NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA, 505(b)(2)
Application Number(s)	NDA 211882/IND 126277
Priority or Standard	Standard
Submit Date(s)	February 22, 2019
Received Date(s)	February 22, 2019
PDUFA Goal Date	December 22, 2019
Division/Office	Dermatology and Dental Products/Office of Drug Evaluation III
Review Completion Date	December 16, 2019
Established/Proper Name	Tazarotene lotion, 0.045%
(Proposed) Trade Name	Arazlo™
Pharmacologic Class	Retinoid
Code name	IDP-123
Applicant	Bausch Health US, LLC
Dosage form	Lotion
Applicant proposed Dosing Regimen	Once daily
Applicant Proposed Indication(s)/Population(s)	For the topical treatment of acne vulgaris
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	88616000 |Acne vulgaris (disorder)|
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Arazlo is indicated for the treatment of acne vulgaris in patients age 9 years and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	88616000 |Acne vulgaris (disorder)|
Recommended Dosing Regimen	Once daily

Table of Contents

Table of Tables

Table of Figures

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DB=Division of Biopharmaceutics
DB III = Division of Biometrics III
DBRR I = Division of Biotechnology Research and Review 1
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DDS = Deputy Director for Safety
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OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OPRO = Office of Program and Regulatory Operations
OSE= Office of Surveillance and Epidemiology
PLT = Patient Labeling Team
PMS = Project Management Staff
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Glossary

Acne-QoL	Acne-Specific Quality of Life Questionnaire
AE	adverse event
ANCOVA	analysis of covariance
AR	adverse reaction
AUC	area under the curve
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CHO/HGPRT	Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl-transferase
C_{max}	observed peak drug concentration
CSR	clinical study report
DMF	drug master file
ECG	electrocardiogram
EGSS	Evaluator's Global Severity Score
FDA	Food and Drug Administration
GLP	good laboratory practice
hERG	human ether-a-go-go-related gene
IC_{50}	half maximal inhibitory concentration
IND	Investigational New Drug
iPSP	Initial Pediatric Study Plan
ISS	integrated summary of safety
LD	listed drug
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	maximum recommended human dose
NDA	new drug application
OCS	Office of Computational Science
OPDP	Office of Prescription Drug Promotion
PI	prescribing information
PK	pharmacokinetics
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PRO	patient-reported outcome
PT	preferred term
RAR	retinoic acid receptor
SAE	serious adverse event
SOC	system organ class
TEAE	treatment-emergent adverse event

1 Executive Summary

1.1. Product Introduction

Arazlo (tazarotene) Lotion, 0.045% is a topical drug product for which the Applicant seeks approval under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for the treatment of acne vulgaris. The listed drug (LD) is Tazorac Cream, 0.1% (new drug application (NDA) 021184), which was approved 9/29/2000.

The Applicant established a clinical bridge between Arazlo Lotion, 0.045% and Tazorac Cream through comparative pharmacokinetics (PK), and proposes to rely on the Agency's finding of safety for nonclinical toxicology (reproductive toxicity, carcinogenesis, mutagenesis, and impairment of fertility) for the LD.

This application is for a new dosage form (lotion) of tazarotene. The proposed dose and administration is a thin layer applied to the affected areas once daily for the indication of topical treatment of acne vulgaris.

The active ingredient in Arazlo Lotion is tazarotene, a prodrug member of the retinoid class of compounds, which is converted to its active form tazarotenic acid. Tazarotene is currently marketed in the United States in various dosage forms (cream, gel, foam) for indications of acne vulgaris, plaque psoriasis, and as an adjunctive agent for use in the mitigation (palliation) of facial fine wrinkling, facial mottled hyperpigmentation and hypopigmentation, and benign facial lentigines in patients who use comprehensive skin care and sunlight avoidance programs.

The Agency concluded that the proposed proprietary name, Arazlo, was acceptable from both a promotional and safety perspective under NDA 211882 (Proprietary Name Review by Madhuri R. Patel, PharmD, Division of Medication Error Prevention and Analysis dated 5/15/2019).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from two adequate and well-controlled trials V01-123A-301 and V01-123A-302 (Trials 301 and 302) which provided evidence of the effectiveness of tazarotene lotion, 0.045% for the topical treatment of acne vulgaris in the target population. Both trials assessed the changes from baseline to Week 12 compared to vehicle, in the following coprimary efficacy endpoints:

- Absolute change in the mean noninflammatory lesion count
- Absolute change in the mean inflammatory lesion count
- Percentage of subjects who achieved an Evaluator's Global Severity Score (EGSS) of clear(0) or almost clear(1), and ≥2 grade improvement(reduction) from baseline

Tazarotene lotion, 0.045% was statistically superior to vehicle on the coprimary efficacy endpoints in both trials. The Applicant has demonstrated that tazarotene lotion, 0.045% is

effective for its intended use in the target population and has met the evidentiary standard required by 21 Code of Federal Regulations (CFR) 314.126 (a)(b) to support approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Bausch Health US, LLC submitted a New Drug Application (NDA) 211882 for Arazlo (tazarotene) Lotion, 0.045% for the treatment of acne vulgaris under the 505(b)(2) regulatory pathway of the Federal Food, Drug and Cosmetic Act. Acne vulgaris is a common, chronic dermatological disorder of sebaceous follicles which primarily affects adolescents and young adults. Arazlo Lotion is a new dosage form of tazarotene and the safety profile of the moiety is well characterized. The Applicant established a clinical bridge to the listed drug Tazorac Cream, 0.1% (NDA 021184, approved 9/29/2000) in order to rely on the Agency's findings of safety (nonclinical toxicology including genotoxicity and reproductive and developmental) to support the safety of their product.

In two, multicenter, randomized, double-blind clinical trials enrolling 1614 subjects age 9 years and older with acne vulgaris, tazarotene lotion was statistically superior to vehicle for the treatment of acne vulgaris. The coprimary efficacy endpoints were absolute change in noninflammatory lesion count, absolute change in inflammatory lesion count, and the proportion of subjects with success on the EGSS (defined as at least a 2-grade improvement from baseline and an EGSS score of clear (0) or almost clear (1)) at Week 12.

The safety profile for tazarotene lotion, 0.045% was adequately characterized during the drug development program. There were no deaths or drug-related serious adverse events (SAEs) in the Phase 3 Trials 301 and 302. In the Phase 3 trials pooled safety analysis set, SAEs occurred with an equal frequency of 0.5% in the tazarotene lotion group and the vehicle lotion group. Adverse Reactions (ARs) occurred at a higher frequency in the Arazlo Lotion group compared to the vehicle lotion group (11.3% vs. 1.1%). Active assessment of local tolerability indicated that the percentage of subjects who reported signs and symptoms (erythema, scaling, itching, burning, and stinging) at any post-baseline visit was greater in the tazarotene lotion group than the vehicle lotion group. The most common ARs occurred at the application site and included the following ARs in the Arazlo Lotion group, compared to the vehicle lotion group: pain (5.3% vs. 0.3%), dryness (3.6% vs. 0.1%), erythema (1.8% vs. 0), exfoliation (2.1% vs. 0), and pruritus (1.2% vs. 0). Review of the data supports including the potential for skin irritation and photosensitivity and risk of sunburn in Section 5 WARNINGS AND PRECAUTIONS of labeling.

Tazarotene lotion, 0.045% provides an additional treatment option for acne vulgaris. The available evidence of safety and efficacy supports the approval of Arazlo (tazarotene) Lotion, 0.045% for the topical treatment of acne vulgaris in the population 9 years of age and older. In view of a favorable overall benefit/risk assessment, the review team recommends approval of this product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acne vulgaris is a common, chronic dermatological disorder of sebaceous follicles which primarily affects adolescents and young adults. Acne occurs most frequently on the face and is characterized by two major types of lesions: noninflammatory (open or closed comedones) and inflammatory lesions (papules, pustules, and nodules). The etiology is multifactorial. Because of the chronic relapsing and remitting course and potential for scarring after lesions resolve, acne may be associated with clinically important impacts.	Acne is a common chronic disorder with a range of disease severities which may impact quality of life.
Current Treatment Options	• Many topical and systemic drugs are available for the treatment of acne vulgaris. Approved therapies for acne vulgaris include oral and topical antibiotics and antimicrobials (e.g., erythromycin, clindamycin, benzoyl peroxide), systemic hormonal therapies (e.g., ethinyl estradiol/norgestimate), and topical retinoids (e.g., tretinoin, tazarotene). Oral formulations of isotretinoin are available for severe, recalcitrant, nodulo-cystic acne. • Treatment is individualized according to the types of lesions, severity of disease, and patient preferences. Topical retinoids are generally considered as part of an initial treatment regimen[1].	There are a number of FDA-approved products with an acceptable risk-benefit profile for the treatment of acne vulgaris in adolescents and adults. Topical retinoids are a mainstay of treatment. However, the response to treatment varies with the lesion type, severity of the disease and compliance with the treatment regimen. Additional retinoid formulations that promote compliance by addressing patient preferences may be needed.
Benefit	• Data from two adequate and well controlled trials (301 and 302) provided substantial evidence of the effectiveness of tazarotene lotion, 0.045% for the treatment of acne vulgaris. These trials enrolled 1614 subjects age 9 years and older with moderate to severe acne vulgaris. Tazarotene lotion, 0.045% was superior to vehicle lotion in both trials for the coprimary efficacy endpoints of	Tazarotene lotion. 0.045% provides an effective and safe treatment option for patients with moderate to severe acne vulgaris.

[1] Zaenglein AL et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. http://dx.doi.org/10.1016/ j. jaad.2015.12.037

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	absolute change in noninflammatory lesion count, absolute change in inflammatory lesion count, and EGSS success (defined as an EGSS score of 0 (clear) or 1 (almost clear), and a ≥2-grade improvement (decrease) from baseline) at Week 12. • Review of the safety data from clinical trials (301 and 302) identified no new safety signals with this new dosage form of tazarotene. Tazarotene lotion was well tolerated in all evaluated subgroups.	
Risk and Risk Management	• The primary safety database (301 and 302) included 1570 subjects who received treatment with tazarotene lotion (n=779) or vehicle lotion (n=791) once daily for 12 weeks. There were no deaths or serious adverse events related to the study drug product. The most common adverse reactions occurring in ≥1% of subjects in Arazlo Lotion group, and more frequent than in vehicle lotion group, was localized to the application site and included the following: pain (5.3%), dryness(3.6%), exfoliation(2.1%), erythema(1.8%), and pruritus(1.2%). Active assessment of local adverse reactions indicated that most were mild or moderate. • Labeling: Prescription labeling adequately addresses the known risks associated with the moiety and those identified during product development. • No issues require further assessment with a postmarketing requirement or postmarketing commitment (PMR/PMC). • A risk evaluation and mitigation strategy (REMS) does not appear necessary and is not recommended.	• The risks associated with the use of tazarotene lotion are similar to other tazarotene drug products. Local adverse reactions such as pain, irritation, dryness, sunburn, application site rash, and/or hypersensitivity may occur during treatment and may be severe. • Prescription labeling, patient labeling, and routine pharmacovigilance are adequate to manage the risks of the product.

1.4. Patient Experience Data

The Applicant conducted a patient-reported outcome (PRO) assessment of the Acne-Specific Quality of Life Questionnaire (Acne-QoL) during the Phase 3 trials, summarized the results using descriptive statistics, and used the data to identify trends between treatment groups.

No inferential analyses were conducted by the Applicant, as the endpoints related to the PROs were not prespecified or controlled for multiplicity. The Acne-QoL data will not be included in labeling or discussed in this review.

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		x	Patient-reported outcome (PRO)	Acne-QoL questionnaire Protocols 301 and 302
		☐	Observer reported outcome (ObsRO)	
		x	Clinician reported outcome (ClinRO)	(Section 8.1.1) Evaluator's Global Severity Score (EGSS), inflammatory lesion count, noninflammatory lesion count
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		

	☐ Observational survey studies designed to capture patient experience data	
	☐ Other: (Please specify):	
☐	**Patient experience data were not submitted as part of this application.**	

2 Therapeutic Context

2.1. Analysis of Condition

Acne vulgaris is a common, chronic dermatological disorder. In the United States, acne affects more than 50 million individuals.[2] The highest prevalence is among adolescents and young adults; however, acne may occur in children and adults at any age. Among adults with acne, females are more commonly affected than males.[3,4]

Acne is an inflammatory disease of sebaceous follicles. Factors which contribute to the complex pathophysiology of acne include bacterial colonization of follicles, hypersecretion of the sebaceous glands, and intrafollicular hypercornification. At adrenarche, increased androgen stimulation may result in both abnormal keratinization of the sebaceous follicle and increased sebum production in the sebaceous gland. Obstruction of the follicular orifice of the sebaceous gland by desquamated keratinocytes produces a microcomedone. Prolonged fundibular blockage, proliferation of *Corynebacterium acnes* (*Propionibacterium acnes*) in the sebaceous follicle, and production of multiple chemoattractant and proinflammatory cytokines may trigger the formation of noninflammatory and inflammatory lesions.[5]

Acne may present with a variety of lesions which may be categorized as one of the following types:

(1) Noninflammatory: Noninflammatory lesions include the open comedones (blackheads) or closed comedones (whiteheads).
(2) Inflammatory: Inflammatory lesions include papules, pustules, nodules, and cysts.

Both lesion types develop from microcomedones[6] and most frequently occur on the face. However, lesions may be localized to other areas with a high density of sebaceous follicles such as the neck, chest and back. Factors which may influence the risk or presentation of acne are age, sex, and genetic predisposition. Variants of acne which may require more aggressive or specialized treatment include acne fulminans, acne conglobate, synovitis/acne/pustulosis/hyperostosis/osteitis syndrome, pyogenic arthritis/pyoderma gangrenosum/acne syndrome, neonatal acne, and acne complicated by Gram-negative folliculitis.

The clinical course is characterized by remissions and recurrences. In some individuals, acne may persist for decades and resolve with scarring. The association of acne with depression,

[2] Bhate K, Williams HC. Epidemiology of acne vulgaris. BJD. 2013 168, pp 474–485.
[3] UpToDate. Thiboutot, D et al. Accessed May 16, 2019.
[4] Zaenglein AL et al. Guidelines of care for the management of acne vulgaris. JAAD. 2016 May, 74 (5):945-73.e33
[5] Brown SK, Shalita AR. Acne vulgaris. Lancet. 1998. 351; 9119:1871-1876.
[6] Dawson AL et al. Acne Vulgaris. BMJ 2013;346: 2634

anxiety and reduced quality of life is well-documented.[7] Successful treatment may produce a significant improvement in self-esteem.[8]

2.2. Analysis of Current Treatment Options

The treatment armamentarium for acne vulgaris includes both topical and systemic products. Treatments target one or more of the primary pathogenic factors: sebaceous gland hypersecretion stimulated by androgen production; bacterial proliferation; and abnormal keratinization with resultant follicular obstruction and inflammation.

Most of the FDA-approved therapies belong to the following pharmacologic classes: antibiotics and antimicrobials (e.g., erythromycin, clindamycin, benzoyl peroxide, dapsone); hormonal agents (e.g., ethinyl estradiol/norgestimate); and retinoids (e.g., tretinoin, tazarotene, isotretinoin). Other treatment options which are used less frequently include: physical modalities (e.g., chemical peels, intralesional corticosteroids and laser therapy), complementary/alternative therapies (e.g., tea tree oil, herbal supplements and biofeedback) and dietary management (e.g., low glycemic index diets and low calcium diets.) Factors which influence the choice of treatment are lesion type(s), disease severity, personal preference, and individual patient characteristics (e.g., age, sex, skin sensitivity, predisposition for hyperpigmentation/scarring.) Topical products such as benzoyl peroxide, retinoids and antibiotics are indicated for acne of mild to moderate severity;[9] whereas, oral formulations of isotretinoin are indicated for severe, recalcitrant, nodulo-cystic acne. Topical products may contain a single active ingredient or two active ingredients which may address different lesion types.

Categories of drug products and examples of topical and systemic therapies currently approved for the treatment of acne vulgaris are presented in the following tables.

[7] Lasek RJ et al. Acne Vulgaris and the Quality of Life of Adult Dermatology Patients. Arch Dermatol. 1998; 134 (4): 454-458.

[8] Newton JN et al. The effectiveness of acne treatment: an assessment by patients of the outcome of therapy. Br J Dermatol. 1997;137 (4):563

[9] Zaenglein AL et al. Guidelines of care for the management of acne vulgaris. JAAD. 2015.

Table 1: Categories of Drug Products for Acne Treatment

Categories	Drug Products
Topical	
Benzoyl peroxide *	Multiple products
Sulfa products	Sulfacetamide, sulfacetamide/sulfur
Azelaic acid	Azelaic acid cream
Antibiotics	Clindamycin, erythromycin, dapsone
Retinoids	Tretinoin, adapalene, tazarotene
Salicylic acid *	Multiple products
Systemic	
Antibiotics[a]	Tetracycline, doxycycline, minocycline
Retinoids	Isotretinoin
Hormonal therapies [b]	Various oral contraceptives

Source: Modified from NDA 209269, Clinical Review by Patricia Brown, MD
*Over-the-counter monograph approved products
[a]: Azithromycin/erythromycin, ampicillin/amoxicillin used off-label
[b]: Spironolactone, flutamide, corticosteroids used off-label

Table 2: Representative Examples of FDA Approved Topical Products for Acne Treatment

Product (s) Name/Year of Approval	Indication	Dosing/ Administration	Efficacy Information From Labeling	Important Safety and Tolerability Issues
Antimicrobials				
Amzeeq (minocycline) foam, 4% (10/2019)	Topical treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older.	Apply to affected areas once daily	3, 12-week, R, DB, VC trials in 2418 subjects: Active vs. vehicle Trial one: • IGA success: 8% vs. 5% • Mean absolute CFB Inflam: 14 vs. 11 Trial two: • IGA success: 16% vs. 8% • Mean absolute CFB Inflam: 14 vs. 11 Trial three • IGA 31% vs. 20% • Mean absolute CFB Inflam: 16 vs. 13	AR: headache W&P: flammability, (from oral minocycline): teratogenicity, tooth discoloration, inhibition of bone growth, Clostridium difficile associated diarrhea, hepatotoxicity; azotemia, hyperphosphatemia, and acidosis (w/ renal impairment), light-headedness, dizziness or vertigo (CNS effects), Intracranial hypertension, autoimmune syndromes, photosensitivity, hypersensitivity reactions (anaphylaxis, SJS, DRESS, EM), tissue hyperpigmentation, potential for drug-resistant bacteria

Product (s) Name/Year of Approval	Indication	Dosing/ Administration	Efficacy Information From Labeling	Important Safety and Tolerability Issues
Aczone (dapsone) Gel, 7.5%, NDA 207154 (2016)	Topical treatment of acne vulgaris in patients 12 years of age and older (expanded to ≥9 years of age in 9/2019)	Apply a pea-sized amount in a thin layer to the entire face once daily	2, 12-week R, DB, VC trials in 4340 subjects Active vs. vehicle Trial one: • GAAS: 30% vs. 21% • Inflam: 56% vs. 49% • Noninflam: 45% vs. 39% Trial two: • GAAS: 30% vs. 21% • Inflam: 54% vs. 48% • Noninflam: 46% vs. 41%	AR: application site dryness and pruritus W&P: Methemoglobinemia, Hemolysis, Peripheral neuropathy, Skin reactions
Evoclin (clindamycin phosphate) foam, 1% NDA 050801 (2004)	Acne vulgaris in patients 12 years and older	Apply once daily to affected areas	A 12-week R, DB, VC trial in 513 subjects with mild to moderate acne. Active vs. vehicle • IGSA: 31% vs. 18% • Inflam: 49% vs. 35% • Noninflam: 38% vs. 27%	AR: headache, application site burning, application site pruritus, application site dryness, application site reactions W&P: colitis, irritation
Azelex (azelaic acid cream) 20% NDA 020428 (1995)	Topical treatment of mild- to moderate inflammatory acne vulgaris	A thin film to affected areas twice daily	Not included AR	AR: pruritus, burning, stinging and tingling W&P: hypopigmentation, sensitivity or irritation
Retinoids				
Fabior (tazarotene) Foam, 0.1% NDA 202428 (2012)	Topical treatment of acne vulgaris in patients 12 years of age or older	Once daily in the evening after washing with a mild cleanser and fully drying the affected area	2, 12-week R, DB, VC trials in 1485 subjects 12 years and older with moderate to severe acne vulgaris Active vs. vehicle Trial one: • IGA: 29% vs. 16% • Inflam: 58% vs. 45% • Noninflam: 55% vs. 33% • Total: 56% vs. 39% Trial two: • IGA: 28% vs. 13% • Inflam: 57% vs. 41% • Noninflam: 46% vs. 41% • Total: 56% vs. 43%	AR: application site irritation, dryness, erythema, exfoliation, pain, photosensitivity, pruritus, dermatitis W&P: fetal risk, local irritation, irritant effect with concomitant topical medications, photosensitivity and risk for sunburn, flammability

Product (s) Name/Year of Approval	Indication	Dosing/ Administration	Efficacy Information From Labeling	Important Safety and Tolerability Issues
Differin (adapalene) Lotion, 0.1% NDA 022502 (2010)	Topical treatment of acne vulgaris in patients 12 years and older	Apply a thin film to the entire face and other affected areas of the skin once daily, after washing gently with a mild soap less cleanser	2, 12-week R, DB, VC trials in 2141 subjects Active vs. vehicle Trial one: • IGA: 26% vs. 17% • Inflam: 55% vs. 40% • Noninflam: 50% vs. 36% • Total: 52% vs. 37% Trial two: • IGA: 24% vs. 16% • Inflam: 46% vs. 37% • Noninflam: 43% vs. 30% • Total: 45% vs. 33%	AR: dry skin, skin irritation, skin burning/skin discomfort, sunburn W&P: UV light and environmental exposure, local cutaneous reactions
Altreno (tretinoin) Lotion, 0.05% NDA 209353 (2018)	Topical treatment of acne vulgaris in patients 9 years and older	Apply a thin layer to affected areas once daily	2, 12-week R, DB, VC trials in 1640 subjects Active vs. vehicle Trial one: • IGA: 17% vs. 7% • Inflam: 51% vs. 40% • Noninflam: 48% vs. 27% Trial two: • IGA: 20% vs. 13% • Inflam: 53% vs. 42% • Noninflam: 46% vs. 32%	AR: application site dryness, pain, erythema, irritation, exfoliation W&P: potential fetal risk, photosensitivity and risk for sunburn, fish allergies
Combination Products				
Acanya Gel (clindamycin phosphate 1.2% and benzoyl peroxide, 2.5%) NDA 050819 (2008)	Topical treatment of acne vulgaris in patients 12 years or older.12 years and older	Apply a pea-sized amount of Acanya Gel to the face once daily	2, 12-week R, DB, VC trials subjects 12 years and older with moderate to severe acne vulgaris Active vs. vehicle • EGSS: 0/1: 29% vs. 14% • 2-grade: 33% vs. 19% • Inflam: 55% vs. 35%	AR: application site pain, exfoliation, irritation W&P: Colitis, UV light exposure

Product (s) Name/Year of Approval	Indication	Dosing/ Administration	Efficacy Information From Labeling	Important Safety and Tolerability Issues
Epiduo Forte (adapalene and benzoyl peroxide) Gel, 0.3%/2.5% NDA 207917 (2015)	Topical treatment of acne vulgaris	Apply a thin layer of Epiduo Forte Gel to affected areas of the face and/or trunk once daily after washing	A 12-week R, DB, VC trial in subjects 12 years and older with moderate to severe acne vulgaris Active vs. vehicle • IGA: 33.7% vs. 11.0% • Inflam: 27.8% vs. 13.2% • Noninflam: 40.5% vs. 19.7%	AR: skin irritation, eczema, atopic dermatitis, and skin burning sensation. W&P: UV light exposure, local cutaneous reactions

Source: Modified from Table 2, NDA 209353, Clinical Review by Melinda Mccord, MD;
Updated by reviewer from "Drugs at FDA," and "DAILYMED" accessed May 17, 2019. Updated information for AMZEEQ approval added on 10/25/19.
Abbreviations: AR=adverse reaction, CFB=change from baseline, CNS=central nervous system, DB=double blind, DRESS=drug reaction with eosinophilia and systemic symptoms, EM= erythema multiforme, EGSS=Evaluator's Global Severity Score, GAAS=Global Acne Assessment Score, IGA=Investigator Global Assessment, IGSA=Investigator Global Static Assessment, Inflam=inflammatory, Noninflam=noninflammatory, R=randomized, SJS=Stevens-Johnson syndrome, UV=ultraviolet, VC=vehicle controlled, W&P=Warnings and Precautions

Table 3: Examples of Systemic Acne Products

Generic Name	Brand Name	Formulations	Applicant	Indication
Oral Antibiotics				
Sarecycline (2018)	Seysara	Tablet	Almirall	Treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older.
Minocycline hydrochloride	Solodyn	Extended release tablets 55 mg, 65 mg, 105 mg, 115 mg	Medicis	Only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older
Doxycycline hyclate	Doryx MPC Doxycycline hyclate	Delayed release tablets, 60 & 120 mg Delayed release tablets, 75, 100, 150, 200 mg	Mayne pharma	In severe acne may be useful adjunctive therapy
Doxycycline monohydrate	Monodox	Capsule; 50 mg, 75 mg, 100 mg	Aqua Pharms	
Tetracycline hydrochloride	Tetracycline hydrochloride	Capsule; 250 mg, 500 mg	Heritage Pharms, Inc	

Generic Name	Brand Name	Formulations	Applicant	Indication
Retinoid				
Isotretinoin	Absorica	Capsules; 10, 20, 25, 30, 35, 40 mg	Ranbaxy	Severe recalcitrant nodular acne in patients 12 years of age and older
	Amnesteem generic	Capsules; 10, 20, 40 mg	Mylan Pharms Inc.	
	Claravis generic	Capsules; 10, 20, 30, 40 mg	Teva Pharms USA	
	Myorisan generic		Douglas Pharm	
	Zenatane generic		Dr Reddy's Labs, Ltd	
Hormonal Therapies				
Drospirenone 3 mg/ethinyl estradiol 0.02 mg	Yaz	Tablets	Bayer Healthcare	Moderate acne for women at least 14 years old only if patient desires an oral contraceptive for birth control
Norgestimate 0.180, 0.215, 0.250 mg/ethinyl estradiol 0.035 mg norgestimate 0.250 mg/ethinyl estradiol 0.035 mg	Ortho-Cyclen Ortho Tri-Cyclen	Tablets	Janssen Pharmaceuticals	Moderate acne vulgaris in females at least 15 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche

Source: Modified from Table 3, NDA 209353, Clinical Review by Melinda Mccord, MD.
Updated by reviewer from "Drugs at FDA," and "DAILYMED" accessed May 17, 2019.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The proposed product, Arazlo (tazarotene) Lotion, 0.045%, is not approved in the U.S. or any other jurisdiction. As there is no marketing history, this section is not applicable.

3.2. Summary of Presubmission/Submission Regulatory Activity

Arazlo (tazarotene, 0.045% lotion) was developed under Investigational New Drug (IND) 126277, submitted on 8/21/2015. The Applicant developed Arazlo for treatment of acne vulgaris under the 505(b)(2) regulatory pathway with Tazorac (tazarotene) cream, 0.1% (NDA 021184) as the reference drug.

The Applicant conducted clinical studies to evaluate efficacy and safety of Arazlo Lotion in their clinical development program but planned to use some of the information required for approval from the studies not conducted by or for the Applicant and for which the Applicant had not obtained a right of reference. The nonclinical pharmacology/toxicology information the Applicant planned to use for the basis of this 505(b)(2) submission are from the LD Tazorac Cream, 0.1% approved for the treatment of plaque psoriasis (9/29/2000), and for the treatment of acne vulgaris (10/11/2001). Milestone interactions with the Applicant are listed below:

Pre-IND:

A teleconference was held with the Applicant on 6/25/2015. The following topics were discussed during this meeting:

- Requirements to establish clinical bridges to reference product under a 505(b)(2) pathway
- Adequacy of nonclinical studies (repeat dose toxicity and local tolerance data from the nonclinical studies conducted in support of the development of IDP-118 Lotion)
- Outline of clinical studies to be conducted under IND 126277, including dermal safety studies, discussion of criteria for maximal use study and PK bridge to LD, and removal of an upper age limit for inclusion of subjects
- Discussion of the overall design of Phase 3 trials, including primary and secondary efficacy endpoints, and EGSS scale.
- Discussion of the Applicant's plan to request waivers for conducting a long-term safety evaluation, a thorough QT study, and a phototoxicity/photoallergenicity study of Arazlo Lotion if the Applicant could establish an adequate clinical bridge to the LD.

EOP2 Meeting:

The Applicant requested cancellation of the EOP2 meeting scheduled for 12/6/2016 following the receipt of preliminary meeting comments sent by the FDA on 12/2/2016. Meeting comments included the following topics:

- Chemistry, manufacturing and control issues related to specifications and stability requirements
- Nonclinical development program required no additional nonclinical studies if an adequate clinical bridge to Tazorac Cream, 0.1% was established
- Phase 3 trial design including subject population, number of subjects, EGSS scale for clinical endpoints assessments, waiver requests (for TQT and long-term safety studies, dermal photosafety studies), and statistical analyses

iPSP:

The FDA agreed with the Applicant's Agreed Initial Pediatric Study Plan (iPSP) on 12/3/2018 following discussion of the Agreed iPSP with the Pediatric Review Committee at its meeting on 11/14/2018. Refer to Section 8.2.9 of this review for additional details.

Pre-NDA:

The Applicant requested cancellation of the pre-NDA meeting scheduled for 11/13/2018 following the receipt of preliminary meeting comments sent by the FDA on 11/8/2018. Meeting comments included the following topics:

- The content and format of the NDA

- Chemistry, manufacturing and controls: Drug substance specifications, stability studies, and USP <905> uniformity
- Pharmacology/toxicology: Clinical bridge adequacy for nonclinical program
- Clinical pharmacology: Maximal use clinical PK study (501)
- Clinical/Biostatistics: Clinical (201) and PK (501) bridging studies, number of subjects exposed to the to-be-marketed formulation per International Conference on Harmonisation E1A guidance, case report forms (for deaths, serious adverse events (SAEs), and discontinuations due to treatment-emergent adverse events (TEAEs)), no long-term safety study required, no TQT study required, statistical analysis plan for pooling of trials 301 and 302 in integrated summary of safety (ISS) and integrated summary of effectiveness

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

The overall quality of the clinical information contained in this submission was adequate. The by-center efficacy results plots for trials 301 and 302 for each of the three coprimary efficacy endpoints were generated by the statistical reviewer for this NDA (Kathleen Fritsch, PhD). In light of the long marketing history of tazarotene (initial approval 1997) and the results of by-center efficacy plots for this product, the clinical and statistical reviewers did not request a clinical study site inspection from the Office of Scientific Investigations.

4.2. Product Quality

The Applicant, Bausch Health U.S., LLC. has submitted this 505(b)(2) application for Arazlo (tazarotene) Lotion, 0.045% indicated for the treatment of acne vulgaris in patients 9 years of age and older. The lotion is intended for topical application as a thin layer to the affected skin area once daily. (b) (4)

The CMC review concluded that:

- The Applicant of this 505(b)(2) NDA has provided sufficient chemistry, manufacturing and controls information to assure the identity, purity, strength, and quality of the drug substance and drug product.
- All labels/labeling issues have been satisfactorily resolved.
- The Office of Process and Facility has made an overall "Acceptable" recommendation regarding the facilities involved in this NDA.
- The claim for categorical exclusion of the environmental assessment has been granted.

Therefore, from the Office of Pharmaceutical Quality perspective, this NDA is recommended for APPROVAL with the drug product expiration dating period of 36 months.

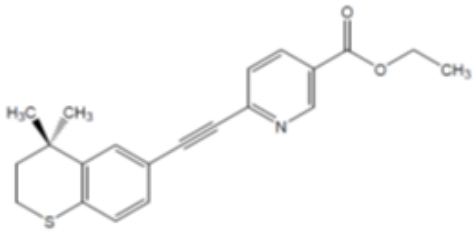
Drug Substance

The drug product Arazlo contains tazarotene as the active ingredient. The active ingredient, tazarotene is a retinoid prodrug that activates three members of retinoic acid receptors (RAR), RARα, RARβ, and RARγ. Due to its antiproliferation, normalizing-of-differentiation, and anti-inflammatory properties, tazarotene has been found to be effective in the treatment of acne vulgaris.

Tazarotene was first approved in 1997, and since its original approval, multiple brand name and generic cream, gel, and foam drug products containing this active ingredient have been approved and are being marketed in the United States.

Tazarotene has the chemical name of 6-[3,4-dihydro-4,4-dimethyl-2H-1-benzothiopyran-6-yl)ethynyl]-3-pyridinecarboxylic acid ethyl ester, molecular formula of $C_{21}H_{21}NO_2S$, molecular weight of 351.46 g/mol, and the molecular structure below:

Figure 1: Molecular Structure of Tazarotene



Tazarotene for this NDA is manufactured by (b) (4) (b) (4) in accordance to current good manufacturing practices. It is produced through a (b) (4) It is tested against an adequate specification that assures identity, strength, purity and quality of the drug substance at release and throughout its proposed retest date of (b) (4) months. Information regarding the manufacture of tazarotene produced by (b) (4) is provided in drug master file (DMF) (b) (4) which has been reviewed and found adequate to support this NDA.

Drug Product

Arazlo (tazarotene) Lotion, 0.045% is a white to off-white lotion and will be packaged and supplied as 3 g for physician samples and as 45 g for commercial use in white aluminum tubes with (b) (4) caps. It is manufactured in accordance to the current good manufacturing practice by Bausch Health Companies Inc., Quebec, Canada.

The drug product is tested and released according to a specification that includes testing and acceptance criteria for all physical and chemical attributes essential for assuring the identity, strength, purity, and quality of the drug product at release and throughout its proposed expiration dating period of 36 months.

Each gram of Arazlo lotion contains 0.45 mg of tazarotene as the active ingredient and diethyl sebacate, light mineral oil, sorbitan monooleate, sorbitol solution (70%), methylparaben, propylparaben, edetate disodium dihydrate, carbomer copolymer type B (b) (4) carbomer homopolymer type A (b) (4) sodium hydroxide (b) (4) as inactive ingredients. Inactive ingredients used in the composition of this lotion are all compendial materials.

4.3. Clinical Microbiology

No Clinical Microbiology studies were conducted during Arazlo development program.

APPEARS THIS WAY ON ORIGINAL

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant submitted a 505(b)(2) application for Arazlo (tazarotene) Lotion, 0.045% for the topical treatment of acne vulgaris in patients 9 years of age and older, using Tazorac Cream, 0.1% as the LD. Tazorac Cream, 0.1% has been approved for the same indication in patients 12 years of age and older under NDA 021184 since 2001.

The Applicant has established an adequate clinical bridge to the LD, Tazorac Cream, 0.1% based on a human maximal use PK study in subjects aged 12 years and older. Refer to the Clinical Pharmacology section of this review for the details. The Applicant is relying on the Agency's finding of safety for the LD. The nonclinical information from the approved label for the LD that the Applicant intends to rely on includes fertility and reproduction, embryofetal development, genetic toxicity, and carcinogenicity. The toxicity of tazarotene is well characterized and typical for the retinoid drug class.

The Applicant conducted a pivotal repeat dose dermal toxicity study with a fixed-dose combination drug product containing halobetasol propionate and tazarotene in a lotion vehicle, and halobetasol and tazarotene monads in a lotion vehicle. The lotion vehicle composition used in this study is the same as used in Arazlo. The Applicant used the toxicity data from the tazarotene portion of this repeat dose dermal toxicity study to support the safety of Arazlo.

The pivotal 3-month repeat dose dermal toxicity study in minipigs was conducted with five treatment groups that included low (halobetasol propionate 0.002%/tazarotene 0.010%), mid (halobetasol propionate 0.01%/tazarotene 0.045%) and high doses (halobetasol propionate 0.02%/tazarotene 0.09%) of the combination product and monad groups containing halobetasol propionate (0.02%) or tazarotene (0.090%) in the lotion vehicle. The mid-dose group is equivalent to the tazarotene concentration used in Arazlo. Topical administration of the three doses of the fixed-dose combination drug product as well as halobetasol propionate and tazarotene monads once daily for 90 days was well tolerated in minipigs. Treatment related effects included body weight decreases, consistent with adverse effects of topical corticosteroids, and correlated to halobetasol propionate systemic exposure. Target organs included those previously reported for tazarotene and halobetasol propionate (i.e., skin dose site, adrenal glands, and thymus). Decreased organ weights and/or microscopic changes observed in target organs showed partial or full reversibility following a 1-month recovery period. There were no test article-related electrocardiogram (ECG) abnormalities in this study. The tazarotene lotion monad used in this study contains 0.090% tazarotene which is twofold higher than the concentration used in Arazlo. The toxicity profile for the tazarotene lotion monad was consistent with that of topical tazarotene or retinoid. Steady state exposures (AUC_{0-24}) at the mid dose (clinical strength) were 20 and 14 ng*hr/mL for tazarotenic acid (the active metabolite of tazarotene) in males and females, respectively, which is 2 and 1.4 times the maximum recommended human dose (MRHD) of Arazlo Lotion (based on area under the curve (AUC) comparison), respectively.

Arazlo does not contain any novel excipients. There are no concerns with any impurities in the drug substance from a pharmacology/toxicology perspective.

Arazlo is approvable for the topical treatment of acne vulgaris in patients 9 years of age and older from a pharmacology/toxicology perspective. There are no recommended nonclinical postmarketing commitments/postmarketing requirements for this NDA.

5.2. Referenced NDAs, BLAs, DMFs

This NDA makes reference to the following DMFs.

- DMF [redacted] (b) (4) aluminum tubes, active, 3/12/1991.
- DMF [redacted] (b) (4) Tazarotene, active, 8/3/2011.

The Applicant intends to rely on the Agency's findings of safety for Tazorac (tazarotene) Cream, 0.1% (NDA 21184, approved for the treatment of plaque psoriasis on 9/29/2000 and for the treatment of acne vulgaris on 10/11/2001) as the LD.

The following nonclinical pharmacology and toxicology studies were reviewed under INDs 111218 or 126779. A summary of these studies is provided below. The code name for this drug product is IDP-123 lotion. IDP-118 lotion is the code name for the fixed-dose combination product (halobetasol and tazarotene lotion, 0.01%/0.045%).

5.3. Pharmacology

Primary Pharmacology

Tazarotene is a retinoid prodrug which is converted to its active form, the carboxylic acid of tazarotene, by deesterification. Tazarotenic acid binds to all three members of the RAR family: RARα, RARβ, and RARγ, but shows relative selectivity for RARβ, and RARγ and may modify gene expression. The clinical significance of these findings for the treatment of acne vulgaris is unknown.

Secondary Pharmacology

N/A

Safety Pharmacology

Study 1 Effects of Tazarotene, Tazarotenic Acid and Halobetasol Propionate and Mixtures on Cloned hERG Potassium Channels Expressed in Mammalian Cells (Study # V01-118A-608, Non-GLP)

The most common mechanism of drug-induced QT interval prolongation is inhibition of the delayed rectifier potassium channel. The potential of halobetasol propionate, tazarotene and tazarotenic acid (the active metabolite for tazarotene) to inhibit potassium channel currents

was evaluated in the in vitro human ether-a-go-go-related gene (hERG) assay. This review will focus on the data available for tazarotene and tazarotenic acid from this study. Tazarotene inhibited hERG current with a half maximal inhibitory concentration (IC_{50}) of 5.7µM; this level of inhibition is considered weak and not a concern because tazarotene is rapidly metabolized in vivo to tazarotenic acid and is essentially not detected in human plasma following dermal administration. An IC_{50}>10µM (the highest concentration tested) was established for tazarotenic acid. Therefore, tazarotenic acid has no hERG inhibition potential based on the results from this in vitro study.

No standalone safety pharmacology studies have been conducted with the drug substances or the drug product. The effects on ECG measurements were evaluated in a 3-month repeat dose minipig dermal toxicity study. There were no test article-related ECG abnormalities in main study animals or in 1-month recovery animals.

5.4. ADME/PK

The Applicant has not conducted nonclinical PK studies with the drug substance or drug product. However, the toxicokinetics of tazarotene and tazarotenic acid (the active metabolite for tazarotene) were determined in the 3-month repeat dose toxicity study in minipigs conducted with three doses of the fixed-dose combination product containing halobetasol propionate and tazarotene in a lotion vehicle, the monad tazarotene in a lotion vehicle, and the monad halobetasol propionate in a lotion vehicle. A summary of the tazarotenic acid toxicokinetic data are provided below. Refer to Section 5.5.1 (General Toxicology) for detailed information concerning the design of the 3-month repeat dose toxicity study in minipigs. The concentration of tazarotene in the low strength, clinical strength, enhanced strength and tazarotene lotion monad in the following table are 0.01%, 0.045%, 0.09%, and 0.09%, respectively. The low strength, clinical strength and enhanced strength products also contained halobetasol propionate at concentrations of 0.002%, 0.01%, and 0.02%. It appears that the presence of halobetasol propionate in the low, clinical, and enhanced strength products increased the systemic exposure to tazarotenic acid compared to the tazarotene lotion monad.

Table 4. TK Data for Tazarotenic Acid From a 3-Month Repeat-Dose Dermal Minipig Toxicity Study

Agent and Test Animal	Major Findings
Tazarotenic acid in male minipigs	**T_{max}:** Low strength: 2 hrs Clinical strength: 8 hrs Enhanced strength: 4 hrs Tazarotene lotion monad: 2 hrs **AUC_{0-24}:** Low strength: 6.1 ng·hr/mL Clinical strength: 32 ng·hr/mL Enhanced strength: 54 ng·hr/mL Tazarotene lotion monad: 26.5 ng·hr/mL **C_{max}:** Low strength: 0.3 ng/mL Clinical strength: 2.1 ng/mL Enhanced strength: 3.0 ng/mL Tazarotene lotion monad: 1.8 ng/mL **Accumulation:** No evidence of systemic accumulation from Day 28 to Day 90, indicating steady-state had been achieved by Day 28. **Dose proportionality:** Systemic exposure increased roughly dose-proportionally
Tazarotenic acid in female minipigs	**T_{max}:** Low strength: 8 hrs Clinical strength: 4 hrs Enhanced strength: 3 hrs Tazarotene lotion monad: 2 hrs **AUC_{0-24}:** Low strength: 4.0 ng·hr/mL Clinical strength: 24 ng·hr/mL Enhanced strength: 42 ng·hr/mL Tazarotene lotion monad: 30.6 ng·hr/mL **C_{max}:** Low strength: 0.23 ng/mL Clinical strength: 1.7 ng/mL Enhanced strength: 3.7 ng/mL Tazarotene lotion monad: 2.4 ng/mL **Accumulation:** No evidence of systemic accumulation from Day 28 to Day 90, indicating steady-state had been achieved by Day 28. **Dose proportionality:** Systemic exposure increased roughly dose-proportionally

[a] A 3-month Study of IDP-118-A by Dermal Administration in Minipigs with a 1-month Recovery Period, Study # V01-118A-605
Abbreviations: AUC=area under the curve, C_{max}=observed peak drug concentration, T_{max}=time at which C_{max} is observed

The Applicant conducted a human maximal use PK study in subjects aged 12 years and older to determine biocomparability between Arazlo and the LD to establish a clinical bridge to the LD. It is determined that the Applicant has established an adequate clinical bridge to the LD, Tazorac Cream, 0.1%. The Applicant also conducted a human maximal use PK study in pediatric subjects (9 years to 11 years 11 months) with Arazlo Lotion. Refer to the Clinical Pharmacology section of this review for the details.

5.5. Toxicology

5.5.1. General Toxicology

Study 1 A 3-month Study of IDP-118-A by Dermal Administration in Minipigs with a 1-month Recovery Period (Study # V01-118A-605, GLP)

This study was conducted with five treatment groups that included low (halobetasol propionate 0.002%/tazarotene 0.010%), mid (halobetasol propionate 0.01%/tazarotene 0.045%) and high doses (halobetasol propionate 0.02%/tazarotene 0.09%) of the fixed-dose combination product, as well as monad groups containing halobetasol propionate (0.02%) or tazarotene (0.090%) in the lotion vehicle. The lotion vehicle used in this study contains the same excipient composition as Arazlo Lotion. The mid-dose group is equivalent to the tazarotene concentration used in Arazlo Lotion. The tazarotene monad group contained 0.090% tazarotene, which is twofold higher than the tazarotene concentration used in Arazlo Lotion.

Administration of the three doses of the fixed-dose combination product as well as halobetasol propionate and tazarotene monads by once daily dermal application for 90 days was well tolerated in minipigs.

Treatment-related effects included body weight decreases, consistent with adverse effects of topical corticosteroids, and correlated to halobetasol propionate systemic exposure. Target organs included those previously reported for tazarotene and halobetasol propionate (i.e., skin dose site, adrenal glands, and thymus). The decreased organ weights and/or microscopic changes observed in target organs showed partial or full reversibility following a 1-month recovery period. The toxicity profile of the tazarotene lotion monad group was consistent with that of topical tazarotene.

ECG measurements were obtained prior to the first dose, during the last week of dosing (Days 85/87), and during the last week of the recovery period (Day 114). There were no test article-related ECG abnormalities in main study animals or in 1-month recovery animals.

Tazarotene is a prodrug of its active metabolite, tazarotenic acid. Tazarotenic acid, but not tazarotene, was detected in plasma. Overall, drug systemic exposure was consistently achieved throughout the dosing interval, with the peak drug concentration (C_{max}) reached within a few hours after dosing. The highest exposures, based on C_{max}, were observed in the high-dose group on Day 90 for tazarotenic acid. There was no evidence of drug systemic accumulation between Days 28 and 90, and steady state appeared to be reached by Day 28. Drug absorption appeared to increase with the combination product as compared to the lotion monads. On Day 90, male and female C_{max} averaged 3.0 and 3.7 ng/mL for tazarotenic acid, respectively. Steady state exposures (AUC_{0-24}) for tazarotenic acid at the mid dose (clinical strength) were 21 and 14 ng*hr/mL for males and females, respectively, which is 2 and 1.4 times the MRHD of Arazlo (based on AUC comparison), respectively.

5.5.2. Genetic Toxicology

The following genetic toxicology information is included in the Tazorac Cream label approved in 2017.

Tazarotene was found to be nonmutagenic in the Ames assay and did not produce structural chromosomal aberrations in a human lymphocyte assay. Tazarotene was nonmutagenic in the CHO/HGPRT mammalian cell forward gene mutation assay and was nonclastogenic in the in vivo mouse micronucleus test.

5.5.3. Carcinogenicity

The following carcinogenicity information is included in the Tazorac Cream label approved in 2017. Please note: there are two human exposure multiples for each animal study in the section 13.1 of the label. The second one is relevant to this NDA because it is the human exposure multiple for acne patients. Therefore, the sentences regarding the irrelevant human exposure multiples in psoriatic patients were omitted in this review.

A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on PK data from a shorter term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to 2 times the maximum systemic exposure in acne patients treated with tazarotene cream, 0.1% cream at 2 mg/cm^2 over a 15% body surface area.

A long-term topical application study of up to 0.1% of tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals. Systemic exposures at the highest dose was 13 times the maximum systemic exposure in acne patients treated with tazarotene cream, 0.1% at 2 mg/cm^2 over a 15% body surface area.

5.5.4. Reproductive and Developmental Toxicology

The following fertility and embryofetal development information is included in the Tazorac Cream label approved in 2017. Please note: there are two human exposure multiples for each animal study in the section 13.1 of the label. The second one is relevant to this NDA because it is the human exposure multiple for acne patients. Therefore, the sentences regarding the irrelevant human exposure multiples in psoriatic patients were omitted in this review.

Fertility and Early Embryonic Development

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating, and continuing through gestation and lactation with topical doses of tazarotene gel up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat would be equivalent to 2 times

the maximum systemic exposure in acne patients treated with tazarotene cream, 0.1% at 2 mg/cm^2 over a 15% body surface area.

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1 mg/kg/day tazarotene. That dose produced a systemic exposure that was 6.3 times the maximum systemic exposure in acne patients treated with tazarotene cream, 0.1% at 2 mg/cm^2 over a 15% body surface area.

No impairment of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through gestation day 7 with oral doses up to 2 mg/kg/day of tazarotene. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose [see Use in Specific Populations (8.1)]. That dose produced a systemic exposure that was (b) (4) times the maximum systemic exposure in acne patients treated with tazarotene cream, 0.1% at 2 mg/cm^2 over a 15% body surface area.

Reproductive capabilities of F1 animals, including F2 survival and development, were not affected by topical administration of tazarotene gel to female F0 parental rats from gestation day 16 through lactation day 20 at the maximum tolerated dose of 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat would be equivalent to 2 times the maximum systemic exposure in acne patients treated with tazarotene cream, 0.1% at 2 mg/cm^2 over a 15% body surface area.

Embryo-Fetal Development

In rats, a tazarotene gel, 0.05% formulation dosed topically during gestation days 6 through 17 at 0.25 mg/kg/day, which represented 2 times the maximum systemic exposure in subjects treated with the MRHD of tazarotene cream, 0.1% (i.e., 2 mg/cm^2 over a 15% body surface area), resulted in reduced fetal body weights and reduced skeletal ossification. Rabbits dosed topically with 0.25 mg/kg/day tazarotene gel, which represented 26 times the maximum systemic exposure in subjects treated with MRHD of tazarotene cream, 0.1%, during gestation days 6 through 18, had a single incident of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies.

When tazarotene was given orally to animals, developmental delays were seen in rats, and malformations and postimplantation loss were observed in rats and rabbits at doses representing 2 and 52 times, respectively, the maximum systemic exposure seen in subjects treated with the MRHD of tazarotene cream, 0.1%.

In female rats orally administered 2 mg/kg/day of tazarotene from 15 days before mating through gestation day 7, which represented 7 times the maximum systemic exposure in subjects treated with the MRHD of tazarotene cream, 0.1%, classic developmental effects of retinoids were observed including decreased number of implantation sites, decreased litter size, decreased numbers of live fetuses, and decreased fetal body weights. A low incidence of retinoid-related malformations was observed at that dose.

In a pre- and postnatal development toxicity study, topical administration of tazarotene gel (0.125 mg/kg/day) to pregnant female rats from gestation day 16 through lactation day 20 reduced pup survival, but did not affect the reproductive capacity of the offspring. Based on data from another study, the maximum systemic exposure in the rat would be equivalent to the maximum systemic exposure in subjects treated with the MRHD of tazarotene cream, 0.1%.

Lactation

After single topical doses of ^{14}C-tazarotene gel to the skin of lactating rats, radioactivity was detected in rat milk.

5.5.5. Other Toxicology Studies

Study 1 A Reduced Local Lymph Node Assay with IDP-118 Lotion (Study # 7001-U6HP-02-10, GLP)

This study was conducted to determine if two IDP-118 Lotion formulations, Formula A and Formula B, would induce a hypersensitivity response in mice as measured by the proliferation of lymphocytes in the draining auricular lymph nodes.

A threefold or greater increase in stimulation index was considered a positive response. Treatment with either of the two lotion formulations of the fixed-dose combination of halobetasol propionate and tazarotene did not result in a stimulation index of greater than or equal to 3 relative to appropriate controls. Therefore, these findings suggest that the two lotion formulations of the fixed-dose combination of halobetasol propionate and tazarotene are not sensitizers.

Study 2 IDP-118 Lotion: Topical Application Ocular Irritation Screening Assay Using the EpiOcular Human Cell Construct (Study # 7001-U6HP-04-10, GLP)

This study was conducted to evaluate the potential ocular irritation of the test articles by measuring 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide dye conversion by the EpiOcular tissue construct after topical exposure to two lotion formulations of the fixed-dose combination of halobetasol propionate and tazarotene, the halobetasol propionate lotion monad and the tazarotene lotion monad. The results from the tazarotene monad lotion will be provided in this review.

Tazarotene were predicted to be minimally irritating to nonirritating to the eye based on the results from this study.

Study 3 Phototoxicity Assay Using the EpiDerm Skin Model (Study # V01-118A-607, GLP)

The phototoxicity potential of IDP-118 Lotion was evaluated in the EpiDerm in vitro skin model by treating tissues and subsequently exposing to ultraviolet-A/visible light, and measuring tissue viability. According to the prediction model presented by (b) (4), IDP-118-A Lotion (lot # DP1615) and IDP-118-A Lotion Vehicle (lot # DP1612) did not show phototoxic potential; whereas Tazorac Cream 0.1% (lot # 81464) exhibited a phototoxic potential (i.e., test article

induced ≥30% decrease in viability in the presence of ultraviolet-A compared to the viability in the absence of ultraviolet-A). The positive control, 0.02% chlorpromazine, met the acceptance criterion for a positive phototoxic response and validated the assay sensitivity.

6 Clinical Pharmacology

6.1. Executive Summary

Tazarotene is a retinoid prodrug which is rapidly metabolized to its active metabolite, tazarotenic acid by deesterification. It activates 3 members of the RAR nuclear receptors (RARα, RARβ, and RARγ), and may modify gene expression. The mechanism of action for tazarotene in the treatment of acne vulgaris is unknown. However, tazarotene's therapeutic effect in acne might be due to its anti-hyperproliferative, normalizing-of-differentiation, and anti-inflammatory effects.

The Applicant's proposed product is a topical lotion containing 0.045% of tazarotene. The proposed proprietary name, Arazlo, has been conditionally accepted. The Applicant is following a 505(b)(2) regulatory pathway and has identified Tazorac Cream, 0.1% as the LD. Tazorac Cream, 0.1% is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older and for the topical treatment of plaque psoriasis in patients 18 years of age and older.

The proposed indication for Arazlo Lotion is the topical treatment of acne vulgaris in patients 9 years of age and older. The proposed dosing regimen is to apply a thin layer of Arazlo Lotion to the affected areas once daily.

The Clinical Pharmacology program in this NDA includes Study V01-123A-501, which was a Phase 1, PK study in patients with moderate or severe acne conducted under the maximal use conditions. The aim of the study was to establish a clinical bridge by evaluating the relative bioavailability of Arazlo Lotion, 0.045% and Tazorac Cream, 0.1% in subjects aged 12 years and older. The study also evaluated the safety and PK of Arazlo Lotion in subjects aged 9 years to <12 years.

The key review findings with specific recommendations and comments are summarized in Table 5.

Table 5: Clinical Pharmacology Review

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Efficacy was not evaluated as a part of the Clinical Pharmacology program. See Section 8.1 for efficacy studies and their results.
General dosing instruction	The proposed dosing regimen of once daily application to the affected areas is acceptable.
Pharmacokinetics (PK)	The PK of tazarotene and tazarotenic acid following once daily application of Arazlo Lotion and Tazorac Cream were evaluated in subjects aged ≥12 years and older to support establishment of a clinical bridge. In addition, the PK of Arazlo Lotion was also evaluated in subjects aged 9 to <12 years. The plasma concentrations of tazarotene and tazarotenic acid were higher in younger subjects (9 to <12 years) compared to older subjects (≥12 years).
Clinical Bridge between Arazlo and the Listed Drug (Tazorac)	The mean systemic exposures of tazarotene and tazarotenic acid following administration of Arazlo Lotion were not greater than those observed following application of Tazorac Cream in subjects aged ≥12 years and older. The clinical bridge between Arazlo Lotion and Tazorac Cream is considered as established.
Pediatric subjects	The PK study was performed in pediatric subjects ≥9 years and older in Study V01-123A-501. A wavier for conducting a pediatric study in subjects 0 to <9 years has been agreed to in the initial Pediatric Study Plan.
Formulations used in clinical trial	To-be-marketed formulation of Arazlo Lotion was used in Study V01-123A-501.

6.1.1. Recommendations

From a clinical pharmacology standpoint, this NDA is acceptable.

6.1.2. Postmarketing Requirement(s) and Commitments(s)

None

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Table 6: Pharmacology and Clinical Pharmacokinetics of Tazarotene

Parameter	Details
Mechanism of action	Tazarotene is rapidly converted to its active metabolite, tazarotenic acid, by deesterification. Tazarotenic acid binds to all three members of the retinoic acid receptor (RAR) family but shows relative selectivity for RARβ and RARγ and may modify gene expression. However, the exact mechanism of action for the treatment of acne vulgaris is unknown.

<table>
<tr><th>Parameter</th><th>Details</th></tr>
<tr><td>PK parameters</td><td>Systemic concentrations of tazarotene were at or near steady state by Day 14. The tables below summarize PK parameters of tazarotene and tazarotenic acid on Days 14-15 following once daily topical application of Arazlo Lotion and Tazorac Cream.
<table>
<tr><th colspan="5">Tazarotene</th></tr>
<tr><th></th><th></th><th>Arazlo Lotion
9 to <12 years</th><th>Arazlo Lotion
≥12 years</th><th>Tazorac Cream
≥12 years</th></tr>
<tr><td rowspan="2">C_{max} (pg/mL)</td><td>Mean (SD)</td><td>17.82 (19.93)</td><td>4.84 (3.97)</td><td>6.25 (4.43)</td></tr>
<tr><td>N (N_{quant})</td><td>8 (6)</td><td>20 (7)</td><td>20 (10)</td></tr>
<tr><td rowspan="2">AUC_{0-t} (h*pg/mL)</td><td>Mean (SD)</td><td>240.98 (239.22)</td><td>67.40 (34.10)</td><td>72.66 (33.30)</td></tr>
<tr><td>N (N_{quant})</td><td>5 (5)</td><td>4 (4)</td><td>5 (5)</td></tr>
<tr><td rowspan="2">AUC_{0-24h} (h*pg/mL)</td><td>Mean (SD)</td><td>447.73 (NA[a])</td><td>126.53 (-)</td><td>-</td></tr>
<tr><td>N (N_{quant})</td><td>2 (2)</td><td>1 (1)</td><td>0 (0)</td></tr>
</table>
[a] SD could not be calculated from two values
Source: Tables 2 and 3 from module 2.7.2
<table>
<tr><th colspan="5">Tazarotenic Acid</th></tr>
<tr><th></th><th></th><th>Arazlo Lotion
9 to <12 years</th><th>Arazlo Lotion
≥12 years</th><th>Tazorac Cream
≥12 years</th></tr>
<tr><td rowspan="2">C_{max} (pg/mL)</td><td>Mean (SD)</td><td>620.88 (532.30)</td><td>262.63 (170.09)</td><td>355.11 (227.56)</td></tr>
<tr><td>N (N_{quant})</td><td>8 (8)</td><td>20 (20)</td><td>20 (20)</td></tr>
<tr><td rowspan="2">AUC_{0-t} (h*pg/mL)</td><td>Mean (SD)</td><td>9702.49 (8420.68)</td><td>4129.33 (2641.35)</td><td>5571.13 (3324.04)</td></tr>
<tr><td>N (N_{quant})</td><td>8 (8)</td><td>20 (20)</td><td>20 (20)</td></tr>
<tr><td rowspan="2">AUC_{0-24h} (h*pg/mL)</td><td>Mean (SD)</td><td>8251.06 (7941.10)</td><td>4195.14 (2851.14)</td><td>5606.80 (3776.02)</td></tr>
<tr><td>N (N_{quant})</td><td>5 (5)</td><td>17 (17)</td><td>11 (11)</td></tr>
</table>
Source: Tables 4 and 5 from module 2.7.2</td></tr>
<tr><td>Relative bioavailability</td><td>In subjects aged ≥12 years and older, the systemic exposure of Arazlo Lotion was lower compared to that of Tazorac Cream. For tazarotene, the ratios of arithmetic mean (Arazlo/Tazorac) were 0.77 and 0.93 for C_{max} and AUC_{0-t}, respectively on Days 14-15. For tazarotenic acid, the ratios were 0.74 for both C_{max} and AUC_{0-t} on Days 14-15.</td></tr>
<tr><td>Pharmacodynamics (PD)</td><td>The PD of tazarotene and tazarotenic acid are unknown. The Applicant did not evaluate the PD in this NDA.</td></tr>
<tr><td>Bioanalytical method</td><td>A liquid chromatography tandem mass spectrometric method was used for quantification of tazarotene and tazarotenic acid in human plasma samples collected from Study V01-123A-501. A full validation report was submitted and bioanalytical method was adequately validated. See Section 13.4.1 for additional details.</td></tr>
</table>

Abbreviations: AUC_{0-t}=area under the curve from time 0 up to the time corresponding to the last quantifiable concentration, AUC_{0-24h}=area under the curve from time 0 through 24 hours, C_{max}=observed peak drug concentration, SD=standard deviation, N_{quant}=number of samples with quantifiable levels of analyte, NDA = new drug application, PK=pharmacokinetics

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant's proposed dosing regimen is to apply a thin layer of Arazlo Lotion to the affected areas once daily. This dosing regimen is supported by systemic safety data from the maximal use study (V01-123A-501) and efficacy and safety data from the Phase 2 comparative safety and efficacy study (V01-123A-201) and the Phase 3 trials (301 and 302). See Section 8 for efficacy and safety findings from the Phase 3 trials.

Therapeutic Individualization

Therapeutic individualization was not evaluated in this NDA.

6.2.3. Outstanding Issues

There are no outstanding issues that would preclude the approval of Arazlo Lotion from a Clinical Pharmacology perspective.

6.2.4. Summary of Labeling Recommendations

The Clinical Pharmacology review team added additional PK information indicating the higher C_{max} and $AUC_{(0-t)}$ of tazarotene and tazarotenic acid observed in subjects aged 9 to less than 12 years compared to those observed in subjects 12 years and older in Section 12.3 of the label.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The PK characteristics of tazarotene and tazarotenic acid following application of Arazlo Lotion were assessed in Study V01-123A-501 under maximal use conditions. This was an open-label study designed to assess the safety and plasma PK of topically applied Arazlo Lotion in comparison to Tazorac Cream.

Eligible subjects for the study were males and females at least 9 years of age for Arazlo Lotion and at least 12 years of age and older for Tazorac Cream. Subjects had a clinical diagnosis of moderate to severe acne vulgaris with a facial acne inflammatory lesion (e.g., papules, pustules, nodules) count of no less than 20 but no more than 40, a facial acne noninflammatory lesion (e.g., open and closed comedones) count of no less than 20 but no more than 100, and 2 or fewer facial nodules.

Subjects applied approximately 4 g of Arazlo Lotion or Tazorac Cream on the face, neck, upper chest, upper back, and shoulders once daily for 14 days at approximately the same time each morning.

A total of 48 subjects were enrolled and all subjects completed the study. Demographic characteristics of these subjects are summarized in Table 7.

Table 7: Demographic Characteristics From Study V01-123A-501

Demographic Characteristic	Arazlo Lotion 9 to <12 years	Arazlo Lotion ≥12 years	Tazorac Cream ≥12 years
Age (years)			
Mean (SD)	10.25 (0.89)	17.45 (6.91)	16.40 (3.20)
Minimum, maximum	9.0, 11.0	12.0, 45.0	12.0, 25.0
Age group n(%)			
9 to <12 years	8 (100.0)	--	--
≥12 years	--	20 (100.0)	20 (100.0)
Sex, n(%)			
Male	1 (12.5)	8 (40.0)	10 (50.0)
Female	7 (87.5)	12 (60.0)	10 (50.0)
Race n(%)			
White	5 (62.5)	20 (100.0)	20 (100.0)
Black or African American	2 (25.0)	0	0
Other	1 (12.5)	0	0
Ethnicity, n(%)			
Hispanic or Latino	3 (37.5)	6 (30.0)	10 (50.0)
Not Hispanic or Latino	5 (62.5)	14 (70.0)	10 (50.0)

Source: Table 11-2 in CSR
Abbreviations: SD=standard deviation

The treatment compliance range was acceptable in all treatment groups as follows:

- Arazlo Lotion in 9 to <12 years: 93 to 100% (mean: 99.1%)
- Arazlo Lotion in ≥12 years: 79 to 100% (mean: 97.5%)
- Tazorac Cream in ≥12 years: 86 to 100% (mean: 96.8%)

The PK samples were collected to measure tazarotene and tazarotenic acid concentrations. The sampling timepoints were different in younger subjects (9 to <12 years) and in older subjects (≥12 years) as shown in Table 8 and Table 9, respectively.

Table 8: Schedule of PK Assessments in Subjects Aged 9 to <12 Years

Assessment Day	Predose[a]	1 hr Postdose	2 hr Postdose	4 hr Postdose	6 hr Postdose	8 hr Postdose	12 hr Postdose	24 hr Postdose
Day 1	X							
Day 2								
Day 12	X							
Day 14	X	X	X	X	X	X	X	
Day 15								X[b]

Source: Table 9-4 in CSR
[a] Prior to the morning application of study drug.
[b] Collected 24-hours after study drug application on Day 14.
Abbreviations: PK=pharmacokinetic

Table 9: Schedule of PK Assessments in Subjects Aged ≥12 Years

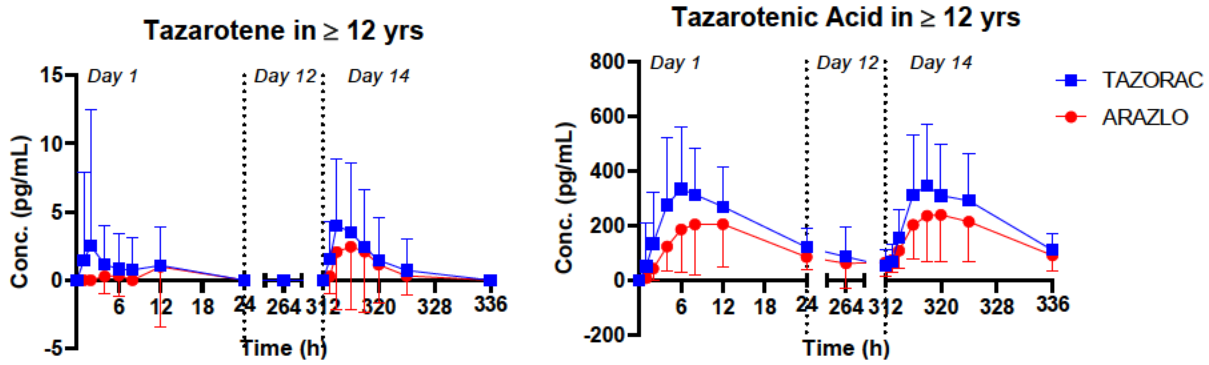
Assessment Day	Predose[a]	1 hr Postdose	2 hr Postdose	4 hr Postdose	6 hr Postdose	8 hr Postdose	12 hr Postdose	24 hr Postdose
Day 1	X	X	X	X	X	X	X	
Day 2	X[b]							
Day 12	X							
Day 14	X	X	X	X	X	X	X	
Day 15								X[c]

Source: Table 9-3 in CSR
[a] Prior to the morning application of study drug.
[b] Collected 24-hours after study drug application on Day 1.
[c] Collected 24-hours after study drug application on Day 14.

Abbreviations: PK=pharmacokinetic

Figure 2 shows the mean and standard deviation of tazarotene and tazarotenic acid plasma concentrations following once daily application of Tazorac Cream and Arazlo Lotion in subjects aged ≥12 years. Only a limited number of samples had quantifiable concentrations, especially for tazarotene. Samples with concentrations below the limit of quantification, 5.00 pg/mL for tazarotene and tazarotenic acid, were reported as zero for calculation. Figure 3 compares plasma concentrations in younger subjects (9 to <12 years) with those of older subjects (≥12 years) following once daily application of Arazlo Lotion, as well as concentrations following use of Arazlo Lotion versus Tazorac Cream.

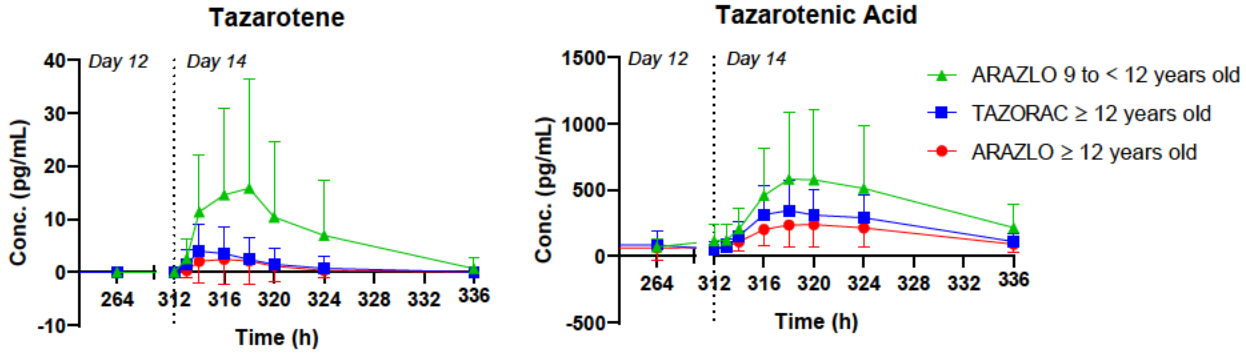
Figure 2: Plasma Concentrations (Mean ± SD) of Tazarotene and Tazarotenic Acid in Subjects Aged ≥12 Years



Source: reviewer's plot
Abbreviations: SD=standard deviation

Reviewer's comment: *The plasma concentrations of both tazarotene and tazarotenic acid are lower following once daily application of Arazlo Lotion, compared to those of Tazorac Cream in subjects aged ≥12 years. For the purpose of systemic safety, the bridge between Tazorac Cream and Arazlo Lotion can be said to be established.*

Figure 3: Plasma Concentrations (Mean ± SD) of Tazarotene and Tazarotenic Acid From Three Treatment Groups



Source: reviewer's plot
Abbreviations: SD=standard deviation

Reviewer's comment: *The plasma concentrations of both tazarotene and tazarotenic acid were higher in younger subjects (9 to <12 years) following once daily application of Arazlo Lotion, compared to the concentrations in older subjects (≥12 years) who following once daily application of Arazlo Lotion or Tazorac Cream. Plots of individual C_{max} and AUC_{all} values for all subjects are available in Figure 17 and Figure 18, respectively in Section 13.4.2. Although only a small number of subjects aged 9 to <12 years were included in the PK assessment (n=8), the higher concentrations observed in younger subjects were not cause for any additional safety concerns (and this was confirmed with clinical reviewers). The percentage of subjects with any TEAE was lower among younger subjects (12.5%) compared to older subjects in the Arazlo treatment group (15%) and to subjects in the Tazorac treatment group (30%) (see Section 8.2 for the summary of safety). This reviewer did additional analysis to assess for correlation between the amount of Arazlo Lotion applied and the systemic exposure (C_{max}) of tazarotenic acid as a potential cause of increase in systemic exposure in the lower age group (see Figure 19 under Section 13.4.2). The results indicated no correlation and thus did not explain the observed increase in systemic exposure in the lower age group. The higher systemic exposure in younger subjects could be due to higher surface-area-to-volume ratio as the daily dose applied was similar in all age groups.*

The PK parameters of tazarotene and tazarotenic acid were evaluated and summarized by the treatment groups and evaluation days in Table 10, Table 11, Table 12 and Table 13. Due to number of samples with concentrations of tazarotene or tazarotenic acid below the limit of quantification, AUC values were calculated in limited number of subjects, especially for tazarotene.

Table 10: PK Parameters of Tazarotene on Days 1 to 2 Per Treatment Groups

Parameter	Arazlo Lotion 9 to <12 years	Arazlo Lotion ≥12 years	Tazorac Cream ≥12 years
T_{max} (h)			
Mean (SD)	-	9.00 (9.00)	6.33 (4.63)
N_{quant}	-	2	6
C_{max} (pg/mL)			
Mean (SD)	-	1.33 (4.60)	4.15 (10.16)
N_{quant}	-	2	6
AUC_{0-t} (h*pg/mL)			
Mean (SD)	-	-	137.87 (-)
N_{quant}	-	0	1
AUC_{0-24} (h*pg/mL)			
Mean (SD)	-	-	-
N_{quant}	-	0	0

Source: Table 14.2.2.1 from CSR
Abbreviations: AUC_{0-t}=area under the curve from time 0 up to the time corresponding to the last quantifiable concentration, AUC_{0-24h}=area under the curve from time 0 through 24 hours, C_{max}=observed peak drug concentration, SD=standard deviation, T_{max}=time at which C_{max} is observed, N_{quant}=number of samples with quantifiable levels of analyte, PK=pharmacokinetics

Table 11: PK Parameters of Tazarotene on Days 14 to 15 Per Treatment Groups

Parameter	Arazlo Lotion 9 to <12 years	Arazlo Lotion ≥12 years	Tazorac Cream ≥12 years
T_{max} (h)			
Mean (SD)	4.67 (1.63)	3.57 (1.99)	3.90 (2.23)
N_{quant}	6	7	10
C_{max} (pg/mL)			
Mean (SD)	17.82 (19.93)	3.22 (5.03)	5.00 (5.58)
N_{quant}	6	7	10
AUC_{0-t} (h*pg/mL)			
Mean (SD)	240.98 (239.22)	67.40 (34.10)	72.66 (33.30)
N_{quant}	5	4	5
AUC_{0-24} (h*pg/mL)			
Mean (SD)	447.73 (NA[a])	126.53 (-)	-
N_{quant}	2	1	0

Source: Table 14.2.2.1 from CSR
[a] SD could not be calculated from two values
Abbreviations: AUC_{0-t}=area under the curve from time 0 up to the time corresponding to the last quantifiable concentration, AUC_{0-24h}=area under the curve from time 0 through 24 hours, C_{max}=observed peak drug concentration, SD=standard deviation, T_{max}=time at which C_{max} is observed, N_{quant}=number of samples with quantifiable levels of analyte, PK=pharmacokinetics

Table 12: PK Parameters of Tazarotenic Acid on Days 1 to 2 Per Treatment Groups

Parameter	Arazlo Lotion 9 to <12 years	Arazlo Lotion ≥12 years	Tazorac Cream ≥12 years
T_{max} (h)			
Mean (SD)	-	9.30 (2.70)	7.10 (2.38)
N_{quant}	-	20	20
C_{max} (pg/mL)			
Mean (SD)	-	226.64 (190.52)	369.75 (239.05)
N_{quant}	-	20	20
AUC_{0-t} (h*pg/mL)			
Mean (SD)	-	3462.02 (2589.02)	5301.12 (3142.50)
N_{quant}	-	20	20
AUC_{0-24} (h*pg/mL)			
Mean (SD)	-	2589.15 (2884.14)	5821.71 (3444.77)
N_{quant}	-	20	20

Source: Table 14.2.2.2 from CSR
Abbreviations: AUC_{0-t}=area under the curve from time 0 up to the time corresponding to the last quantifiable concentration, AUC_{0-24h}=area under the curve from time 0 through 24 hours, C_{max}=observed peak drug concentration, SD=standard deviation, T_{max}=time at which C_{max} is observed, N_{quant}=number of samples with quantifiable levels of analyte, PK=pharmacokinetics

Table 13: PK Parameters of Tazarotenic Acid on Days 14 to 15 Per Treatment Groups

Parameter	Arazlo Lotion 9 to <12 years	Arazlo Lotion ≥12 years	Tazorac Cream ≥12 years
T_{max} (h)			
Mean (SD)	7.50 (2.98)	6.90 (1.89)	6.70 (2.85)
N_{quant}	8	20	20
C_{max} (pg/mL)			
Mean (SD)	620.88 (532.30)	262.63 (170.09)	355.11 (227.56)
N_{quant}	8	20	20
AUC_{0-t} (h*pg/mL)			
Mean (SD)	9702.49 (8420.68)	4129.33 (2641.35)	5571.13 (3324.04)
N_{quant}	8	20	20
AUC_{0-24} (h*pg/mL)			
Mean (SD)	8251.06 (7941.10)	4195.14 (2851.14)	5606.80 (3776.02)
N_{quant}	5	20	11

Source: Table 14.2.2.2 from CSR
Abbreviations: AUC_{0-t}=area under the curve from time 0 up to the time corresponding to the last quantifiable concentration, AUC_{0-24h}=area under the curve from time 0 through 24 hours, C_{max}=observed peak drug concentration, SD=standard deviation, T_{max}=time at which C_{max} is observed, N_{quant}=number of samples with quantifiable levels of analyte, PK=pharmacokinetics

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Not applicable. The purpose of the pivotal Clinical Pharmacology study was to assess PK of Arazlo Lotion under maximal use conditions, assess systemic safety and establish a clinical bridge between the Applicant's product, Arazlo Lotion, and the LD, Tazorac Cream. This study did not directly provide efficacy data.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Based on the systemic safety and bridging study results from V01-123A-501 and the efficacy and safety results from Phase 3 trials, the proposed dosing regimen is appropriate.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The effect of intrinsic and extrinsic factors was not evaluated in this NDA. A dose adjustment is not needed based on efficacy and safety data from Phase 3 trials.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food-drug interaction studies are not needed for topical products. Drug-drug interaction assessment was not needed for this product as this is a 505(b)(2) application.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The development program for Arazlo Lotion for the topical treatment of acne vulgaris included the following 6 studies:

- Phase 3 Trials 301 and 302
- Phase 2 Efficacy/Safety/Clinical Bridging Study V01-123A-201 (Study 201)
- Phase 1 Maximal use/PK Bridging Study V01-123A-501 (Study 501)
- Phase 1 Provocative Dermal Safety Studies V01-123A-101 (Study 101, cumulative irritation patch test) and V01-123A-102 (Study 102, repeat insult patch test)

The following table provides a summary of all clinical studies pertinent to the evaluation of the efficacy and safety of Arazlo Lotion for the topical treatment of acne vulgaris.

Table 14: Clinical Trials Relevant to NDA 211882

Trial Identity	NCT no.	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
V01-123A-301	NCT 03168321	Phase 3, MC,R,DB,VC,PG	Applied topically to face, once daily in the evening	3 coprimary efficacy endpoints: • Absolute change in mean noninflammatory lesion count from Baseline to Week 12 • Absolute change in mean inflammatory lesion count from Baseline to Week 12 • Proportion of subjects with ≥2-grade reduction from Baseline in EGSS and EGSS=0, “clear” or 1, “almost clear” at Week 12	12 weeks, No follow-up	N=813 A:402 L: 411	Male/ female ≥9 YO, moderate to severe facial acne (EGSS=3,4) 20≤ inflammatory lesions ≤50 25≤ noninflammatory lesions ≤100 ≤2 nodules	U.S. (41), Canada 4)
V01-123A-302	NCT 03168334	Phase 3, MC,R,DB,VC,PG	Applied topically to face, once daily in the evening	Same as Trial 301	12 weeks, No follow-up	N=801 A:397 L: 404	Same as Trial 301	U.S. (39), Canada 5)
V01-123A-201	NCT 02938494 NCT 02525822	Phase 2, MC,R,DB,VC,PG (Clinical Bridging Study)	Applied topically to face, once daily in the evening	Same as Trial 301	12 weeks, No follow-up	N=210 A: 69 TC: 72 L: 34 ehicle cream: 35	Male/female ≥12 YO, moderate to severe facial acne (EGSS=3,4) 20≤ inflammatory lesions ≤40 20≤ noninflammatory lesions ≤100 ≤2 nodules	U.S.(16)

Trial Identity	NCT no.	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Studies to Support Safety								
V01-123A-501 (MuST PK/ Bridging Study)	NCT 02849873	Phase 1b, OL, R, MuST	Applied topically to the face, neck, upper chest, upper back, and shoulders once daily	Absorption and systemic PK, safety	14 days	A(9 to <12 O):8 A(≥12 O):20 TC(≥12 O):20	same as Trial -201 except for minimum age of: A: ≥9 O TC: ≥12 YO	U.S.(5)
V01-123A-101 (CIPT)		Phase 1, R,VC	A,VL, positive control, negative control patches applied to infrascapular skin daily	Cumulative irritation, TEAEs	21 days	42	Healthy adult subjects	U.S.(1)
V01-123A-102 (RIPT)		Phase 1, R,VC	A,VL, negative control patches applied x 3/week, x 3 weeks to infrascapular skin during induction phase. 1 patch application to a naïve (opposite infrascapular) site and assessment for up to 72 hours during challenge phase.	Sensitization potential, Cumulative irritation, TEAEs	6 weeks, induction: 3 weeks, Rest: 2 weeks, Challenge: Week 6 No Rechallenge	235	Healthy adult subjects	U.S.(1)

Source: Adapted from Applicant's submission, Section 2.5 (Clinical Overview), Table 1, Pages 8-9.
Study V01-123A-302 was identical in design to Study V01-123A-301.
Abbreviations: A=Arazlo Lotion, CIPT=Cumulative Irritation Patch Test, DB=double blind, EGSS=Evaluator's Global Severity Score, MC=multicenter, MuST=Maximum use Study, NDA=new drug application, OL=open-label, PG=parallel-group, PK=pharmacokinetics, R=randomized, RIPT=Repeat Insult Patch Test, TC=Tazorac Cream, TEAE=treatment-emergent adverse event, 0.1%, VC=vehicle-controlled, VL=vehicle-lotion, YO=years-old

7.2. Review Strategy

Data Sources

The data sources used for the evaluation of the efficacy and safety of tazarotene lotion 0.045% included the Applicant's clinical study reports (CSRs), datasets, clinical summaries, and proposed labeling. The submission was submitted in electronic common technical document format and was entirely electronic. Both Study Data Tabulation Model and analysis datasets were submitted. The analysis datasets used in this review are archived at \\cdsesub1\evsprod\nda211882\0001\m5\datasets.

Data and Analysis Quality

A consultation for review of data fitness was obtained from CDER Office of Computational Sciences (OCS).

OCS performed exploratory safety analysis and data fitness analysis for trials V01-123A-201, V01-123A -301, and V01-123A -302 for this NDA and found the data quality acceptable.

In collaboration with the OCS (JumpStart Data Fitness Consult Response dated 3/14/2019), the Statistical and Clinical reviewers held the following meetings with the JumpStart team:

- 4/1/2019 Study Data Tabulation Model assessment
- 4/2/2019 Traceability and ISS assessments
- 4/4/2019 Exploratory safety analysis assessment

Assessments evaluated the data fitness, whether certain common analyses could be performed, and other data quality metrics including:

- Availability of appropriate variables
- Variables populated by expected data points
- Appropriate use of standard terminology
- Data well described by metadata

In general, the data submitted by the Applicant to support the efficacy and safety of Arazlo Lotion for the proposed indication appeared adequate.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Design of Trials 301 and 302

Trial Design

Trials 301 and 302 were identical randomized, double-blind, vehicle-controlled, Phase 3 trials evaluating tazarotene lotion, 0.045% in the treatment of acne. The trials enrolled subjects 9 years of age and older with moderate to severe acne. Subjects were to have a score of 3 (moderate) or 4 (severe) on the EGSS. Subjects also were to have 20 to 50 facial inflammatory lesions, 25 to 100 facial noninflammatory lesions, and no more than 2 facial nodules.

Each trial was designed to randomize approximately 800 subjects in a 1:1 ratio to tazarotene lotion or vehicle lotion in the United States and Canada. Subjects applied treatment once daily for 12 weeks. Subjects were evaluated at screening, baseline, and Weeks 2, 4, 8, and 12.

Study Endpoints

Efficacy was assessed using the EGSS and inflammatory and noninflammatory lesion counts. The EGSS is as follows

Table 15: Evaluator's Global Severity Score (EGSS)

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost Clear	Rare noninflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red
2	Mild	Some noninflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	Noninflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be one nodulocystic lesion
4	Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be up to 2 nodulocystic lesions

Source: Protocols 301 and 302

Inflammatory lesion counts (papules and pustules) and noninflammatory lesion counts (open and closed comedones) were evaluated on the subject's face. Nodules were counted separately.

The coprimary efficacy endpoints were:

- The absolute change in noninflammatory lesions at Week 12
- The absolute change in inflammatory lesions at Week 12
- Clear or almost clear on the EGSS with at least 2 grades improvement at Week 12

The secondary endpoints were:

- The percent change in noninflammatory lesions at Week 12
- The percent change in inflammatory lesions at Week 12
- At least 2 grades improvement on the EGSS from baseline to Week 12
- The percent change in noninflammatory lesions at Week 8
- The percent change in inflammatory lesions at Week 8
- The percent change in noninflammatory lesions at Week 4
- The percent change in inflammatory lesions at Week 4

The supportive endpoints were:

- The percent change in noninflammatory lesions at Week 2
- The percent change in inflammatory lesions at Week 2
- At least 2 grades improvement on the EGSS from baseline to Week 8
- At least 2 grades improvement on the EGSS from baseline to Week 4
- At least 2 grades improvement on the EGSS from baseline to Week 2

Statistical Analysis Plan

The absolute changes in lesion counts were analyzed with either analysis of covariance (ANCOVA) or ANCOVA on the ranks depending on the results of a skewness test. Specifically, the absolute change values or the ranks were analyzed with ANCOVA with terms for treatment, analysis center, and baseline lesion count as a covariate. If the treatment-by-analysis center interaction was significant at alpha level 0.10, then the effect was included in the model, otherwise it was removed. A skewness test was applied to the residuals of the ANCOVA model using Zar's test.[10] If the two-sided p-value was significant at 0.01, then the analysis based on ranks was considered the primary analysis. Missing data were handled with Markov Chain Monte Carlo (MCMC) multiple imputation conducted separately for each treatment group. The number of imputations was 5 × *nmiss* where *nmiss* is the maximum number of missing Week 12 values between the treatment groups. After the lesion count values were imputed, each imputed dataset was analyzed with the ANCOVA procedure and combined into a single result.

Success on the EGSS was analyzed using logistic regression with terms for treatment and analysis center. If the treatment-by-analysis center interaction was significant at alpha level 0.10, then the effect was included in the model, otherwise it was removed. Missing data were handled using MCMC multiple imputation similarly to the lesion count endpoints, except using logistic regression rather than ANCOVA.

As sensitivity analyses, the change in lesion count endpoints were analyzed using repeated measures ANCOVA with terms for treatment analysis center, visit, and baseline lesion count. A second sensitivity analysis used model-based multiple imputation with ANCOVA rather than

[10] Zar, JH. Biostatistical analysis. 2nd Edition. Englewood Cliffs, NJ: Prentice-Hall. Pg. 118-119. 1984.

MCMC. For EGSS success, the first sensitivity analysis was a repeated measures logistic regression model (generalized estimating equations) with terms for treatment, analysis center, and visit. A second sensitivity analysis used model-based multiple imputation via logistic regression.

The secondary and supportive endpoints were analyzed in the same way as the primary endpoints. All three coprimary endpoints needed to demonstrate statistical significance. The secondary endpoints were analyzed sequentially in the order listed above.

The intent-to-treat population was defined as all randomized subjects who receive study medication. The per protocol (PP) population is defined as all subjects in the intent-to-treat population except those subjects who failed any of the inclusion/exclusion criteria, took interfering concomitant medications, did not attend the Week 12 visit (unless due to an adverse event (AE) related to study treatment or documented lack of treatment effect), missed more than one postbaseline visit prior to Week 12, were noncompliant with the dosing regimen, or who were out of window at the Week 12 visit (-3 to +5 days).

The study was intended to enroll a minimum of five subjects per treatment arm per center. If too few subjects were enrolled at a center, then the subjects from the smallest center were combined with the center with the largest enrollment. This pooling procedure continued with the next smallest and next largest center until all analysis centers had a minimum of five subjects per arm.

Protocol Amendments

The development plan for tazarotene lotion, 0.045% was discussed with the FDA at a pre-IND meeting on 6/17/2015. An end-of-phase 2 meeting was scheduled for 12/6/2016. However, this meeting was cancelled by the Applicant after receipt of the preliminary comments because the comments were well understood. The Applicant submitted protocols for Trials 301 and 302 on 6/5/2017. The protocols were amended on 8/24/2017 do provide additional details on the use of allowable concomitant products. The amendment did not impact the study design, endpoints, or analysis.

8.1.2. Results of Trials 301 and 302

Compliance With Good Clinical Practices

The Applicant stated that all six clinical studies in their Arazlo development program were conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, and with Good Clinical Practice, as required by the US CFR applicable to clinical studies. For Financial Disclosure information, refer to Section 13.2 of this review.

Patient Disposition

Trial 301 enrolled 813 subjects (402 on tazarotene and 411 on vehicle) and Trial 302 enrolled 801 subjects (397 on tazarotene and 404 on vehicle). Approximately 13% of subjects in Trial 301 and 11% of subjects in Trial 302 discontinued. The most common reasons for discontinuation were loss to follow-up and subject request (Table 16).

Table 16: Disposition of Subjects in Trials 301 and 302

	Trial 301		Trial 302	
Disposition	**Tazarotene Lotion**	**Vehicle**	**Tazarotene Lotion**	**Vehicle**
Subjects randomized	402	411	397	404
Discontinued, n (%)	55 (14%)	55 (13%)	52 (13%)	38 (9%)
Lost to follow-up	22 (6%)	35 (9%)	23 (6%)	21 (5%)
Subject request	17 (4%)	11 (3%)	17 (4%)	12 (3%)
Withdrawal by parent or guardian	--	2 (<1%)	1 (<1%)	1 (<1%)
Adverse event	10 (3%)	2 (<1%)	9 (2%)	2 (<1%)
Pregnancy	3 (<1%)	3 (<1%)	--	--
Protocol violation	1 (<1%)	1 (<1%)	--	--
Other	2 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)

Source: pg. 47 of Study Report 301 and pg. 47 of Study Report 302 and reviewer analysis.

Protocol Violations/Deviations

Approximately 29% of tazarotene subjects and 28% of vehicle subjects in Trial 301 were excluded from the PP population due to protocol violations. Approximately 30% of tazarotene subjects and 28% of vehicle subjects in Trial 302 were excluded from the PP population due to protocol violations. The most common reasons for exclusion were not attending the Week 12 visit and Week 12 visit out of window (Table 17). Two subjects in Trial 301 received an incorrect treatment during at least one visit. Subject (b) (6) was randomized to vehicle and used vehicle treatment from Day 1 to Day 55 and Day 83 to 89, but received tazarotene lotion at the Week 8 visit and used tazarotene lotion from Day 57 to Day 76. The primary reason that this subject was excluded from the PP analysis set was due to noncompliance with dosing regimen (missing more than 5 consecutive doses); receiving the wrong treatment was a secondary reason. Subject (b) (6) was randomized to tazarotene lotion and used tazarotene lotion from Day 1 to Day 55, but received vehicle lotion at the Week 8 visit and used vehicle lotion from Day 56 to Day 84. The primary reason that this subject was excluded from the PP analysis set was having received the incorrect treatment during part of the study (classified as “other”).

Table 17: Per Protocol (PP) Analysis Set in Trials 301 and 302

	Trial 301		Trial 302	
Disposition	**Tazarotene Lotion N=402, n (%)**	**Vehicle N=411, n (%)**	**Tazarotene Lotion N=397, n (%)**	**Vehicle N=404, n (%)**
Subjects included in the PP analysis set	287 (71%)	297 (72%)	278 (70%)	293 (73%)
Subjects excluded from the PP analysis set	115 (29%)	114 (28%)	119 (30%)	111 (28%)
Primary reason for exclusion				
No postbaseline safety evaluation	10 (3%)	12 (3%)	10 (3%)	12 (3%)
Violated inclusion/exclusion criteria	13 (3%)	7 (2%)	3 (1%)	13 (3%)
Used an interfering Con Med	12 (3%)	15 (4%)	16 (4%)	16 (4%)
Did not attend Week 12 visit	31 (8%)	38 (9%)	32 (8%)	23 (6%)
Not compliant with dosing regimen	13 (3%)	6 (2%)	22 (6%)	10 (3%)
Week 12 visit out of window	35 (9%)	36 (9%)	36 (9%)	37 (9%)
Other	1 (<1%)	--	--	--

Source: pg. 48 of Study Report 301 and pg. 48 of Study Report 302 and reviewer analysis.
Note: for subjects with more than one reason for exclusion, the primary reason was assigned within the order listed in the table.

Table of Baseline Demographic Characteristics

Baseline demographics were generally balanced across the treatment groups in the two studies (Table 18). Although the inclusion criteria allowed enrollment of subjects as young as 9 years, all subjects in the two studies were at least 10 years old, with 1.7% of subjects aged 10 to 11 years. The mean age was 20 years. Approximately 66% of subjects were female, 74% were white, and 22% were Hispanic/Latino.

Table 18: Demographic Characteristics of Subjects in Trial 301 and 302

	Trial 301		Trial 302	
Characteristic	**Tazarotene Lotion N=402**	**Vehicle N=411**	**Tazarotene Lotion N=397**	**Vehicle N=404**
Age (years)				
Mean	20.8	20.4	20.1	20.5
Range	10 to 50	10 to 65	10 to 54	10 to 53
9-11 years	8 (2%)	9 (2%)	6 (2%)	4 (1%)
12-17 years	158 (39%)	163 (40%)	172 (43%)	164 (41%)
18+ years	236 (59%)	239 (58%)	221 (55%)	236 (58%)
Gender, n (%)				
Female	280 (70%)	271 (66%)	251 (63%)	262 (65%)
Male	122 (30%)	140 (34%)	146 (37%)	142 (35%)
Race, n (%)				
White	293 (73%)	297 (72%)	298 (75%)	303 (75%)
Black or Afric.-Amer.	76 (19%)	83 (20%)	49 (12%)	54 (13%)
Am. Ind./ AK Native	3 (1%)	3 (1%)	6 (2%)	3 (1%)
Asian	15 (4%)	13 (3%)	27 (7%)	23 (6%)
Native HI/ Pac. Isl.	--	2 (<1%)	--	2 (<1%)
Other	15 (4%)	13 (3%)	17 (4%)	19 (5%)
Ethnicity, n (%)				
Hispanic or Latino	67 (17%)	76 (18%)	101 (25%)	108 (27%)
Not Hispanic or Latino	335 (83%)	335 (82%)	296 (75%)	296 (73%)

Source: pg. 50 of Study Report 301 and pg. 50 of Study Report 302 and reviewer analysis.
Percentages may not sum to 100% due to rounding

Other Baseline Characteristics

Baseline disease characteristics were balanced across treatment arms. Subjects in the two studies had a mean of approximately 41 noninflammatory lesions and 28 noninflammatory lesions at baseline. Approximately 91% of subjects were classified as moderate on the EGSS in both studies (Table 19).

Table 19: Baseline Disease Characteristics

	Trial 301		Trial 302	
Characteristic	**Tazarotene Lotion N=402**	**Vehicle N=411**	**Tazarotene Lotion N=397**	**Vehicle N=404**
Noninflammatory lesions				
Mean (SD)	41.1 (15.7)	40.7 (16.3)	41.8 (17.9)	40.6 (16.3)
Median	36	34	36	35
Range	25 to 100	25 to 99	25 to 100	23 to 98
Inflammatory lesions				
Mean (SD)	28.5 (7.0)	28.1 (7.0)	28.0 (7.3)	27.9 (7.1)
Median	26	26	26	26
Range	20 to 50	20 to 50	20 to 50	20 to 50
EGSS, n (%)				
3 – moderate	368 (92%)	384 (93%)	358 (90%)	357 (88%)
4 - severe	34 (9%)	27 (7%)	39 (10%)	47 (12%)

Source: pg. 51 of Study Report 301 and pg. 51 of Study Report 302 and reviewer analysis.
Percentages may not sum to 100% due to rounding
Abbreviations: EGSS= Evaluator's Global Severity Score, SD=standard deviation

Efficacy Results – Primary Endpoint

In Trials 301 and 302, tazarotene lotion was superior to vehicle for the three coprimary efficacy endpoints of absolute change in noninflammatory lesion count, absolute change in inflammatory lesion count and EGSS success at Week 12. The results are presented in Table 20.

The final primary analyses for the primary endpoints depended on the results of a skewness test (lesion count endpoints only) and whether the treatment-by-analysis center interactions were significant. Zar's test for skewness was statistically significant for both change in lesion count endpoints (noninflammatory and inflammatory) in both studies (P<0.001). Thus, the primary analysis for the change in lesion count endpoints was based on the ranks in all four cases. Treatment-by-analysis center interactions were not significant in any of the ranked ANCOVA analyses, however, the unranked analysis for the change in noninflammatory lesions was significant in Trial 302.

Multiple imputation datasets were used for all key analyses of the three primary endpoints (skewness tests, primary analyses based on ranks, and supportive analyses based on the unranked data values). The p-values from unranked analyses for the absolute change in noninflammatory and inflammatory lesions were similar to the p-values for the ranked analyses in both studies (P<0.001).

Table 20: Primary Efficacy Endpoints (Trials 301 and 302)

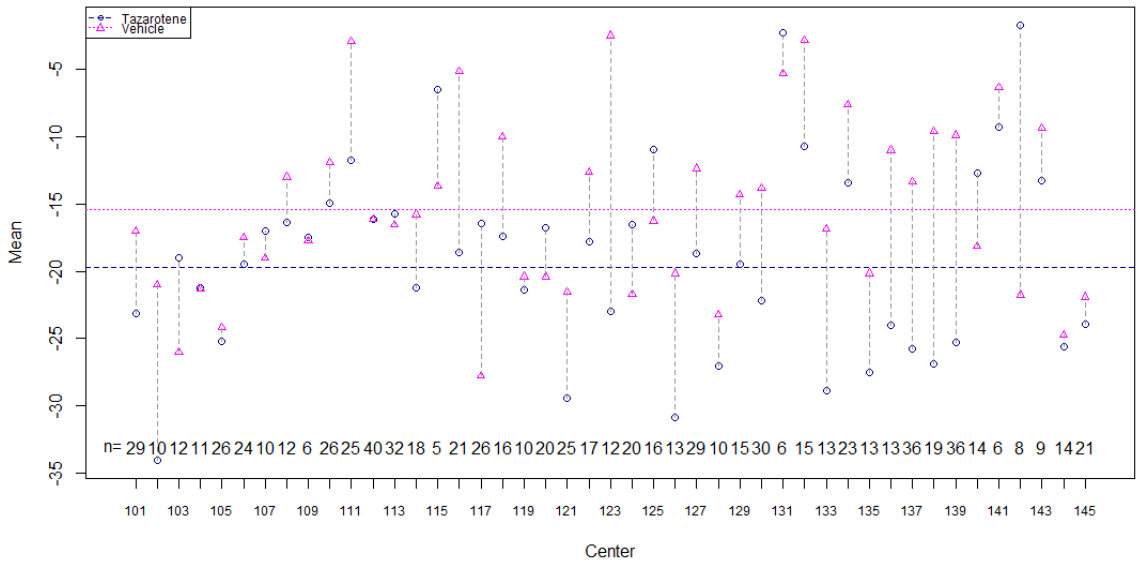
	Trial 301		Trial 302	
Endpoint	**Tazarotene Lotion N=402**	**Vehicle N=411**	**Tazarotene Lotion N=397**	**Vehicle N=404**
Noninflammatory lesions				
Baseline mean	41.1 (15.7)	40.7 (16.3)	41.8 (17.9)	40.6 (16.3)
Week 12 mean	19.9 (16.2)	24.2 (17.5)	16.8 (14.8)	24.2 (20.9)
LSMean change	-21.0 (14.7)	-16.4 (14.5)	-24.6 (15.3)	-16.6 (15.5)
p-value	<0.001		<0.001	
Difference (95% CI)	-4.5 (-6.4, -2.6)		-8.1 (-10.2, -5.9)	
Inflammatory lesions				
Baseline mean	28.5 (7.0)	28.1 (7.0)	28.0 (7.3)	27.9 (7.1)
Week 12 mean	12.8 (9.7)	15.9 (12.3)	11.0 (9.5)	14.1 (10.5)
LSMean change	-15.6 (10.4)	-12.4 (10.4)	-16.7 (9.5)	-13.4 (9.4)
p-value	<0.001		<0.001	
Difference (95% CI)	-3.3 (-4.7, -1.9)		-3.2 (-4.5, -1.9)	
EGSS				
Success	25.5%	13.0%	29.6%	17.3%
p-value	<0.001		<0.001	
Difference (95% CI)	12.5% (7.1%, 17.9%)		12.3% (6.5%, 18.1%)	

Source: pg. 53, 97-98,105-106 of Study Report 301 and pg. 53, 96-97,104-105 of Study Report 302 and reviewer analysis.
Abbreviations: CI=confidence interval, EGSS= Evaluator's Global Severity Score, LSMean=least squares mean

Treatment-by-Center Interactions

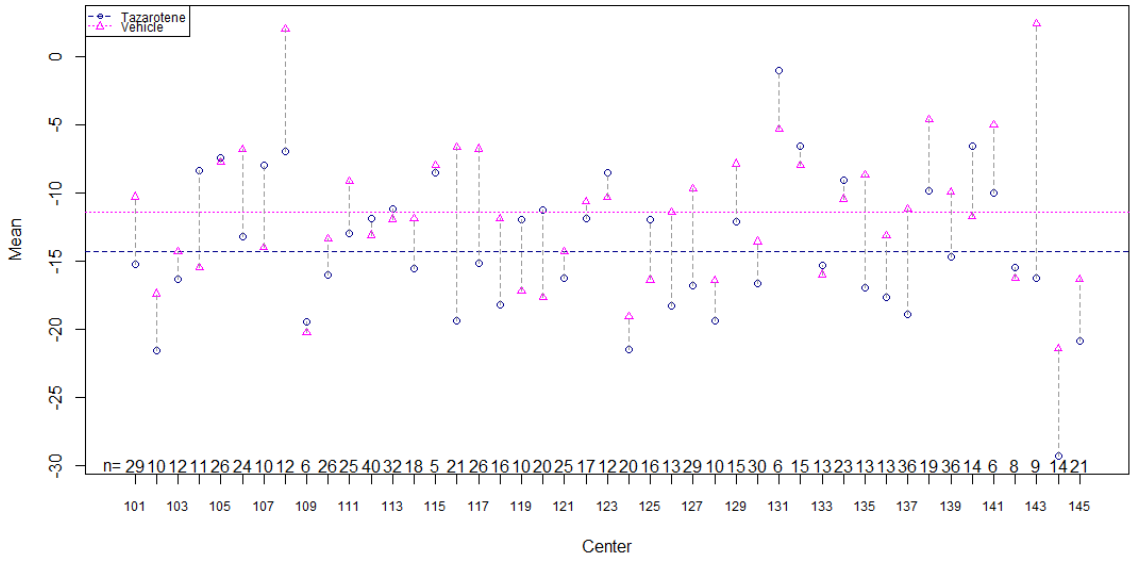
Trial 301 had 45 centers that were combined into 42 analysis centers. Trial 302 had 44 centers that were combined into 41 analysis centers. Treatment-by-analysis center interactions were not significant in any of the ranked ANCOVA analyses or the EGSS success analyses, however, the unranked analysis for the change in noninflammatory lesions was significant in Trial 302. Because none of the treatment-by-center interactions were significant for the primary analyses (ranked ANCOVA or logistic regression for EGSS success), the Applicant did not conduct additional analyses to identify centers with extreme results. The results by center for the three coprimary endpoints are presented in Figure 4 through Figure 9.

Figure 4: Absolute Change in Noninflammatory Lesions by Center (Trial 301)



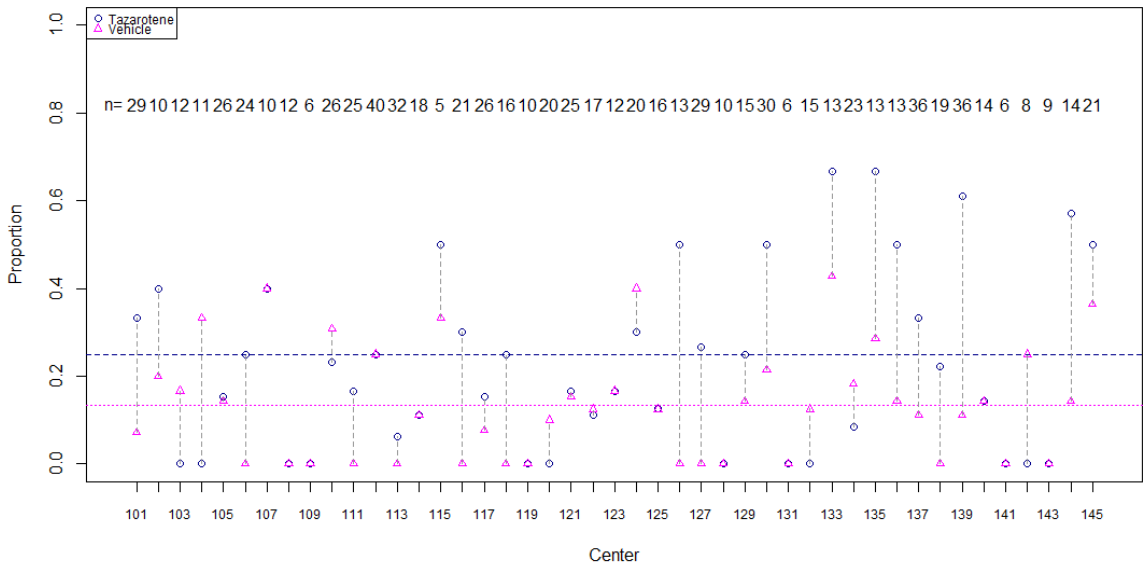
Source: Reviewer analysis.

Figure 5: Absolute Change in Inflammatory Lesions by Center (Trial 301)



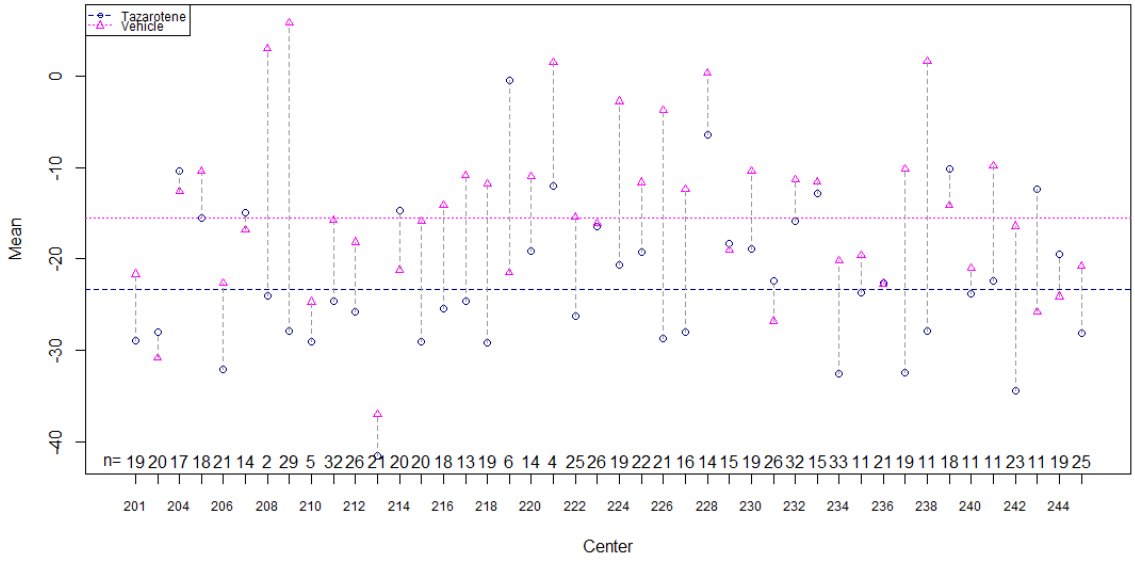
Source: Reviewer analysis.

Figure 6: EGSS Success by Center (Trial 301)



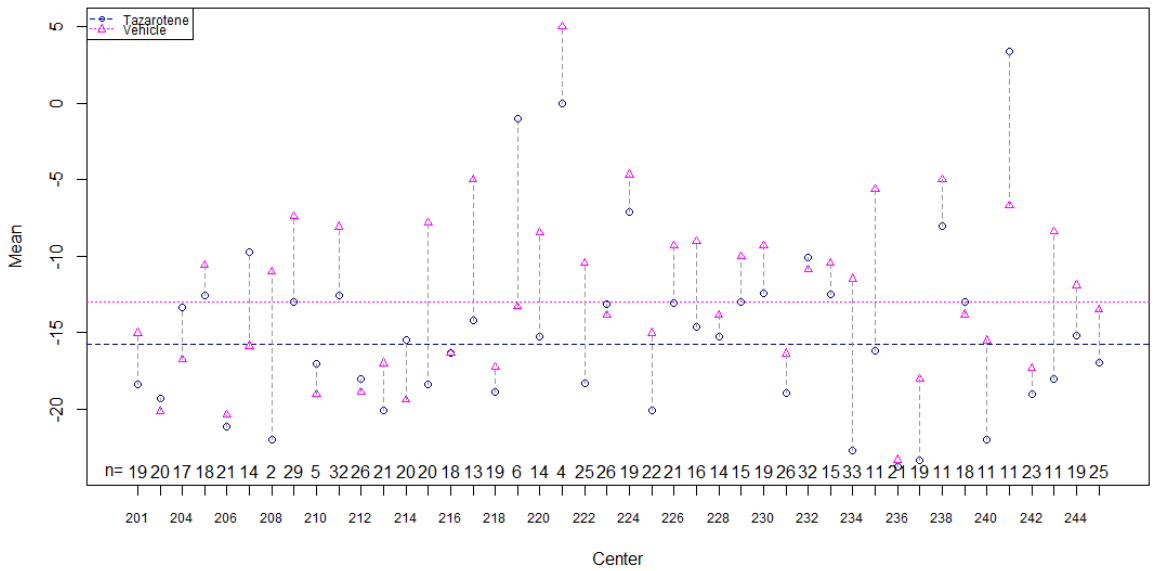
Source: Reviewer analysis.
Abbreviations: EGSS= Evaluator's Global Severity Score

Figure 7: Absolute Change in Noninflammatory Lesions by Center (Trial 302)



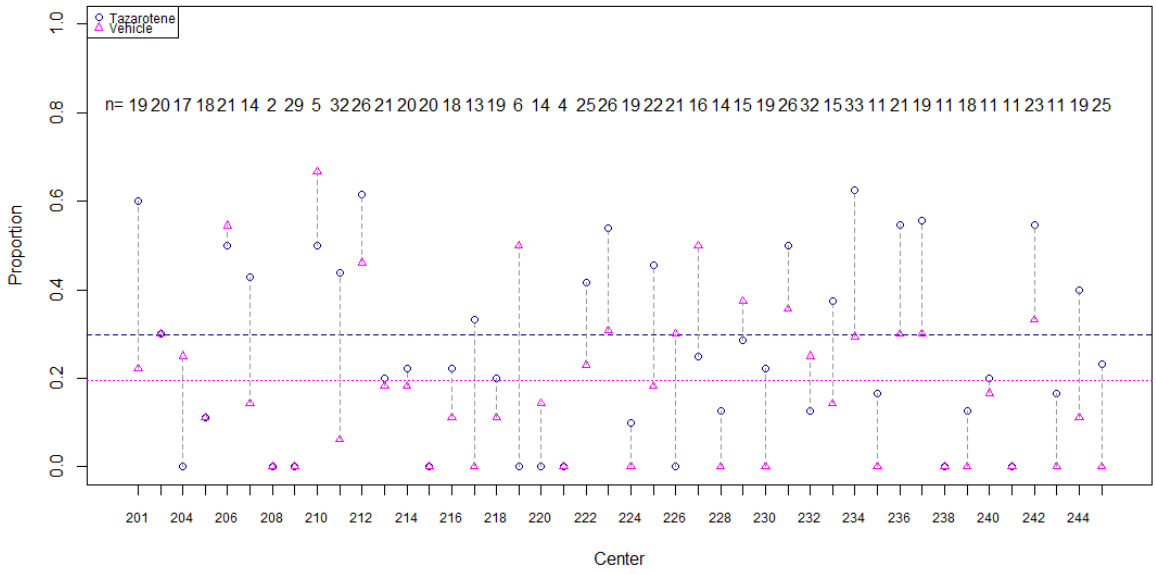
Source: Reviewer analysis.

Figure 8: Absolute Change in Inflammatory Lesions by Center (Trial 302)



Source: Reviewer analysis.

Figure 9: EGSS Success by Center (Trial 302)



Source: Reviewer analysis.
Abbreviations: EGSS= Evaluator's Global Severity Score

Missing Data Handling

The primary method of handling missing data were MCMC multiple imputation. As sensitivity analyses, the primary endpoints were analyzed using repeated measures (ANCOVA for the change in lesion count endpoints and logistic regression model (generalized estimating

equations) for EGSS success). A second sensitivity analysis used model-based multiple imputation using ANCOVA or logistic regression rather than MCMC. The Applicant's sensitivity analyses produced results similar to the primary analyses. All p-values for these sensitivity analyses were <0.001 (Table 21).

Table 21: Sensitivity Analysis Results

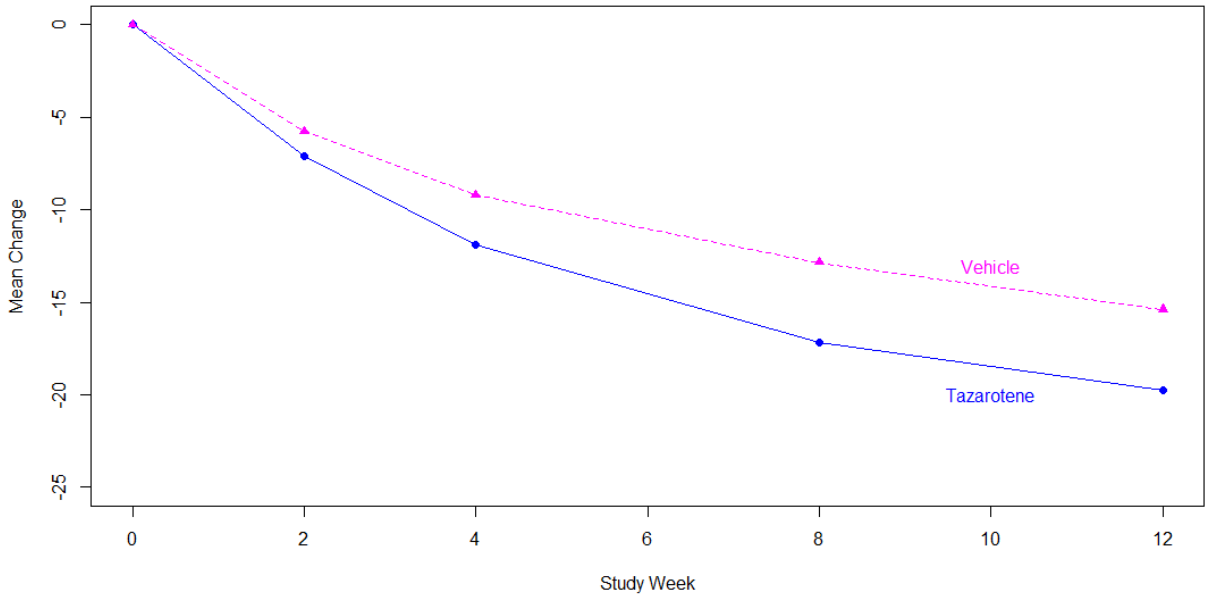
	Trial 301		Trial 302	
Endpoint	**Tazarotene Lotion N=402**	**Vehicle N=411**	**Tazarotene Lotion N=397**	**Vehicle N=404**
Noninflammatory lesions				
Repeated measures	-21.0 (13.3)	-16.3 (13.2)	-24.8 (14.8)	-16.3 (14.6)
Model MI	-21.1 (14.8)	-16.5 (14.6)	-24.7 (15.5)	-16.3 (15.3)
Inflammatory lesions				
Repeated measures	-15.4 (9.7)	-12.3 (9.7)	-16.6 (9.3)	-13.5 (9.1)
Model MI	-15.6 (10.5)	-12.5 (10.3)	-16.6 (9.4)	-13.5 (9.3)
EGSS				
Repeated measures	28.1%	14.4%	33.5%	21.2%
Model MI	26.8%	13.0%	29.8%	17.6%

Source: pg. 133-135 of Study Report 301 and pg. 132-134 of Study Report 302 and reviewer analysis.
Abbreviations: EGSS= Evaluator's Global Severity Score, MI=Multiple Imputation

Efficacy Results Over Time

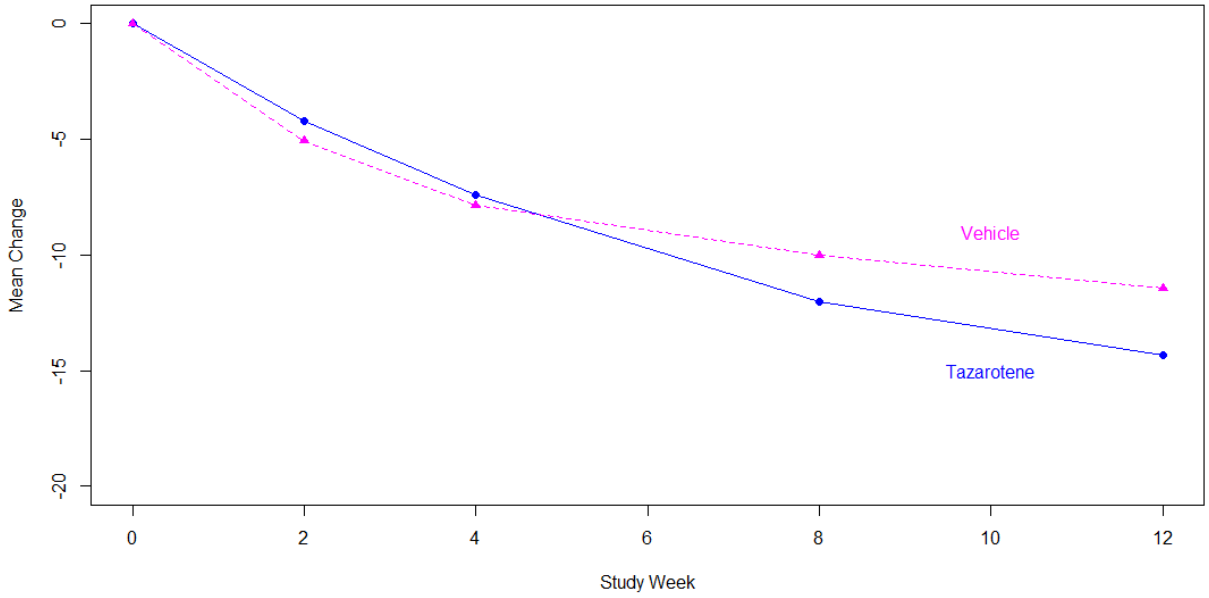
The efficacy results for the tazarotene and vehicle treatment arms gradually separated over time through Week 12. See Figure 10 through Figure 15.

Figure 10: Change in Noninflammatory Lesions Over Time (Trial 301)



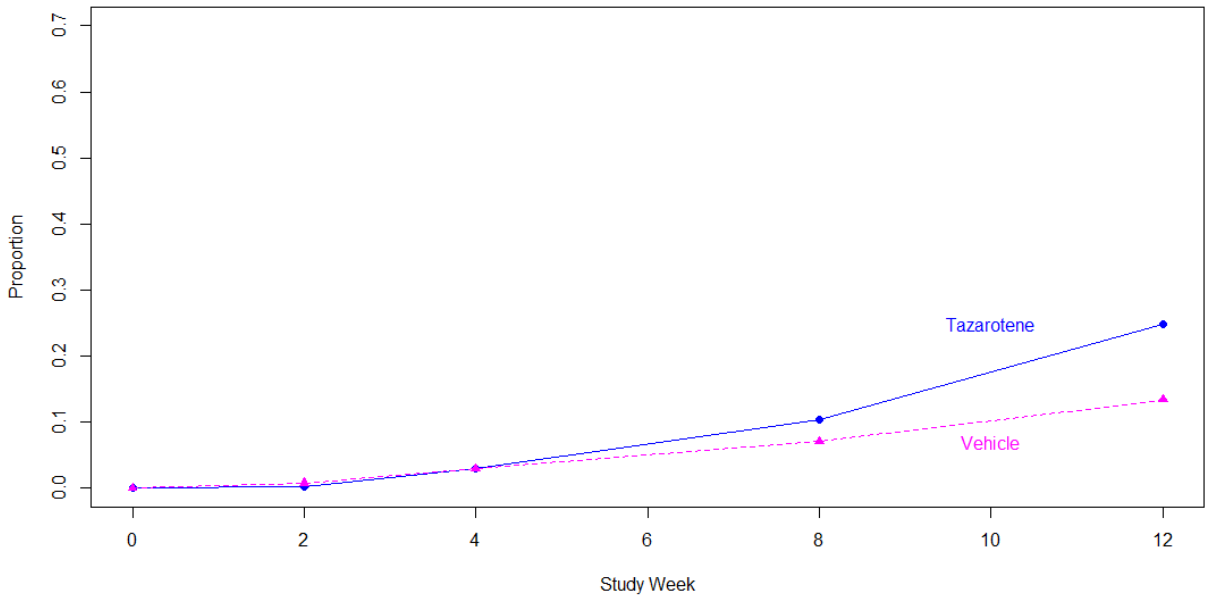
Source: Reviewer analysis.

Figure 11: Change in Inflammatory Lesions Over Time (Trial 301)



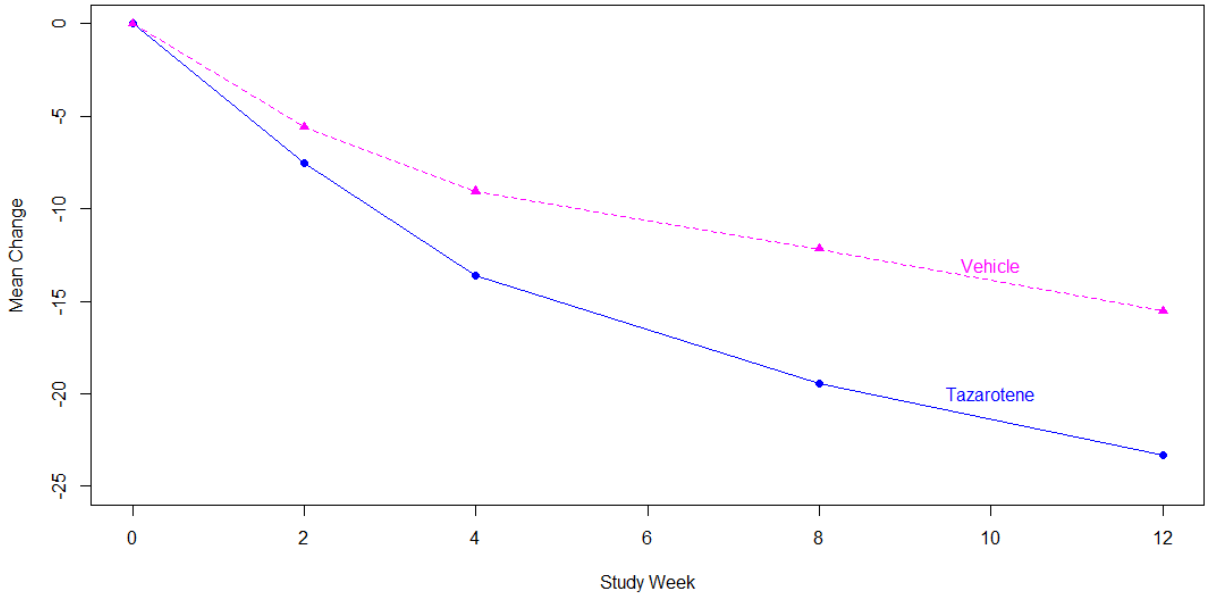
Source: Reviewer analysis.

Figure 12: EGSS Success Over Time (Trial 301)



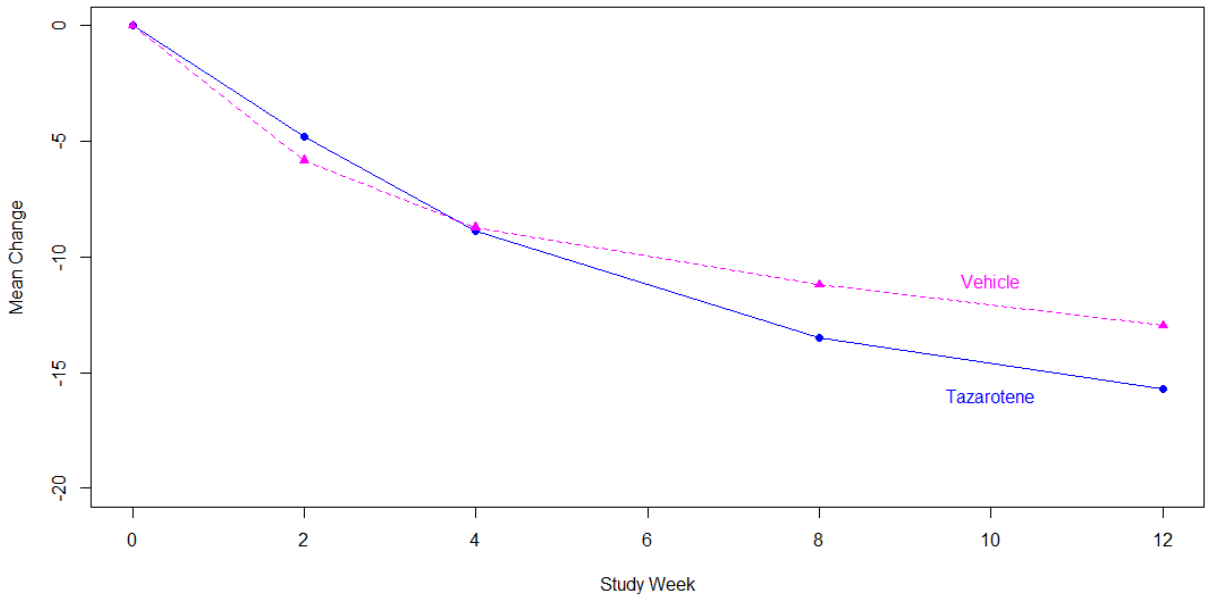
Source: Reviewer analysis.
Abbreviations: EGSS= Evaluator's Global Severity Score

Figure 13: Change in Noninflammatory Lesions Over Time (Trial 302)



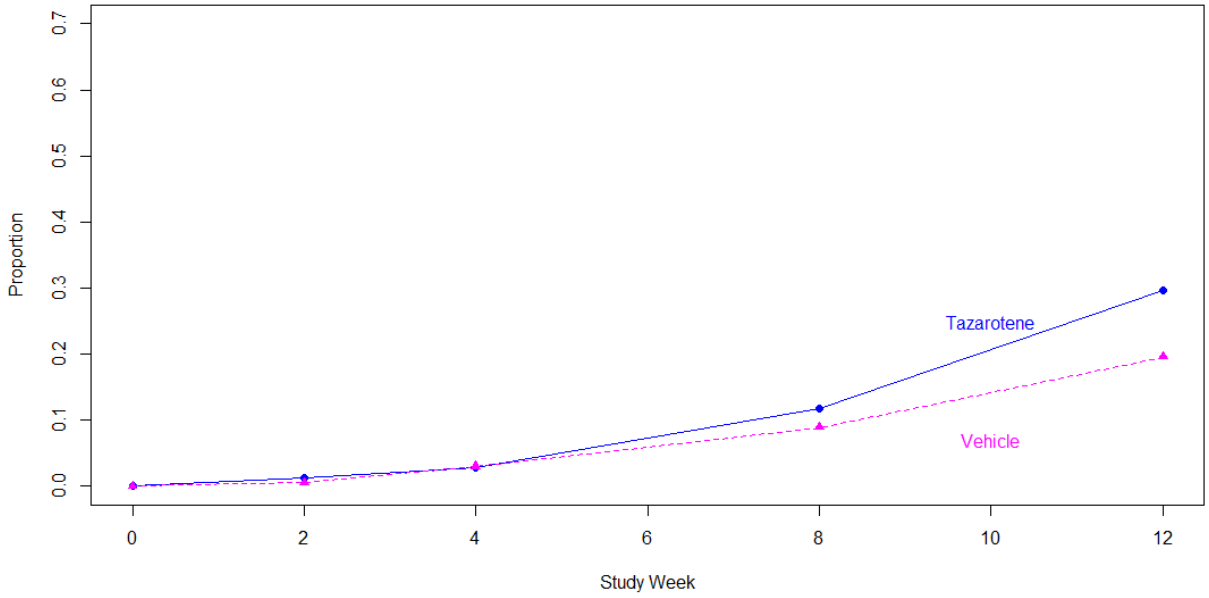
Source: Reviewer analysis.

Figure 14: Change in Inflammatory Lesions Over Time (Trial 302)



Source: Reviewer analysis.

Figure 15: EGSS Success Over Time (Trial 302)



Source: Reviewer analysis.
Abbreviations: EGSS= Evaluator's Global Severity Score

Efficacy Results – Secondary and Supportive Endpoints

Trials 301 and 302 included 7 secondary endpoints related to the primary endpoints. These endpoints were analyzed in sequential order and are:

- The percent change in noninflammatory lesions at Week 12
- The percent change in inflammatory lesions at Week 12
- At least 2 grades improvement on the EGSS from baseline to Week 12
- The percent change in noninflammatory lesions at Week 8
- The percent change in inflammatory lesions at Week 8
- The percent change in noninflammatory lesions at Week 4
- The percent change in inflammatory lesions at Week 4

The results for these endpoints are presented in Table 22. These endpoints are all closely related to the three coprimary endpoints. The endpoints are assessed using the same statistical methodology as the primary endpoints. The endpoints based on lesion counts were evaluated using ranked ANOVA. Evaluated in the prespecified order, all of the secondary endpoints are statistically significant except for the final endpoint of percent change in inflammatory lesions at Week 4 in both studies.

Table 22: Secondary Efficacy Endpoint Results

	Trial 301		Trial 302	
Endpoint	**Tazarotene Lotion N=402**	**Vehicle N=411**	**Tazarotene Lotion N=397**	**Vehicle N=404**
Week 12				
Percent change noninflammatory	-51.4 (36.4)	-41.5 (35.2)	-60.0 (34.7)	-41.6 (35.2)
p-value		<0.001		<0.001
Percent change inflammatory	-55.5 (36.5)	-45.7 (37.0)	-59.5 (33.4)	49.0 (33.0)
p-value		<0.001		<0.001
At least 2-grade reduction in EGSS	28.3%	15.2%	34.5%	20.9%
p-value		<0.001		<0.001
Week 8				
Percent change noninflammatory	-43.1 (32.4)	-34.3 (31.7)	-48.5 (36.5)	-30.9 (36.8)
p-value		<0.001		<0.001
Percent change inflammatory	-45.3 (34.4)	-39.0 (34.5)	-50.4 (32.9)	-41.7 (32.9)
p-value		0.015		<0.001
Week 4				
Percent change noninflammatory	-29.4 (32.4)	-23.3 (31.8)	-35.0 (32.8)	24.1 (33.0)
p-value		0.004		<0.001
Percent change inflammatory	-27.3 (35.0)	-29.7 (34.4)	-32.3 (32.9)	-31.6 (33.0)
p-value		0.735		0.435

Source: pg. 54 of Study Report 301 and pg. 54 of Study Report 302 and reviewer analysis.
Abbreviations: EGSS= Evaluator's Global Severity Score

Findings in Special/Subgroup Populations

Treatment effects were generally consistent across age, gender, race, ethnicity, and geographic region subgroups, with some variability from the smaller subgroups, such as race. The studies enrolled few subjects in the American Indian/Alaskan native and Native Hawaiian/Pacific Islander groups. Treatment effects were also consistent across baseline disease severity (moderate versus severe on the EGSS). See Table 23 and Table 24.

Table 23: Efficacy Results by Subgroup (Trial 301)

	Change in Noninflammatory Lesions		Change in Inflammatory Lesions		EGSS Success	
Subgroup	**Tazarotene Lotion N=402**	**Vehicle N=411**	**Tazarotene Lotion N=402**	**Vehicle N=411**	**Tazarotene Lotion N=402**	**Vehicle N=411**
Age (years)						
9-17 (N=194/194)	-20.5	-14.3	-15.3	-10.2	21.8%	7.5%
18+ (N=208/217)	-21.9	-18.4	-16.0	-14.1	32.4%	20.8%
Gender						
Female (N=280/271)	-22.2	-17.3	-15.8	-13.5	28.9%	17.1%
Male (N=122/140)	-18.9	-14.9	-15.3	-9.9	23.7%	9.4%
Race						
White (N=293/297)	-22.1	-15.9	-15.5	-14.9	21.9%	19.2%
Black /Afr.-Am. (N=76/83)	-19.5	-17.8	-16.0	-11.5	30.5%	13.0%
Am. Ind./ AK Nat. (N=3/3)	-12.4	-22.4	-13.2	-11.2	2.6%	9.8%
Asian (N=15/13)	-13.6	17.9	-11.2	-13.7	6.8%	21.0%
Native HI/ Pac. Isl. (N=0/2)	--	-40.0	--	-12.0	--	0%
Other (N=15/13)	-23.1	-14.9	-13.6	-12.4	17.0%	17.2%
Ethnicity						
Hispanic or Latino (N=67/76)	-20.1	-16.5	-17.4	-12.0	32.2%	13.2%
Not Hisp. or Latino (N=335/335)	-21.5	-16.5	-15.3	-12.3	26.3%	14.8%
Baseline severity						
Moderate (N=368/384)	-21.3	-16.3	-15.5	-12.2	29.1%	15.0%
Severe (N=34/27)	-21.0	-19.0	-16.7	-13.4	7.2%	7.9%

Source: pg. 135-142 of Study Report 301 and reviewer analysis.
Means are calculated across the multiply imputed datasets.
The notation N=XXX/YYY indicates the sample size for tazarotene lotion and vehicle, respectively
Abbreviations: EGSS=Evaluator's Global Severity Score

Table 24: Efficacy Results by Subgroup (Trial 302)

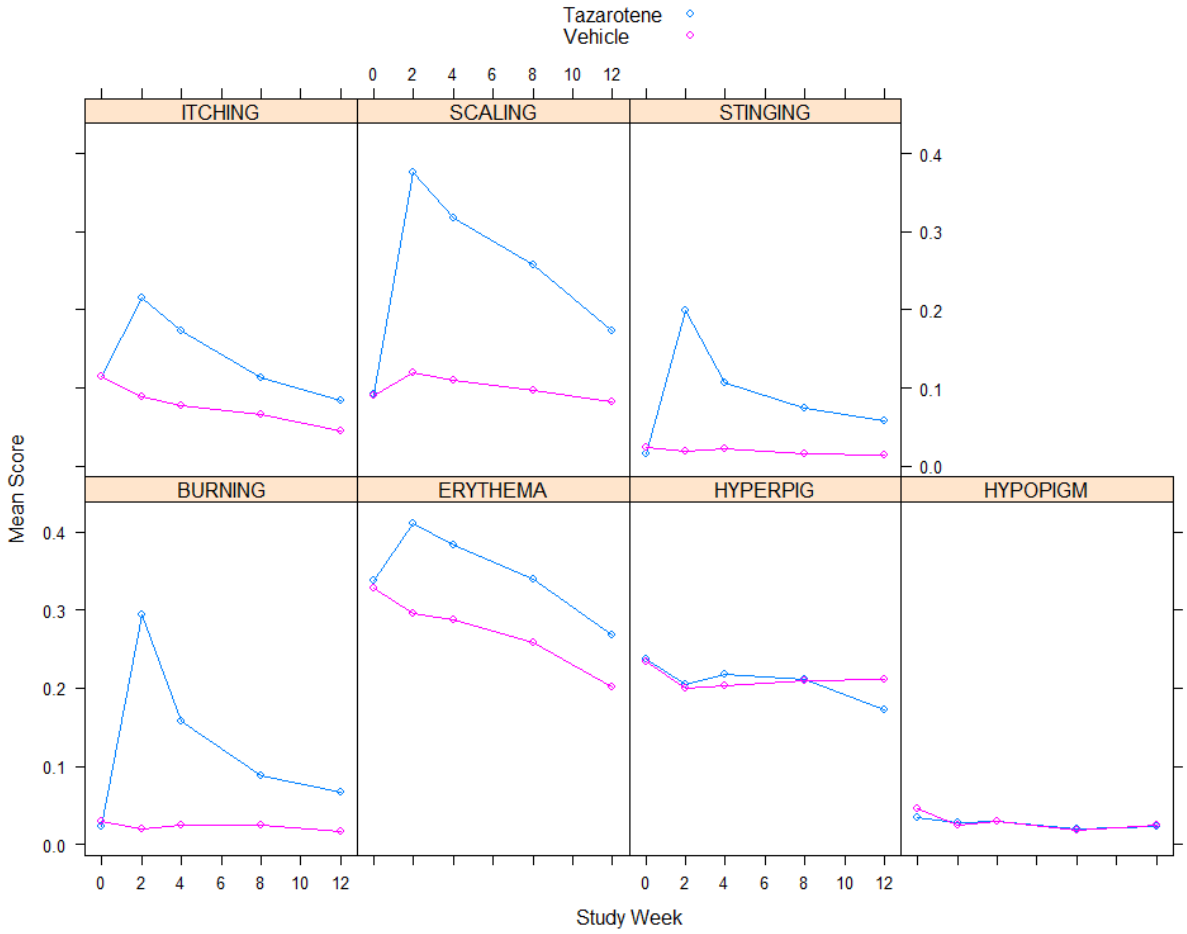
	Change in Noninflammatory Lesions		Change in Inflammatory Lesions		EGSS Success	
	Tazarotene Lotion	Vehicle	Tazarotene Lotion	Vehicle	Tazarotene Lotion	Vehicle
Subgroup	**N=397**	**N=404**	**N=397**	**N=404**	**N=397**	**N=404**
Age (years)						
9-17 (N=178/168)	-25.0	-13.3	-15.3	-12.4	24.8%	13.5%
18+ (N=219/236)	-25.0	-18.6	-18.4	-14.7	40.5%	26.8%
Gender						
Female (N=251/262)	-25.2	-14.0	-16.4	-12.7	26.2%	15.9%
Male (N=146/142)	-24.9	-17.7	-17.3	-14.3	37.7%	24.1%
Race						
White (N=298/303)	-23.4	-15.8	-16.6	-13.5	31.8%	20.4%
Black /Afr.-Am. (N=49/54)	-26.2	-16.5	-18.2	-14.7	41.1%	19.8%
Am. Ind./ AK Nat. (N=6/3)	-41.3	-21.4	-21.7	-15.8	33.3%	37.6%
Asian (N=27/23)	-28.0	-16.7	-18.3	-15.7	40.7%	39.1%
Native HI/ Pac. Isl. (N=0/2)	--	-40.3	--	-9.4	--	6.4%
Other (N=17/19)	-38.5	-22.1	-16.6	-13.4	29.4%	17.1%
Ethnicity						
Hispanic or Latino (N=101/108)	-24.7	-19.4	-17.8	-16.3	35.3%	29.9%
Not Hisp. or Latino (N=296/296)	-25.1	-15.3	-16.7	-12.8	32.9%	18.1%
Baseline severity						
Moderate (N=358/357)	-24.2	-16.0	-16.4	-13.6	34.4%	22.3%
Severe (N=39/47)	-33.1	-19.4	-22.9	-14.6	25.2%	13.1%

Source: pg. 135-142 of Study Report 302 and reviewer analysis.
Means are calculated across the multiply imputed datasets.
The notation N=XXX/YYY indicates the sample size for tazarotene lotion and vehicle, respectively
Abbreviations: EGSS=Evaluator's Global Severity Score

Local Cutaneous Safety and Tolerability Assessments

Local skin reactions and tolerability were actively assessed on 4-point scales (0=none, 1=mild, 2=moderate, 3=severe) at baseline and Weeks 2, 4, 8, and 12. The mean scores for itching, scaling, stinging, burning, and erythema were higher on the tazarotene arm than the vehicle arm and generally peaked at Week 2 and decreased thereafter. The mean scores for hyperpigmentation and hypopigmentation were similar on the tazarotene and vehicle arms. The mean scores were <0.5 at each visit for all signs and symptoms. See Figure 16.

Figure 16: Mean Local Cutaneous Safety and Tolerability Assessments by Visit (Trials 301 and 302 Combined)



Source: reviewer analysis.

The maximum severity experienced postbaseline by a subject for each sign and symptom is presented in Table 25. Most subjects did not experience cutaneous tolerability events, and of those subjects who did experience cutaneous tolerability events, the events were usually of mild or moderate severity. Approximately 0.6% of tazarotene subjects and 0.25% of vehicle subjects in the safety population did not have any local cutaneous safety and tolerability assessments.

Table 25: Maximum Postbaseline Local Cutaneous Safety and Tolerability Assessments (Trials 301 and 302 Combined, Safety Population)

	Tazarotene Lotion N=774[a]				Vehicle N=789[a]			
Symptom/Sign	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
Erythema	51%	37%	12%	<1%	62%	32%	6%	<1%
Scaling	49%	40%	10%	<1%	77%	22%	1%	0%
Hypopigmentation	96%	4%	<1%	0%	96%	4%	<1%	0%
Hyperpigmentation	75%	19%	7%	<1%	76%	17%	6%	<1%
Itching	71%	22%	7%	<1%	86%	11%	2%	<1%
Burning	70%	20%	9%	1%	94%	5%	<1%	<1%
Stinging	78%	16%	6%	<1%	95%	4%	<1%	0%

Source: Reviewer analysis
[a] Subjects with at least one local cutaneous safety and tolerability assessment (5 subjects on the tazarotene arm and 2 subjects on the vehicle arm did not have any local cutaneous safety and tolerability assessments.

Data Quality and Integrity

The databases required minimal data management prior to performing analyses. The Applicant submitted statistical programs for generating the multiple imputations for missing data. No clinical site inspections were requested for this application.

8.1.3. Study 201

Trial Design and Endpoints

Study V01-123A-201 (referred to as Study 201) was a Phase 2, randomized, double-blind study to compare the efficacy and safety of tazarotene lotion 0.045% to Tazorac (tazarotene) cream 0.1%, vehicle lotion, and vehicle cream. The objective of the study was to establish a component of the clinical bridge to Tazorac Cream. Only a high-level summary of the study design and efficacy results will be presented in this review.

The trial enrolled subjects 12 years of age and older with moderate to severe acne. Subjects were to have a score of 3 (moderate) or 4 (severe) on the EGSS. Subjects also were to have 20 to 40 facial inflammatory lesions, 20 to 100 facial noninflammatory lesions, and no more than 2 facial nodules.

The trial was designed to randomize approximately 210 subjects in a 2:2:1:1 ratio to tazarotene lotion, tazarotene cream, vehicle lotion, or vehicle cream in the United States. Subject applied treatment once daily for 12 weeks. Subjects were evaluated at screening, baseline, and Weeks 2, 4, 8, and 12. Efficacy was assessed using the EGSS and inflammatory and noninflammatory lesion counts.

The coprimary efficacy endpoints were:

- The absolute change in noninflammatory lesions at Week 12
- The absolute change in inflammatory lesions at Week 12
- Clear or almost clear on the EGSS with at least 2 grades improvement at Week 12

The absolute changes in lesion counts were to be analyzed with ANCOVA with terms for treatment and baseline lesion count as a covariate Success on the EGSS was to be analyzed using the Cochran-Mantel-Haenszel test. These analyses compared tazarotene lotion versus the combined lotion and cream vehicle group. No other formal comparisons were made. Missing data were handled using last observation carried forward. The sample size was selected based on clinical considerations and the study was not powered for efficacy.

Study Results

The protocol stated that the formal comparisons (with p-value) would be made only between tazarotene lotion and the combined vehicle arm. The results for the three coprimary endpoints are presented in Table 26. For the lesion count endpoints, the table presents the means for all four treatment arms and the least squares means (adjusted for baseline value covariate) for the tazarotene lotion and combined vehicle arms. The results on the two vehicle arms are similar. The results on the tazarotene lotion and tazarotene cream arm are also similar, though the Applicant did not conduct any formal comparisons. The nominal p-values for the tazarotene lotion versus combined vehicle for the change in inflammatory and noninflammatory lesions were <0.05. The p-value for success on the EGSS was >0.05.

Table 26: Efficacy Results (Study 201)

Endpoint	Tazarotene Lotion, 0.045% N=69	Tazarotene Cream, 0.1% N=72	Lotion Vehicle N=34	Cream Vehicle N=35	Combined Vehicle N=69	P-value[a]
Inflammatory						
Mean (SD)	-18.1 (9.0)	-16.8 (11.0)	-14.3 (8.7)	-13.7 (8.7)	-14.0 (8.6)	
LSMean (SD)	-17.8 (8.2)				-14.3 (8.2)	0.013
Noninflamm.						
Mean (SD)	-21.6 (14.0)	-20.3 (13.7)	-12.6 (14.9)	-13.6 (12.4)	-13.1 (13.6)	
LSMean (SD)	-21.3 (12.3)				-13.4 (12.3)	<0.001
EGSS Success						
Percent	18.8%	16.7%	11.8%	8.6%	10.1%	0.148

Source: pg. 63, 91, 99, and 107 of Study Report 201 and reviewer analysis.
[a] For the comparison of tazarotene lotion vs. combined vehicle.
Abbreviations: EGSS=Evaluator's Global Severity Score, LSMean=least squares mean, SD=standard deviation

8.1.4. Assessment of Efficacy Across Trials and Integrated Assessment of Effectiveness

Primary Endpoints

The results for the primary efficacy endpoints were consistent across Trials 301 and 302. Both studies demonstrated statistical significance for the three coprimary endpoints of change in noninflammatory lesions, change in inflammatory lesions, and EGSS success at Week 12 in both studies. The efficacy results are summarized in Table 27.

Table 27: Primary Efficacy Endpoints (Trials 301 and 302)

	Trial 301		Trial 302	
Endpoint	**Tazarotene Lotion N=402**	**Vehicle N=411**	**Tazarotene Lotion N=397**	**Vehicle N=404**
Noninflammatory lesions				
LSMean Change	-21.0 (14.7)	-16.4 (14.5)	-24.6 (15.3)	-16.6 (15.5)
p-value	<0.001		<0.001	
Difference (95% CI)	-4.5 (-6.4, -2.6)		-8.1 (-10.2, -5.9)	
Inflammatory lesions				
LSMean Change	-15.6 (10.4)	-12.4 (10.4)	-16.7 (9.5)	-13.4 (9.4)
p-value	<0.001		<0.001	
Difference (95% CI)	-3.3 (-4.7, -1.9)		-3.2 (-4.5, -1.9)	
EGSS				
Success	25.5%	13.0%	29.6%	17.3%
p-value	<0.001		<0.001	
Difference (95% CI)	12.5% (7.1%, 17.9%)		12.3% (6.5%, 18.1%)	

Abbreviations: CI=confidence interval, EGSS=Evaluator's Global Severity Score, LSMean=least squares mean, SD=standard deviation

The results for the secondary endpoints and subgroup analyses were supportive of the primary efficacy endpoints.

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary review of safety for Arazlo Lotion relied on the evaluation of pooled safety data from two Phase 3 controlled trials (V01-123A-301 and V01-123A-302) that comprised the Applicant's ISS database and shared identical inclusion/exclusion criteria, study designs, dosing regimen, and primary and secondary efficacy endpoints.

The combined Phase 3 trials study population included a total of 1614 subjects age 9 years and above with moderate to severe acne vulgaris (defined as EGSS of 3 (moderate) or 4 (severe) on 5-point scale). Enrolled subjects had an inflammatory lesion count of 20 to 50, noninflammatory lesion count of 25 to 100, and ≤ 2 nodules. In both trials, subjects were randomized in a 1:1 ratio to receive Arazlo Lotion or vehicle lotion applied as a thin layer to the face, once daily in the evening, for 12 weeks.

The safety population for combined Phase 3 trials (ISS) included all randomized subjects who used the study drug at least once and provided at least 1 post-baseline evaluation. The ISS included 1570 pediatric and adult subjects. Investigators conducted safety assessments at screening, baseline, Weeks 2, 4, 8, and 12 visits.

The Applicant also submitted supportive safety data from a Phase 2 trial (201), a PK/Bioavailability maximal use study (501), and 2 dermal safety studies (101, 102).

To determine the safety profile of Arazlo Lotion, the review team analyzed the pooled data for exposure, demographics, baseline characteristics, TEAEs, SAEs, TEAEs leading to discontinuation, local skin reactions (scaling, erythema, hypopigmentation, and hyperpigmentation), tolerability assessments (itching, burning, and stinging), abbreviated physical examinations, clinical laboratory measurements (chemistry, hematology, urine or serum pregnancy tests for female subjects of child-bearing potential), and vital signs.

As there were no ongoing trials for Arazlo at the time of this NDA submission, the Applicant did not submit a 120-day safety update.

Because safety data are available for the LD (Tazorac Cream, 0.1%) for almost twenty years, the Applicant requested waivers for the conduct of the following studies to evaluate Arazlo Lotion:

- Long-term safety study
- Thorough QT study
- Phototoxicity and photoallergy studies.

In view of the limited systemic absorption of Arazlo Lotion and available referenced safety data from LD (Tazorac Cream, 0.1%), the Agency agreed to grant waivers for conducting photosensitivity/photoallergenicity studies and to grant waivers for conducting the long-term safety and Thorough QT (TQT) studies if the Applicant could establish a clinical bridge for Arazlo Lotion to the Reference Drug, Tazorac Cream, 0.1%. Refer to Section 8.2.4 of this review for further details about a waiver for TQT study.

During the pre-NDA meeting with the Applicant, the Agency agreed that the Applicant's statistical analysis plan for the ISS (to provide descriptive safety summaries for the pooled Phase 3 studies) appeared reasonable. For a detailed description of the study designs, refer to Section 8.1, Review of relevant individual trials used to support efficacy.

8.2.2. Review of the Safety Database

Overall Exposure

Overall exposure to Arazlo Lotion in terms of frequency, duration and target population was adequate for the evaluation of safety. A total of 868 subjects were exposed to the to-be-marketed formulation of Arazlo Lotion applied once daily for up to 12 weeks, including 69 subjects in Phase 2 trial (201), and 799 in combined Phase 3 trials. The extent of exposure for combined Phase 3 trials is summarized in the following table:

Table 28: Extent of Exposure, Combined Trials 301 and 302 (Safety Analysis Set)

Exposure Parameter	Arazlo Lotion (N=779)	Vehicle Lotion (N=791)
Total amount of study drug used (g)		
N	704	716
Mean (SD)	37.11 (20.1)	40.50 (21.0)
Median	32.80	36.30
Minimum to maximum	0.3 to 122.0	0.3 to 138.0
Total number of days of exposure		
N	734	746
Mean (SD)	81.8 (15.10)	83.4 (10.43)
Median	84.0	84.0
Minimum to maximum	3 to 120	3 to 129
Total number of applications		
N	733	746
Mean (SD)	79.7 (15.61)	81.3 (10.87)
Median	83.0	83.5
Minimum to maximum	3 to 117	3 to 126
Compliant[a], n (%)		
N	733	746
Yes	672 (91.7)	719 (96.4)
No	61 (8.3)	27 (3.6)

Source: NDA 211882, Section 2.7.4, Table 2 (adapted from ISS, Table 14.3.0.3)
[a] A subject was considered compliant with the application regimen if the subject did not miss >5 consecutive days of dosing and applied 80% to 120% of expected number of applications while participating in the study.
Abbreviations: SD=standard deviation

Table 29: Summary of Exposure by Age Group, Combined Trials 301 and 302 (Safety Analysis Set)

	Arazlo Lotion (N=779)			Vehicle Lotion (N=791)			Total N=1570
Duration of Exposure	9 to <12 (n=14)	12 to <18 (n=326)	≥18 (n=439)	9 to <12 (n=12)	12 to <18 (n=324)	≥18 (n=455)	n
≥4 weeks (≥ 25 days)	12	307	392	11	312	414	1448
≥8 weeks (≥ 53 days)	12	306	382	11	312	406	1429
≥12 weeks (≥81 days)	12	293	366	10	300	392	1373

Source: Clinical Reviewer's analysis,(JMP Clinical 7.0), and analysis by Statistical Reviewer (Kathleen Fritsch, PhD). Full safety analysis set with cutoffs of 25, 53, and 81 days (using the Applicant's specified -3 days from the acceptable window of -3 to +5 days).

Adequacy of the Safety Database:

The safety database presented by the Applicant is sufficient to characterize the safety profile of Arazlo Lotion for the treatment of acne vulgaris in subjects 9 years of age and older:

- The size of safety database is adequate.
- The total subject exposure to Arazlo Lotion, applied once daily for 12 weeks, provides adequate data for the evaluation of safety.
- The demographics of the study population are sufficiently representative of the target population as presented in the following Table:

Table 30: Demographic Characteristics of Subjects, Combined Trials 301 and 302 (Safety Analysis Set)

Characteristic	Arazlo Lotion (n=779)	Vehicle Lotion (n=791)	Total (N=1570)
Age			
Mean (SD)	20.5 (6.93)	20.4 (6.86)	20.4 (6.90)
Median	18.0	19.0	18.0
Minimum to maximum	10 to 54	10 to 65	10 to 65
Sex, n (%)			
Male	263 (33.8)	275 (34.8)	538 (34.3)
Female	516 (66.2)	516 (65.2)	1032 (65.7)
Ethnicity, n (%)			
Hispanic or Latino	163 (20.9)	178 (22.5)	341 (21.7)
Not Hispanic or Latino	616 (79.1)	613 (77.5)	1229 (78.3)
Race, n (%)			
American Indian or Alaska Native	9 (1.2)	4 (0.5)	13 (0.8)
Asian	42 (5.4)	36 (4.6)	78 (5.0)
Black or African American	121 (15.5)	132 (16.7)	253 (16.1)
Native Hawaiian/ Other Pacific Islander	0 (0.0)	4 (0.5)	4 (0.3)
White	575 (73.8)	584 (73.8)	1159 (73.8)
Other/multiple	32 (4.1)	31 (3.9)	63 (4.0)

Source: NDA 211882, Section 2.7.4, Table 5 (adapted from ISS, Table 14.1.1.3)
Abbreviations: SD=standard deviation

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of data submitted is adequate to characterize the safety and efficacy of Arazlo. Data quality and fitness were evaluated in conjunction with the JumpStart team. The review team discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

An AE was defined as any untoward medical occurrence, including illness, sign, symptoms, clinically significant laboratory abnormalities, or disease temporally associated with the use of the drug, in a subject administered the drug product. AEs did not necessarily have a causal relationship to the study drug. AEs were recorded from the time the informed consent was signed. TEAEs were AEs that occurred after the first administration of the study drug. AEs were documented at each study visit as observed by the investigators or reported by subjects.

The investigators categorized AEs by system organ class (SOC) and preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 (for Trials 201, 501), MedDRA version 19.0 (for Study 101), and MedDRA version 20.0 (for Trials 102, 301, 302). The Applicant assessed TEAEs by the number of subjects reporting one or more AEs. Each subject reporting a TEAE was counted once at each level of MedDRA summarization (PT or SOC). Both verbatim terms and preferred terms were included in the data files for phase 3 trials, and there was good correlation between the verbatim and preferred terms used. No safety signal emerged from the review of TEAEs.

Investigators categorized AEs for seriousness, causality, event name (diagnosis/signs and symptoms), duration, maximum intensity (severity), action taken regarding the study drug (including any treatment given), and outcome of AEs. Subjects were followed to resolution of the AE (return to normal/baseline or stabilization for up to 30 days after last study visit) by the investigators.

SAEs were any AE that resulted in death, was immediately life-threatening, required (or prolonged) hospitalization, resulted in persistent disability or incapacity, resulted in a congenital anomaly or birth defect, or a medically important event that may have required medical or surgical intervention to prevent one of the outcomes listed above.

Severity of AEs were assessed by investigators as mild, moderate, or severe. Causality was assessed as related or unrelated based on positive temporal relationship to the study drug, reasonable possibility of association of AE with underlying or concomitant illness or therapy, whether the AE was related to study procedures or lack of efficacy, and existence of a likely alternative etiology/lack of temporal relationship of the AE to the study drug.

The Applicant's assessment of AEs conducted for all the studies in the Arazlo development program, appears reasonable and appropriate. The Applicant reported accurate definitions of TEAEs, SAEs, and severity of AEs .

Routine Clinical Tests

The Applicant performed clinical laboratory evaluations (chemistry, hematology, and pregnancy tests), local skin reactions and tolerability assessments, TEAE assessment, abbreviated physical examinations, and vital signs measurements during the Phase 2 study and Phase 3 trials.

8.2.4. Safety Results

Deaths

No deaths were reported in any studies during the Arazlo development program.

Serious Adverse Events

Combined Trials V01-123A-301 and V01-123A-302 (ISS)

This pooled safety analysis set of 1570 subjects included 779 subjects in the Arazlo Lotion group and 791 subjects in the vehicle lotion group. Four (4) SAEs were reported in each treatment group. The investigators assessed all 8 SAEs as not related to the study drug or vehicle. In the vehicle lotion groups 4 SAEs (1 SAE in each subject) were reported as the following: abortion induced, suicidal ideation, appendicitis, and rhabdomyolysis. In the Arazlo Lotion group, the following 4 SAEs were reported (1 SAE in each subject):

(1) Abortion induced (Subject V01-123A-301-(b) (6))

A 29-year-old African American female discontinued the trial on Day 19 due to pregnancy. On Day 20, the subject experienced an induced abortion (elective abortion) which was considered an SAE. The final outcome was reported as recovered/resolved.

(2) Abortion spontaneous (Subject: V01-123A-301-(b) (6))

A 22-year-old white female completed the trial on Day 84. On Day 89, the subject experienced a spontaneous abortion (miscarriage) which was considered an SAE. At the time of the event, the subject had completed study medication and the final outcome was reported as recovered/resolved.

(3) Suicidal ideation (Subject: V01-123A-301-(b) (6))

A 14-year-old white male (with a medical history that included general anxiety, depression, and suicidal ideation), completed the trial on Day 104. On Day 55, the subject experienced suicidal ideation (worsening of suicidal ideation) which was considered an SAE. The subject was on treatment with Arazlo and was taking concomitant trazadone when the event occurred. The trial medication was interrupted, and the subject was hospitalized and treated with concomitant medication. On Day 61, the final outcome was reported as recovered/resolved.

(4) Abortion induced (Subject: V01-123A-302(b) (6))

A 20-year-old white female completed the trial on Day 90. On Day 100, the subject experienced an induced abortion (pregnancy termination) which was considered an SAE. At the time of the event, the subject had completed study medication and the final outcome was reported as recovered/resolved.

Reviewer's comment: This reviewer agrees with the investigators' assessments that the SAEs were not related to the study drugs. A plausible explanation for the occurrences of suicidal ideation in subject V01-123A-301-(b) (6) is this subject's psychiatric history and concomitant treatment with trazodone.

No SAEs occurred in studies V01-123A-201, V01-123A-501, V01-123A-101, or V01-123A-102.

Dropouts and/or Discontinuations Due to Adverse Effects

Combined Trials V01-123A-301 and V01-123A-302 (ISS)

Disposition of all randomized subjects for combined Phase 3 trials is summarized in the following table:

Table 31: Subject Disposition, Combined Trials 301 and 302 (All Randomized Subjects)

Disposition	Arazlo Lotion (N=799) n (%)	Vehicle Lotion (N=815) n (%)
Subjects completed	692 (86.6)	722 (88.6)
Subjects withdrawn	107 (13.4)	93 (11.4)
Reason for discontinuation		
Adverse event	19 (2.4)	4 (0.5)
Subject request	34 (4.3)	23 (2.8)
Withdrawal by parent or guardian	1 (0.1)	3 (0.4)
Protocol violation	1 (0.1)	1 (0.1)
Lost to follow-up	45 (5.6)	56 (6.9)
Pregnancy	3 (0.4)	3 (0.4)
Other	4 (0.5)	3 (0.4)

Source: Applicant's submission, Section 2.7.4, Table 3, Page 29, and ISS, Table 14.0.1.

Reviewer's comment:

A similar proportion of subjects in the Arazlo Lotion groups, compared to the vehicle lotion groups completed Phase 3 trials. However, a slightly higher proportion of subjects in the Arazlo Lotion groups (2.4%) discontinued the trials due to AEs, compared to subjects in the vehicle lotion groups (0.5%).

In the safety analysis set (ISS), the TEAEs leading to discontinuation that were more common in the Arazlo Lotion group than the vehicle lotion group were application site pain (1.7% versus 0) and application site erythema (0.8% versus 0). The incidence of TEAEs that led to drug discontinuation was 22/779 (2.8%) in Arazlo Lotion group compared to 4/791 (0.5%) in the vehicle lotion group. The TEAEs related to the study drug (ARs) leading to discontinuation are summarized according to the SOC and PT in the following table.

Table 32: Treatment-Emergent Adverse Reactions Leading to Discontinuation (ISS)

System Organ Class Preferred Term	Arazlo Lotion, (N=778), n (%)	Vehicle Lotion, (N=790), n (%)
General disorders and administration site conditions		
Application site pain	13 (1.7)	0
Application site erythema	6 (0.8)	0
Application site pruritus	2 (0.3)	0
Application site rash	2 (0.3)	0
Application site exfoliation	1 (0.1)	0
Application site hypersensitivity	1 (0.1)	0
Application site irritation	1 (0.1)	0
Application site oedema	1 (0.1)	0
Application site acne	1 (0.1)	1 (0.1)
Application site dryness	1 (0.1)	0
Application site dermatitis	1 (0.1)	0
Skin and subcutaneous tissue disorders		
Acne	0	1 (0.1)
Urticaria	0	1 (0.1)

Source: Reviewer's JMP Clinical 7.0 Analysis. Study: NDA 211882-ISS. Adverse Events Distribution. Analysis population: Safety. Event Type: Treatment-emergent events. Additional filter to include Adverse Events: AEREL='RELATED' AND AEACN='DRUG WITHDRAWN'. Treatment emergence determined using AE.AETRTEM.
Abbreviations: ISS=integrated summary of safety, PT=preferred term, SOC=system organ class

Trial V01-123A-201

Ninety percent (189/210) of the randomized subjects completed this study. The percentages of subjects who completed the study were similar across treatment groups (88.2% to 94.2%). The only TEAE that led to study drug discontinuation in this trial (elevated liver enzymes at baseline) occurred in one subject in the Tazorac Cream, 0.1% group.

Study V01-123A-501

No TEAEs led to subject discontinuation of the study drug.

Study V01-123A-101

No TEAEs led to subject discontinuation of the study drug.

Study V01-123A-102

A TEAE of contact dermatitis (to adhesive tape), considered by the investigator not to be related to study medication, led to one subject (V01-123A-102-01-(b) (6)) discontinuing from the study.

Significant Adverse Events

Severe TEAEs

In the combined Phase 3 trials (ISS), the incidence of severe TEAEs in the Arazlo Lotion group 10/779 (1.3%), was higher than vehicle lotion group 4/791 (0.5%). Application-site pain occurred in 2 subjects and was the only severe TEAEs in the Arazlo Lotion group that was deemed related to the study drug by the investigators occurring in >1 subject.

Human Reproduction and Pregnancy

Pregnant or lactating subjects were excluded from studies in the Arazlo Lotion development program. Female subjects of childbearing potential were required to use effective forms of contraception and have negative serum pregnancy tests at screening and urine pregnancy tests at all study visits. Subjects who became pregnant discontinued treatment.

No subjects became pregnant during studies 501, 201, 102, and 101. A total of 12 subjects became pregnant during Phase 3 studies (11 subjects during Trial 301, 1 additional pregnancy detected at screening, and 1 subject in Trial 302). Of the 12 pregnancies, 8 occurred in the Arazlo Lotion groups (outcomes: 3 elective abortions, 1 spontaneous abortion, 1 normal birth, 2 lost to follow-up, 1 withdrew consent) and 4 in the vehicle lotion groups (outcomes: 1 elective abortion, 2 normal live births, 1 lost to follow-up).

There were no reports of congenital malformations.

Treatment-Emergent Adverse Events and Adverse Reactions

TEAEs in Combined Trials V01-123A-301 and V01-123A-302 (ISS)

The incidence of TEAEs in the Arazlo Lotion group was 209/779 (26.8%), compared to 151/791 (19.1%) in the vehicle lotion group.

Most TEAEs that occurred in ≥1% of the subjects in the Arazlo Lotion group were associated with application-site reactions (included in the SOC of general disorders and administration site conditions), occurred at higher frequencies than in the vehicle lotion group, and were TEAEs expected to occur with the application of a topical retinoid. Other TEAEs that occurred in ≥1% of the subjects in the Arazlo Lotion group were respiratory (included in the SOC of Infections and Infestations) and occurred at similar frequencies in both treatment groups. The results are summarized in the following table:

Table 33: Treatment-Emergent Adverse Events (TEAEs) Occurring in ≥1% of the Subjects in Either Treatment Group (Safety Analysis Set)

System Organ Class/ Preferred Term	Arazlo Lotion (N=779), n (%)	Vehicle Lotion (N=791), n (%)
Subjects reporting any TEAE	209 (26.8)	151 (19.1)
General disorders and administration site conditions	99 (12.7)	13 (1.6)
Application site pain	41 (5.3)	2 (0.3)
Application site dryness	30 (3.9)	1 (0.1)
Application site exfoliation	16 (2.1)	0 (0.0)
Application site erythema	15 (1.9)	0 (0.0)
Application site pruritus	10 (1.3)	0 (0.0)
Infections and infestations	76 (9.8)	80 (10.1)
Viral upper respiratory tract infection	36 (4.6)	31 (3.9)
Upper respiratory tract infection	13 (1.7)	14 (1.8)

Source: Applicant's submission (Section 2.7.4, Table 8, Page 40) and Reviewer's analysis, JMP Clinical 7. Study: NDA 211882 -ISS Analysis Population: Safety

Adverse Reactions in Combined Trials V01-123A-301 and V01-123A-302 (ISS)

Adverse reactions (ARs) occurred at a higher frequency in the Arazlo Lotion group 88/779 (11.3%) compared to vehicle lotion group 9/791 (1.1%). The results are summarized in the following table:

Table 34: Adverse Reactions (ARs) Occurring in ≥1% of Subjects Treated With Arazlo Lotion and at Higher Frequency Compared to Vehicle Lotion Group (Safety Analysis Set)

Preferred Term	Arazlo Lotion (N=779), n (%)	Vehicle Lotion (N=791), n (%)
Subjects reporting any AR	88 (11.3)	9 (1.1)
Application site pain	41 (5.3)	2 (0.3)
Application site dryness	28 (3.6)	1 (0.1)
Application site exfoliation	16 (2.1)	0 (0.0)
Application site erythema	14 (1.8)	0 (0.0)
Application site pruritus	9 (1.2)	0 (0.0)

Source: Applicant's submission, Section 2.7.4, Modified from Table 10, Page 43 (similar to results of Clinical Reviewer's analysis, JMP Clinical 7.0)

Reviewer comment: The higher incidence of application site-related ARs in subjects treated with Arazlo Lotion, compared to subjects treated with vehicle lotion, is consistent with the known ARs associated with the use of topical tazarotene drug products. This reviewer agrees with the inclusion of the Table of ARs in Section 6.1 of the Arazlo label.

Adverse Reactions in Trial V01-123A-201

The only AR in the Arazlo Lotion group was application-site pain, which occurred in 2/68 (2.9%) subjects, compared to 3/71 (4.2%) subjects in the Tazorac Cream, 0.1% group, and no subjects in combined vehicles groups.

Adverse Reactions in Study V01-123A-501

The only ARs that occurred in more than 1 subject in Arazlo Lotion group was application-site pruritus in 2/28 (7.1%) of subjects, compared to 1/20 (5%) subjects in Tazorac Cream, 0.1% group.

Adverse Reactions in Study V01-123A-101

No ARs were reported for any subject in this Study.

Adverse Reactions in Study V01-123A-102

No ARs were reported for any subject in this Study.

Laboratory Findings

Combined Trials V01-123A-301 and V01-123A-302 (ISS)

Specimens for laboratory tests were collected at the baseline and Week 12 visits. No clinically significant treatment-related abnormalities in hematology or clinical chemistry laboratory results was reported in any subject in the Arazlo Lotion group. One (1) subject (V01-123A-301-(b) (6)) in the vehicle lotion group, with slightly elevated baseline creatinine kinase value of 220 [normal range 33 to 211 U/L], had an SAE of nontraumatic rhabdomyolysis with creatinine kinase value of 45,170 U/L at week 12. The subject completed the study and the investigators considered this SAE as not related to the study drug.

Study V01-123A-201

Specimens for laboratory tests were collected at screening and at Weeks 4, 8, and 12 visits. No clinically significant treatment-related abnormalities in laboratory results was reported for any subject in this study (one subject with elevated liver enzymes at baseline in the Tazorac Cream, 0.1% group was discontinued from the study).

Study V01-123A-501

Specimens for laboratory tests were collected at screening and Day 15 visits. No clinically significant treatment-related abnormalities in laboratory results occurred in any subject in this study.

Study V01-123A-101

No clinical laboratory tests were conducted during this study.

Study V01-123A-102

No clinical laboratory tests were conducted during this study.

Vital Signs

Combined Trials V01-123A-301 and V01-123A-302 (ISS)

Vital sign measurements (temperature, respiration rate, heart rate, systolic and diastolic blood pressures) were recorded at baseline and at Week 12 visits. The mean values for each parameter in the two treatment groups were similar, and changes observed from baseline to Week 12 were small and not clinically significant.

Trial V01-123A-201

Vital sign measurements were recorded at screening, baseline, and Week 12 visits. No clinically significant differences in vital signs were observed between treatment groups.

Study V01-123A-501

Vital sign measurements were recorded at screening, baseline, and Day 15 visits. No clinically significant differences in vital signs were observed between treatment groups.

Study V01-123A-101

Vital sign measurements were not recorded for this study.

Study V01-123A-102

Vital sign measurements were not recorded for this study.

Electrocardiograms

No ECGs were recorded during studies conducted in the Arazlo development program.

QT

The Applicant requested a waiver to conduct a thorough QT/QTc clinical study for Arazlo Lotion, and provided the following reasons in support of their request:

- Nonclinical study (Study V01-118A-608), an in vitro patch clamp test on HEK293 human embryonic kidney cells conducted by the Applicant, included tazarotene and tazarotenic acid at concentrations up to 10 µM. Tazarotene inhibited hERG current with an IC_{50} of 5.7µM (tazarotene is rapidly metabolized to tazarotenic acid and is essentially not detected in humans). Tazarotenic acid inhibited hERG current minimally with IC_{50}>10µM. Tazarotene and tazarotenic acid are highly bound (>90%) to human plasma proteins which further reduces the amount of free drug and the potential of hERG inhibition in vivo.
- Lack of observed ECG abnormalities in a 3-month dermal toxicity study (V01-118A-605) in Gottingen minipigs conducted by the Applicant.
- The Applicant performed a literature search (Pubmed 1/24/2019) which did not identify an increased risk of QT/QTc prolongation associated with the use of topical tazarotene, or other retinoids.

The Applicant cited the long marketing history of tazarotene (since 1997) and the absence of any postmarketing reports of cardiovascular safety signals, including arrhythmias possibly related to QT/QTc prolongation, in several public databases (the FDA Postmarket drug safety information for patients and providers, FDA Adverse Event Reporting System database, and the CredibleMeds organization QT drug database).

In the memorandum of pre-IND meeting minutes letter of 6/25/2015 and the EOP2 preliminary meeting minutes letter of 12/6/2016, the Agency informed the Applicant that a determination for waiver would be made after submission of the study results from the maximal use PK trial in subjects with acne. The Agency stated that a waiver of thorough QT trial would be reasonable if the results from the maximal use PK trial confirm that the systemic exposure from tazarotene and tazarotenic acid following Arazlo Lotion treatment under maximal use conditions was similar to or lower than the systemic exposure from LD Tazorac Cream, 0.1%.

Reviewer's comment:

A consultation was requested from the Division of Cardiovascular and Renal Products QT-Interdisciplinary Review Team(QT-IRT) On 4/16/2019 regarding the Applicant's TQT waiver request for NDA 211882. In a memorandum dated 7/1/2019, the QT-IRT determined that a TQT study was not required:

" Yes, we agree with the sponsor's proposal. The low systemic exposures tazarotene and tazarotenic acid associated with the topical application of IDP-123 (tazarotene 0.045% w/w) lotion at the planned doses are unlikely to cause clinically relevant QT/QTc prolongation."

The following comment was made by the QT-IRT reviewer, Girish K Bende:

"In a maximal use PK study, the plasma concentrations of tazarotene and tazarotenic acid were comparable between the LD and the to-be marketed lotion formulation."

8.2.5. Analysis of Submission-Specific Safety Issues

Cutaneous Safety and Tolerability Assessments

Cutaneous safety evaluations included assessment of scaling, erythema, hypo-pigmentation and hyper-pigmentation. Cutaneous tolerability evaluations included assessment of itching, burning and stinging at the drug application site. The following grading scales were used (Refer to Study V01-123A-301 Protocol, Sections 11.3.1 and 11.3.2):

Safety:

Scaling:

- 0 – None No scaling
- 1 – Mild Barely perceptible, fine scales present on limited areas of the face
- 2 – Moderate Fine scale generalized to all areas of the face
- 3 – Severe Scaling and peeling of skin over all areas of the face

Erythema:

- 0 – None No evidence of erythema present
- 1 – Mild Slight pink coloration
- 2 – Moderate Definite redness
- 3 – Severe Marked erythema, bright red to dusky dark red in color

Hypo-pigmentation:

- 0 – None No evidence
- 1 – Mild Slight, barely perceptible
- 2 – Moderate Definite, evident
- 3 – Severe Marked, prominent

Hyper-pigmentation:

- 0 – None No evidence
- 1 – Mild Slight, barely perceptible
- 2 – Moderate Definite, evident
- 3 – Severe Marked, prominent

Tolerability:

Itching:

- 0 – None No itching
- 1 – Mild Slight itching, not really bothersome
- 2 – Moderate Definite itching that is somewhat bothersome
- 3 – Severe Intense itching that may interrupt daily activities and/or sleep

Burning:

- 0 – None No burning
- 1 – Mild Slight burning sensation; not really bothersome
- 2 – Moderate Definite warm, burning sensation that is somewhat bothersome
- 3 – Severe Hot burning sensation that causes definite discomfort and may interrupt daily activities and/or sleep

Stinging:

- 0 – None No stinging
- 1 – Mild Slight stinging sensation, not really bothersome
- 2 – Moderate Definite stinging sensation that is somewhat bothersome
- 3 – Severe Stinging sensation that causes definite discomfort and may interrupt daily activities and/or sleep

Combined Trials V01-123A-301 and V01-123A-302 (ISS)

Subjects treated with Arazlo Lotion had transient increases in the severity of local cutaneous signs or symptoms that peaked about Week 2 and were generally mild or moderate in severity. At Week 12, most subjects showed small changes compared to baseline scores in nearly all assessed parameters. Cutaneous safety and tolerability results for combined Phase 3 trials at any post-baseline visit are presented in the following table:

Table 35: Incidence of Local Mild, Moderate, or Severe Cutaneous Irritation at Any Post Baseline Visit (Safety Population)

Dermal Reaction	Arazlo (N=779) n (%)	Vehicle (N=791) n (%)
Erythema	379 (48.9%)	300 (38.0%)
Scaling	394 (50.8%)	180 (22.8%)
Itching	227 (29.3%)	108 (13.7%)
Burning	237 (30.6%)	46 (5.8%)
Stinging	175 (22.6%)	38 (4.8%)

Source: Adapted from ISS Table 14.1.1 AH2

Study V01-123A-201

Cutaneous safety and tolerability assessments (erythema, scaling, hypopigmentation, hyperpigmentation, itching, burning, and stinging) were assessed at baseline and Weeks 2, 4, 8, and 12 visits. At all postbaseline visits, the proportion of subjects with no cutaneous signs or

symptoms were similar in the Arazlo Lotion and Tazorac Cream groups, and less than the combined vehicle group.

Treatment-emergent Grade 3 (severe) findings occurred with similar frequency (<3%) in the Arazlo Lotion and Tazorac Cream groups and included combined burning/stinging/itching (4.4% versus. 5.6%), hypopigmentation (1.5% versus 0), hyperpigmentation (0 versus 1.4%) in the Arazlo Lotion and Tazorac Cream groups, respectively.

Study V01-123A-501

In the maximal use Study 501, cutaneous safety and tolerability assessments included erythema, scaling, itching, burning, and stinging (assessments did not include hyper-pigmentation or hypo-pigmentation) graded on a 4-point scale (0= none, 1= mild, 2= moderate, or 3= severe) at baseline, Days 2, 12, 14, and 15. The frequency and severity of all local skin reactions increased in both Arazlo Lotion and Tazorac Cream treatment groups and in all age cohorts over the 2-week treatment period, consistent with results expected from treatment with topical retinoids. The most frequently observed skin reactions were mild erythema, and mild or moderate scaling. No severe reaction was reported for any subject at Day 15 visit.

Study V01-123A-101 and Study V01-123A-102

Dermal safety studies 101 and 102 did not include cutaneous safety and tolerability assessments.

Reviewer's comment: For Phase 3 Trials 301 and 302, the frequency of moderate to severe cutaneous safety/tolerability ARs were generally low and comparable at the beginning and at the end of the trials. For the Phase 2 Trial 201, the frequency of severe cutaneous safety/tolerability ARs were generally low and comparable between Arazlo and the reference product, tazarotene cream, 0.1%.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

The Phase 3 protocols 301 and 302 included the Acne-QoL, a PRO. No primary or secondary endpoints were based on this PRO, and it was not included in the multiplicity testing strategy or proposed product labeling. Therefore, data and endpoints based on this PRO are considered exploratory and will not be included in this review.

8.2.7. Safety Analyses by Demographic Subgroups

The safety population for combined Phase 3 trials (ISS, Safety Analysis Set) included 778 subjects in the Arazlo Lotion and 790 subjects in the vehicle lotion groups. For subjects included in the combined Phase 3 trials, the Applicant conducted safety analyses based on age category, sex, and race (per 21 CFR 314.50 (d)(5)(vi)(a)), and ethnicity/geographic region. The results indicated that there were no substantial differences in the risk of ARs in demographic subgroups. However, because the trials were not powered for these analyses, the data must be

interpreted with caution. Treatment-emergent ARs by demographic subgroups are presented in the following tables by age category, sex, race, ethnicity, and geographic location.

TEAEs and ARs by Age Group:

Subjects ≥9 years of age were included in the Arazlo Lotion groups in Study 501 and Phase 3 Trials 301 and 302. (Only subjects ≥12 years of age were included in the Tazorac Cream, 0.1% groups in Studies 501 and 201, per approved label for Tazorac Cream, 0.1% for acne vulgaris.)

The Applicant reported no clinically significant differences in the incidence of TEAEs by age category (<18 years compared to ≥18 years of age) in the Arazlo Lotion group. In addition, the Applicant conducted comparisons of safety assessments by age category (9 to <12 years versus ≥12 years) for subjects in the Arazlo Lotion group for Study 501 and combined Phase 3 trials (ISS) and found no clinically significant differences in the incidence of TEAEs, clinical laboratory results, and vital signs between these age groups.

For combined Phase 3 trials, 36% of subjects <12 years of age and 27% of subjects ≥12 years of age reported ≥1 TEAEs. No subject <12 years of age reported an SAE or a severe TEAE. One subject <12 years of age (V01-123A-301-(b) (6)) experienced 3 TEAEs and discontinued from the trial. A summary of ARs for subjects in combined Phase 3 trials by age group is presented in the following table:

Table 36: Treatment-Emergent Adverse Reactions Occurring in ≥2 Subjects in Any Subgroup Treated With Arazlo Lotion or Vehicle Lotion, by Age Group (ISS, Safety Analysis Set)

	Age 9 to <12 Years (N=26)		Age ≥12 Years (N=1542)	
Preferred Term	**Arazlo Lotion, n=14 n (%)**	**Vehicle Lotion, n=12 n (%)**	**Arazlo Lotion, n=764 n (%)**	**Vehicle Lotion, n=778 n (%)**
Application site pain	1 (7.1)	0	40 (5.2)	2 (0.3)
Application site dryness	0	0	28 (3.7)	1 (0.1)
Combined PTs for application site: rash/dermatitis/erythema/hypersensitivity	1 (7.1)	0	24 (3.1)	0
Application site exfoliation	0	0	16 (2.1)	0
Application site pruritus	2 (14.3)	0	7 (0.9)	0
Application site irritation	0	0	6 (0.8)	0
Application site acne	0	0	1	2 (0.3)

Source: Adapted from ISS (Table 14.3.1.2.3.2. AH1) and Reviewer's JMP Clinical 7 Analysis. Adverse Events Distribution Report Results. Analysis population: Safety. Event Type: Treatment-emergent events. Additional filter to include Adverse Events: AEREL="RELATED." Treatment emergence determined using AE.AETRTEM. MedDRA version 20.0.
Abbreviations: ISS=integrated summary of safety, PT=preferred term

Reviewer's comment: Among subjects treated with Arazlo Lotion, the incidence of most ARs is higher in subjects aged 9 to <12 years of age than in subjects ≥12 years of age. However, the subgroup analysis was not powered for safety analyses, and because of small number of subjects in the younger age group no meaningful conclusions can be drawn by comparing the incidence of ARs between the age subgroups.

TEAEs and ARs by Gender:

Subjects treated with Arazlo Lotion in combined Phase 3 trials reported ≥1 TEAEs in 19% of male and 30.8% of female subjects, and ARs in 4.6% of male and 14.7% of female subjects. The frequency of TEAEs and ARs (other than application-site reactions) were similar between female and male subjects treated with Arazlo Lotion. Female subjects treated with Arazlo Lotion reported a higher frequency of application-site reactions compared to male subjects as presented in the following table.

Table 37: Treatment-Emergent Adverse Reactions Occurring in ≥2 Subjects in Any Subgroup Treated With Arazlo Lotion or Vehicle Lotion, by Gender (ISS, Safety Analysis Set)

	Female (N=1030)		Male (N=538)	
Preferred Term	**Arazlo Lotion, n=515 n (%)**	**Vehicle Lotion, n=515 n (%)**	**Arazlo Lotion, n=263 n (%)**	**Vehicle Lotion, n=275 n (%)**
Application site pain	34 (6.6)	2 (0.4)	7 (2.7)	0
Application site dryness	26 (5.0)	1 (0.2)	2 (0.8)	0
Combined PTs for application site: rash/dermatitis/erythema/hypersensitivity	22 (4.3)	0	3 (1.1)	0
Application site exfoliation	15 (2.9)	0	1 (0.4)	0
Application site pruritus	8 (1.6)	0	1 (0.4)	0
Application site irritation	6 (1.2)	0	0	0
Application site acne	1 (0.2)	2 (0.4)	0	0

Source: Adapted from ISS (Table 14.3.1.2.1.4, Table 14.3.1.2.3.4) and Reviewer's JMP Clinical 7 Analysis. Adverse Events Distribution Report Results. Analysis population: Safety. Event Type: Treatment-emergent events. Additional filter to include Adverse Events: AEREL="RELATED." Treatment emergence determined using AE.AETRTEM. MedDRA version 20.0.
Abbreviations: ISS=integrated summary of safety, PT=preferred term

Reviewer's comment: The incidence of ARs was higher in female subjects compared to male subjects treated with Arazlo Lotion. However, the subgroup analysis was not powered for safety analyses, and no meaningful conclusions can be drawn by comparing the incidence of ARs between the gender subgroups.

TEAEs and ARs by Race:

Subjects treated with Arazlo Lotion in combined Phase 3 trials with ≥1 TEAEs included 30/120 (25%) of Black/African American and 165/575 (28.7%) of white subjects. No trends were reported for SAEs, severe TEAEs, TEAEs that led to treatment discontinuation, or ARs between Black/African American and white subjects. Other races included ≤42 subjects each in the Arazlo Lotion treatment groups. A summary of ARs by race is presented in the following table.

Table 38: Treatment-Emergent Adverse Reactions Occurring in ≥2 Subjects in Any Subgroup Treated With Arazlo Lotion or Vehicle Lotion, by Race (ISS, Safety Analysis Set)

	White (N=1158)		Black or African American (N=252)	
Preferred Term	**Arazlo Lotion, n=575 n (%)**	**Vehicle Lotion, n=583 n (%)**	**Arazlo Lotion, n=120 n (%)**	**Vehicle Lotion, n=132 n (%)**
Application site pain	30 (5.2)	2 (0.3)	8 (6.7)	0
Application site dryness	22 (3.8)	1 (0.2)	4 (3.3)	0
Combined PTs for application site: rash/dermatitis/erythema/hypersensitivity	22 (3.8)	0	2 (1.6)	0
Application site exfoliation	8 (1.4)	0	6 (5.0)	0
Application site pruritus	6 (1.0)	0	3 (2.5)	0
Application site irritation	6 (1.0)	0	0	0

Source: Adapted from ISS (Table 14.3.1.2.1.9, Table 14.3.1.2.3.9) and Reviewer's JMP Clinical 7 Analysis. Adverse Events Distribution Report Results. Analysis population: Safety. Event Type: Treatment-emergent events. Additional filter to include Adverse Events: AEREL="RELATED." Treatment emergence determined using AE.AETRTEM. MedDRA version 20.0.
Abbreviations: ISS=integrated summary of safety, PT=preferred term

Reviewer's comment: The incidence of ARs was generally similar in white and Black/African American subjects treated with Arazlo Lotion. The number of subjects of other races included in ISS (American Indian or Alaskan native (13), Asian (78), Native Hawaiian or Pacific Islander (4), Multiple (24), Other(39)) were too small for inclusion in the table, and the subgroup analysis was not powered for safety analyses. Therefore, no meaningful conclusions can be drawn by comparing the incidence of ARs between the race subgroups.

TEAEs and ARs by Ethnicity

Subjects treated with Arazlo Lotion in combined Phase 3 trials with ≥1 TEAEs included 33/163 (20.2%) of Hispanic/Latino and 176/615 (28.6%) of non-Hispanic/non-Latino subjects. No SAEs were reported for subjects in the Hispanic/Latino group, compared to 4/615 (0.6%) of subjects in the non-Hispanic/non-Latino group. No trends were reported for severe TEAEs, TEAEs that led to treatment discontinuation, or ARs between Hispanic/Latino and non-Hispanic/non-Latino subjects treated with Arazlo Lotion. A summary of ARs by Ethnicity is presented in the following table.

Table 39: Treatment-Emergent Adverse Reactions Occurring in ≥2 Subjects in Any Subgroup Treated With Arazlo Lotion or Vehicle Lotion, by Ethnicity (ISS, Safety Analysis Set)

	Hispanic or Latino (N=341)		Non-Hispanic or Latino (N=1227)	
Preferred Term	**Arazlo Lotion, n=163 n (%)**	**Vehicle Lotion, n=178 n (%)**	**Arazlo Lotion, n=615 n (%)**	**Vehicle Lotion, n=612 n (%)**
Application site pain	10 (6.1)	0	31 (5.0)	2 (0.3)
Application site dryness	4 (2.5)	0	24 (3.9)	1 (0.2)
Combined PTs for application site: rash/dermatitis/erythema/hypersensitivity	4 (2.5)	0	21 (3.4)	0
Application site exfoliation	4 (2.5)	0	12 (1.9)	0
Application site pruritus	2 (1.2)	0	7 (1.1)	0
Application site irritation	1 (0.6)	0	5 (0.8)	0

Source: Adapted from ISS (Table 14.3.1.2.1.7, Table 14.3.1.2.3.2) and Reviewer's JMP Clinical 7 Analysis. Adverse Events Distribution Report Results. Analysis population: Safety. Event Type: Treatment-emergent events. Additional filter to include Adverse Events: AEREL="RELATED." Treatment emergence determined using AE.AETRTEM. MedDRA version 20.0.
Abbreviations: ISS=integrated summary of safety, PT=preferred term

Reviewer's comment: The incidence of ARs was generally similar in Hispanic/Latino subjects compared to non-Hispanic/non-Latino subjects treated with Arazlo Lotion.

TEAEs and ARs by Geographic Location:

Subjects treated with Arazlo Lotion in combined Phase 3 trials with ≥1 TEAEs included 39/82 (47.6%) of subjects in Canada and 170/696 (24.4%) of subjects in the United States. In general, the frequencies of reported SAEs, severe TEAEs, TEAEs that led to treatment discontinuation, or ARs for subjects treated with Arazlo Lotion were slightly higher for subjects in Canada, compared to subjects in the United States. The Applicant concluded that because of the large difference between the number of subjects treated with Arazlo in the United States, compared to Canada, no definitive conclusions could be made. A summary of ARs by geographic region is presented in the following table.

Table 40: Treatment-Emergent Adverse Reactions Occurring in ≥2 Subjects in Any Subgroup Treated With Arazlo Lotion or Vehicle Lotion, by Geographic Region (ISS, Safety Analysis Set)

	United States (N=1409)		Canada (N=159)	
Preferred Term	**Arazlo Lotion, n=696 n (%)**	**Vehicle Lotion, n=713 n (%)**	**Arazlo Lotion, n=82 n (%)**	**Vehicle Lotion, n=77 n (%)**
Combine PTs for application site: pain/discomfort	37 (5.3)	1 (0.1)	5 (6.1)	1 (1.3)
Application site dryness	24 (3.4)	1 (0.1)	4 (4.9)	0
Combined PTs for application site: rash/dermatitis/erythema/hypersensitivity	18 (2.6)	0	7 (8.5)	0
Application site exfoliation	13 (1.9)	0	3 (3.7)	0
Application site pruritus	9 (1.3)	0	0	0
Application site irritation	6 (0.8)	0	0	0

Source: Adapted from ISS (Table 14.3.1.2.1.10, Table 14.3.1.2.3.10) and Reviewer's JMP Clinical 7 Analysis. Adverse Events Distribution Report Results. Analysis population: Safety. Event Type: Treatment-emergent events. Additional filter to include Adverse Events: AEREL="RELATED." Treatment emergence determined using AE.AETRTEM. MedDRA version 20.0.
Abbreviations: ISS=integrated summary of safety, PT=preferred term

Reviewer's comment: The frequencies of ARs related to the application-site for subjects treated with Arazlo Lotion were generally higher for subjects in Canada compared to subjects in the U.S. However, the subgroup analysis was not powered for safety analyses, and because of small number of subjects treated with Arazlo Lotion in Canada, no meaningful conclusions can be made by comparing the incidence of ARs between the geographic subgroups.

8.2.8. Specific Safety Studies/Clinical Trials

Photosafety Studies:

The Applicant requested a waiver for conducting clinical studies to evaluate the potential for phototoxicity or photoallergenicity of Arazlo Lotion, and provided the following points in support of their position during the pre-IND meeting:

- Tazarotene cream (the reference LD for Arazlo) was previously evaluated in human dermal safety studies and was assessed not to induce phototoxicity or photoallergy.
- Per recommendations of International Conference on Harmonisation guidance (S10), the Applicant evaluated the photoabsorbance and in vitro phototoxic potential of Arazlo Lotion and confirmed that only tazarotene (not vehicle lotion) absorbs light in the 290 to 700 nm range.
- The Applicant proposed similar AE/AR labeling to the referenced product, Tazorac Cream.

The Agency agreed with the Applicant not to conduct additional photosafety studies, provided that the Applicant incorporates all of the cautionary language (related to UV light exposure in the label for Tazorac Cream) into the Arazlo label.

Clinical Dermal Safety Studies:

The Applicant conducted two phase 1, provocative dermal safety studies in healthy adult subjects (V01-123A-101 and V01-123A-102) with the to-be-marketed formulation to support the dermal safety of Arazlo Lotion. The trials evaluated the potential of Arazlo Lotion for irritation and sensitization. The results are presented in this section.

Study V01-123A-101 (Cumulative Irritation Patch Test)

This study was a 21-day, randomized, single-center, vehicle-controlled, evaluator-blinded, within-subject study to evaluate the skin irritation potential of Arazlo Lotion in healthy adult male and female subjects ≥18 years of age. Forty-two (42) subjects were randomized and 38 subjects completed the study.

Each subject received 0.2 mL per patch of each of the following test drugs:

- Arazlo Lotion
- Vehicle lotion
- 0.5% sodium lauryl sulfate (positive control)
- 0.9% saline (negative control)

Semi-occlusive patches were applied to randomly assigned, 2 cm x 2 cm adjacent areas on one side of the infrascapular area of each subject once daily for 21 consecutive days and removed after 24 hours (21 applications). Each test site was assessed and a fresh patch containing the same study product was re-applied to the same location. Dermal reactions at the application sites were assessed daily by a blinded assessor before each patch application, using a visual scale for erythema, edema, and irritation. The actual patch test grades were calculated as the sum of numerical grades and letter grades (converted to numerical equivalents), according to the following tables:

Table 41: Response Symbols and Numerical Responses

Grade	Definition	Score
0	No evidence of irritation	0
1	Minimal erythema; barely perceptible	1
2	Definite erythema, readily visible; or minimal edema; or minimal papular response	2
3	Erythema and papules	3
4	Definite edema	3
5	Erythema, edema, and papules	3
6	Vesicular eruption	3
7	Strong reaction spreading beyond test site	3

Source: Applicant's submission, protocol V01-123A-101, Table 9-3. Page 28.

Table 42: Effects on Superficial Layers of the Skin

Symbol	Numerical Equivalent	Response
A	0	Slight glazed appearance
C	1	Marked glazing
E	2	Glazing with peeling and cracking
F	3	Glazing with fissures
G	3	Film of dried serous exudate covering all or portion of the patch
H	3	Small petechial erosions and/or scabs

Source: Applicant's submission, protocol V01-123A-101, Tables 9-4, Page 29.

Of the 42 enrolled subjects, 9 (21.4%) experienced a total of 10 nonserious TEAEs. All TEAE resolved, were mild, and considered not related to the study drug. No TEAEs occurred in more than 1 subject or led to study discontinuation or changes in any study product application.

Results

Under the exaggerated conditions of this dermal provocative irritancy study, Arazlo Lotion was assessed as slightly irritating. The results are summarized in the following table:

Table 43: Mean and Total Irritation Score, Study 101 (N=42) (Safety Population)

Subgroup	Irritation Score, Mean (SD)	Total Irritation Score, Mean (SD)
Arazlo Lotion	0.54 (0.44)	11.33 (9.17)
Vehicle Lotion	0.08 (0.20)	1.71 (4.19)
0.5% SLS	0.34 (0.37)	6.98 (7.67)
0.9% Saline	0.04 (0.11)	0.93 (2.36)

Source: Applicant's submission, protocol V01-123A-101, Tables 12-1, Page 40.
Abbreviations: SD=standard deviation, SLS=sodium lauryl sulfate

Reviewer Comment: The Applicant's proposed label for Arazlo Lotion appears adequate to convey the risk of potential skin irritation.

Study V01-123A-102 (Repeat Insult Patch Test)

This study was a single-center, 6-week, randomized, controlled, evaluator-blinded, within-subject comparison study of sensitization potential of Arazlo Lotion compared to Arazlo vehicle lotion and negative control (0.9% Saline) to induce sensitization, using a repeat insult patch test design based on the Modified Draize Procedure.

Two hundred thirty-five (235) healthy male and female subjects 18 years of age or older were randomized. The analysis of cumulative irritation and analysis of sensitization included 210 and 206 subjects, respectively. A rechallenge phase was not required in this study. One subject discontinued the study due to a mild TEAE (contact dermatitis to tape) not related to the study drug.

Each subject received a total of 10 applications (0.2 mL of each test drug applied to semi-occlusive patches) of each of the following solutions: Arazlo Lotion, Arazlo vehicle lotion, and 0.9% saline (negative control).

During the induction phase of the study, patches were applied to randomly assigned, adjacent sites on the infrascapular areas of the subjects on Mondays, Wednesdays, and Fridays of 3 consecutive weeks (9 applications) and remained in place until removed and the next patch was applied. Dermal reactions were assessed using a visual scale, similar to the scale used for study 101, after each patch removal and prior to application of an identical patch to the same patch site. A 10 to 14-day rest period (with no patch application) followed the completion of the induction phase, prior to the start of the challenge phase. Based on mean and total cumulative irritation scores in the induction phase, the investigators classified Arazlo Lotion and Arazlo vehicle lotion as having no meaningful irritation.

During the challenge phase, a 48-hour application of each test patch was performed at a naïve site on the opposite side of the subjects' infrascapular areas. Test sites were evaluated, using the same dermal irritation scoring grade used in the induction phase, at 30 minutes, 24 hours, 48 hours, and 72 hours after patch removal. During this phase, no subject had a reaction indicating sensitization, and no subject required a rechallenge.

Reviewer's comment: This reviewer agrees with the Applicant's conclusion that Arazlo Lotion did not show potential for skin sensitization under the exaggerated conditions of this repeat insult patch test study.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The applicant did not conduct a specific clinical trial to evaluate human carcinogenicity or tumor development. During the development of Arazlo lotion, the trial designs did not include specific assessments to evaluate for carcinogenicity or screen for safety signals related to malignancy. However, no subjects enrolled in the Phase 3 trials reported malignant neoplasms. The applicant obtained a right of reference to nonclinical carcinogenicity studies conducted to support Tazorac cream, 0.1% (NDA 021184). This information is included in Section 13.1 of labeling. Refer to Section 5.5.3 of this review for a discussion of the nonclinical data.

Human Reproduction and Pregnancy

Refer to the Subsection "Significant Adverse Events (Human Reproduction and Pregnancy)" under Section 8.2.4 of this review.

Pediatrics and Assessment of Effects on Growth

Clinical studies for Arazlo were conducted in subjects ≥9 years of age. Because Arazlo is a new dosage form for tazarotene, this NDA is required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric subjects, under the Pediatric Research Equity Act (21 U.S.C. 355c).

The Division agreed with the Applicant's Agreed iPSP on 12/3/2018, following discussion of the Agreed iPSP with the Pediatric Review Committee on 11/14/2018. The Agreed iPSP included a request for partial waiver to conduct clinical studies in subjects less than 9 years of age. The prevalence of moderate to severe acne vulgaris in pediatric population in this age group is low. Therefore, studies would be impossible or highly impracticable (Section 505B (a)(4)(B)(i) of the Act).].

The Applicant did not request a deferral of clinical assessments in any pediatric age group. The Phase 3 trials and the Phase 1 MuST Study (-501) included subjects in the target pediatric age group (≥9 years of age).

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No subject in any clinical studies conducted with Arazlo Lotion experienced an overdose, and no information regarding Arazlo overdose is available. No unexpected TEAE occurred under maximal use conditions (Study 501) in which approximately 4 g of study drug applied once daily for 14 days. The Applicant omitted Section 10 OVERDOSE in labeling for Arazlo Lotion.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Arazlo Lotion has not been marketed in any country, and there are no postmarketing safety data available.

Expectations on Safety in the Postmarket Setting

The comprehensive analysis of the Arazlo Lotion safety data identified no safety signals. There are no safety concerns that are expected to change the favorable risk/benefit assessment or lead to increased risk with administration of Arazlo Lotion in the postmarket setting.

8.2.11. Integrated Assessment of Safety

The safety profile for Arazlo Lotion was adequately characterized during the drug development program. The primary safety database consisted of 1570 subjects from Phase 3 Trials 301 and 302 (the pooled safety analysis set, ISS). All randomized subjects who were included in the safety analysis set used the study drug at least once and provided at least 1 post-baseline evaluation.

The safety profile for Arazlo Lotion was similar to the safety profile for other marketed topical tazarotene products. Review of the safety data did not reveal any new safety concerns or suggest additional contraindications (other than contraindication in Pregnancy) to treatment with Arazlo Lotion to be included in Section 4 of product labeling.

Review of the data supports including the potential for skin irritation and photosensitivity and risk of sunburn in Section 5 WARNINGS AND PRECAUTIONS of labeling. Active assessment of

local tolerability indicated that the percentage of subjects who reported signs and symptoms (erythema, scaling, itching, burning, and stinging) at any post-baseline visits was greater in the Arazlo Lotion group than the vehicle lotion group.

The most common ARs which occurred in ≥1 % of subjects treated with Arazlo Lotion and greater than vehicle lotion were related to the application site, and included pain (5%), dryness (4%), erythema (2%), exfoliation (2%), and pruritus (1%).

The pooled safety analysis set (ISS) included 779 subjects who were treated with Arazlo Lotion once daily for 12 weeks. There were no deaths or drug-related SAEs. SAEs occurred at an equal frequency of 4 (0.5%) in both the Arazlo Lotion group and the vehicle lotion group. SAEs among subjects in the Arazlo Lotion group included 3 pregnancies (2 abortions induced, 1 abortion spontaneous), and 1 suicidal ideation (subject was hospitalized).

The Applicant's proposed Sections 4 and 8 of labeling states that Arazlo Lotion is contraindicated during pregnancy (based on animal data for tazarotene) and conveys the lack of human data for the use of Arazlo Lotion during pregnancy and the uncertainty regarding a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Available safety data from the two Phase 3 trials demonstrate that Arazlo Lotion appears safe for the treatment of acne vulgaris in subjects 9 years of age and older. Postmarketing risk management will include professional labeling and routine pharmacovigilance. As the moiety is well characterized, the review team recommends no other risk management tools and assessments (REMS or clinical postmarketing studies).

8.3. Conclusions and Recommendations

To establish the effectiveness of Arazlo Lotion, the Applicant submitted data from two randomized, multicenter, vehicle-controlled, Phase 3 trials (301 and 302). The trials enrolled subjects 9 years of age and older with moderate (3) or severe (4) facial acne vulgaris on the EGSS. Enrolled subjects had 20 to 50 inflammatory lesions (papules, pustules, and nodules), 25 to 100 noninflammatory lesion (open and closed comedones) and two or fewer facial nodules.

In both trials, subjects were randomized in a 1:1 ratio to receive Arazlo Lotion or vehicle applied once daily for 12 weeks in a sufficient amount to cover the entire face, excluding the mouth, eyes, inside the nose, and lips. The coprimary efficacy endpoints were the absolute change in noninflammatory lesion count, absolute change in inflammatory lesion count, and "treatment success" at Week 12. Treatment success was defined as at least a 2-grade improvement from Baseline in EGSS and an EGSS score of clear (0) or almost clear (1).

Secondary efficacy endpoints included percent change in noninflammatory lesion counts and percent change in inflammatory lesion counts from baseline to Weeks 12, 8, and 4; and the proportion of subjects with ≥2 points improvement in EGSS from baseline to Week 12.

The Applicant conducted a maximal use PK Study V01-123A-501, and established a clinical bridge by evaluating the relative bioavailability of Arazlo Lotion, 0.045% and Tazorac Cream,

0.1% in subjects 12 years of age and older. The clinical bridge allows the Applicant to rely on the Agency's finding of safety for the LD via the 505(b)(2) regulatory pathway.

Study V01-123A-501 also evaluated the safety and PK of Arazlo Lotion in subjects 9 years to <12 years of age. The plasma concentrations of both tazarotene and tazarotenic acid were higher in younger subjects (9 to <12 years) following once daily application of Arazlo Lotion, compared to the concentrations in older subjects (≥12 years) following once daily application of Arazlo Lotion or Tazorac Cream. The Clinical Pharmacology reviewer for this NDA concluded that the higher concentrations observed in younger subjects could be due to higher surface area to volume ratio and did not cause any additional safety concerns.

The Applicant conducted a comprehensive assessment of the safety of Arazlo Lotion in the target population. The size of the safety database and the safety evaluations were adequate to identify local and systemic treatment-emergent ARs.

Submitted safety and efficacy data support approval of this NDA for Arazlo Lotion for the topical treatment of acne vulgaris in the population age 9 years and older.

9 Pediatrics

The applicant established the safety and efficacy of Arazlo lotion for use in the target pediatric population age 9 to less than 17 years for the treatment of acne vulgaris in their development program. The applicant requested a partial waiver of assessments in pediatric subjects from birth to less than 9 years of age because "Necessary studies are impossible or highly impracticable because the number of patients in this age group is so small (section 505B(a)(4)(B)(i) of the Act)."

The PeRC agreed with the Division that the assessments were adequate (Meeting of December 10, 2019). Therefore, no postmarketing requirements or commitments for deferred pediatric studies are needed under the Pediatric Research Equity Act (21 CFR 314.55(b) and 601.27(b)). Refer to Pediatrics and Assessment of Effects on Growth in Section 8.2.9 of this review for a discussion regarding the Pediatric Study Plan.

10 Labeling Recommendations

10.1. Prescription Drug Labeling

Prescribing Information

The Applicant submitted proposed Patient Package Insert (PPI), Prescribing Information (PI) and carton/container labels for Arazlo Lotion. The review team provided recommendations regarding PI.

Madhuri R. Patel, PharmD, from the Division of Medication Error Prevention and Analysis reviewed the proposed container label, carton labeling, professional sample container label and carton labeling, PPI, and PI, and provided comments. Division of Medication Error Prevention and Analysis concluded that the PPI and PI were acceptable from a medication error perspective (See Review dated 9/13/2019). Dr. Patel reviewed the container labels and carton labeling for Arazlo and recommended improvements to allow for consistent dosing recommendations with the PI and to facilitate product identification from a medication error perspective.

Laurie Buonaccorsi, PharmD, from the Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the proposed PI. OPDP had no comments regarding the carton/container labeling (See Review dated 11/21/2019).

Other Prescription Drug Labeling

The Applicant submitted a proposed PPI for Arazlo Lotion. Susan Redwood, MPH, BSN, RN from the Division of Medical Policy Programs and Laurie Bounaccorsi, PharmD from OPDP reviewed and provided comments regarding the PPI (See Review dated 11/25/2019). The final labeling will reflect their recommendations.

11 Risk Evaluation and Mitigation Strategies

Based on the favorable safety profile of this product, risk mitigation measures beyond professional labeling and standard postmarketing surveillance are not warranted at this time. As no additional risk management strategies are required, the subsequent subsections are not applicable for this review and are omitted.

12 Postmarketing Requirements and Commitment

No Post marketing requirements are recommended.

13 Appendices

13.1. References

The references are included as footnotes.

13.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and subinvestigators who participated in covered clinical studies for Arazlo Lotion. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4 (a)(3) (i-iv).

The covered clinical studies as defined in 21 CFR 54.2 (e) were Trial V01-123A-301, V01-123A-302, which provided the primary data to establish effectiveness and safety of this product. Refer to Section 8.1 of this review for the trial designs. The Applicant provided the following disclosures:

Significant payments of other sorts from the Applicant of the covered study[21 CFR 54.4 (a)(3)(ii), 54.2 (f)]

- V01-123A-301:
    - (b) (6) Site (b) (6) (Received $37,565 in 2016 and $24,805 in 2017 from Applicant for honoraria, consulting, advisory boards, paid lectures, and reimbursement for travel)
    - (b) (6) – Site (b) (6) (Consultant and speaker on behalf of Valeant Pharmaceuticals North America LLC)
- V01-123A-302:
    - (b) (6) – Site (b) (6) (Consulting engagement fee ($6,195) not ongoing past 11/2017)
    - (b) (6) – Site (b) (6) (Received a one-time consulting income of $2,055 for participation in a round-table discussion on (b) (6))
    - (b) (6) – Site (b) (6) (Received honoraria for consultation under the reportable amount)

Significant equity interest in the Applicant of the covered study product (21 CFR 54.4 (a)(3) (iv), 54.2 (b))

- V01-123A-301:
    - [redacted] – Site [redacted] (investigator owned Valeant stock at a value of $11,664)

The Applicant adequately disclosed financial interests involving clinical investigators. Because the number of investigators with financial disclosures was limited and assessments were blinded, the strategies employed by the Applicant to minimize potential bias arising from investigator financial interests/arrangements appear reasonable.

Covered Clinical Study: V01-123A-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 45		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2 (a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 45		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2 (a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Nonclinical Pharmacology/Toxicology

13.3.1. Multiple of Human Exposure Calculations

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

13.3.2. Recommended Revision to the Nonclinical Portions of Labeling

Revisions to the Applicant's proposed wording for the nonclinical and related sections of the label are provided below. It is recommended that the underlined wording be inserted into and the ~~strikethrough~~ wording be deleted from the Arazlo Lotion label text.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

Arazlo (b) (4) is a retinoid indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

8.1 Pregnancy
Risk Summary

(b) (4) Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, Arazlo (b) (4) may

cause fetal harm when administered to a pregnant female and is contraindicated during pregnancy. Safety in pregnant females has not been established. The potential risk to the fetus outweighs the potential benefit to the mother from Arazlo ~~Lotion~~ during pregnancy; therefore, Arazlo ~~-~~ (b) (4) should be discontinued as soon as pregnancy is recognized *[see Contraindications (4.1), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*.

(b) (4)

In animal reproduction studies with pregnant rats, reduced fetal body weights and reduced skeletal ossification were observed after topical administration of a tazarotene gel formulation during the period of organogenesis at a dose equivalent to the maximum recommended human dose (MRHD) (based on AUC comparison). In animal reproduction studies with pregnant rabbits, single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were observed after topical administration of a tazarotene gel formulation at 15 times the MRHD (based on AUC comparison) *(see Data)*.

In animal reproduction studies with pregnant rats and rabbits, malformations, fetal toxicity, developmental delays, and/or behavioral delays were observed after oral administration of tazarotene during the period of organogenesis at doses 1 and 30 times, respectively, the MRHD (based on AUC comparison). In pregnant rats, decreased litter size, decreased numbers of live fetuses, decreased fetal body weights, and increased malformations were observed after oral administration of tazarotene prior to mating through early gestation at doses 6 times the MRHD (based on AUC comparison) *(see Data)*.

Data

Animal Data

In an embryofetal development study in rats, (b) (4) a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rats during gestation days 6 through 17. (b) (4) R~~r~~educed fetal body weights and reduced skeletal ossification occurred at this dose (equivalent to the MRHD based on AUC comparison). In an embryofetal development study in R~~r~~abbits, a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rabbits (b) (4) during gestation days 6 through 18. (b) (4) S~~s~~ingle incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were noted at this dose (15 times the MRHD based on AUC comparison). (b) (4) ~~,~~

(b) (4)

(b) (4), ~~W~~when tazarotene was given orally to (b) (4) animals, developmental delays were seen in rats; (b) (4) malformations and postimplantation loss were observed in rats and rabbits at doses producing (b) (4) 1 and (b) (4) 30 times, respectively, the MRHD (based on AUC comparison) (b) (4).

In female rats orally administered 2 mg/kg/day of tazarotene from 15 days before mating through gestation day 7, (b) (4) classic developmental effects of retinoids (b) (4) including decreased number of implantation sites, decreased litter size, decreased numbers of live fetuses, and decreased fetal body weights were observed at this dose (6 times the MRHD based on AUC comparison). A low incidence of retinoid-related malformations (b) (4) was observed at this dose. (b) (4)

In a pre- and postnatal development toxicity study, topical administration of a tazarotene gel formulation (0.125 mg/kg/day) to pregnant female rats from gestation day 17 through lactation day 20 reduced pup survival, but did not affect the reproductive capacity of the offspring. Based on data from another study, the systemic drug exposure in the rat at this dose would be equivalent to the MRHD (based on AUC comparison).

8.2 Lactation

Risk Summary

After single topical doses of a ^{14}C-tazarotene gel formulation to the skin of lactating rats, radioactivity was detected in rat milk (b) (4)

12.1 Mechanism of Action

Tazarotene is a retinoid prodrug (b) (4) which is converted (b) (4) to its active form, tazarotenic acid, (b) (4) the carboxylic acid of tazarotene, by deesterification. Tazarotenic acid binds to all three members of the retinoic acid receptor (RAR) family: RARα, RARβ and RARγ, but shows relative selectivity for RARβ, and RARγ and may modify gene expression. The clinical significance of these findings for the treatment of acne vulgaris is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter-term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give (b) (4) systemic exposure in the rat equivalent to (b) (4) the MRHD (based on AUC comparison). (b) (4)

A long-term study with topical application (b) (4) of up to 0.1% of tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals. Tazarotenic acid systemic exposures at the highest (b) (4) dose was 7 (b) (4) times the MRHD (based on AUC comparison). (b) (4)

(b) (4)

No impairment of fertility occurred in rats when male animals were (b) (4)

treated for 70 days prior to mating and (b) (4) female (b) (4) animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of a tazarotene gel formulation up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat (b) (4) at the highest dose was equivalent to the MRHD (based on AUC comparison) (b) (4)

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1 mg/kg/day tazarotene (b) (4) which produced a

systemic exposure (b) (4) 4 times the MRHD (based on AUC comparison). (b) (4)

No impairment of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through gestation day 7 with oral doses of tazarotene up to 2 mg/kg/day (b) (4). However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose, (b) (4) (b) (4) which produced a systemic exposure (b) (4) 6 times the MRHD (based on AUC comparison). (b) (4)

(b) (4)

Clean version of the recommended nonclinical portions of labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

Arazlo is a retinoid indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, Arazlo may cause fetal harm when administered to a pregnant female and is contraindicated during pregnancy. Safety in pregnant females has not been established. The potential risk to the fetus outweighs the potential benefit to the mother from Arazlo during pregnancy; therefore, Arazlo should be discontinued as soon as pregnancy is recognized *[see Contraindications (4), Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]*.

In animal reproduction studies with pregnant rats, reduced fetal body weights and reduced skeletal ossification were observed after topical administration of a tazarotene gel formulation during the period of organogenesis at a dose equivalent to the maximum recommended human

dose (MRHD) (based on AUC comparison). In animal reproduction studies with pregnant rabbits, single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were observed after topical administration of a tazarotene gel formulation at a 15 times the MRHD (based on AUC comparison) *(see Data)*.

In animal reproduction studies with pregnant rats and rabbits, malformations, fetal toxicity, developmental delays, and/or behavioral delays were observed after oral administration of tazarotene during the period of organogenesis at doses 1 and 30 times, respectively, the MRHD (based on AUC comparison). In pregnant rats, decreased litter size, decreased numbers of live fetuses, decreased fetal body weights, and increased malformations were observed after oral administration of tazarotene prior to mating through early gestation at doses 6 times the MRHD (based on AUC comparison) *(see Data)*.

Data

Animal Data

In an embryofetal development study in rats, a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rats during gestation days 6 through 17. Reduced fetal body weights and reduced skeletal ossification occurred at this dose (equivalent to the MRHD based on AUC comparison). In an embryofetal development study in rabbits, a tazarotene gel formulation, 0.5% (0.25 mg/kg/day tazarotene) was topically administered to pregnant rabbits during gestation days 6 through 18. Single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were noted at this dose (15 times the MRHD based on AUC comparison).

When tazarotene was given orally to animals, developmental delays were seen in rats; and malformations and postimplantation loss were observed in rats and rabbits at doses producing 1 and 30 times, respectively, the MRHD (based on AUC comparison).

In female rats orally administered 2 mg/kg/day of tazarotene from 15 days before mating through gestation day 7, classic developmental effects of retinoids including decreased number of implantation sites, decreased litter size, decreased numbers of live fetuses, and decreased fetal body weights were observed at this dose (6 times the MRHD based on AUC comparison). A low incidence of retinoid-related malformations was observed at this dose.

In a pre- and postnatal development toxicity study, topical administration of a tazarotene gel formulation (0.125 mg/kg/day) to pregnant female rats from gestation day 16 through lactation day 20 reduced pup survival, but did not affect the reproductive capacity of the offspring. Based on data from another study, the systemic drug exposure in the rat at this dose would be equivalent to the MRHD (based on AUC comparison).

8.2 Lactation

Risk Summary

After single topical doses of a ^{14}C-tazarotene gel formulation to the skin of lactating rats, radioactivity was detected in rat milk.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tazarotene is a retinoid prodrug which is converted to its active form, tazarotenic acid, the carboxylic acid of tazarotene, by deesterification. Tazarotenic acid binds to all three members of the retinoic acid receptor (RAR) family: RARα, RARβ and RARγ, but shows relative selectivity for RARβ, and RARγ and may modify gene expression. The clinical significance of these findings for the treatment of acne vulgaris is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to the MRHD (based on AUC comparison).

A long-term study with topical application of up to 0.1% of tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals. Tazarotenic acid systemic exposures at the highest dose was 7 times the MRHD (based on AUC comparison).

Tazarotene was nonmutagenic in the Ames assay and did not produce structural chromosomal aberrations in human lymphocytes. Tazarotene was nonmutagenic in CHO/HGPRT mammalian cell forward gene mutation assay and was nonclastogenic in an in vivo mouse micronucleus test.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of a tazarotene gel formulation up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat at the highest dose was equivalent to the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1 mg/kg/day tazarotene, which produced a systemic exposure 4 times the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through gestation day 7 with oral doses of tazarotene up to

2 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose, which produced a systemic exposure 6 times the MRHD (based on AUC comparison).

13.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

13.4.1. Summary of Bioanalytical Method Validation and Performance

The concentrations of tazarotene and tazarotenic acid in human plasma were quantified using a validated LC-MS/MS method. The method validation results are summarized in Table 45. The bioanalysis performance results are summarized in Table 46.

The bioanalytical method was adequately validated and met the acceptance criteria suggested in the FDA Bioanalytical Method Validation Guidance. Incurred sample reanalysis for plasma samples were acceptable in terms of both sample size (at least 10% of the first 1000 samples and 5% of the remaining samples) and the results (>67% of the study samples evaluated within ±20% of the original sample concentrations). All samples were analyzed within the established long-term stability window.

Table 45: Summary of LC-MS/MS Bioanalytical Method Validation

Validation Report	VVALN1404P3	
Matrix	Human plasma	
Anticoagulant	Dipotassium Ethylene Diamine Tetra Acetic Acid (K_2EDTA)	
	Analyte	
	Tazarotene	Tazarotenic Acid
Internal standard (ISTD)	Tazarotene-d8	Tazarotenic Acid-d8
Linearity (calibration curve range)	5.00 to 2500 pg/mL	5.00 to 2500 pg/mL
LLOQ	5.00 pg/mL	5.00 pg/mL
Precision (% CV)		
Intra-assay	• LLOQ: 7.1 to 11.7% • Above LLOQ: 1.7 to 9.3%	• LLOQ: 4.6 to 13.8% • Above LLOQ: 1.1 to 8.9%
Inter-assay	• LLOQ: 12.4% • Above LLOQ: 2.9 to 6.2%	• LLOQ: 7.1 to 13.2% • Above LLOQ: 3.4 to 6.6%
Accuracy (% Nominal)		
Intra-assay	• LLOQ: -15.7 to 4.0% • Above LLOQ: -4.8 to 0.5%	• LLOQ: -9.0 to 11.2% • Above LLOQ: -5.21 to -0.2%
Inter-assay	• LLOQ: -7.5% • Above LLOQ: -2.6 to -0.6%	• LLOQ: -0.6% Above LLOQ: -3.8 to -1.7%
Reproducibility (% Bias)		
Individual sample	-5.2 to 3.3%	0.4 to 10.0%
Whole batch	-10.1 to 0.1%	-4.0 to 4.1%

Freeze/Thaw stability	Stable over 4 cycles of freeze (-70°C or -20°C) and thaw (room temperature)
Bench-top stability	6.5 hours at room temperature under normal laboratory lighting
Long-term stability	Stable over 330 days at -70°C or -20°C
Sample collection and process stability	Stable up to 1 h in an ice-water bath and at room temperature unprotected from light
In-autosampler stability	Stable over 3 days and 21 h at room temperature
Stability when refrigerated	Stable over 3 days and 21 h

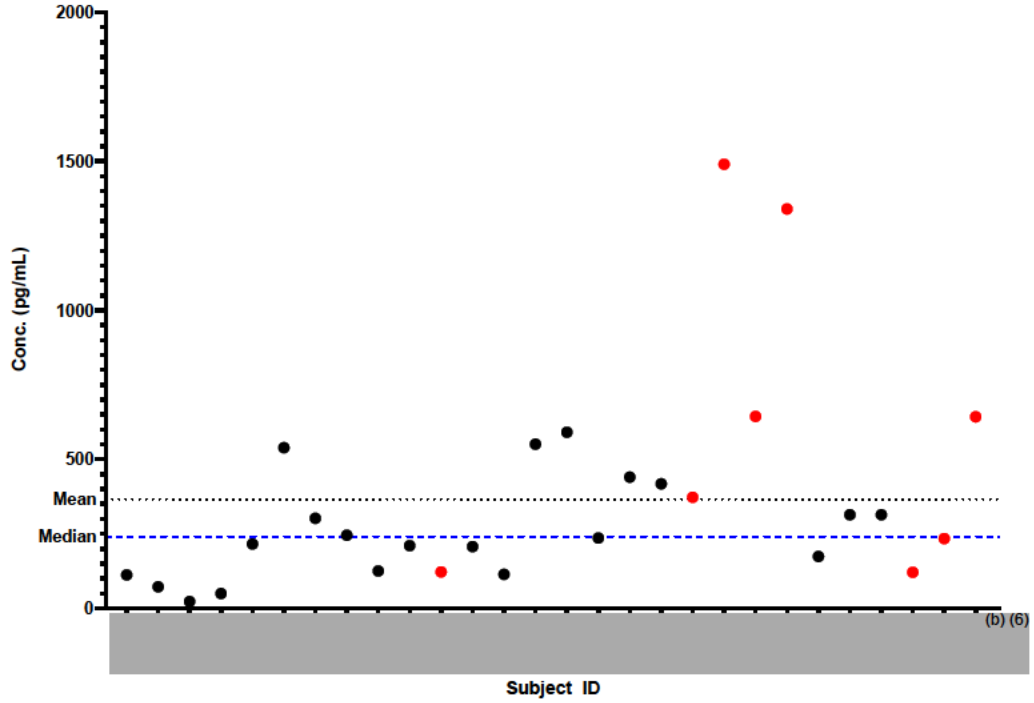
Abbreviations: LLOQ = lower limit of quantification

Table 46: Summary of Bioanalysis Performance

Relevant Clinical Trial	V01-123A-501
Bioanalytical method ID	BVALN1601P1
Matrix	Human plasma
Anticoagulant	Dipotassium Ethylene Diamine Tetra Acetic Acid (K_2EDTA)
Analytes	Tazarotene and tazarotenic acid
Internal standard	Tazarotene-d8 and tazarotenic acid-d8
Linearity (calibration curve range)	5.00 to 2500 pg/mL
Incurred Sample Reanalysis - Tazarotene	
Total no. of incurred sample reanalysis	78 (10.2% of samples)
Total no. of sample whose % differences are within 20%	75
% of total no. of samples whose % differences are within 20 %	96
Incurred Sample Reanalysis – Tazarotenic Acid	
Total no. of incurred sample reanalysis	95 (12.4% of total samples)
Total no. of sample whose % differences are within 20%	94
% of total no. of samples whose % differences are within 20 %	99
Duration from time sample was first drawn to date of last sample analysis including ISR	210 days (within the established stability window of 330 days)
Actual sample storage temperature	-20°C or below

13.4.2. Supporting Graphs

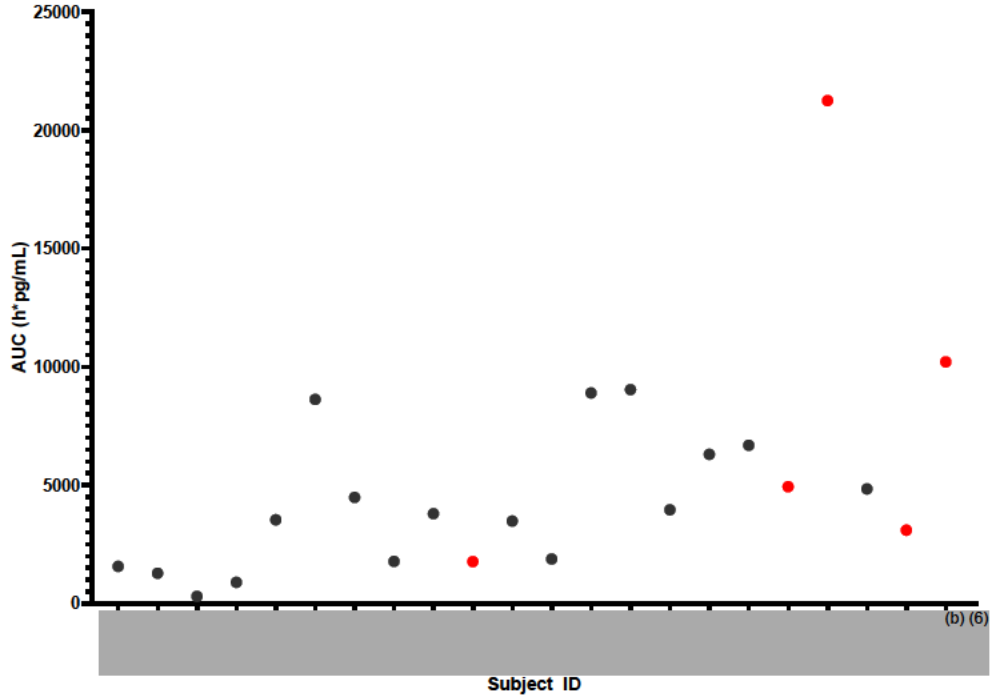
Figure 17: C_{max} of Tazarotenic Acid on Days 14 to 15 From Individual Subjects From the Arazlo Lotion Treatment Group



Source: reviewer's plot
Data in red dots represent subjects aged 9 to <12 years and black dots represent subjects aged ≥12 years.
Abbreviations: C_{max}=observed peak drug concentration

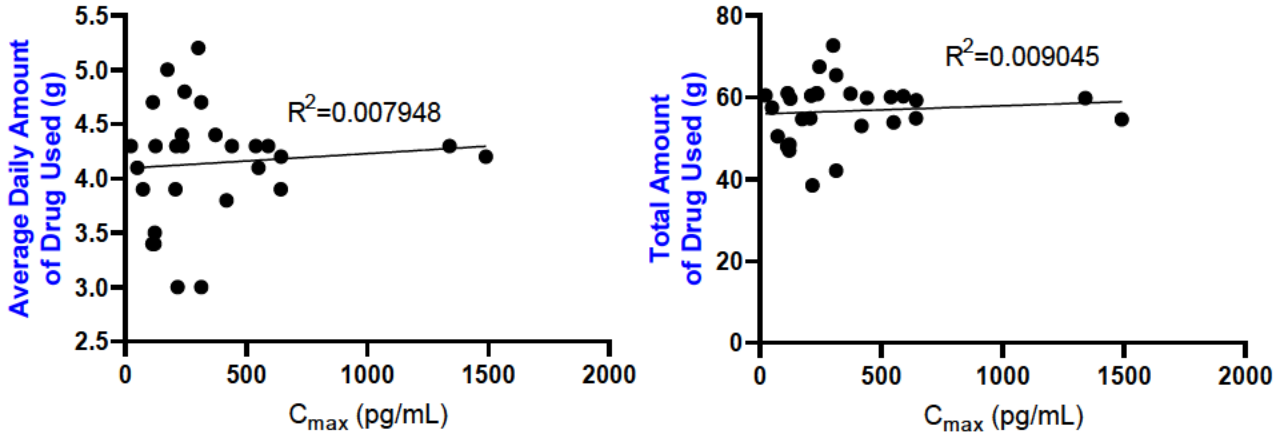
Reviewer's comments: *In subjects 9 to <12 years old, 62.5% (5 out of 8) of C_{max} values were above the mean, whereas in subjects 12 years and older, only 25% (5 out of 20) of C_{max} values were above the mean. This analysis suggests that the systemic exposure following daily application of Arazlo Lotion is higher in younger subjects compared to older subjects.*

Figure 18: AUC_{all} of Tazarotenic Acid on Days 14 to 15 From Individual Subjects From the Arazlo Lotion Treatment Group



Source: reviewer's plot
Data in red dots represent subjects aged 9 to <12 years and black dots represent subjects aged ≥12 years. Data are from 22 subjects (out of 28) as AUC values could not be calculated in all subjects.
Abbreviations: AUC=area under the curve

Figure 19: Relationship Between Dose of Arazlo Lotion and C_{max} of Tazarotenic Acid on Days 14 to 15



Source: reviewer's plot
Abbreviations: C_{max}=observed peak drug concentration, R^2=coefficient of determination

Reviewer's comments: The systemic exposure, as evaluated by the observed C_{max} of tazarotenic acid on Days 14 to 15, does not appear to be related to the average daily amount of Arazlo Cream applied nor the total amount of Arazlo Cream applied over the treatment period.

13.5. Additional Clinical Outcome Assessment Analyses

Refer to Section 1.4 of this review.

APPEARS THIS WAY ON ORIGINAL

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/s/

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12/16/2019 07:57:36 PM

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