tazarotene foam	Application site pruritus	INT	4 / ong	DC-AE[c] – D12
211-0043	F/31/BL	Tazarotene foam	Application site irritation	INT	23 / 24	Completed
704-0030	M/15/NA	Tazarotene foam	Application site dryness	INT	4(1)/16 (13)	WD – D22
			Application site erythema	INT	4(1)/16 (13)	
203-0032	F/18/WH	Vehicle foam	Application site dryness	NC	1 / 11	Completed

Source: NDA 202-428: ISS, table 25, page 38

Reviewer's Comment: *Although there were only 4 subjects listed as having withdrawn due to a severe adverse event, 4 other subjects who also had severe adverse events withdrew their consent. On review of the CRFs, these subjects had their medication interrupted due to the adverse event. Thus, in this reviewer's opinion, their withdrawal of consent amounts discontinuation because of a severe adverse event. Finally, subject 203-0010, although discontinued because of not meeting the eligibility requirements, nevertheless, received at least 2 weeks of product application and in that*

time had a severe reaction, so should be counted. Therefore, a total of 9/744 (1.2%) subjects discontinued because of a severe adverse reaction; all related to application site reactions. One other subject, subject 211-0038, did have a severe adverse event, but discontinued because of mild application site discoloration. I agree with the applicant that 10 subjects did complete the trials in spite of the severe application site reactions.

7.3.5 Submission Specific Primary Safety Concerns

Retinoids as a class have been associated with photosensitivity. In the two pivotal trials, 9/744 (1.2%) on tazarotene foam had either a photosensitivity reaction (burning sensation at the application site due to sun exposure) or frank sunburn. All of the reactions were either mild or moderate and resolved. There were 3 [3/741(0.4%)] instances of sunburn in the vehicle foam arm (see table 37).

Reference ID: 3109305

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Table 37
List of Photosensitivity Reaction and Sunburn Adverse Events
Phase 3 Trials – ITT Population

Subject Number	Sex/Age/ Race	Study Group	Preferred Term (Verbatim)	Severity	Causality	AE Day Start/Stop
Study W0260-301						
104-0005	M/15/WH	Tazarotene foam	Application site photosensitivity reaction (burning sensation on face due to sun exposure)	Moderate	Yes	10/ 13
111-0034	F/17/WH	Tazarotene foam	Sunburn (on arms and legs)	Moderate	No	76/ 77
111-0045	F/22/WH	Tazarotene foam	Application site photosensitivity reaction (sunburn at applic site-face)	Moderate	No	7/ 9
112-0021	F/20/WH	Tazarotene foam	Sunburn (facial)	Mild	No	52/ 53
112-0031	F/15/WH	Tazarotene foam	Sunburn (treatment area)	Moderate	No	53/55
114-0002	F/12/WH	Tazarotene foam	Sunburn (at study drug application site)	Mild	No	59/ 87 (1)
114-0006	M/15/WH	Tazarotene foam	Sunburn (at study drug application site-entire face)	Mild	No	63/ 88 (1)
114-0013	M/19/WH	Vehicle foam	Sunburn (entire face)	Mild	No	30/ 81 (1)
116-0028	F/21/WH	Tazarotene foam	Application site photosensitivity reaction (sunburn-application site)	Moderate	Yes	10/ 20 (11)
116-0032	M/17/WH	Vehicle foam	Sunburn (on face; sunburn while at lake, wore sunscreen but did not reapply frequently)	Moderate	No	56/ 60
118-0020	F/14/WH	Vehicle foam	Sunburn (entire body; went to softball tournament without sunscreen)	Mild	No	79/ ong
Study W0260-302						
207-0031	M/15/WH	Tazarotene foam	Sunburn (redness on face from sun at study application site)	Mild	No	4/ 8
211-0016	M/19/WH	Tazarotene foam	Application site photosensitivity reaction (facial sunburn-at the study product treatment area)	Mild	Yes	6/ 10

Source: NDA 202-428: ISS, table 31, page 45

Reviewer's Comment: *Although the investigators only attributed 3 of the 9 photoreactions to the product, it is not clear to this reviewer that tazarotene as a culprit can be definitively ruled out in any of the cases except subject 111-0034, where the sunburn occurred on the arms and legs, far from the application site of the face. Thus, in this reviewer's opinion, 8/744 (1.0%) of the subjects on tazarotene foam had a photosensitivity reaction. There were 3 subjects with sunburn in the vehicle foam arm. Two of the subjects had plausible reasons for sunburn, at the lake all day without reapplying sunscreen and at a softball game without sunscreen and was sunburned to all exposed areas. One subject had sunburn on the face without any explanation.*

Thus, if 2 subjects are excluded, then 1/741(0.1%) had sunburn without a explanation of non-compliance. This difference does suggest that the chemical moiety may have contributed to the photosensitivity experienced by those on tazarotene foam. This adverse event is addressed in topical retinoid labeling, and should also be addressed in this one.

Local Tolerability

Local skin tolerability assessments were completed at Baseline and all subsequent study visits (Weeks 2, 4, 8, and 12) during the phase 3 trials. The investigator/assessor evaluated the severity of the dryness, erythema, and peeling and the subject evaluated the severity of burning/stinging and itching using the scales in Table 5 and Table 6, respectively, under section 5.3 of this review. To the fullest extent possible, the same assessor was to perform all assessments on the same subject at all visits to ensure consistency in the evaluations. Table 38 shows the results of these tolerability assessments.

Reference ID: 3109305

Table 38
Summary of Change from Baseline in Local Tolerability Assessments
ITT Population – Phase 3 Trials

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		Tazarotene Foam N=744		Vehicle Foam N=741	
Investigator Assessments					
Dryness		n		n	
Baseline	Mean (SD)	744	0.18 (0.50)	741	0.18 (0.49)
Week 2 Change	Mean (SD)	672	0.91 (1.04)	691	0.18 (0.62)
Week 4 Change	Mean (SD)	644	0.64 (0.99)	695	0.10 (0.57)
Week 8 Change	Mean (SD)	621	0.43 (0.91)	666	0.05 (0.60)
Week 12 Change	Mean (SD)	611	0.20 (0.83)	661	-0.06 (0.58)
Erythema		n		n	
Baseline	Mean (SD)	744	0.55 (0.90)	741	0.54 (0.87)
Week 2 Change	Mean (SD)	672	0.66 (0.98)	691	0.11 (0.69)
Week 4 Change	Mean (SD)	644	0.47 (0.97)	695	0.05 (0.68)
Week 8 Change	Mean (SD)	621	0.28 (0.89)	666	0.02 (0.73)
Week 12 Change	Mean (SD)	611	0.10 (0.92)	661	-0.09 (0.69)
Peeling		n		n	
Baseline	Mean (SD)	744	0.10 (0.37)	741	0.11 (0.42)
Week 2 Change	Mean (SD)	672	0.78 (0.97)	691	0.10 (0.49)
Week 4 Change	Mean (SD)	644	0.56 (0.92)	695	0.05 (0.49)
Week 8 Change	Mean (SD)	621	0.35 (0.81)	666	0.03 (0.56)
Week 12 Change	Mean (SD)	611	0.19 (0.73)	661	-0.03 (0.51)
Subject Assessments					
Burning/Stinging		n		n	
Baseline	Mean (SD)	743	0.25 (0.57)	741	0.27 (0.55)
Week 2 Change	Mean (SD)	671	1.23 (1.20)	691	0.36 (0.78)
Week 4 Change	Mean (SD)	643	0.67 (0.99)	695	0.22 (0.73)
Week 8 Change	Mean (SD)	620	0.41 (0.91)	666	0.15 (0.71)
Week 12 Change	Mean (SD)	610	0.33 (0.90)	661	0.13 (0.74)
Itching		n		n	
Baseline	Mean (SD)	743	0.50 (0.68)	741	0.50 (0.67)
Week 2 Change	Mean (SD)	671	0.48 (1.00)	691	0.01 (0.72)
Week 4 Change	Mean (SD)	643	0.35 (0.93)	695	0.00 (0.73)
Week 8 Change	Mean (SD)	620	0.16 (0.87)	666	-0.03 (0.72)
Week 12 Change	Mean (SD)	610	0.01 (0.82)	661	-0.10 (0.78)

Source: NDA 202-428: ISS, table 34, page 52.

The tazarotene foam group had greater mean changes in each tolerability parameter from Baseline to Week 2 than the vehicle foam group; changes were still greater at Week 4. The median change from Baseline in the tazarotene foam group was 1.0 at Week 2 for dryness, peeling, and burning/stinging and was 1.0 at Week 4 for burning/stinging only; the median change from Baseline was 0 for all assessments at Week 8 and Week 12.

Reviewer's Comment: *The table shows that for all of the local tolerability signs, there was not a difference between vehicle and tazarotene foam at baseline, as would be expected. This table also reveals that all the changes in the local tolerability parameters are due to the drug moiety itself, as there was not much change in the vehicle arm for any of the local parameters. The changes also peaked at week 2, and then slowly dissipated over time, consistent with the retinization effect of the family of topical retinoids.*

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The incidence of study product-related AEs was greater in the tazarotene foam group (22%) than in the vehicle foam group (3%). The most frequently reported, product-related events were in the tazarotene foam group and included application site irritation (14%), application site dryness (7%), application site erythema (6%), and application site exfoliation (6%). No other individual, product-related event was reported by more than 1% of subjects within either of the study product groups. Most AEs were mild to moderate in severity and typically resolved in 2 -6 days. Table 39 shows the adverse reactions that occurred with a 1% or greater incidence in the tazarotene foam arm as compared to the vehicle foam arm.

Table 39
Incidence of Adverse Reactions
Phase 3 Trials – ITT Population

System Organ Class **Preferred Term**	**Tazarotene Foam N=744**	**Vehicle Foam N=741**
Subjects with any related adverse event, n (%)	163 (22)	19 (3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	163 (22)	19 (3)
Application site irritation (includes burning and stinging)	107 (14)	9 (1)
Application site dryness	50 (7)	8 (1)
Application site erythema	48 (6)	3 (<1)
Application site exfoliation	44 (6)	3 (<1)
Application site pain	9 (1)	0
Application site pruritus	7 (1)	3 (<1)
Application site dermatitis (including rash)	7 (1)	1 (<1)
Application site photosensitivity reaction (including sunburn)	8 (1)	3 (<1)
Source: NDA 202-428: ISS: Adapted from table 23, page 34 and table 31, page 43		

Reviewer's Comment: *These adverse events can reasonably be attributed to the drug product tazarotene foam and thus would be classified as adverse reactions and should be included in the label. There were no other adverse events with a difference of ≥ 1% between tazarotene foam and vehicle foam. Application site photosensitivity is being added to the applicant's table, even though the incidence difference is not greater than*

Reference ID: 3109305

1% because topical retinoids do have the potential to cause photoreactions (see section 7.3.5).

7.4.2 Laboratory Findings

All urine pregnancy testing for the phase 1 dermal trials and the bioavailability trial were negative. See section 7.6.2 for the pivotal trials pregnancy data.

7.4.3 Vital Signs

Topical application of tazarotene has not been associated with adverse effects on vital signs. There were no effects on vital signs or physical examination findings during studies of tazarotene capsules for oral administration in the treatment of psoriasis [Allergan 2004]. Vital signs and physical examinations were not evaluated in the phase 1 dermal safety trials or the phase 3 safety and efficacy trials.
Vital sign measurements were performed in the comparative bioavailability trial in acne subjects at days 1 (baseline), on days 8, 12, 15, 18, 20, and 22; and at 24, 48, and 72 hours after application during the 72-hour PK blood sample collection (days 22 through 25). Mean vital sign measurements at baseline and after dosing were similar in each group, and mean changes from baseline in vital sign measurements following application of study product were also similar in each group. No vital sign measurement or physical examination finding was reported as an AE.

7.4.4 Electrocardiograms (ECGs)

ECGs were not conducted in this trial.

7.4.5 Special Safety Studies/Clinical Trials

Four (4) dermal safety studies were performed for the tazarotene foam formulation, cumulative irritation (W0260-101), contact sensitization (W0260-102), phototoxicity (W0260-103), and photoallergy (W0260-104).

<u>Cumulative Irritation – W0260-101</u>

A total of 39 subjects were enrolled in this trial and exposed to study product but 30 subjects completed the trial. Reasons for premature discontinuation included withdrawn consent (n = 1) and “other” (including being unable to attend visits [n = 5], missed visit [n = 2], investigator discretion [n = 1]). Table 40 shows the disposition of the subjects.

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Table 40
Disposition of Subjects
Safety Analysis Set – W0260-101

Disposition	Number (%) of Subjects
Enrolled	39
Exposed to Study Product	39 (100)
Completed	30 (76.9)
Discontinued	9 (23.1)
Reason for Discontinuation	
Adverse event	0
Lost to follow-up	0
Noncompliance	0
Withdrew consent	1 (2.6)
Other	8 (20.5)

Source: NDA 202-428: Study Report W0260-101, table 6, page 30.

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Contact Irritation Evaluation

In the 21- day cumulative irritation trial, tazarotene foam showed potential to induce irritation. Mean converted cumulative irritation score statistically differed among study products ($p<0.0001$) and, in pairwise comparisons, was statistically higher with tazarotene foam than the positive control ($p<0.0001$), the negative control ($p<0.0001$), and vehicle foam ($p<0.0001$). Maximum mean converted cumulative irritation score was attained by Day 10 for tazarotene foam, Day 12 for the positive control, Day 8 for the negative control, and Day 15 for vehicle foam (see table 41).

Table 41
Mean Converted Cumulative Irritation Score
Per Protocol Analysis Set – W0260-101

	Tazarotene Foam 0.1%	Positive Control (Sodium Lauryl Sulfate 0.5%)	Negative Control (Distilled Water)	Vehicle Foam
N	24	24	24	24
Mean (SD)	2.72 (0.2)	1.62 (0.95)	0.23 (0.27)	2.02 (0.83)
Median (range)	2.80 (2.1, 3.0)	1.90 (0, 2.9)	0.10 (0, 1.0)	2.40 (0, 2.8)
ANOVA p-value	<0.0001			
Fisher's protected LSD one-sided p-value	tazarotene foam 0.1% versus positive control <0.0001			
	tazarotene foam 0.1% versus negative control <0.0001			
	tazarotene foam 0.1% versus vehicle foam <0.0001			

Source: NDA 202-428: Final Study Report, W0260-101, table 8, page 34

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Reviewer's Comment: *As expected, the cumulative irritation trial supports the clinical findings that the chemical moiety, tazarotene, is a cutaneous irritant. It also reveals that the vehicle, itself is more irritating than the positive control but not as irritating as the drug product.*

Contact Sensitization – W0260-102

A total of 254 subjects were enrolled in the study and exposed to study product; 215 subjects completed the study. The primary reason for discontinuation was "other" which included a missed visit(s) for 29 subjects, violation of exclusion criterion #10 for 2 subjects, and violation of exclusion criterion #11 for 2 subjects (see table 42).

Table 42
Disposition of Subjects
Safety Analysis Set – W0260-102

Disposition	Number (%) of Subjects
Enrolled	254
Exposed to Study Product	254 (100)
Completed	215 (84.6)
Discontinued	39 (15.4)
Reason for discontinuation	
Adverse event	3 (1.2)
Lost to follow-up	0
Noncompliance	0
Death	1 (0.4)
Withdrew consent	2 (0.8)
Other	33 (13.0)

Source: NDA 202-428: Final Study Report W0260-102, table 8, page 29.

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Contact Sensitization Evaluation
The Per-Protocol analysis set comprised all subjects exposed to study product for the full 21-day Induction Phase and for 48 hours during the Challenge Phase, and who returned for evaluation 24 hours after removal of the challenge patch. However, if a patch was removed before 48 hours due to a sensitization reaction in the Challenge Phase, the patch site was evaluated and the last observation carried forward method was used for the follow-up evaluation time points. Forty-six enrolled subjects were excluded from the Per-Protocol analysis set: 37 subjects did not complete the Induction Phase and 9 subjects did not participate in the Challenge Phase, did not have 48 hours of exposure during Challenge, or missed the 24-hour evaluation. The Per-Protocol analysis set was used for the primary analysis of the primary endpoint.

In the challenge phase, the majority of subjects (64.5%) had no visible reaction (score of 0) at all 4 assessment times. Smaller percentages of subjects had slight (17.0%) or mild (13.0%) erythema (scores of + or 1). Relatively few subjects (5.5%) had moderate

erythema (score of 2) at any evaluation time, and only 1 subject (0.5%) had strong erythema (score of 3) at any time (the 48-hour evaluation).
Results for the vehicle foam patch sites showed a slightly lower overall occurrence of irritation than the tazarotene foam patch sites. The majority of subjects (81.3%) had no visible reaction (score of 0) at all 4 assessment times. Smaller percentages of subjects (13.5%) had slight or mild erythema (scores of + or 1). Relatively few subjects (1.4%) had moderate erythema (score of 2) at any evaluation time, and no subject had strong erythema (score of 3) at any time. Table 43 describes the number and percentage of subjects with each erythema grade at challenge and Table 44 describes the local skin reactions and superficial effects.

Table 43
Number and Percentage of Subjects
With Erythema Grade at Challenge
Per Protocol Population – W0260-102

Best Available Copy

	Patch Site Assessment at Challenge			
Erythema Grade	30 Min. n (%)	24 Hr. n (%)	48 Hr. n (%)	72 Hr. n (%)
Tazarotene foam (N = 200[a])				
0 = no visible reaction	136 (68.00)	129 (64.50)	145 (72.50)	171 (85.50)
+ = slight, confluent, or patchy	29 (14.50)	34 (17.00)	25 (12.50)	11 (5.50)
1 = mild (pink)	26 (13.00)	26 (13.00)	25 (12.50)	16 (8.00)
2 = moderate (definite redness)	9 (4.50)	11 (5.50)	4 (2.00)	2 (1.00)
3 = strong (very intense redness)	0	0	1 (0.50)	0
Vehicle foam (N = 208)				
0 = no visible reaction	169 (81.25)	181 (87.02)	191 (91.83)	199 (95.67)
+ = slight, confluent, or patchy	28 (13.46)	15 (7.21)	10 (4.81)	7 (3.37)
1 = mild (pink)	8 (3.85)	11 (5.29)	5 (2.40)	2 (0.96)
2 = moderate (definite redness)	3 (1.44)	1 (0.48)	2 (0.96)	0
3 = strong (very intense redness)	0	0	0	0

[a]Eight subjects did not have the tazarotene foam patch applied during Challenge due to strong irritation scores that were observed after the first or second induction application.
Source: NDA 202-428: Final Study Report W0260-102, table 10, page 32

Table 44
Number and Percentage of Subjects With Local Skin Reactions and Superficial Effects at Challenge Per Protocol Population – W0260-102

Best Available Copy

	Patch Site Assessment at Challenge			
	30 Min. n (%)	24 Hr. n (%)	48 Hr. n (%)	72 Hr. n (%)
Tazarotene foam (N = 200[a])				
Local Skin Reaction:				
No local skin reactions	198 (99.00)	198 (99.00)	196 (98.00)	198 (99.00)
P = papule	2 (1.00)	2 (1.00)	4 (2.00)	2 (1.00)
Superficial Effects:				
No superficial effects	198 (99.00)	199 (99.50)	196 (98.00)	196 (98.00)
c = scab	0	0	1 (0.50)	1 (0.50)
g = glazing	2 (1.00)	0	0	0
gy = glazing, peeling	0	1 (0.50)	2 (1.00)	2 (1.00)
gyf = glazing, peeling, fissuring	0	0	0	1 (0.50)
y = peeling	0	0	1 (0.50)	0
Vehicle foam (N = 208)				
Local Skin Reaction:				
No local skin reactions	207 (99.52)	207 (99.52)	207 (99.52)	206 (99.04)
P = papule	1 (0.48)	1 (0.48)	1 (0.48)	2 (0.96)
Superficial Effects:				
No superficial effects	208 (100)	208 (100)	208 (100)	208 (100)

[a]Eight subjects did not have the tazarotene foam patch applied during Challenge due to strong irritation scores that were observed after the first or second induction application.
Source: NDA 202-428: Final Study Report W0260-102, table 11, page 33

The investigator elected to rechallenge 3 subjects based on their scores. But upon rechallenge, it was concluded outright that 2 of the subjects did not show any evidence of reactions suggestive of contact sensitization. One subject had reactions to both tazarotene foam and vehicle foam but it was thought to be irritant in nature, as there was no edema, papules, or absence of reaction spreading beyond the application site and the peak response was at 24 hours with subsequent fading.
None of the subjects had a conclusive positive sensitization reaction to either tazarotene foam or to vehicle foam. While several subjects had visible skin reactions during challenge, the investigator determined the reactions were due to irritation rather than sensitization. Under the conditions of this study, tazarotene foam and vehicle foam did not appear to induce allergic contact dermatitis and were considered to have a low potential for contact sensitization reactions.

Reviewer's Comment: *I agree with the assessment of the investigator that tazarotene foam does not appear to induce allergic contact dermatitis. There were no cases of this in the clinical trials.*

Phototoxicity – W0260-103

A total of 38 subjects were enrolled in the study and exposed to study product; 36 subjects completed the study. Reasons for premature discontinuation included withdrawn consent (n = 1) and "other" (ie, late for study visit, unable to accommodate due to treatment schedule [n = 1]). See table 45.

Table 45
Disposition of Subjects
Safety Analysis Set – W0260-103

Best Available Copy

Disposition	Number (%) of Subjects
Enrolled	38
Exposed to Study Product	38 (100)
Completed	36 (94.7)
Discontinued	2 (5.3)
Reasons for Discontinuation	
Adverse event	0
Lost to follow-up	0
Noncompliance	0
Withdrew consent	1 (2.6)
Other	1 (2.6)

Source: NDA 202-428, Final Study Report W0260-103, table 5, page 31.

Phototoxic Evaluation
More than 90% of subjects were scored by the investigators as having no phototoxic reaction at the UV only irradiated site with tazarotene foam or vehicle foam. Approximately 89% of subjects were scored by the investigators as having no phototoxic reaction at the UV plus VIS irradiated site with tazarotene foam or vehicle foam. No phototoxic reactions were observed with the blank patch (see table 46).

Table 46
Frequency Distribution of Investigator Assessment of Phototoxicity
By Study Product and Irradiation Type
Per Protocol Population

Best Available Copy

	Tazarotene Foam 0.1%		Vehicle Foam		Blank Patch (no foam)	
Reaction	UV plus VIS Irradiation n (%)	UV Irradiation n (%)	UV plus VIS Irradiation n (%)	UV Irradiation n (%)	UV plus VIS Irradiation n (%)	UV Irradiation n (%)
N	36	36	36	36	36	36
Yes	1 (2.78)	1 (2.78)	2 (5.56)	0	0	0
No	32 (88.89)	33 (91.67)	32 (88.89)	33 (91.67)	36 (100)	36 (100)
Unclear	3 (8.33)	2 (5.56)	2 (5.56)	3 (8.33)	0	0

Abbreviations: VIS = visible light; UV = ultraviolet light (UVA, UVB/UVA)

Source: NDA 202-428: Final Study Report,- W0260-103, table 8, page 35

Three subjects had a possible photoirritation/phototoxicity reaction: 1 subject at both tazarotene foam UV only and UV plus VIS sites and 2 subjects at vehicle foam UV plus VIS sites.
An additional 7 subjects had an unclear reaction at 1 or 2 sites; however, the results did not show a consistent pattern of increased reactivity at tazarotene foam irradiated sites compared with vehicle foam irradiated sites or at UV plus VIS irradiated sites compared with UV only irradiated sites.
Under the conditions of this study, tazarotene foam and vehicle foam did not appear to be major photoirritants and were determined to have a low potential for phototoxic reactions.

Photoallergy – W0260-104
A total of 59 subjects were enrolled in the study and exposed to study product;
51 subjects completed the study. Reasons for premature discontinuation included AE, withdrawn consent, and "other" (which was due to a missed visit in all cases). See table 47.

Table 47
Disposition of Subjects
Safety Analysis Population – W0260-104

Best Available Copy

Disposition	Number (%) of Subjects
Enrolled	59
Exposed to study product	59 (100)
Completed	51 (86.4)
Discontinued	8 (13.6)
Reason for discontinuation	
Adverse event	1 (1.7)
Lost to follow-up	0
Noncompliance	0
Withdrew consent	3 (5.1)
Other (missed visit)	4 (6.8)

Source: NDA 202-428: Final Study Report, W0260-104, table 8, page 35

Photoallergic Evaluation
The number and percentage of subjects with each erythema grade at the Challenge Phase evaluations, by study product, are presented in Table 48 for UV only irradiated test sites, in Table 49 for UV plus VIS irradiated test sites, and in Table 50 for nonirradiated test sites.

Reference ID: 3109305

Table 48
Number (%) of Subjects with Each Erythema Grade.
Challenge Phase, UV Only Irradiation
Per Protocol Population – W0260-104

Best Available Copy

Patch Type Erythema Grade	Patch Site Assessment Immed n (%)	1 Hour n (%)	24 Hours n (%)	48 Hours n (%)	72 Hours n (%)
Tazarotene foam					
0 = no visible reaction	8 (15.69)	2 (3.92)	4 (7.84)	10 (19.61)	27 (52.94)
+ = slight, confluent, or patchy	4 (7.84)	6 (11.76)	6 (11.76)	11 (21.57)	11 (21.57)
1 = mild (pink)	20 (39.22)	21 (41.18)	19 (37.25)	15 (29.41)	10 (19.61)
2 = moderate (definite redness)	19 (37.25)	20 (39.22)	20 (39.22)	13 (25.49)	3 (5.88)
3 = strong (very intense redness)	0	2 (3.92)	2 (3.92)	2 (3.92)	0
Vehicle foam					
0 = no visible reaction	30 (58.82)	13 (25.49)	4 (7.84)	13 (25.49)	28 (54.90)
+ = slight, confluent, or patchy	10 (19.61)	22 (43.14)	7 (13.73)	14 (27.45)	9 (17.65)
1 = mild (pink)	6 (11.76)	12 (23.53)	24 (47.06)	11 (21.57)	11 (21.57)
2 = moderate (definite redness)	5 (9.80)	4 (7.84)	16 (31.37)	13 (25.49)	3 (5.88)
3 = strong (very intense redness)	0	0	0	0	0
Blank patch					
0 = no visible reaction	31 (60.78)	21 (41.18)	8 (15.69)	21 (41.18)	36 (70.59)
+ = slight, confluent, or patchy	12 (23.53)	20 (39.22)	14 (27.45)	17 (33.33)	9 (17.65)
1 = mild (pink)	8 (15.69)	10 (19.61)	17 (33.33)	9 (17.65)	5 (9.80)
2 = moderate (definite redness)	0	0	11 (21.57)	3 (5.88)	1 (1.96)
3 = strong (very intense redness)	0	0	1 (1.96)	1 (1.96)	0

Source: NDA 202-428: Final Study Report, W0260-104, table 10, page 38

Table 49
Number (%) of Subjects with Each Erythema Grade, Challenge Phase, UV plus VIS Irradiation Per Protocol Population – W0260-104

Best Available Copy

Patch Type Erythema Grade	Patch Site Assessment Immed n (%)	1 Hour n (%)	24 Hours n (%)	48 Hours n (%)	72 Hours n (%)
Tazarotene foam					
0 = no visible reaction	9 (17.65)	4 (7.84)	3 (5.88)	13 (25.49)	25 (49.02)
+ = slight, confluent, or patchy	5 (9.80)	11 (21.57)	8 (15.69)	13 (25.49)	12 (23.53)
1 = mild (pink)	15 (29.41)	17 (33.33)	16 (31.37)	8 (15.69)	10 (19.61)
2 = moderate (definite redness)	20 (39.22)	18 (35.29)	23 (45.10)	16 (31.37)	4 (7.84)
3 = strong (very intense redness)	2 (3.92)	1 (1.96)	1 (1.96)	1 (1.96)	0
Vehicle foam					
0 = no visible reaction	23 (45.10)	18 (35.29)	6 (11.76)	11 (21.57)	30 (58.82)
+ = slight, confluent, or patchy	10 (19.61)	14 (27.45)	6 (11.76)	13 (25.49)	7 (13.73)
1 = mild (pink)	13 (25.49)	15 (29.41)	17 (33.33)	16 (31.37)	10 (19.61)
2 = moderate (definite redness)	4 (7.84)	4 (7.84)	21 (41.18)	9 (17.65)	4 (7.84)
3 = strong (very intense redness)	1 (1.96)	0	1 (1.96)	2 (3.92)	0
Blank patch					
0 = no visible reaction	34 (66.67)	21 (41.18)	10 (19.61)	20 (39.22)	36 (70.59)
+ = slight, confluent, or patchy	12 (23.53)	18 (35.29)	15 (29.41)	14 (27.45)	9 (17.65)
1 = mild (pink)	4 (7.84)	12 (23.53)	14 (27.45)	12 (23.53)	6 (11.76)
2 = moderate (definite redness)	1 (1.96)	0	12 (23.53)	5 (9.80)	0
3 = strong (very intense redness)	0	0	0	0	0

Source: NDA 202-428: Final Study Report, W0260-104, table 11, page 39

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Table 50
Number (%) of Subjects with Each Erythema Grade, Challenge Phase, No Irradiation Per Protocol Population – W0260-104

Patch Type Erythema Grade	Patch Site Assessment Immed n (%)	1 Hour n (%)	24 Hours n (%)	48 Hours n (%)	72 Hours n (%)
Tazarotene foam					
0 = no visible reaction	8 (15.69)	6 (11.76)	11 (21.57)	16 (31.37)	31 (60.78)
+ = slight, confluent, or patchy	8 (15.69)	9 (17.65)	11 (21.57)	10 (19.61)	9 (17.65)
1 = mild (pink)	17 (33.33)	18 (35.29)	11 (21.57)	13 (25.49)	8 (15.69)
2 = moderate (definite redness)	17 (33.33)	16 (31.37)	17 (33.33)	11 (21.57)	3 (5.88)
3 = strong (very intense redness)	1 (1.96)	2 (3.92)	1 (1.96)	1 (1.96)	0
Vehicle foam					
0 = no visible reaction	30 (58.82)	30 (58.82)	29 (56.86)	28 (54.90)	43 (84.31)
+ = slight, confluent, or patchy	6 (11.76)	9 (17.65)	11 (21.57)	8 (15.69)	3 (5.88)
1 = mild (pink)	9 (17.65)	7 (13.73)	4 (7.84)	9 (17.65)	4 (7.84)
2 = moderate (definite redness)	6 (11.76)	5 (9.80)	7 (13.73)	6 (11.76)	1 (1.96)
3 = strong (very intense redness)	0	0	0	0	0
Blank patch					
0 = no visible reaction	39 (76.47)	39 (76.47)	40 (78.43)	42 (82.35)	48 (94.12)
+ = slight, confluent, or patchy	9 (17.65)	9 (17.65)	8 (15.69)	5 (9.80)	2 (3.92)
1 = mild (pink)	3 (5.88)	2 (3.92)	3 (5.88)	4 (7.84)	0
2 = moderate (definite redness)	0	1 (1.96)	0	0	1 (1.96)
3 = strong (very intense redness)	0	0	0	0	0

Source: NDA 202-428: Final Study Report, W0260-104, table 12, page 40

Eight subjects were rechallenged. Following review of all data, the investigator found that there were no subjects who exhibited a conclusive positive photoallergic reaction to tazarotene foam or vehicle foam under UV only or UV plus VIS irradiation. Table 51 presents the number and percentage of investigator-determined photoallergic reactions (yes, no, or unclear).

Table 51
Frequency Distribution of Investigator Assessment Of Photoallergy by Study Product and Irradiation Type Per Protocol Population – W0260-104

Best Available Copy

	Tazarotene Foam 0.1%		Vehicle Foam		Blank Patch (no foam)	
Reaction	UV plus VIS Irradiation n (%)	UV Irradiation n (%)	UV plus VIS Irradiation n (%)	UV Irradiation n (%)	UV plus VIS Irradiation n (%)	UV Irradiation n (%)
N	51	51	51	51	51	51
Yes	0	0	0	0	0	0
No	50 (98.04)	50 (98.04)	50 (98.04)	50 (98.04)	51 (100)	51 (100)
Unclear	1 (1.96)	1 (1.96)	1 (1.96)	1 (1.96)	0	0

Source: NDA 202-428: Final Study Report, W0260-104, table 13, page 42

Reviewer's Comment: *Agree with the investigator's assessment of the results that tazarotene foam did not appear to be a major photoirritant or photosensitizer, but does have the potential for phototoxic/photosensitive reactions, as a low incidence of photoreactive (sunburn) adverse events did occur in the phase 3 trials.*

7.4.6 Immunogenicity

Immunogenicity was not evaluated in this trial. None of the topical tazarotene products have been evaluated for immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency for adverse events is not applicable to this topical drug product, where subjects apply a thin film to the affected areas of the face q hs.

7.5.2 Time Dependency for Adverse Events

The adverse reactions of irritation, erythema, dryness, and exfoliation were most frequently reported during the first 2-4 weeks of application. Severe adverse events occurred within the first 6 days of treatment for 16 subjects, between 17 and 23 days for 4 subjects, and after 60 days for 1 subject.

7.5.3 Drug-Demographic Interactions

For the tazarotene foam phase 3 trials, the proportions of AEs overall and study product-related AEs reported by subjects were compared on the basis of age, sex, race (Black, White, and other than Black or White), ethnicity (Hispanic or Latino, or not Hispanic or Latino), and Baseline ISGA (3 or 4). Within the tazarotene foam group, there were no notable differences between subgroups for sex, race, or Baseline ISGA. The incidence of AEs overall and of related AEs was lower for Hispanic or Latino subjects (26% and 11%, respectively) than for subjects who were not Hispanic or Latino (40% and 24%, respectively). The incidence of related AEs was lower for subjects 12 to 17 years (22%) and 18 to 25 years (19%) than for subjects 26 to 35 years (29%) and 36 to 45 years (27%) (see table 52).

Table 52
Incidence of Treatment-Emergent Adverse Events by Subgroups for Phase 3 Trials – ITT Population

Best Available Copy

		Any Adverse Event Occurring in ≥1% of Subjects per Group		Any Related Adverse Event	
		Tazarotene Foam N=744	Vehicle Foam N=741	Tazarotene Foam N=744	Vehicle Foam N=741
		n/n (%)	n/n (%)	n/n (%)	n/n (%)
Age:					
12 to 17 years	(n=860)	152/428 (36)	78/432 (18)	93/428 (22)	5/432 (1)
18 to 25 years	(n=428)	88/221 (40)	46/207 (22)	43/221 (19)	10/207 (5)
26 to 35 years	(n=143)	30/73 (41)	18/70 (26)	21/73 (29)	2/70 (3)
36 to 45 years	(n=54)	7/22 (32)	9/32 (28)	6/22 (27)	2/32 (6)
Sex:					
Male	(n=729)	132/365 (36)	59/364 (16)	79/365 (22)	7/364 (2)
Female	(n=756)	145/379 (38)	92/377 (24)	84/379 (22)	12/377 (3)
Ethnicity:					
Hispanic or Latino	(n=260)	34/133 (26)	27/127 (21)	14/133 (11)	1/127 (1)
Not Hispanic or Latino	(n=1225)	243/611 (40)	124/614 (20)	149/611 (24)	18/614 (3)
Race:					
Black	(n=219)	47/112 (42)	21 /107(20)	27/112 (24)	4/107 (4)
White	(n=1150)	204/563 (36)	121 /587(21)	120/563 (21)	15/587 (3)
Other than Black or White	(n=116)	26/69 (38)	9/47 (19)	16/69 (23)	0/47 (0)
Baseline ISGA:					
3	(n=1192)	226/599 (38)	116/593 (20)	136/599 (23)	18/593 (3)
4	(n=293)	51/145 (35)	35/148 (24)	27/145 (19)	1/148 (1)

Source: NDA 202-428: ISS, table 38, page 58.

Reviewer's Comment: *Although there are some differences in terms of demographic-drug interaction, given that the adverse reactions are non-serious and rarely severe in nature, this reviewer believes that it does not offer further clarity to try to label the drug for these small differences.*

7.5.4 Drug-Disease Interactions

There was no special investigation for drug-disease interactions. However, subjects with some other facial dermatitis that may have interfered with evaluation for efficacy, such as rosacea; or who had a photosensitive disease, such as lupus were excluded from the trial.

7.5.5 Drug-Drug Interactions

Drug interactions were not specifically evaluated in the studies conducted with tazarotene foam, but a review of concomitant medication usages and reported AEs did not indicate any trends or signals suggestive of drug interactions. Subjects were prohibited from using concomitant medications during the studies that could have interfered with the application of tazarotene foam or the evaluation of its safety or efficacy.
Concomitant dermatologic medications and cosmetics that have a strong drying effect should be avoided. It is also advisable to "rest" a patient's skin until the effects of such preparations subside before use of tazarotene foam is begun.

Reviewer's Comment: *Agree with the sponsor. It should certainly be noted in the label and in the information for patients concerning concomitant use of other dermatologic drying agents.*

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The international birth date of tazarotene is December 3, 1996, first approved in a gel formulation in Germany. The sponsor has compiled an extensive database from the clinical trials and from post-marketing data and the sponsor does not report any instances of tazarotene being associated with the development of cancer in humans.

7.6.2 Human Reproduction and Pregnancy Data

There were 5 pregnancies reported during the phase 3 trials. All subjects were discontinued when their pregnancies were reported. Only 1 pregnancy of these 5 was

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exposed to tazarotene foam. It was for 25 days. The subject delivered a full term healthy infant.
Tazarotene is a teratogenic substance and as such females of childbearing potential should have a negative urine pregnancy test and not start the drug product until their next menses.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Division met with PeRC on February 15, 2012. The sponsor asked for a partial waiver for pediatric subjects less than 12 years of age. Tow reasons were checked to support the request: 1) Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small) and 2) The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric subjects and is unlikely to be used in a substantial number of pediatric subjects < 12 years of age.
The PeRC committee agreed with the waiver request and that the applicant did not have any further obligations under PREA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No instances of overdose were reported during the tazarotene foam clinical trials. No instances of drug abuse were reported during the tazarotene foam clinical studies. Tazarotene, the active ingredient, does not have any known potential for abuse.
No instances of withdrawal or rebound effects were reported during the tazarotene foam clinical studies. However, the last observation of the studies occurred at the end of the 12-week application period, limiting the opportunity to assess the potential for withdrawal or rebound effects. Tazarotene, the active ingredient, does not have any known potential for withdrawal or rebound effects.

7.7 Additional Submissions / Safety Issues

The 120-day safety update did not provide any additional clinical data. There were no additional clinical trials conducted and no additional recent literature revealed anything that would impact the safety of topical application of tazarotene foam.

8 Postmarket Experience

The international birth date for tazarotene is 03 December 1996. Tazarotene was first approved as a gel formulation in 1996 in Germany and is currently marketed worldwide in gel and cream formulations (0.05% and 0.1%) for the topical treatment of plaque psoriasis under the internationally-licensed proprietary names Zorac, Tazorac, and

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Suretin. Tazarotene 0.1% was approved for the treatment of acne in the US and Canada in a gel formulation in 1997 and in a cream formulation in 2001, both under the proprietary name Tazorac. Tazarotene cream 0.1% is also marketed in some countries for the topical treatment of signs and symptoms (appearance and texture) of premature aging of the skin due to overexposure to the sun, including fine wrinkling, mottled hyperpigmentation, lentigines, elastosis, pore size and irregular depigmentation. Allergan's marketing research has indicated that approximately (b) (4) of all prescriptions for tazarotene in the US are for the acne indication.

Allergan has compiled an extensive safety database for tazarotene through clinical studies for psoriasis, acne, and photoaging, and through more than 14 years of postmarketing experience. Tazarotene cream has been registered by Allergan in 10 countries and is marketed in 9 countries. Tazarotene gel has been registered by Allergan in 20 countries and is marketed in 10 countries; tazarotene gel has also been registered by Pierre-Fabre (the license holder in most European countries) in 27 countries and is marketed for psoriasis in 12 countries.

During the postmarketing period, the most frequently-reported nonserious AEs worldwide have been in the skin and subcutaneous tissues disorders system organ class, which is consistent with the approved prescribing information.

9 Appendices

9.1 Literature Review/References

Literature review did not reveal any additional safety issues for the chemical moiety, tazarotene.

9.2 Labeling Recommendations

Clinical has the following major recommendations for changes to the label. The applicant's language is provided and changes are delineated by strikeout (for suggested deletions) and underline for additions.

In the Highlight Section:

Dosage and Administration
Apply a [redacted] (b) (4) thin layer to the entire affected area once daily in the evening. [redacted] (b) (4)

Warnings and Precautions

- Fetal Risk: Tradename is contraindicated in pregnancy. Females of childbearing potential should have a negative pregnancy test within 2 weeks prior to initiating treatment and use an effective method of contraception during treatment. (5.1)

Dosage and Administration
[redacted] (b) (4)

Reviewer's Comment: *This sentence was deleted because* [redacted] (b) (4)

In the Warnings and Precautions Section:

Fetal Risk
There were five reported pregnancies in patients who participated in clinical trials for topical tazarotene foam. One of the patients was found to have been treated with topical tazarotene for 25 days, two were treated with vehicle foam and the other two did not receive study product. The patients were discontinued from the trials when their pregnancy was reported. The one pregnant woman who was inadvertently exposed to topical tazarotene foam during the clinical trial delivered a full-term healthy infant.

Adverse Reactions
6.1 Clinical Trials

The safety data reflect exposure to [redacted] (b) (4) -Trade name Foam in 744 patients with acne vulgaris. Patients were 12 years to 45 years of age and were treated once daily in the evening for 12 weeks. [redacted] (b) (4) Adverse reactions reported in ≥1% of patients treated with [redacted] (b) (4) -Trade name Foam [redacted] (b) (4) studies are presented in Table 1. Most adverse reactions were mild to moderate in severity. Overall, 2.6% (20/744) of patients discontinued FABIOR foam because of local skin reactions.

The following was added to Table 1: Incidence of Adverse Reactions in ≥ 1 % of Patients with TRADENAME Foam:

Application site photosensitivity (including sunburn): 8/744 (1%) for Trade name foam and 3 (<1%) for vehicle foam.

Additional [redacted] (b) (4) adverse reactions that were reported in <1% of patients treated with [redacted] (b) (4) Trade name Foam included application site reactions (including [redacted] (b) (4) discoloration, discomfort, edema, rash, and swelling), dermatitis, impetigo, and pruritus.

Local skin reactions, dryness, erythema, and peeling actively assessed by the investigator and burning/stinging and itching reported by the patient were evaluated at baseline and during treatment, [redacted] (b) (4) During the 12 weeks of treatment, each local skin reaction peaked at week 2 and gradually reduced thereafter with the continued use of [redacted] (b) (4) Trade name Foam.

Reviewer's Comment: *The* [redacted] (b) (4) *proposed by the sponsor* [redacted] (b) (4) *was deleted,* [redacted] (b) (4)

[redacted] (b) (4)

(b) (4)

Reviewer's Comment: *Recommend deleting* (b) (4)

14 Clinical Studies

Absolute and percent reductions in lesion counts and the IGA scale after 12 weeks of treatment in these two studies are shown in Table 3. (b) (4) Each study needed to have a statistically significant reduction in two out of three lesion counts at Week 12.

Reviewer's Comment: *The applicant's table was replaced with the following table (all numbers were rounded to the nearest 0.5 in the labeling):*

Table 3: Reductions in Lesion Counts and Improvements in Investigator's Global Assessment at Week 12

	Study 1		Study 2	
	(b) (4) Trade name Foam N=371	Vehicle Foam N=372	(b) (4) Trade name Foam N=373	Vehicle Foam N=369
Inflammatory Lesions				
Mean absolute reduction from Baseline	18.0	14.1	17.8	14.7
Mean percent reduction from Baseline	57.5%	45.2%	54.5%	45.3%
Non-inflammatory Lesions				
Mean absolute reduction from Baseline	27.9	16.7	25.6	18.2
Mean percent reduction from Baseline	55.1%	33.2%	56.7%	41.2%
Total Lesions				
Mean absolute reduction from Baseline	45.8	30.8	43.3	32.9
Mean percent reduction from Baseline	56.3%	39.0%	56.0%	42.6%
Investigator's Global Assessment (IGA), n (%)				
Minimum 2-grade improvement *and* IGA of 0 or 1	107 (28.9%)	60 (16.1%)	103 (27.6%)	49 (13.3%)

17 Patient Counseling Information

The following statements were recommended to be added to this section:

- Fetal risk associated with (b) (4) Trade name for females of childbearing potential. Advise patients to use an effective method of contraception during treatment to avoid pregnancy. Advise the patient to stop medication if she becomes pregnant and call her doctor.

- If undue irritation (redness, peeling, or discomfort) occurs, reduce frequency of application or temporarily interrupt treatment. Treatment may be resumed once irritation subsides.
- Avoid contact with the eyes.
- Keep out of the reach of children.

9.3 Advisory Committee Meeting

There was not an advisory committee meeting in association with this NDA.

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/s/

DENISE COOK
03/30/2012

GORDANA DIGLISIC
03/30/2012

DDDP CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Yes	No	N/A	Comment
FORMAT/ORGANIZATION/LEGIBILITY				
1. Identify the general format that has been used for this application, e.g. electronic CTD.	Electronic CTD			
2. On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
3. Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4. For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5. Are all documents submitted in English, or are English translations provided when necessary?	X			
6. On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING				
7. Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57, current divisional and Center policies, and the design of the development package?	X			
SUMMARIES				
8. Has the applicant submitted all the required discipline summaries (*i.e*, Module 2 summaries)?	X			
9. Has the applicant submitted the integrated summary of safety (ISS)?	X			
10. Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11. Has the applicant submitted a benefit-risk analysis for the product?	X			
12. Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505 (b)(1)			
DOSE				
13. If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	The sponsor performed a comparative bioavailability study with Tazorac Gel, 0.1%.
EFFICACY				
14. On its face, do there appear to be the requisite number of adequate and well controlled studies in the application? Pivotal Study #1 W0260-301 Indication: Topical treatment of facial acne vulgaris in patients 12 years or older Pivotal Study #2 W0260-302 Indication: Topical treatment of	X			

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

facial acne vulgaris in patients 12 years or older				
15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	Only 7 sites out of 39 (18%) foreign, in Canada. Pop. is similar.
SAFETY				
18. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19. Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (*e.g.*, QT interval studies, if needed?			X	
20. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?			X	Submitted a letter of authorization to NDA 20-600 and NDA 21-184 (tazarotene gel and cream)
OTHER STUDIES				
21. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	X			
22. For an Rx-to-OTC switch application, are the necessary special OTC studies included (*e.g.*, labeling comprehension)?			X	
PEDIATRIC USE				
23. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY				
24. If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES				
25. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS				
26. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
27. Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
28. Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
29. Are all datasets to support the critical safety analyses available and complete?	X			

30. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?	X			
CASE REPORT FORMS				
31. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
32. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE				
33. Has the applicant submitted the required Financial Disclosure information for study investigators?	X			
GOOD CLINICAL PRACTICE				
34. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			
CONCLUSION				
35. From a clinical perspective, is this application fileable? If "no", please state why it is not?	X			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer

Clinical Team Leader

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

/s/

DENISE COOK
09/13/2011

GORDANA DIGLISIC
09/13/2011